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2019 年度新药报告

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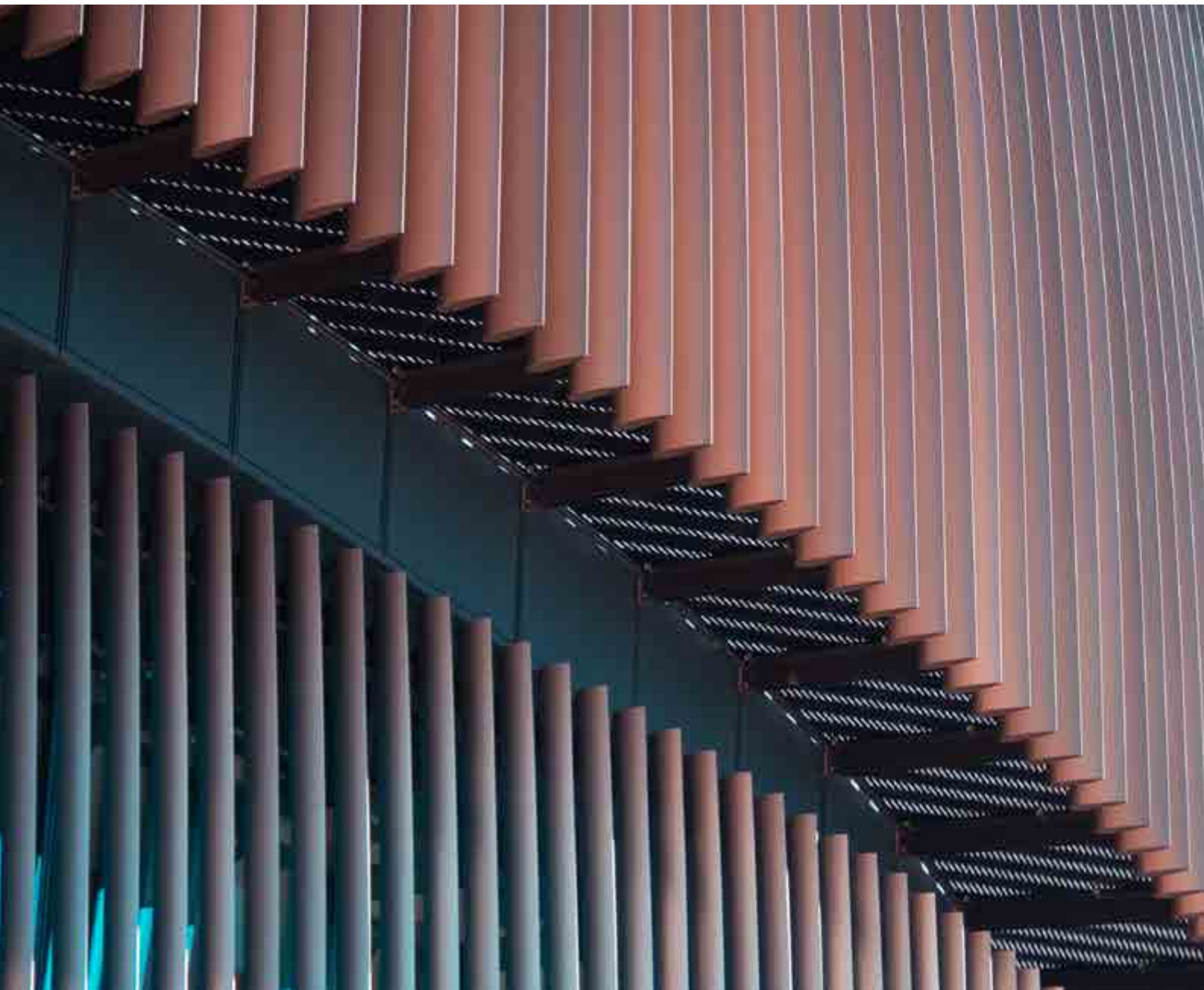

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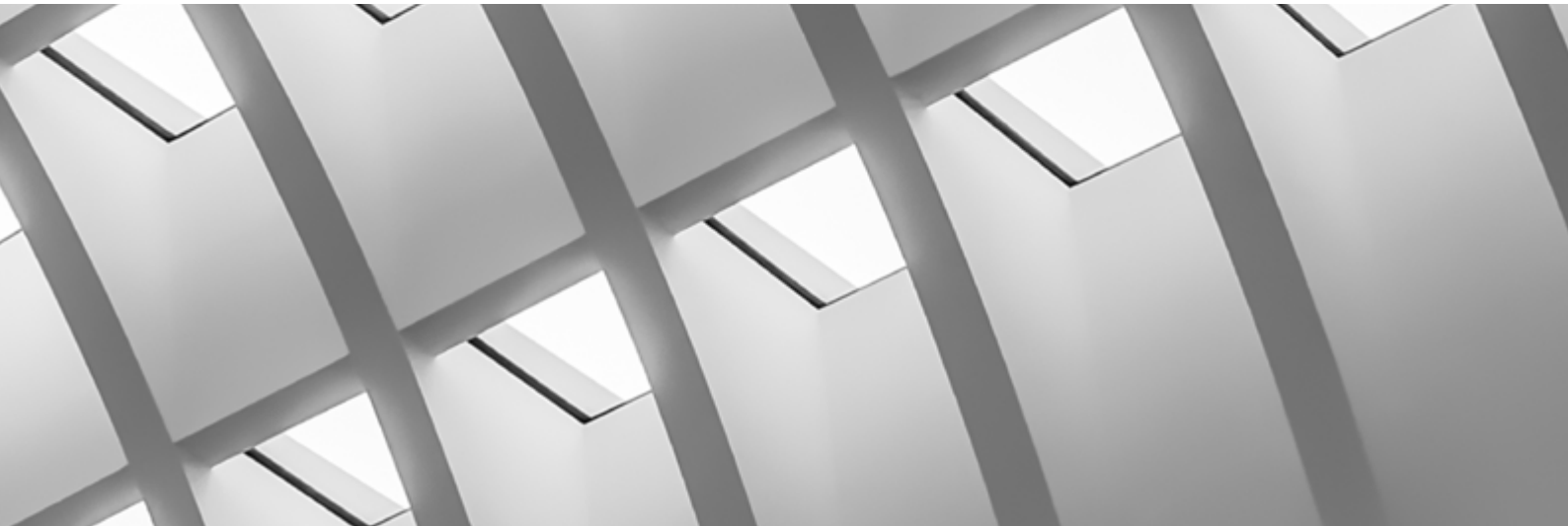

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摘要

我们对全球药品市场上新获批和新上市的药物进行了年度综述,重点内容包括目前为止在囊性纤维化治疗中应用最广泛的Trikafta的获批和上市;首款常规(非应急)接种用的埃博拉疫苗的获批;全球首款疟疾疫苗在三个非洲国家的试点推广;一种新型多药耐药细菌感染治疗药物的获批;首款阿尔茨海默病原研药在中国获批上市,结束了全球十余年来相关领域无新药上市的历史。多款新型免疫检查点抑制剂和抗体药物偶联物的恶性肿瘤适应症相继获批,这证实了生物制药行业对恶性肿瘤免疫疗法的投入热情持续上涨。2019年最引人瞩目的趋势是美国食品药品管理局(FDA)授予了创纪录数量的加速审评,其中多项审评的批准早于预期批准日期多达数月。

关键词:新药上市;新药获批;产品线拓展产品;新剂型;新适应症;新联合用药;孤儿药;同类首创新药;加速审批

引言

年度新药报告已有32年历史,从历史和研究的角度对在过去一年中首次在多个国家上市或获批的化学药物和生物药物进行了介绍。

2019年,在全球范围内共有56种新分子实体和生物药首次获批上市(见表I)。此外,有24项重要的新产品拓展(此报告的专用说法,指既往上市药物的新联合用药、新制剂和新适应症)

表 I. 2009 - 2019 年上市的化学药和生物药分类 *

治疗领域	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
中枢神经系统	7	4	5	2	4	3	4	7	6	6	8
呼吸系统	2	1	1	2	1	5	3	1	1	2	1
心血管系统	1	1	1	1	2	1	1	2	0	1	3
肾 - 泌尿系统	2	0	2	1	0	2	1	1	0	1	1
血液系统	3	1	3	2	1	7	7	4	2	7	6
胃肠道系统	1	1	0	1	4	1	4	1	4	2	1
内分泌系统	3	2	1	4	4	6	3	1	3	4	5
皮肤病	1	0	1	2	1	1	2	4	3	3	5
感染性疾病	1	2	6	0	5	11	5	5	6	10	3
肌肉骨骼系统	3	0	1	2	0	1	1	1	3	1	3
免疫系统	17	5	4	5	11	2	5	10	8	5	4
恶性肿瘤	6	7	7	10	12	10	14	5	18	18	13
眼科疾病	1	1	2	0	1	2	0	1	2	3	1
代谢性疾病	3	4	2	2	7	3	5	4	4	5	2
中毒和药物滥用	0	0	0	1	1	0	0	1	0	0	0
口腔和牙科	0	0	0	0	1	0	0	0	0	0	0
诊断试剂	0	0	0	1	1	3	0	2	1	1	0
合计	51	29	36	36	56	58	55	50	61	69	56

* 不包括产品拓展药物。

在全球范围内获得推广。另有26种新产品,包括化学新药、生物制剂以及新产品拓展获批,但无法确认这些产品是否在2019年12月31日前上市。

最为活跃的治疗类药物仍为抗肿瘤药物,有13种新产品获批,其次是中枢神经系统(CNS)疾病治疗药物,有8种。

2019年有9种首创新药首次上市,其中包括治疗阿尔茨海默病(AD)、血友病和性欲减退的新药,以及数款首创的恶性肿瘤治疗药物。

2019年,美国再次成为最活跃的新药市场,其所上市新药占全球新上市产品的56%(图1)。美国食品药品监督管理局(FDA)一直致力于加快新药审批的进程。2017年,美国研究人员发现,2011～2015年间FDA的审批时间比欧洲药品管理局(EMA)平均短60天[1];此后,美国监管机构的审批速度进一步加快。FDA正在采用快速通道和加速审批的方式批准更多的新药,而拒绝的药物数量越来越少,这导致有人指责其已成为被监管行业的合作伙伴。同样值得注意的是,中国本土制药行业涌现出的化学新药和生物制剂的数量在持续增加。在去年首次上市的产品中有7个来自中国,占全球总量的12%。

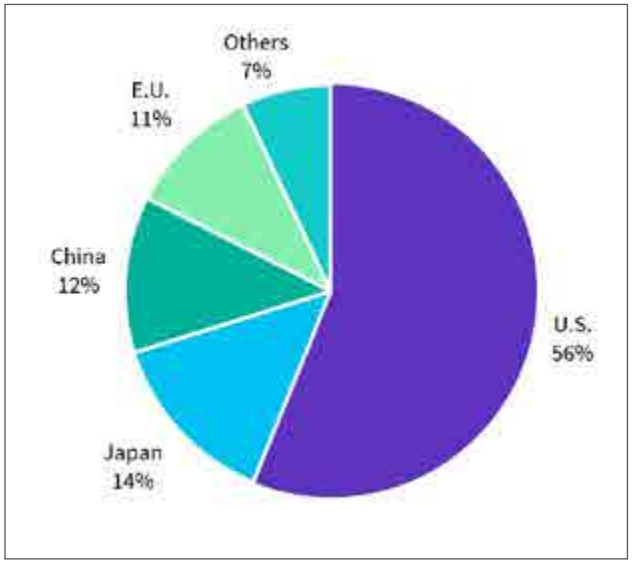

图 1. 2019年上市新药国家分布图

监管机构(主要为FDA,尽管其他国家也设立了相应的程序)可加快新药的开发和审批进程,并通过更多的特殊资格认证为制药公司提供激励。美国国会授权的第一个此类项目是1983年出台的孤儿药法案,该法案的构思和实施旨在促进对罕见病疗法的研究。紧随这项举措之后的是1988年实施的"快速通道"资格认定程序,旨在促进和加速药物开发和审批的进程,以治疗严重疾病并解决未满足的医疗需求。在1992年,通过了对处方药申报者付费法案(PDUFA)的修订,其中包括"加速审批"和"优先审评"程序(而且,并非偶然地首次要求制药公司向监管机构支付审评费用)。1997年,PDUFA法案将目标审评时间从1年缩短至10个月。2012年,美国国会增加了"突破性疗法"的资格认定,这使得FDA能够对现有疗法有实质性改善的新药免除正常的审批程序和要求。美国批准的新药中约有3/4获得某种类型的加速审评资格[2]。在欧盟,优先审评药物(PRIME)资格的实施现已进入第三个年头,其重点关注的药物是对现有疗法的疗效具有显著改善或为无药可用的患者带来获益的药物。2014年3月至2016年8月期间,欧盟药品管理局(EMA)开展了一项试点项目,以评估适应性路径的方法,该方法是一种药物开发和数据生成的科学概念,在高医疗需求的疾病领域,允许早期和进展期的患者有机会更快使用新药。EMA还实施了"加速评估"项目,对于未满足医疗需求的药物的审评时间从210天缩短到150天。在日本,Sakigake资格认定系统于2015年建立,旨在促进创新药物、器械和再生药物的开发。多年来,许多国家纷纷效仿美国孤儿药项目的实施,也设立了类似的激励项目。

从这些加速审评项目中获益最大的两类疾病为恶性肿瘤和罕见病。*The Wall Street Journal*开展的一项研究发现,2015～2018年间获批的大多数恶性肿瘤治疗药物均获得了快速通道资格认定,其中仅有19%在获批时提供了证据,表明其具有显著延长总生存期的疗效[2]。而监管机构要求的上市后研究的结果,与加速审评时提供的小样本研究结果并不总是相符,因为这些小样本研究往往采用的是替代终点[3]。

表 II. 加速路径的药物开发：授予 2019 年新上市产品的特殊资格认定 *

药物名称	适应症	孤儿药	突破性疗法	加速审批	快速通道	优先审评	实时肿瘤学	QIDP	罕见儿科疾病	Sakigake 资格认定
Alpelisib	伴 HR+/HER2-、PIK3CA 突变的晚期或转移性乳腺癌					X	X			
Apremilast	贝赛特氏症	X								
Beperminogene perplasmid	慢性动脉闭塞症（闭塞性动脉硬化症和血栓闭塞性脉管炎）				X					
Brexanolone	产后抑郁		X			X				
Dupilumab	慢性鼻窦炎伴鼻息肉					X				
Eculizumab	视神经脊髓炎谱系疾病	X								
Elexacaftor/tezacaftor/ivacaftor	囊性纤维化	X				X				
Emapalumab	原发性淋巴组织细胞增生症	X	X			X			X	
Entrectinib	伴 *NTRK* 基因融合实体瘤	X	X							
	伴 *ROS1* 基因融合非小细胞肺癌	X								
Erdafitinib	尿路上皮癌		X							
Esketamine hydrochloride	难治性抑郁症		X							
Evocalcet	甲状旁腺癌或原发性甲状旁腺功能亢进合并高钙血症	X								
Fedratinib	骨髓纤维化	X								
Golodirsen	杜氏肌营养不良症	X		X	X	X				
Lefamulin	社区获得性细菌性肺炎				X	X		X		
Luspatercept	β- 地中海贫血	X			X	X				
Nintedanib	系统性硬化症相关性间质性肺病	X	X			X				

表 II. 加速路径的药物开发：授予 2019 年新上市产品的特殊资格认定 *（续）

药物名称	适应症	孤儿药	突破性疗法	加速审批	快速通道	优先审评	实时肿瘤学	QIDP	罕见儿科疾病	Sakigake资格认定
Omadacycline	社区获得性细菌性肺炎和急性皮肤和皮肤结构感染				X			X		
Onasemnogene abeparvovec	脊髓性肌萎缩症	X	X							
Pexidartinib hydrochloride	腱鞘巨细胞瘤	X	X							
Polatuzumab vedotin	弥漫性大 B 细胞淋巴瘤	X		X						
Pretomanid	广泛耐药和多药耐药结核	X			X			X		
Quizartinib	急性髓性白血病	X								
Ravulizumab	阵发性睡眠性血红蛋白尿症	X				X				
	非典型溶血性尿毒症综合征	X								
Rifamycin	旅行者腹泻				X			X		
Ropeginterferon alfa-2b	真性红细胞增多症	X								
Ruxolitinib phosphate	移植物抗宿主病	X	X			X				
Selinexor	多发性骨髓瘤	X		X	X					
Solriamfetol hydrochloride	发作性嗜睡病	X								
Stemirac	脊髓损伤									X
Tagraxofusp	母细胞性浆细胞样树突状细胞瘤	X								
Treosulfan	异体造血干细胞移植前的预处理	X								
Volanesorsen	家族性乳糜微粒血症	X								
Voxelotor	镰状细胞病	X	X	X	X	X			X	
Rifamycin	套细胞淋巴瘤		X	X						

QIDP，合格感染性疾病产品。

* 资格认定仅适用于适应症和上市国家。本表包括产品拓展。

总体而言,2019年在全球范围内上市的所有化学新药、生物制剂和产品拓展中,约有半数在上市国家被授予至少一项特殊资格认定,如表II所示。

镇痛剂和麻醉剂

神经性疼痛是无法用单一病因或解剖学病变解释的一组异质性慢性疾病。它的发生涉及多种病因和潜在机制;典型的神经病理性疼痛综合征包括带状疱疹后遗神经痛、糖尿病神经病变、三叉神经痛、中枢性疼痛综合征、幻肢痛和格林-巴利综合征。所有神经性疼痛均以神经过度兴奋为特征,但疼痛类型和程度可能有所不同,具体取决于患者的整体健康状况和潜在的神经系统疾病等多种因素。2019年,电压依赖性钙通道亚基α-2/δ-1配体**mirogabalin besylate**(Tarlige;日本第一三共)在日本获批上市,用于治疗外周神经痛(PNP),包括糖尿病性PNP和带状疱疹后遗神经痛。

Lasmiditan hydrochloride(Reyvow;礼来)是一种口服5-HT1F受体激动剂,属于一种新型神经作用型抗偏头痛药物(NAAMA)。前几代抗偏头痛药物的作用机制均涉及血管收缩作用,而NAAMA类药物则可以在不引起血管收缩的前提下发挥疗效。Lasmiditan可选择性地靶向作用于三叉神经通路中的5-HT1F受体。2019年10月,该药被美国FDA批准用于成人偏头痛(伴或不伴先兆症状)急性治疗。礼来公司预计,该药在经过美国毒品管理局(DEA)审评后,将于2020年初上市。

正如去年新药报告中重点关注的那样[4],降钙素基因相关肽(CGRP)是一个颇具前景的抗偏头痛药物的新靶标。CGRP是一个由37个氨基酸组成的血管舒张神经肽,广泛分布于中枢和外周神经系统以及心血管系统,其在这些系统中发挥一系列生物学效应和生理功能,这对偏头痛的病理生理机制(包括神经调节和血管舒张)起着至关重要的作用。2018年推出了3款抗CGRP受体单克隆抗体(MAb),适应症均为偏头痛的预防性治疗,给药途径为注射。2019年,FDA批准了首款口服CGRP受体小分子抑制剂:**ubrogepant**(Ubrelvy)的适应症为成人偏头痛(伴或不伴先兆症状)的急性治疗。Ubrogepant由默克公司发现并于2015年授权艾尔建公司在全球进行开发和商业化。该药物计划于2020年上半年上市。

江苏恒瑞开发的**remimazolam tosylate**是一种苯二氮卓类和γ-氨基丁酸(GABAa)BZ位点受体激动剂,于2019年12月下旬在中国获批,适应症为接受诊断性上消化道内镜检查时的全身麻醉。

精神药理学药物

根据世界卫生组织(WHO)的数据,全球范围内有超过3亿人(不分年龄段)受到抑郁症的困扰,相当于全球人口总数的4.4%。尽管患病率如此之高,但目前的疗法通常无效或仅部分有效,或者会引起无法忍受的副作用。数十年来,抑郁症的治疗药物始终是三环类抗抑郁药、单胺氧化酶抑制剂或神经递质再摄取抑制剂。去年,两种具有新作用机制的新型抗抑郁药上市[5]。这两种药物均获得突破性疗法资格认定,且只能在医生监督下使用。

N-甲基-d-天冬氨酸(NMDA)受体拮抗剂**盐酸艾司氯胺酮**(Spravato;杨森)的新型鼻喷剂已获得FDA批准,于去年在美国上市;该药与口服抗抑郁药联合使用,用于治疗成人难治性抑郁症(定义为对任何两种抗抑郁药治疗均无应答)。这是艾司氯胺酮的一个新适应症,该药此前作为静脉全身麻醉药已于1997年上市。在入组了1,700余例难治性抑郁症患者的临床试验中,艾司氯胺酮以亚麻醉剂量经鼻腔给药,与新上市的口服抗抑郁药联用,可缓解抑郁症状并延迟症状复发。值得注意的是,至少有一名FDA精神类药物咨询委员会成员认为该药物的疗效并不显著,该名成员因美国政府停摆而未出席本次会议[6]。此外,艾司氯胺酮可引起严重的副作用,包括镇静效应、解离、自杀的意念和行为[5]。2019年12月下旬,艾司氯胺酮获得欧盟委员会(EC)批准,与选择性5-羟色胺再摄取抑制剂或5-羟色胺和去甲肾上腺素再摄取抑制剂联用,用于成人难治性重度抑郁症的治疗。

四氢孕酮是突触和突触外GABAa受体的正变构调节剂,是一种在研的潜在抗抑郁药。**别孕烯醇酮**(Zulresso;Sage Therapeutics)是四氢孕酮的静脉注射制剂,已于去年在美国获批上市,这是首款也是唯一一款专门用于治疗女性产后抑郁症的药物。产后抑郁症是分娩时最常见的医学并发症,在美国,每年约有40万名女性受其困扰。别孕烯醇酮使用Ligand公司开发的半合成辅料Captisol制成,这是一种经化学修饰的环糊精,其结构设计可以增加药物的溶解度和稳定性。该药的使用需要在已通过Zulresso风险评估和缓解策略(REMS)项目认证的治疗中心,在医务人员的监督下为患者连续静脉输注2.5天。

近几十年来,精神分裂症的治疗取得了很大进展,尤其是通过靶向多巴胺D_2受体来治疗阳性症状。但是,该疾病有一系列其他症状,这些症状严重影响患者的生活质量,因而需要使用其他治疗策略或其他靶标。去年,一种旨在填补这一空白的新药首次获批,即IntraCellular Therapies公司开发的**lumateperone tosylate**(Caplyta)。

Lumateperone通过多种系统协同作用,因此代表了一种针对多种精神神经疾病的独特的治疗和管理方法。其对血清素5-HT2A受体具有强效拮抗活性,还可与多巴胺(D1和D2)受体结合,是突触前D2受体的部分激动剂和突触后多巴胺受体的拮抗剂。此外,临床前数据表明,lumateperone作为谷氨酸能磷蛋白的间接调节剂具有独特的作用机制,其可通过哺乳动物雷帕霉素(mTOR)通路靶蛋白,增加受体D1依赖的NMDA和AMPA活性,这种作用机制可带来强效和快速的抗抑郁效果[7]。Lumateperone在两项安慰剂对照试验中显示出疗效,证实了其与安慰剂相比在主要终点,即阳性和阴性症状量表总评分方面具有显著的统计学差异。该药将于2020年上市。

今年3月,FDA批准了Jazz Pharmaceuticals公司开发的具有双重作用机制的多巴胺和去甲肾上腺素再摄取抑制剂**solriamfetol hydrochloride**(Sunosi),用于改善与发作性睡病或阻塞性睡眠呼吸暂停(OSA)相关的成人日间过度嗜睡患者的醒觉状态。FDA对Sunosi的批准是基于名为TONES的III期临床试验数据,其中包括4项随机安慰剂对照研究,证实了Sunosi相对于安慰剂的优效性。在为期12周的临床研究中,根据患者总体印象评分表的评估结果,在分别服用75 mg和150 mg Sunosi的两个治疗组中报告整体临床状况有所改善的受试者比例分别约为68%～74%和78%～90%。第12周时,通过醒觉维持试验进行疗效评估;该试验分为5次进行,第一次试验自给药后约1小时进行,第五次试验自给药后约9小时进行。在服用150mg solriamfetol的发作性睡病患者和服用各种剂量的OSA患者的醒觉状况较安慰剂对照组均有所改善。在发作性睡病和OSA研究人群中报告的最常见不良反应(发生率≥5%且高于安慰剂组)为头痛、恶心、食欲减退和焦虑。根据美国DEA最终的计划决定,该药已于2019年7月上市。Solriamfetol也于2020年1月在欧洲获批用于相同的适应症。

2019年12月,FDA批准了第二种针对睡眠障碍的新型药物:双重食欲素受体拮抗剂**lemborexant**(Dayvigo;日本卫材),适应症为以入睡和/或睡眠维持困难为特征的成人失眠症。食欲素神经肽信号系统在醒觉维持中发挥作用。阻断促进觉醒的神经肽食欲素A和食欲素B与食欲素受体OX_1和OX_2的结合被认为可抑制觉醒驱动。Lemborexant可与OX_1和OX_2受体结合,并作为竞争性拮抗剂发挥更强效的OX_2抑制作用。Lemborexant是继2014年suvorexant上市之后第二款上市的食欲素拮抗剂。根据DEA的计划,Lemborexant将在获批90天内在美国上市。

神经系统药物

近年来,肠道微生物菌群在人类健康和疾病中的关键作用日益受到关注。微生物组定义为定植于肠道、呼吸道、皮肤和人类机体其他部位的所有共生微生物的遗传物质,已知其可作为信号传导中枢,对环境刺激与宿主遗传和免疫信号进行整合以调节宿主的代谢和免疫功能,以及协调其对感染的应答。最近,有研究表明,肠道菌群的改变通过多种作用机制在阿尔茨海默病(AD)等神经系统疾病中发挥作用[8]。2019年11月,中国国家药品监督管理局(NMPA)条件性批准了治疗AD的首创新药**GV-971**(甘露寡糖),该药被认为通过调节肠道菌群的微生态失调发挥作用(图2)。本品为分离自褐藻的酸性线状寡糖的混合物,由上海绿谷制药公司研发,适用于中轻度AD的治疗和认知功能的改善。一项在中国轻度至中度AD患者中开展的III期试验发现,GV-971治疗开始后仅4周,患者的认知功能既得到统计学意义的改善,并且在为期36周的研究全程期间,每次随访访视时均观察到持续获益。根据阿尔茨海默病评定量表认知分量表(ADAS-Cog12),治疗组和安慰剂对照组间评分的平均差值为2.54分。GV-971安全且耐受良好。GV-971在中国获得有条件的批准需要进一步评价其作用机制、安全性和疗效。一项将在美国、欧洲和亚洲开展的全球多中心III期临床试验计划于2020年初启动,以支持该产品在全球进行法规注册,预计在5年内完成。GV-971于去年12月底在中国上市。

Acorda Therapeutics公司开发的Inbrija是标准抗帕金森病药物**levodopa**的一种新型吸入制剂,去年已在美国上市,用于使用卡比多巴/左旋多巴治疗的帕金森病患者出现关闭期症状时的间歇性治疗。关期症状发作的特征是在规律服用抗帕金森病药物期间出现运动和非运动症状,这些症状通常会随着疾病进展而逐渐恶化。2019年下半年,Inbrija也获得了欧盟的批准。

Cenobamate(Xcopri)是韩国SK生物制药公司发现并开发的一种新型抗惊厥药,于2019年11月获得美国FDA批准,适应症为成人部分发作性癫痫。虽然cenobamate发挥疗效的确切作用机制尚不清楚,但认为该药物可通过抑制电压门控钠电流减少神经元重复放电。该药也是GABAA受体的正变构调节剂。预计cenobamate将在通过DEA的计划审评后于2020年第二季度上市。

第二代鞘氨醇-1-磷酸(S1P)受体调节剂**siponimod fumarate**(Mayzent;诺华)于去年春季在美国获批并上市,用于治疗成人复发型多发性硬化症,包括临床孤立综合征、复发-缓解型多发性硬化症和活动性继发性进行性多发性硬化症(SPMS)。2019年下半年,EMA人用药品委员会(CHMP)采纳了肯定意见,将siponimod用于治疗有活动性疾病的SPMS成人患者,其表现为复发或有炎症活动的影像学特征,如钆增强的T1病变或活动性、新发或扩大的T2病变。该适应症于2020年1月在欧洲获批。

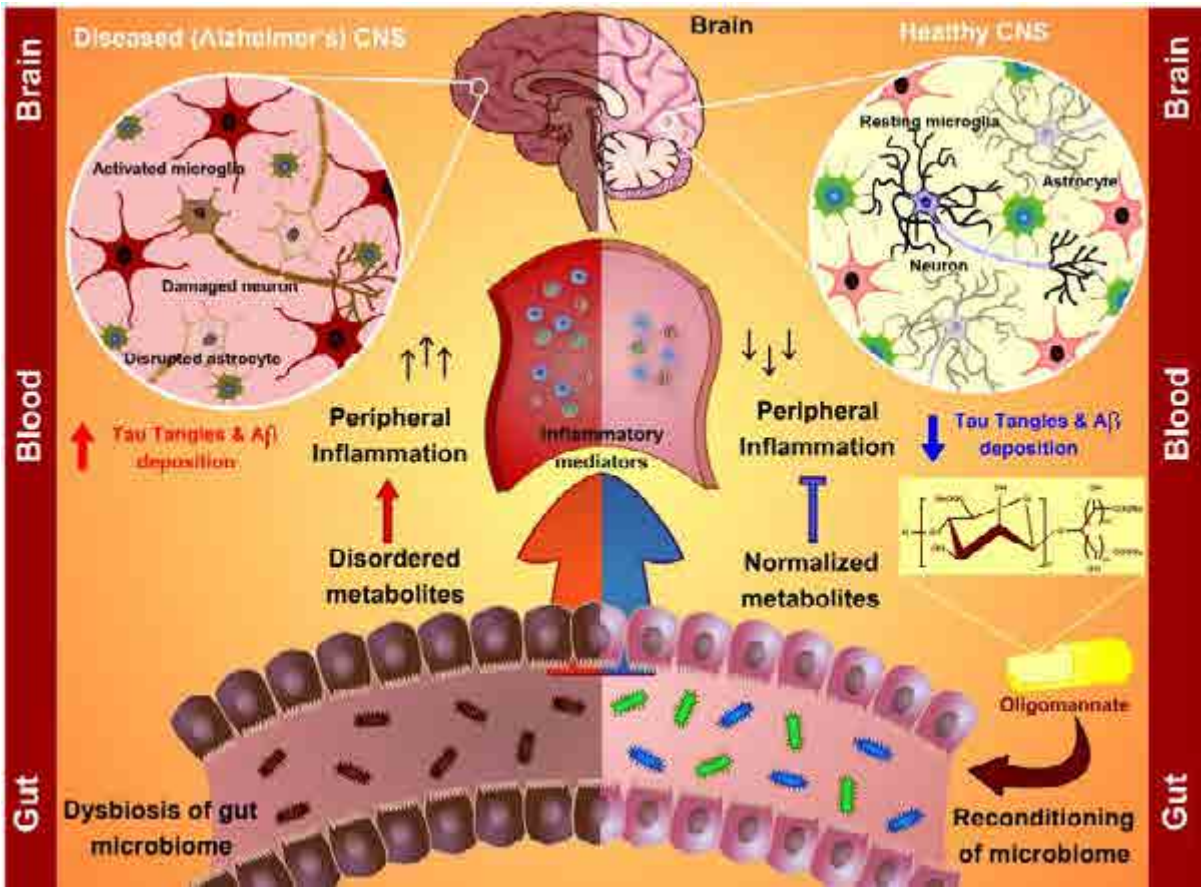

图 2. Oligomannate(GV-971)为首创新药,从海藻中提取,用于治疗阿尔茨海默病。该药通过口服给药,能够将肠道菌群恢复到共生状态,从而减轻外周和中枢神经系统的炎症。这反过来可以调节中枢神经系统(CNS),减少淀粉样蛋白沉积和tau蛋白过度磷酸化,并改善认知功能。

Stemirac(STR-01)是日本札幌医科大学发现并由Nipro公司开发的一种新型细胞疗法,去年已在日本获批并上市,用于脊髓损伤的治疗。Stemirac由在人自体血清中扩增的自体人骨髓来源的间充质干细胞组成。根据日本在2015年创建的Sakigake(创新药物)资格认定系统,该细胞疗法被认定为创新药物。

脊髓性肌萎缩症(SMA)是一种罕见的常染色体隐性神经退行性疾病,主要在儿童期发病,累及脊髓和脑干的运动神经元。SMA在全球范围内均有发病,其在活产婴儿中的发病率约为1/11,000,人群携带率为1/50。约有95%的SMA亚型涉及运动神经元存活基因1(*SMN1*)突变。直到两年前,SMA的唯一治疗方法是支持性疗法;2017年,疾病缓解性药物nusinersen的

上市从根本上改变了I型SMA的治疗现状。2019年,随着**onasemnogene abeparvovec**(Zolgensma,由诺华子公司AveXis开发的基于腺相关病毒载体的基因疗法)在美国获批和上市,该病治疗前景进一步得到改善。Zolgensma适用于2岁以下携带*SMN1*基因双等位基因突变的SMA儿童患者的治疗。该药旨在通过单次一次性静脉输注人*SMN*基因的功能性拷贝,持续表达SMN蛋白,从而阻止疾病进展,针对SMA的遗传学发病机制从根本上进行治疗。该疗法具有潜在的治愈效果,这一点被用于支持其创纪录的210万美元定价的合理性。该产品在美国获得孤儿药和突破性疗法的资格认定。

2016年,尽管外周和中枢神经系统咨询委员会提出了负面建议,但FDA仍加速批准了Sarepta Therapeutics公司的首创外显子跳跃型药物eteplirsen用于治疗特定基因突变者的杜氏肌营养不良症(DMD)[9]。3年后,该咨询委员会在数月前发表了否定意见(完整的回复函),FDA仍再次批准了Sarepta公司的第二款外显子跳跃型反义药物**golodirsen**(Vyondys 53),适用于治疗那些已证实携带了适合53号外显子跳跃的基因突变的患者。根据FDA的数据,仅有约8%的DMD患者存在这种基因突变;因此,golodirsen被认定为孤儿药。外显子跳跃疗法是基于内部缺失的抗肌萎缩蛋白可能保留其部分功能这一发现;因此,如果被破坏了的开放阅读框可以得到恢复,则可以恢复至少具有部分功能的抗肌萎缩蛋白的生成。与eteplirsen的情况相同,golodirsen获得加速审批是基于替代终点,即在一些接受该药物治疗的患者中观察到骨骼肌中的抗肌萎缩蛋白生成量出现增加。FDA得出以下结论:Sarepta公司提交的数据表明,抗肌营养不良蛋白生成量的增加"有可能合理地预测DMD患者的临床获益,这些患者已证实携带了适合53号外显子跳跃的基因突变"[10],尽管该药物的临床获益,包括运动功能的改善尚未得到确定。FDA在作出这一决定时表示,还考虑了与该药物相关的潜在风险(感染和肾毒性),以及该疾病可危及生命和使人衰弱的特点以及缺乏可用疗法的现实状况。Sarepta宣布,将立即开始对golodirsen进行商业分销。该药物后续是否能获得批准可能取决于是否能够通过验证性试验对临床获益进行验证。

视神经脊髓炎谱系疾病(NMOSD),又称Devic病,是一种累及大脑和脊髓的慢性、复发性自身免疫性炎性疾病,以单侧或双侧视神经炎和/或脊髓炎发作为特征。NMOSD是一种罕见病,根据美国国家罕见病组织(NORD)的数据,全球患病率为1-10/100,000[11]。该病病因尚不明确,但在大约2/3的病例中,患存在水通道蛋白-4(AQP4-IgG)抗体以及补体介导的CNS损伤,通常采用免疫抑制剂或泼尼松治疗。去年夏季,FDA批准了NMOSD的新型治疗药物,即Alexion公司的补体抑制剂**eculizumab**(Soliris)。这是该抗C5单克隆抗体药物的新适应症,该药已上市,适应症包括阵发性睡眠性血红蛋白尿症(PNH)、非典型溶血性尿毒症综合征(aHUS)和重症肌无力。Eculizumab在美国被立即用于新适应症且已获得孤儿药认定;在日本,其适应症NMOSD正在接受监管审批。

呼吸系统药物

变应原特异性免疫治疗是一种逐渐得到广泛应用的治疗选择,用于治疗已证实对一种或几种变应原敏感的患者。Itulazax是ALK-Abell公司推出的一种**新型树花粉舌下免疫疗法**(SLIT),去年在欧盟(17个国家)获批,并首次在德国上市。舌下片剂疫苗适用于治疗由来自桦木科树木(包括桦木、赤杨、山毛桃、榛树、角树和橡树)的花粉引起的中度至重度过敏性鼻炎和/或结膜炎,且症状不能通过药物充分控制的成人患者。与可导致不良反应且必须由医生给药的皮下免疫治疗相比,SLIT疗法耐受性良好,患者可在家中服用。

2019年12月,Glenmark Pharmaceuticals公司宣布获得澳大利亚药品管理局(TGA)对固定剂量复方制剂Ryaltris(**盐酸奥洛他定/糠酸莫米松**)的上市许可,该复方制剂适用于治疗12岁以上过敏性鼻炎和鼻结膜炎患者。固定剂量的鼻喷剂可单次给予抗组胺药奥洛他定和皮质类固醇糠酸莫米松。该药将在澳大利亚上市,澳大利亚是全球过敏性鼻炎指数最高的国家之一(接近20%,数据来自Seqirus)。

抗白介素-4(IL-4)受体单克隆抗体**dupilumab**(Dupixent;Regeneron/赛诺菲)于2017年获批用于治疗特应性皮炎,2018年获批用于治疗哮喘,第三个适应症于2019年获批并上市,即与其他药物联合治疗病情未得到控制的成人慢性鼻窦炎伴鼻息肉(CRSwNP)。在dupilumab上市前,CRSwNP的唯一治疗选择是鼻用皮质类固醇或短程全身使用皮质类固醇。美国FDA经过优先审评后,基于两项关键研究(24周SINUS-24和52周SINUS-52研究)批准了dupilumab的新适应症,该两项试验评价了dupilumab 300 mg每2周一次给药加标准疗法糠酸莫米松喷鼻剂(MFNS)相较于安慰剂注射加MFNS(ClinicalTrials.gov识别码NCT02912468和NCT02898454)的疗效。在这些研究中,dupilumab显著改善了关键疾病指标,并达到了所有主要和次要终点:治疗减小了息肉大小,减轻了鼻窦浑浊程度和症状的严重程度,且耐受性良好。EMA在今年下半年也批准了这一新适应症。

Breztri Aerosphere(**布地奈德/格隆溴铵/富马酸福莫特罗**)是

由阿斯利康子公司Pearl Therapeutics公司开发的三联疗法，去年在日本获批上市，用于缓解慢性阻塞性肺病（COPD）的症状。该疗法通过使用基于Aerosphere递送技术的加压定量吸入器单次吸入Breztri，递送吸入性皮质类固醇布地奈德、长效毒蕈碱激动剂格隆溴铵和长效β2激动剂富马酸福莫特罗。该三联疗法越来越多地用于COPD的治疗，在日本有超过500万人患有此症，因此，Breztri Aerosphere是首个在日本获批的此类产品。该疗法在欧盟和中国的申请正在审评中；美国FDA已于10月签发了一份完整的回复函。

囊性纤维化跨膜传导调节因子（CFTR）蛋白嵌入在体内多种细胞的细胞膜中，在囊性纤维化（CF）的发病机制中发挥关键作用。CFTR在胰腺、汗腺、唾液腺、肠道和生殖器官内壁被覆的上皮细胞以及气道粘膜下腺中表达水平最高，而这些恰恰是CF患者体内受累及程度最高的器官和组织。CFTR最直接的作用是作为一种受cAMP调节的氯离子通道，促进氯离子双向流动。除了充当氯离子通道本身，CFTR还充当通道调节剂，影响其他氯离子通道和位于附近细胞膜上的钠离子通道的功能。以缺陷型CFTR蛋白为靶点的新药发现标志着CF治疗的新纪元。该类药物中的第一种药物ivacaftor（Kalydeco）于2012年上市，改变了携带某些特定CFTR突变的CF亚组患者的治疗状况。含Ivacaftor的两药联合（Orkambi和Symdeko）为更广泛的CF患者人群增加了治疗选择。FDA于2019年10月批准了首个含ivacaftor的三药复方制剂Trikafta（**elexacaftor/ivacaftor/tezacaftor**）（在新药申请 [NDA] 提交后仅3个月获批），并几乎立即上市。Trikafta适用于治疗年满12岁并且携带至少1个CFTR基因F508del突变拷贝的患者（无论其是否携带第2个突变）。这意味着约有90%的CF患者适合接受该三联疗法。

2019年9月，FDA批准三重激酶（血管内皮生长因子受体[VEGFR]、成纤维细胞生长因子受体 [FGFR] 和血小板衍生生长因子受体[PDGFR]）抑制剂**nintedanib**（Ofev；中文名：尼达尼布，勃林格殷格翰）的新适应症，即减缓系统性硬化症相关间质性肺病患者肺功能下降的速度。该药是FDA批准的首个用于治疗这种罕见肺部疾病的药物，在美国的审批过程中，该药经过优先审评后同时被认定为孤儿药和突破性疗法，这一结果基于一项在576例20～79岁该疾病患者中进行的随机、双盲、安慰剂对照试验（NCT02597933）而得出。患者接受了52周的治疗，部分患者的治疗时间长达100周。疗效的主要评价指标为用力肺活量；结果显示，使用**nintedanib**的患者肺功能下降的程度低于安慰剂组[12]。在活性药物治疗组中观察到的总体安全性特征与该治疗的已知安全性特征一致。尼达尼布治疗组报告的最常见严重不良事件为肺炎，发生率为2.8%，安慰剂组为0.3%。报告了导致永久性治疗药物减量这一不良反应的患者比例分别为：34%（尼达尼布治疗组）和4%（安慰剂组）；腹泻是活性药物治疗组最常见的不良反应。**nintedanib**于2014年获批用于特发性肺纤维化成人患者的治疗，2015年获批用于非小细胞肺癌的治疗。

心血管系统药物

Azurity公司的Katerzia（**苯磺酸氨氯地平**）已于去年在美国获批上市。这种新型钙通道阻滞剂是第一款也是唯一一款氨氯地平口服混悬剂。它可单独使用或与其他抗高血压药和抗心绞痛药联合使用，适用于治疗成人和儿童高血压以及成人冠心病。Katerzia为年满6岁需要或偏好氨氯地平口服液剂型的儿童提供了一种安全有效的即用型口服混悬液。

Daiichi Sankyo公司的**esaxerenone**（Minnebro）是与Exelixis公司进行研究合作期间发现的一种非甾体类、选择性盐皮质激素受体阻滞剂，于去年在日本上市。本品适用于治疗原发性高血压，目前仅为本类药物中的第三款上市药物。盐皮质激素参与电解质和水平衡的调节；它们影响上皮细胞和肾小管中的离子转运，导致钠潴留和钾流失。

2019年3月，AnGes公司的**beperminogene perplasmid**（编码肝细胞生长因子基因 [HGF] 的DNA质粒）获得日本厚生劳动省（MHLW）的有条件批准，用于治疗重症肢体缺血（CLI）患者。**Beperminogene perplasmid**是在日本获批的首个基因疗法产品，适用于改善慢性动脉闭塞症（闭塞性动脉硬化症和Buerger病）患者的溃疡程度，这些患者对标准药物治疗反应不足，且难以进行血运重建。该药基于在日本进行的一项随机安慰剂对照III期试验和研究者主导的研究结果而获批。在该批准条件下，AnGes将对所有接受该有条件批准药物的患者进行验证性研究，并将在5年内提交解除批准条件的申请。AnGes已授权田边三菱制药公司在日本和美国对beperminogene perplasmid进行商业化，用于治疗包括CLI在内的外周动脉疾病。田边三菱于2019年9月上市了该产品，商品名为Collategene。

肾 - 泌尿系统药物

在获得欧盟批准后将近1年，阿斯利康公司的**磷酸盐结合剂环硅酸钠锆**（Lokelma）于2019年初在斯堪的纳维亚首次上市。该药的适应症为高钾血症，高钾血症是一种严重疾病，特征为与心血管、肾脏和代谢疾病相关的血钾水平升高。对于患有慢性肾脏疾病（CKD）的患者和服用常见治疗心力衰竭药物例如肾素-血管紧张素-醛固酮系统（RAAS）抑制剂的

患者，高钾血症的发病风险显著增加。为了防止高钾血症复发，RAAS抑制剂疗法因其可能会损害心肾功能并增加死亡风险而经常被调整剂量或停止用药。三项双盲、安慰剂对照试验和一项开放临床试验的数据支持了Lokelma的上市申请，其中高钾血症患者接受了长达12个月的治疗。在这些试验中，接受Lokelma治疗的患者血钾达正常水平的中位时间为2.2小时，98%的患者血钾水平在48小时内从基线值达到正常水平。Lokelma表现出长达1年的持续血钾水平控制效果。

血液系统疾病药物

去年，首创新药缺氧诱导因子脯氨酰羟化酶（HIF-PH）抑制剂**roxadustat**（Airuizhuo；中文名：艾瑞卓）在中国首次上市（图3）。HIF-PH抑制剂是一类新型口服活性促红细胞生成药物，通过稳定HIF复合物和刺激促红细胞生成素的内源性生成而发挥作用。Roxadustat的适应症为透析依赖性（血液透析/腹膜透析）CKD患者的贫血治疗。该药由FibroGen公司开发，并授权阿斯利康公司在中国市场进行销售。

2019年6月，EC授予Bluebird Bio公司的**betibeglogene darolentivec**（Zynteglo）有条件上市许可，该基因疗法适用于年满12岁的非β^0/β^0基因型的输血依赖性β-地中海贫血（TDT）患者；这些患者适合接受造血干细胞移植（HSC），但苦于找不到合适的人白细胞抗原（HLA）配型的HSC供体而无法接受移植术。一次性基因疗法采用编码$\beta^{A\text{-}T87Q}$-球蛋白基因的自体$CD34^+$细胞，对TDT的潜在遗传学病因进行纠治，使符合治疗标准的患者有可能终生摆脱输血依赖。Betibeglogene darolentivec由EMA公司的PRIME项目开发；该药也被选为EMA的自适应路径试点项目。EMA于2019年10月下旬批准了Zynteglo的精炼生产工艺，为公司在2020年初开始上市该药品做好了准备。

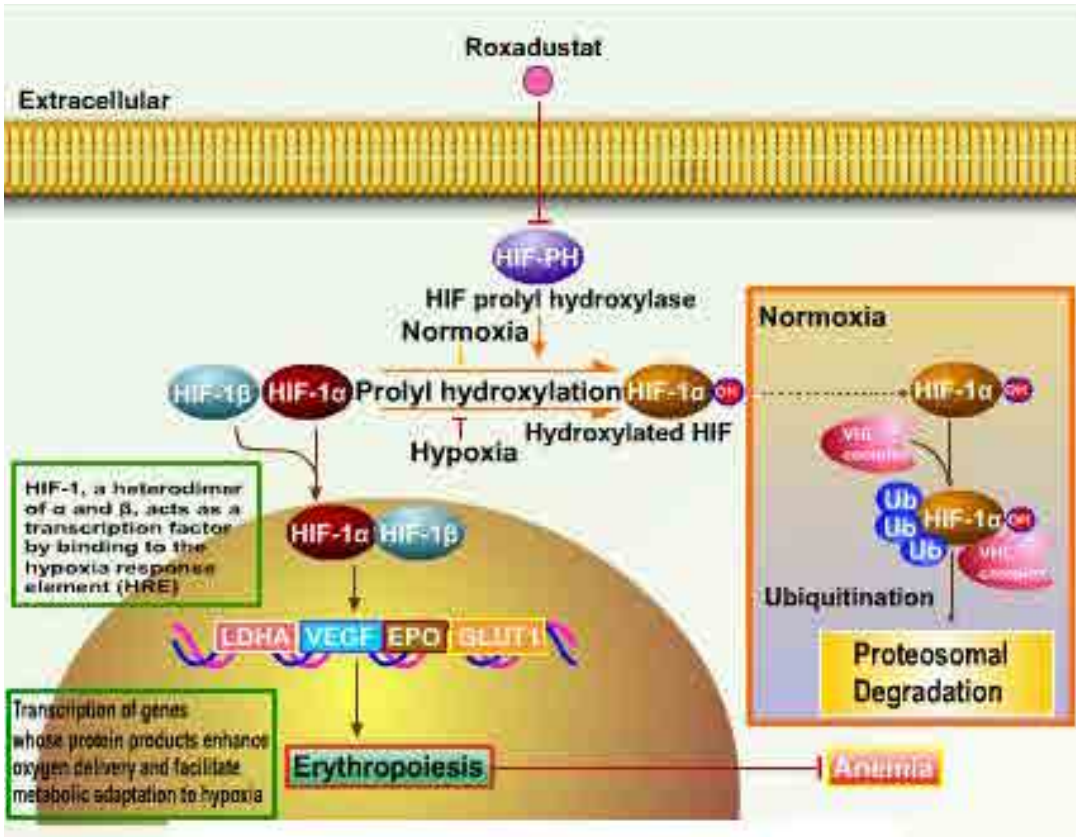

图 3. 缺氧诱导因子（HIF）可调节肾脏和肝脏中促红细胞生成素基因（EPO）的表达。HIF-1α的氧依赖降解通过脯氨酰羟基化介导，该过程反过来可抑制肝脏和肾脏中EPO的表达。HIF稳定剂roxadustat通过抑制HIF脯氨酰羟化酶（PH）发挥作用，旨在稳定和上调EPO基因转录，从而刺激内源性红细胞生成并逆转贫血程度。

FDA于2019年11月批准**luspatercept**(Reblozyl;Acceleron Pharma/Celgene)的适应症,即需要定期输注红细胞(RBC)的β-地中海贫血成人患者的贫血治疗。Luspatercept是首个转化生长因子β(TGF-β)抑制性红细胞成熟剂,代表一类新型疗法,其通过调节红细胞成熟后期阶段帮助患者减轻红细胞输注负荷(图4)。该药经过优先审评后,基于一项关键性、随机、双盲、安慰剂对照的多中心III期BELIEVE研究(NCT02604433)结果获批;该研究评价了luspatercept对于需要定期输注RBC(定义为每24周输注6-20个单位的RBC,并且在5个周期无输血期≥35天)的β-地中海贫血成人患者的贫血治疗疗效。该试验的主要终点达到了具有临床意义和统计学意义的改善。在lus-patercept组中,21.4%的患者在随机化后第13～24周期间达到了RBC输血负荷较基线降低≥33%(至少降低2个单位),相比之下,安慰剂组降低了4.5%。该研究还达到了关键次要终点,包括第37～48周期间输血负荷至少降低33%(至少降低2个单位),输血负荷降低的比例在luspatercept组中为19.6%,安慰剂组为3.6%。其他有效性终点包括第13～24周和第37～48周期间输血负荷至少降低50%(至少降低2个单位)。第13～24周时,观察到luspatercept治疗组中有7.6%的患者(安慰剂组中有1.8%的患者)输血负荷降低≥50%;第37～48周时,这一比例分别为10.3%和0.9%。该药被认定为孤儿药,获批后1周内在美国上市。

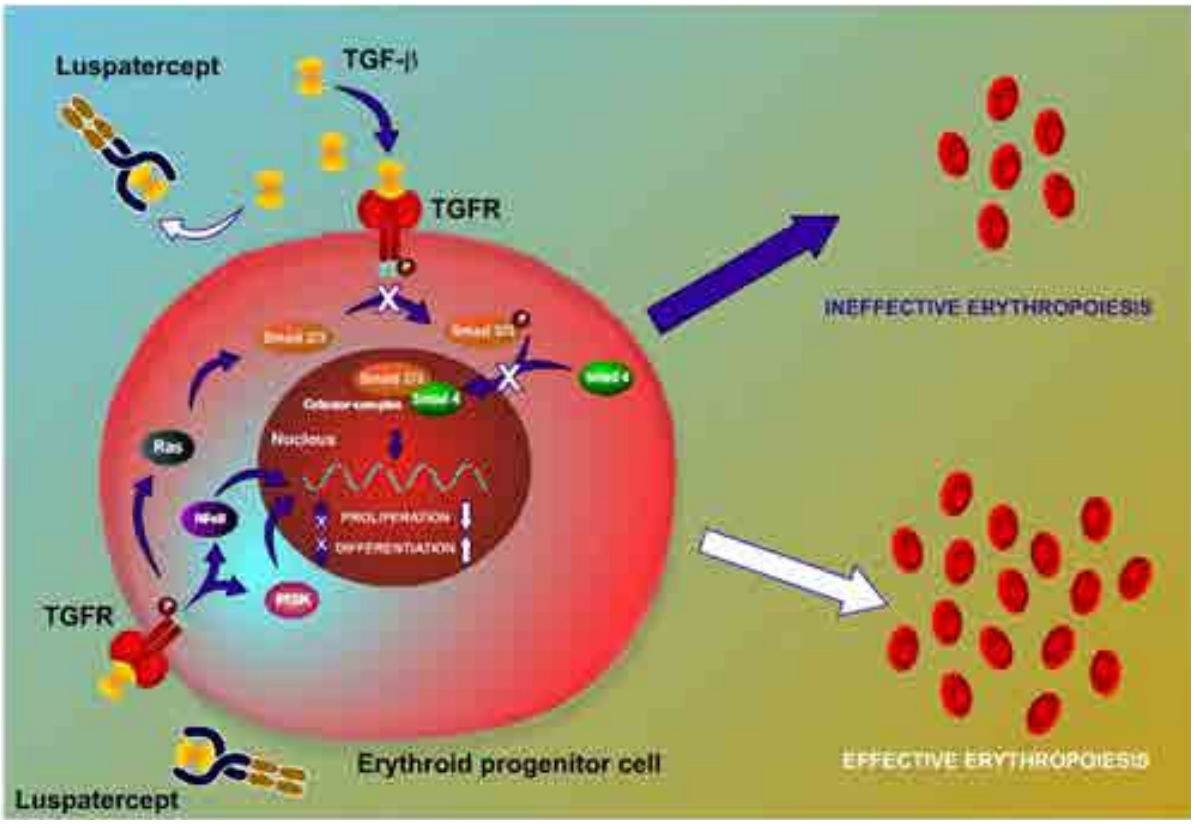

图 4. Luspatercept是一种红细胞成熟剂首创新药,适应症为红细胞生成障碍相关的严重血液疾病。该药物可与多个转化生长因子β(TGF-β)超家族配体结合,从而减弱Smad2/3信号传导。这反过来会降低晚期红细胞前体的增殖并促进其分化,从而恢复红细胞的生成。

先天性甲型血友病的主要治疗方法是在必要时给予凝血因子替代治疗联合重组凝血因子VIII(rFVIII)以达到止血或预防出血发作的目的。现有凝血因子浓缩制剂的一个主要缺点是需要频繁(通常为每日1次)给药,因此许多患者最终需要放置中心静脉通路装置。这些器械可能导致严重不良事件,如感染和血栓形成,这是该疗法的一个严重缺陷,尤其是用于儿童患者时。因此,开发长效rFVIII制剂已成为一个重要目标。去年,一种此类生物制剂已在包括美国、欧盟、加拿大和日本在内的多个国家获批,即诺和诺德公司的糖基化rFVIII,**turoctocog α pegol**(Esperoct)。该药于第三季度在德国和瑞士市场首次上市,用于治疗和预防年满12岁的甲型血友病(先天性凝血因子FVIII缺乏症)患者的出血。虽然该药已于2012年在欧盟获得孤儿药认定,但在2019年5月批准上市许可时,诺和诺德要求撤销这一认定。

真性红细胞增多症(PV)是一种罕见的血液病,患者体内往往生成过量的RBC。这会导致血液变得比正常情况下更粘稠,更容易形成血凝块,并增加卒中和心肌梗死的发生风险。EC已于2019年2月批准PharmaEssentia公司的**ropeginterferon alfa-2b**(Besremi)单药治疗不伴有症状性脾肿大的成人PV。Besremi是首款也是唯一一款获批的PV治疗药物,无论患者既往是否暴露于羟基脲均可使用。该批准适用于所有28个欧盟成员国以及冰岛、挪威和列支敦士登;Besremi在欧洲的上市许可持有者为AOP Orphan Pharmaceuticals公司。该药首先在奥地利和德国上市。

镰状细胞病(SCD)是一种累及红细胞的慢性、终身遗传性血液疾病。由于基因突变,SCD患者的红细胞中含有异常类型的血红蛋白,称为镰状血红蛋白(HbS)。在低氧张力状态下,这些红细胞发生聚集并变成镰状或新月形,使其难以通过小血管。镰状红细胞还表现出一种逐渐增加的倾向,即相互黏附和黏附于血管内皮细胞。SCD患者会发生血管阻塞性危象(VOC),当红细胞变硬、变黏和失去韧性时阻塞血管时就发生这种危象,导致剧烈疼痛。镰状红细胞危象可导致器官损伤、卒中、肺部并发症和包括急性胸部综合征在内的其他不良后果,而这些可能是导致该患者群体死亡的主要原因[12]。如去年报告[4]所示,2018年上市了50年来的首款新型SCD疗法。2019年批准了另外两种新的治疗选择。

SCD与慢性炎症相关,可引起细胞黏附蛋白(包括P-选择素)水平上升;这会进一步增加血管和血细胞的黏性,加速血流中血细胞的黏附和聚集。这种情况可能会引起疼痛和危及生命的VOC。诺华公司的**crizanlizumab**(Adakveo)是一种新型SCD靶向疗法,已在PDUFA日期前2个月,即2019年11月获得FDA批准。Crizanlizumab是一种可与P-选择素结合的单克隆抗体。该批准基于一项为期52周的随机安慰剂对照SUSTAIN研究结果的支持;该研究结果显示,与安慰剂相比,crizanlizumab可使VOC的中位年发生率显著降低45%(1.63 vs 2.98)。此外,患者每年的中位住院天数也减少了42%(4天 vs 6.87天)(13)。

FDA在同月晚些时候(远早于PDUFA日期)授予了另一种SCD抗镰变首创新药**voxelotor**(Oxbryta;Global Blood Therapeutics[GBT]公司)加速审批资格。Voxelotor是一种血红蛋白聚合反应抑制剂,可直接发挥抗镰变作用(图5),已经在动物模型以及SCD患者中证实其具有疗效。Voxelotor通过增加血红蛋白与氧气的亲和力,防止镰状血红蛋白发生聚合反应以及红细胞镰变。该药的批准基于一项III期研究HOPE(NCT03036813)的数据,该研究入组了274例年满12岁的SCD患者。研究显示,治疗24周后,voxelotor治疗组中有51%的患者达到血红蛋白升高>1 g/dL的终点(替代终点),而安慰剂组中有6.5%的患者达到血红蛋白升高>1g/dL[14]。但是,该研究未发现VOC发生率降低。Voxelotor治疗组≥10%的患者中发生的最常见不良反应(与安慰剂组相比发生率差值>3%)为头痛(26% vs. 22%)、腹泻(20% vs. 10%)、腹痛(19% vs. 13%)、恶心(17% vs. 10%)、乏力(14% vs. 10%)、皮疹(14% vs. 10%)和发热(12% vs. 7%)。作为加速审批的一个条件,GBT公司将在HOPE-KIDS 2研究中继续获批后的验证性研究,旨在采用经颅多普勒血流速度证明其可降低2-15岁儿童卒中的发生风险。该产品已于2019年12月上市。

2019年初,抗补体5(C5)单克隆抗体**ravulizumab**(Ultomiris;Alexion)在美国上市,用于治疗成人PNH患者。这种极其罕见的导致人体衰弱的血液疾病以溶血为特征,即红细胞被补体系统所破坏。PNH在所有种族、背景和年龄的男性和女性中均可发病,平均发病年龄在30岁左右。症状包括疲劳、吞咽困难、呼吸急促、腹痛、勃起功能障碍、排深色尿和贫血。慢性溶血的最严重后果是血栓形成,可累及全身血管,损害重要器官并可能导致过早死亡。FDA已授予ravulizumab优先审评资格,并认定其为孤儿药。2019年下半年,ravulizumab在欧盟和日本获批用于治疗PNH。

2019年10月,FDA批准了**ravulizumab**的第二个适应症:用于治疗成人和≥1个月的儿童非典型溶血尿毒综合征(aHUS)患者,以抑制补体介导的血栓性微血管病。aHUS是一种罕见疾病,可导致肾脏小血管中形成异常的血凝块。如果这些血凝块阻

塞或影响了血流,可能会引起严重的医学问题,包括溶血性贫血、血小板减少症和肾衰竭。aHUS可发生于任何年龄,通常由环境因素和遗传因素共同引起[15]。Ravulizumab的这个第二适应症也获得了孤儿药认定,并立即在aHUS人群中进行推广使用。

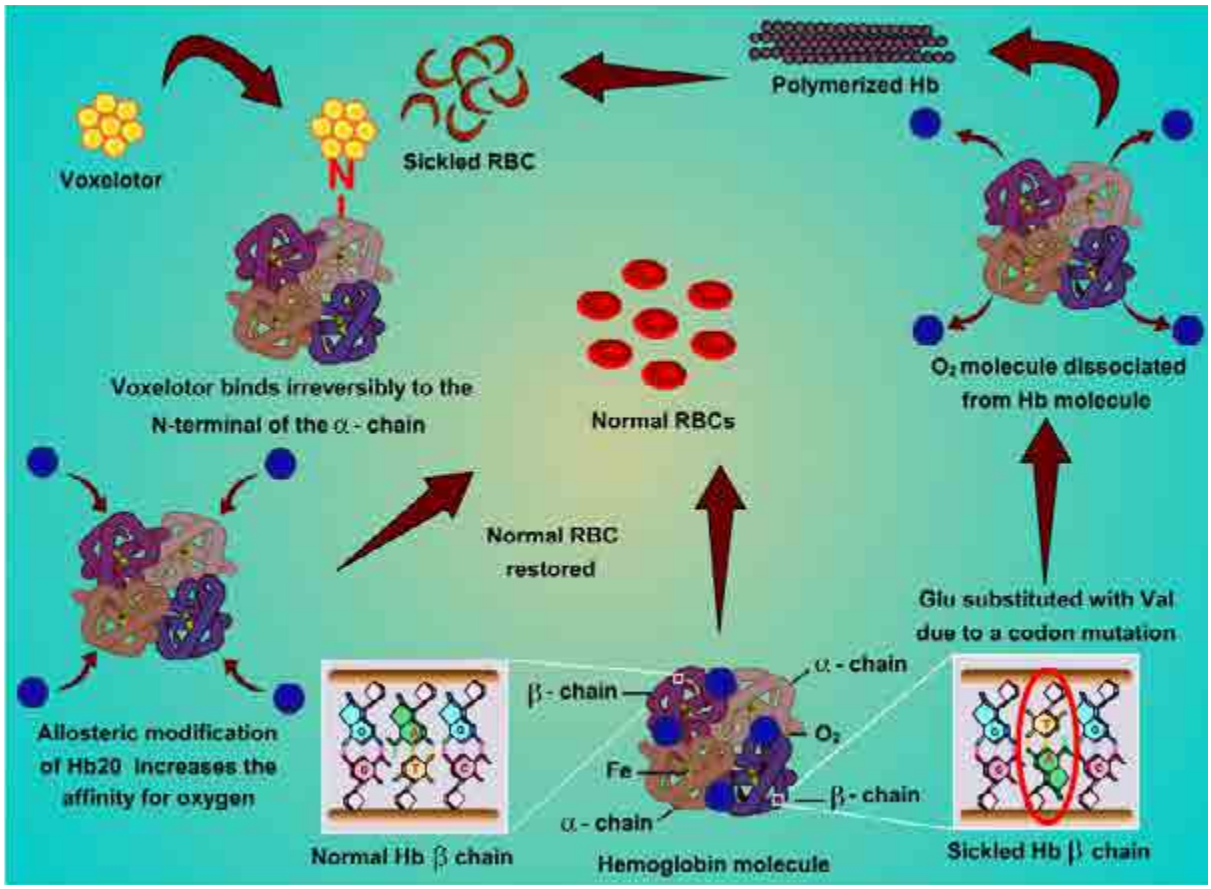

图5. 镰状血红蛋白(HbS)聚合反应是镰状细胞病的致病因素。血红蛋白分子β链密码子突变,导致谷氨酸(Glu)被缬氨酸(Val)替代,这可降低与O2分子的亲和力,导致氧分子解离。而这反过来又会导致异常的镰状红细胞(RBC)形成,进而引起红细胞聚集和全身血管阻塞。Voxelotor是首创的小分子新药,可与血红蛋白α链的N端缬氨酸发生不可逆性结合,导致血红蛋白Hb20构象变化,增加对氧气的亲和力。氧合的镰状血红蛋白不会发生聚合反应。Voxelotor通过直接阻断镰状血红蛋白(HbS)聚合,可逆转HbS与O2分子的亲和力,从而使血流恢复正常。

胃肠道药物

质子泵（H+/K+-ATP酶）抑制剂（PPI）广泛用于治疗胃溃疡和胃食管反流病（GERD）。通常认为这些药物具有安全性，但长期使用可能会导致骨折风险增加，因为它们可能干扰钙吸收。为了克服现有PPI的缺点，新一代钾离子竞争性酸阻滞剂（P-CAB）已被开发出来，并在临床试验中进行了疗效评价。P-CAB在 pKa值较高的情况下以钾离子竞争性的方式可逆性地抑制H+/K+-ATP酶的活性，且在低pH值条件下可提高药物的稳定性。这些特性使得P-CAB具有更好的药代动力学特征，表现为起效时间差异较小、胃酸分泌减少、24小时内疗效延长以及在各种类型的患者中获得一致的疗效。去年，CJ HealthCare公司在韩国上市了P-CAB药物**tegoprazan**（K-CAB）。该药物的适应症为GERD，包括糜烂性食管炎和非糜烂性食管反流病。

2019年11月，FDA批准RedHill Biopharma公司的三联药物Talicia（**奥美拉唑镁/阿莫西林/利福布汀**）用于治疗成人*幽门螺杆菌*感染。Talicia是唯一获批用于治疗*幽门螺杆菌*感染的含利福布汀的治疗药物，旨在消除*幽门螺杆菌*对当前基于克拉霉素的标准治疗的高耐药性。RedHill预计将于2020年第一季度在美国推出Talicia。

Aemcolo是Cosmo Pharmaceuticals公司开发的**利福霉素**的新型制剂，已获得RedHill Biopharma的销售和市场化许可并在美国上市销售，其新适应症为成人旅行者腹泻。Aemcolo是一种胃肠道吸收量最小的抗生素缓释剂，可以递送至结肠。该药尤其适用于非侵袭性*大肠埃希菌*菌株引起的旅行者腹泻；为避免产生耐药菌，Aemcolo应仅用于治疗或预防已证实或强烈怀疑由敏感菌引起的感染。FDA授予Aemcolo合格感染性疾病产品（QIDP）和快速通道资格。

Ardelyx公司的**tenapanor**（Ibsrela）于2019年9月获批用于治疗成人便秘性肠易激综合症。Tenapanor是一种几乎不被人体吸收的小分子药物，可通过抑制钠/氢交换蛋白3（NHE-3）在胃肠道局部发挥作用。膜蛋白NHE-3在大肠和结肠中高度表达，可调节肠道对盐和水的吸收。肠道对钠过度吸收，减少粪便中的含水量从而导致便秘发生。NHE-3抑制剂通过减少整个胃肠道对钠的吸收，帮助恢复或增加肠道中的肠液含量，从而恢复肠道内容物的正常水合，加速肠道的粪便转运并缓解疼痛。Ardelyx公司目前正在与潜在的战略合作伙伴讨论有关Ibsrela在美国上市的事宜。

内分泌药物

在胰岛素促泌剂类降糖药物中，肠促胰素类似物是一种重要且应用日益广泛的治疗选择。去年，Hansoh Pharma公司在中国上市了长效胰高血糖素样肽1（GLP-1）受体激动剂**聚乙二醇洛赛那肽**（孚来美）；中国糖尿病的患病率接近10%。本品适用于单药治疗或与二甲双胍联合使用，结合饮食控制和运动来改善成人2型糖尿病（T2D）患者的血糖控制。

去年美国上市了另一种GLP-1激动剂，诺和诺德的**索马鲁肽**（Rybelsus），此次上市的是片剂新剂型。该药活性成分注射剂之前已获批上市（Ozempic）。Rybelsus是首款口服GLP-1受体激动剂，适用于在饮食控制和运动基础上作为辅助治疗药物改善成人2型糖尿病患者的血糖控制。FDA批准该药是基于10项PIONEER试验的结果，其中包含9,543例成人2型糖尿病患者。Rybelsus的降糖效果优于西格列汀和恩格列净。Rybelsus治疗可使患者体重减轻多达4.4 kg。Rybelsus在PIONEER研究中安全性和耐受性表现良好，最常见的不良事件为轻中度恶心，并可随时间推移而减轻。

虽然钠/葡萄糖协同转运蛋白（SGLT）抑制剂上市时间不足10年，但其作为2型糖尿病的口服降糖药已得到广泛应用。2019年，SGLT抑制剂仍是引人瞩目的降糖药物：Glenmark Pharmaceuticals公司的Remo（**remogli-flozin etabonate**）在印度获批上市以及复方制剂Remo-M（**remogliflozin etabonate/二甲双胍**）获批，同时**sotagliflozin**（Zynquista；Lexicon）在欧盟获批。

阿斯利康公司的Qternmet XR是一种三联药物，由SGLT抑制剂**达格列净**、DPP-4抑制剂**沙格列汀**和胰岛素增敏剂**二甲双胍**组成，已于去年5月获得FDA批准用于治疗成人2型糖尿病患者。该复方制剂已于2019年11月在欧盟获批上市，商品名为Qtrilmet，适应症为当二甲双胍联合或不联合磺酰脲类药物且沙格列汀或达格列净无法充分控制血糖时，或当2型糖尿病患者已接受二甲双胍、沙格列汀和达格列净治疗时，用于改善成人2型糖尿病患者的血糖控制。

在相关的新闻报道中，基于其对糖尿病患者心血管疾病的获益，FDA批准了已上市的SGLT抑制剂**坎格列净**（Invokana；田边三菱/杨森）的新适应症：降低成人2型糖尿病和伴有蛋白尿的糖尿病肾病患者的终末期肾病、血清肌酐翻倍、心血管死亡以及因心力衰竭住院的风险。新适应症是基于在2型糖尿病和糖尿病肾病患者中进行的一项III期CREDENCE研究的结果，该研究在达到预先设定的疗效标准后提前终止

(NCT02065791)。在该项随机、双盲、事件驱动、安慰剂对照、平行设计、双臂多中心研究中,SGLT抑制剂显示出主要复合终点(终末期肾病、血清肌酐翻倍和肾死亡或心血管死亡)风险降低30%的疗效。结果还表明,坎格列净可降低次要心血管终点的风险,包括因心力衰竭住院的风险降低39%。总体而言,不良事件和严重不良事件相似,但坎格列净治疗组的发生率低于安慰剂组。在治疗组中,糖尿病酮症酸中毒和生殖器真菌感染的发生率更高,这与其他临床试验中观察到的结果一致。此外,两组试验中下肢截肢或骨折的发生率相似,未发现新的安全性相关信号[16]。

低血糖定义为血糖水平低于54 mg/dL(3 mmol/L),是运动、饮酒或长期禁食以及血糖控制不佳或血糖控制过严导致的潜在危险后果,最常见于接受胰岛素治疗的糖尿病患者。低血糖可引起一系列症状,从头晕、焦虑和意识模糊直到出现身体协调性问题、视力模糊、意识丧失和痉挛。长期低血糖可对认知功能和大脑显微解剖结构产生严重不良影响,尤其是在1型糖尿病儿童中,严重的低血糖可危及生命。轻度低血糖可通过口服碳水化合物(糖果、果汁、苏打水或葡萄糖片)逆转,而更严重的低血糖则可能需要肌内注射胰高血糖素。2019年上市了两种用于治疗低血糖的新型胰高血糖素制剂,极大地改善了低血糖的治疗现状。2019年7月,FDA批准了礼来公司的**Baqsimi**,这是一种胰高血糖素鼻粉剂,通过鼻内递送装置单剂量给药。该药适用于治疗4岁以上糖尿病患者发生的严重低血糖,并已于2019年8月上市。2019年10月,FDA批准了Xeris Pharmaceuticals公司开发的**Gvoke**,这是一种单剂量预填充针剂或HypoPen自动注射装置,用于2岁以上患者的治疗。Gvoke已于2019年11月上市。

2019年4月,TherapeuticsMD公司宣布Bijuva(**17β-雌二醇/孕酮**)上市,这是FDA批准的首款也是唯一一款以单个口服胶囊形式递送雌二醇和孕酮复方制剂的生物相同(bio-identical)激素的组合疗法。该药的适应症为保留有子宫的女性因更年期引起的中重度血管舒缩症状。该药获批是基于Bijuva临床开发计划,其中包括关键的ReplenishIII期临床试验(NCT01942668),旨在评估Bijuva用于治疗健康且绝经后保留有子宫的女性中重度潮热症状的安全性和有效性[17]。与安慰剂相比,Bijuva在降低子宫内膜病变风险的同时,在降低潮热的发生频率和严重程度方面均较基线有显著改善。最常见的不良反应为乳房压痛、头痛、阴道出血、阴道分泌物异常和盆腔疼痛。与安慰剂相比,在血脂、凝血或血糖参数方面未见有临床意义的变化,并且未观察到非预期的安全性信号。

屈螺酮(Slynd;Exeltis USA)为首款仅含孕激素的口服避孕药,于2019年5月获得FDA批准,用于避孕。这种新型的不含雌激素的避孕药是一种以"24(片,含活性药物)+4(片,不含活性药物)"方案给药的片剂。值得注意的是,这种给药方案为漏服药物的情况设计了24小时的时间窗。这不仅意味着该药具有良好的安全性和疗效,而且可改善出血特征并在发生延迟给药或漏服药物的情况下可维持长达24小时的避孕效果。Slynd于2019年9月在美国上市。

美国人口理事会的Annovera(**醋酸烯诺孕酮-乙炔雌二醇阴道系统**)于去年在美国上市,该避孕环为在美国上市的首款可由使用者自行控制、无需其他操作以及可逆性的长效处方避孕用具。Annovera是一个小而柔软的可弯曲圆环,用于抑制排卵,每个环可重复使用1年(13个周期),由女性使用者自行决定放置和取出;每个周期为28天,可重复使用。该避孕环中含有低剂量的新型孕酮,即醋酸烯诺孕酮和已得到广泛使用的雌激素乙炔雌二醇。该避孕环的获批基于17项临床试验的部分数据,包括两项关键的III期安全性和有效性研究。该III期研究在美国、拉丁美洲、欧洲和澳大利亚的27个研究中心共招募了2,308名女性。所纳入的女性受试者年龄为18～40岁,她们按照研究方案在13个月经周期(1年)内使用该用具。研究数据显示,Annovera在按说明使用时避孕成功率可达97.3%。Annovera的风险特征与其他激素复方避孕药相似,并且说明书中有警告框提示吸烟时使用Annovera可增加心血管相关疾病的发病风险。TherapeuticsMD公司已获得Annovera在美国的商业化权益。

2019年夏季,美国FDA批准了**bremelanotide** (Vyleesi; Palatin Technologies/AMAG Pharmaceuticals),这是一种同类首创的黑皮质素MC_3/MC_4受体激动剂(图6),适用于治疗患有获得性、广义的机能减退性性欲障碍的绝经前女性。Vyleesi由女性使用者通过自动注射器皮下注射给药,需要在性活动前至少提前45分钟给药。该药的批准基于从两项关键性、双盲、安慰剂对照III期试验(RECONNECT)中约1,200例女性获得的数据。在两项注册试验中,bremelanotide达到预先设定的共同的主要终点,即性欲增加和性交痛减轻,并通过经验证的患者报告的结局方法进行评估,结果显示具有良好的安全性。该研究完成后,参与的女性可以选择继续参加一项为期12个月的自愿参加的开放安全性扩展研究。完成该III期试验的患者中有近80%的患者选择继续参加这项开放性的后续研究,所有受试者均接受了活性药物治疗。Bremelanotide已于2019年8月下旬上市。

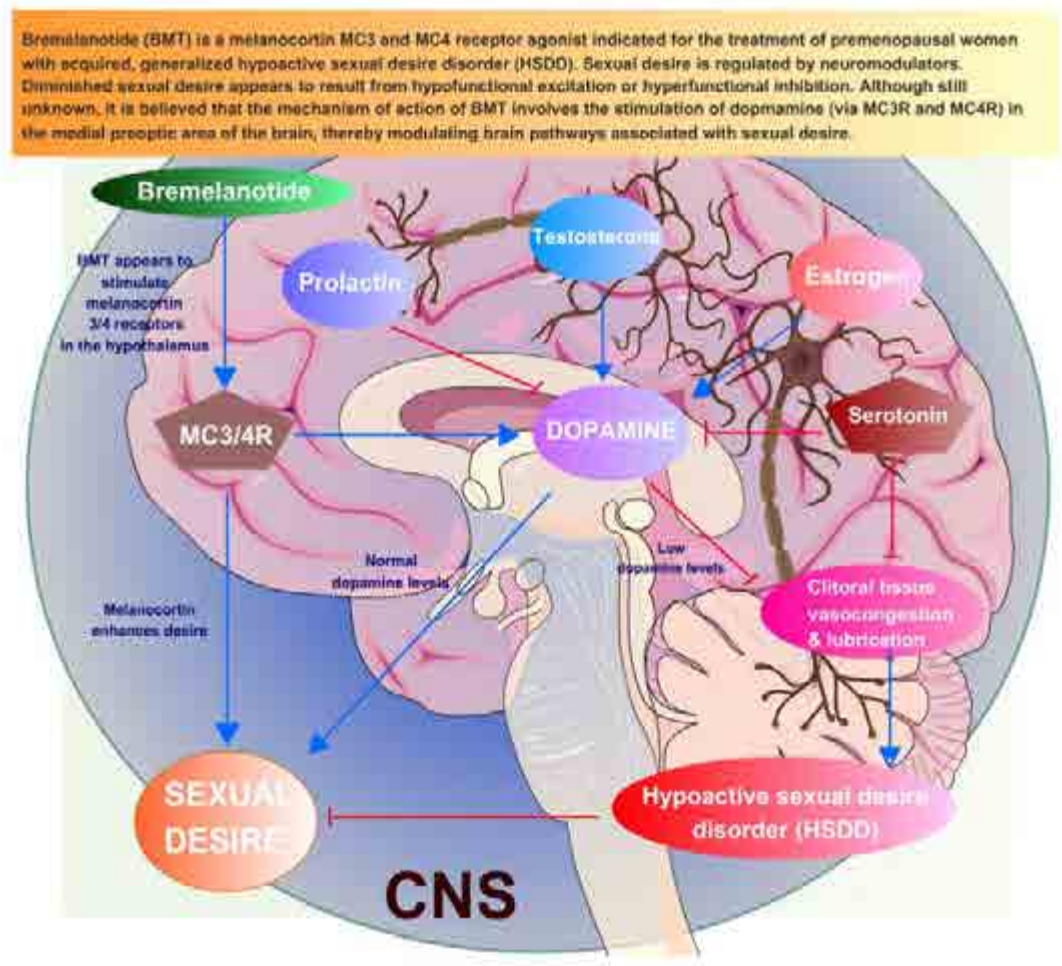

图6. Bremelanotide（BMT）是一种黑皮质素MC3和MC4受体激动剂，适用于治疗患有获得性、广义的机能减退性性欲障碍的绝经前女性。性欲受神经调节物质的调节。性欲减退似乎是由性兴奋功能减退或抑制功能亢进所引起。尽管该病的发病机制尚不明确，但认为bremelanotide的作用机制涉及大脑中脑视前区的多巴胺的刺激（通过MC3和MC4），从而调节与性欲相关的大脑通路。

武田公司的促性腺激素释放激素（GnRH）受体拮抗剂**relugolix**（Relumina）已于去年在日本获批上市，用于缓解子宫肌瘤的症状。武田公司基于在子宫肌瘤患者中开展的日本III期临床试验（TAK-385/CCT-002研究和3008研究），于2018年2月提交了申请。2018年5月，武田公司将该适应症在日本的独家销售权许可给Aska公司。Evocalcet（**Orkedia；Kyowa Kirin**）是一种口服钙敏感受体（CaSR）激动剂，于2018年首次获批用于治疗继发性甲状旁腺功能亢进，2019年底新适应症在日本获批并上市，用于治疗无法接受甲状旁腺切除术或甲状旁腺切除术后复发的甲状旁腺癌或原发性甲状旁腺功能亢进患者的高钙血症。根据一项III期试验的结果，日本MHLW将该药授予“部分变更批准”。Evocalcet该新适应症在日本被认定为孤儿药。

皮肤科用药

2019年1月,Almirall公司在美国上市了每日一次口服窄谱四环素衍生抗生素sarecycline hydrochloride(Seysara),适用于治疗9岁以上的中重度非结节性炎症性寻常性痤疮患者。Sarecycline对主要的皮肤/软组织感染病原体显示出抗菌活性,对*痤疮杆菌*(一种与痤疮皮损相关的革兰阳性厌氧菌)具有靶向活性[18]。与治疗寻常型痤疮的其他四环素类药物相同,该药还具有抗炎作用。与广谱四环素类药物相比,sarecycline对**革兰阴性需氧杆菌和与内源性肠道微生物菌群**相关的厌氧菌的作用较弱。这使其具有特异性抗菌谱,发生不良脱靶抗菌作用的几率更低,因此,与同类其他药物相比是一种更具前景的治疗选择。已证实该药比其他四环素类抗生素的耐药倾向低,且对四环素耐药的金黄色葡萄球菌以及红霉素和克林霉素耐药的痤疮杆菌菌株具有抗菌活性。Sarecycline由Paratek公司发现,并授权给艾尔建公司,后者艾尔建又将其美国医学皮肤病产品组合剥离给Almirall公司。

Galderma公司的**trifarotene**(Aklief)于去年在美国获批上市,用于9岁以上痤疮患者的局部治疗。Trifarotene是唯一一款可选择性靶向皮肤中最常见的维甲酸受体(RAR)-γ的外用维甲酸类药物,是20多年来FDA批准的用于治疗痤疮的首款新型维甲酸类药物。

IL-17家族有6个已知成员(IL-17A-F);IL-17A是主要的辅助性T细胞17(Th17)效应细胞因子。已在多种自身免疫性疾病(包括银屑病)中发现了Th17/IL-17应答的激活,靶向该细胞因子的几种生物制剂已作为银屑病药物上市销售。**Netakimab**(Efleira;Biocad)是最近在抗IL-17A单克隆抗体家族中新增加的一个成员,该药于去年在俄罗斯首次获批上市,用于治疗中重度斑块型银屑病。

IL-23作为IL-17的上游因子可有效抑制下游细胞因子,同时可以降低给药频率。**Risankizumab**(Skyrizi)是由勃林格殷格翰和艾伯维公司联合开发的一种靶向IL-23的人源化单克隆抗体,由艾伯维公司在美国和英国上市,用于治疗准备接受全身性治疗的成人中重度斑块状银屑病患者。Risankizumab已在日本上市,用于治疗银屑病关节炎和斑块状、脓疱性或红皮病性银屑病成年患者,这些患者通常对常规治疗应答不足。靶向IL-17/IL-23信号通路的药物的上市改变了银屑病治疗现状。

Duobrii是由**Bausch Health**(原名Valeant)开发的丙酸氯倍他索和他扎罗汀固定剂量复方制剂,于2019年在美国上市,用于成人斑块状银屑病的局部治疗。Duobrii是首款也是唯一一款外用乳液,含有丙酸氯倍他索(一种皮质类固醇)和他扎罗汀(一种维甲酸)的独特复方制剂。当两种药物分别单独用于治疗斑块状银屑病时,按照FDA标签,丙酸氯倍他索的持续使用时间不得超过2~4周;而他扎罗汀由于耐受性问题,应限制使用。相比之下,在安全性研究中,Duobrii已成功使用长达52周。

Tapinarof是一种天然来源的局部抗炎药,作为芳香烃受体(AhR)激动剂发挥作用。2019年5月,该药在中国获批,用于治疗成人中度稳定性寻常型银屑病。2019年7月,由冠昊生物技术股份有限公司子公司天济医药针对该适应症上市。

白塞病是一种罕见的、慢性易复发、特发性自身免疫性疾病,可导致全身小血管发炎,即血管炎。该病的症状因受累部位的不同而异,包括复发性口腔和/或生殖器溃疡、其他皮肤病变、葡萄膜炎和可能导致失明的眼部病变。白塞病的治疗通常基于经验,治疗目标是控制症状、抑制炎症进程和预防器官损伤。主要治疗手段包括各种抗炎和免疫抑制剂,但这些药物均无法有效控制所有症状。基于小分子磷酸二酯酶4(PDE4)抑制剂**apremilast**在其他适应症中的抗炎活性,对该药在治疗白塞病患者的口腔溃疡方面的疗效进行了评价。Apremilast可通过抑制PDE4提高细胞(尤其是免疫细胞)中的环磷腺苷水平。这导致促炎细胞因子(肿瘤坏死因子a[TNF-α]、IL-23和干扰素γ[IFN-γ])水平降低以及抗炎细胞因子(如IL-10)水平升高。去年,基于随机安慰剂对照的双盲RELIEF III期试验结果,apremilast(Otezla;Celgene)在美国获批上市,用于治疗白塞病患者的口腔溃疡。该产品的这一新适应症被认定为孤儿药。Apremilast于2014年上市,用于治疗银屑病和银屑病性关节炎。

抗感染药物

几十年来,专家们始终对缺乏新型抗生素无法应对日益紧迫的多药耐药的威胁而深感担忧。因此,当去年全球有多个新型抗感染药物和复方制剂获得监管机构的批准时,人们认为发生了令人鼓舞的进展。

截短侧耳素类抗生素通过与细菌50S核糖体亚基的23S rRNA发生特异性相互作用而干扰细菌的蛋白质合成。这类抗生素具有独特的抗菌特性,并且与任何其他种类的抗生素没有交叉耐药性[19]。2019年8月,美国FDA批准将截短侧耳素类抗生素**lefamulin**(Xenleta; Nabriva Therapeutics)的口服和

静脉制剂用于治疗成人社区获得性细菌性肺炎(CABP)。因此,lefamulin成为近20年来FDA批准的首个具有新作用机制的静脉注射和口服抗生素制剂。Lefamulin的静脉注射和口服制剂均已获得FDA的合格感染疾病产品(QIDP)和快速通道资格认定。lefamulin通过QIDP获得的优先审评于2019年9月上市。

2019年6月,FDA批准了默克公司的新型复方抗菌药物Recarbrio(**亚胺培南/西司他丁钠/relebactam**),用于治疗替代疗法有限或无其他治疗选择的18岁以上成人患者,可治疗由易感革兰阴性菌如*阴沟肠杆菌、大肠埃希菌、好氧性克雷伯氏菌、肺炎克雷伯菌和铜绿假单胞菌引起的包括肾盂肾炎在内的复杂性尿路感染(cUTI)*。Recarbrio也适用于治疗18岁以上、替代疗法有限或无其他治疗选择的患者,可治疗敏感的革兰阴性菌如*粪拟杆菌、脆弱拟杆菌、卵形拟杆菌、粪便拟杆菌、多形拟杆菌、单形拟杆菌、普通拟杆菌、弗氏柠檬酸杆菌、阴沟肠杆菌、大肠埃希菌、具核梭杆菌、产气克雷伯菌、产酸克雷伯菌、肺炎克雷伯菌、狄氏副拟杆菌和铜绿假单胞菌引起的复杂性腹腔内感染*。基于Recarbrio有限的临床安全性和疗效数据,这些适应症通过优先审评获批。为减少耐药菌的形成和维持Recarbrio及其它抗菌药物的有效性,Recarbrio应仅用于治疗或预防已证实或强烈疑似由敏感细菌引起的感染。2019年12月中旬,EMA的CHMP采纳了肯定意见,建议批准Recarbrio用于治疗选择有限的成人革兰阴性需氧菌感染。

2019年11月中旬,FDA批准了Shionogi公司的**cefiderocol**(Fetroja),用于治疗选择有限或无其他治疗选择的18岁以上的成人患者,治疗大肠埃希菌、肺炎克雷伯菌、奇异变形杆菌、铜绿假单胞菌和阴沟肠杆菌复合菌引起的cUTI,包括肾盂肾炎。Cefiderocol为头孢菌素类药物,可作为铁载体与细胞外游离铁结合而发挥作用。除了通过孔蛋白通道被动扩散外,cefiderocol还通过铁载体的铁摄取机制主动穿过细菌的细胞外膜进入细胞周质间隙。该药物通过与青霉素结合蛋白结合,抑制细菌细胞壁的生物合成而发挥杀菌作用。Cefiderocol被FDA认定为QIDP资格,从而获得快速通道认定和优先审评资格。值得注意的是,一项在碳青霉烯类耐药革兰阴性菌感染的重症患者中开展的多国随机开放的试验(NCT02714595)发现,与现有最佳疗法相比,cefiderocol治疗患者的全因死亡率增加;因此,该药应仅限于治疗选择有限或无其他治疗选择的患者使用。Shionogi预计cefiderocol将在2020年初上市销售。

新型四环素类抗生素**omadacycline**(Nuzyra;Paratek)在2018年底获批后,已于2019年初在美国上市,适用于治疗急性细菌性皮肤及皮肤结构感染以及由敏感微生物引起的成人CABP患者。Omadacycline在美国获得快速通道和QIDP认定资格,适用于治疗上述两种适应症。Paratek也已在欧盟提交omadacycline这些适应症的申请;但是,Paratek于2019年10月,继EMA要求在CABP患者中额外进行一项临床研究后,决定撤回这两项申请,以待后期获得同步审批。

喹诺酮类抗菌药**lascufloxacin hydrochloride**(Lasvic;Kyorin)已于去年获得日本MHLW批准,用于治疗呼吸道和耳鼻喉感染。该药物的适应症包括咽炎、口腔炎、扁桃腺炎、急性支气管炎、感染性肺炎、慢性呼吸道疾病继发感染、中耳感染和鼻窦炎,适用于治疗*葡萄球菌、链球菌、肺炎球菌、卡他莫拉菌(布兰汉氏菌属)、克雷伯菌、肠杆菌属、流感嗜血杆菌、嗜肺军团菌、普氏菌属和肺炎支原体等敏感菌株引起的感染*。

Dovato是HIV整合酶抑制剂**多替拉韦**和逆转录酶抑制剂**拉米夫定**的固定剂量复方制剂,去年在美国、欧盟和加拿大获批,用于治疗对其中任何一种药物均无已知耐药性且未经治疗的成人HIV-1感染者。该复方制剂由ViiV Healthcare研发,旨在简化抗HIV治疗方案,并于2019年4月首次在美国上市。

非洲锥虫病(俗称昏睡病)是由布氏冈比亚锥虫引起的寄生虫病,通过受感染的舌蝇叮咬传播给人类。因该寄生虫会侵入中枢神经,昏睡病患者如果得不到及时诊治通常会致命。2019年,抗锥虫药**fexinidazole**(Fexinidazole Winthrop)在刚果民主共和国(DRC)和欧盟(后者被批准用于欧盟以外地区)获批,成为这种被忽视的热带病的首款全口服治疗药物。2019年7月,WHO在成人和儿童的基本药物清单中增加了fexinidazole,用于治疗昏睡病的第一阶段(血液淋巴期)和第二阶段(神经期)。在受忽视疾病药物研发倡议(DNDi)的推动下,使用新的药物开发模式开发了Fexinidazole,该开发过程最终涉及15个政府、私人企业和民间社会团体合作伙伴,其中,赛诺菲是来自药企的主要合作伙伴。

Pretomanid是一种干扰细胞壁生物合成的小分子抑制剂,去年8月获得FDA批准,作为贝达喹啉和利奈唑胺口服联合治疗方案(BPaL方案),用于治疗成人广泛耐药肺结核(XDR-TB)和治疗不耐受或无应答的多药耐药肺结核(MDR-TB)。Pretomanid于2019年10月,即获批后仅2个月,被添加至遏制结核病伙伴关系全球药物机构(GDF)药物目录中,从而使该药在全球150个国家和地区得以应用。Pathogenesis公司首先发现了pretomanid,随后授权给TB Drug Development(TB Alliance)

进行开发,并承诺以免除专利费的方式提供给结核病流行国家使用。2019年,TB Alliance公司签署了一项《许可和合作协议》,授权Mylan公司将pretomanid(作为BPaL方案的一部分)商业化,用于治疗XDR-TB和MDR-TB。Pretomanid已在美国获得孤儿药、快速通道和QIDP资格认定。

肌肉骨骼与结缔组织疾病药物

Janus激酶(JAK1、JAK2、JAK3和Tyk2)与关节炎相关细胞因子(包括IL-6、IFN-γ、IL-12、IL-15和IL-23)的不同受体有关。因此,JAK抑制剂作为潜在的疾病缓解性抗风湿药物已得到广泛研究,并最终于2012年开发出同类首创药物托法替尼。去年上市了两种新型JAK抑制剂,用于治疗类风湿性关节炎:**peficitinib hydrobromide**(Smyraf;Astellas)在日本上市,**upadacitinib tartrate**(Rinvoq;AbbVie)在美国上市。

如上所述(见皮肤科用药章节),IL-23/IL-17可调节获得性免疫以及促炎性反应和过敏反应,已被确定为强直性脊柱炎(AS)的重要炎症信号途径。2019年,抗IL-17A单抗**ixekizumab**(Taltz;礼来)获批并上市,用于治疗成人活动性强直性脊柱炎(又称为放射学轴向脊椎关节炎)。该病为ixekizumab单克隆抗体的新适应症,此前该单抗已上市用于治疗银屑病、斑块状银屑病和银屑病关节炎。

2019年8月,日本第一三共宣布,FDA已批准**pexidartinib**(Turalio)作为成人症状性腱鞘巨细胞瘤(TGCT,一组可累及大小关节的罕见非恶性肿瘤)的首款也是唯一一款治疗药物。研究人员已经确定TGCT中的少数细胞在染色体1和2的特定区域发生特定的染色体易位。携带这种染色体易位的细胞过度表达集落刺激因子1(CSF-1)[20],因此会吸引表达CSF-1受体(CSF 1R)的其他细胞,例如巨噬细胞。这些其他的细胞构成TGCT的主体,并且最有可能引起与这些肿瘤相关的炎性改变。Pexidartinib是一种小分子CSF-1R抑制剂,由Plexxicon公司发现。Plexxicon于2011年被日本第一三共收购,但继续作为一个独立的部门运营。Pexidartinib适用于治疗病情严重或功能受限且不适合通过手术改善病情的TGCT患者。由于该药存在肝毒性风险,因此只能通过风险评估和缓解策略项目(Turalio REMS)获得,并且只能由具有资质的医务人员开具处方。由于TGCT为一种罕见病(在美国人群中的发病率为1.8/1,000,000),pexidartinib已获得孤儿药和突破性疗法资格认定。

免疫调节剂和免疫治疗药物

噬血细胞性淋巴组织细胞增生症(HLH)是一种极其罕见、进展迅猛且通常可能致死的过度炎症反应综合征,其中,IFN-γ的过量高表达被认为可驱动免疫系统过度激活,最终导致器官衰竭。该病分为原发性(家族性)和继发性(获得性)两种类型。根据免疫缺陷基金会[21]报道,原发性HLH是一种罕见病,全球每年新生儿中的新发病率约为1/50,000。2018年年底,FDA批准了**emapalumab**(Gamifant),这是一种能与IFN-γ结合并对后者的作用进行中和的单克隆抗体,是近25年来上市的首款HLH新型治疗药物。在该药物上市前,HLH的标准治疗包括类固醇、化疗和造血干细胞移植。Emapalumab由NovImmune公司发现并进行开发,由Sobi公司上市;该产品于2019年第一季度上市。Emapalumab在美国获得孤儿药资格以及突破性疗法和罕见儿科疾病资格认定,并获得了FDA的优先审评资格。

Asceniv(**静脉注射用免疫球蛋白,human-slra**)是ADMA Biologics公司生产的血浆来源的多克隆静脉注射用免疫球蛋白。该产品于2019年4月获得FDA批准,用于治疗成人和青少年(12~17岁)原发性体液免疫缺陷(PI)或原发性免疫缺陷病。PI包括但不限于先天性无丙种球蛋白血症、常见变异型免疫缺陷病(CVID)、X-连锁无丙种球蛋白血症、Wiskott-Aldrich综合征和重度联合免疫缺陷病(SCID)中的体液免疫缺陷。Asceniv在其生产工艺获得优化后,于2019年10月在美国首次上市。

去年夏季,Grifols公司的Xembify(**皮下注射用免疫球蛋白,human-klhw**)获得FDA批准,Xembify是一种皮下注射用免疫球蛋白,也适用于治疗PI,包括但不限于先天性无丙种球蛋白血症、CVID、X连锁无丙种球蛋白血症、Wiskott-Aldrich综合征和SCID。该产品适用于年满2岁的患者,于2019年12月中旬上市。

JAK抑制剂**磷酸芦可替尼**(Jakafi;Incyte)的新适应症于去年在美国获批并上市,用于成人及儿童(年满12岁)类固醇难治性急性移植物抗宿主病(GvHD)。该药通过优先审评获批是基于REACH1的数据,该研究是一项在类固醇难治性II-IV级急性GvHD患者中评价芦可替尼与皮质类固醇联合用药疗效的开放性、单臂、多中心研究(NCT02953678)。在入组REACH1的71例患者中,49例为类固醇单药难治性患者,12例患者既往接受过≥2种抗GvHD治疗,10例患者在其他方面不符合FDA有关类固醇难治性的定义。根据第28天的总缓解率(ORR)

评价疗效,ORR定义为根据国际血液和骨髓移植研究中心(CIBMTR)标准判定的完全缓解(CR)、非常好的部分缓解或部分缓解。49例类固醇单药难治性患者在治疗第28天的ORR为57%,CR为31%。在所有71例受试者中,最常见的不良反应为感染(55%)和水肿(51%),最常见的实验室指标异常为贫血(75%)、血小板减少(75%)和中性粒细胞减少(58%)。芦可替尼2011年被批准用于治疗骨髓纤维化以及2014年被批准用于真性红细胞增多症。该药物用于GvHD已被认定为孤儿药,获得突破性疗法资格认定。

Medac公司的DNA烷化剂**treosulfan**(卵巢癌适应症早已上市)去年在欧盟获批用于治疗新适应症:与氟达拉滨联合使用,作为恶性和非恶性疾病成人患者以及恶性疾病儿童患者接受异体造血干细胞移植前的预处理药物。与其他预处理方案相比,含treosulfan的方案可在维持较高的预处理强度和抗白血病作用的同时减少毒副作用。该药物的新适应症采用Trecondi为商品名,于2019年第三季度在德国上市。其在欧盟和美国的该适应症被认定为孤儿药。

2019年,WHO在收到CHMP的肯定性科学意见的4年后,宣布了一项具有里程碑意义的试点项目:在马拉维上市**RTS,S/AS01E**疟疾疫苗Mosquirix,以此为长达30年之久的疫苗研发工作划上了圆满的句号。马拉维是三个非洲国家中第一个向≤2岁的儿童提供疫苗接种的国家;此后不久,该疫苗也会相继在加纳和肯尼亚上市。该试点计划将招募约36万名儿童受试者。该计划旨在获得证据和经验,从而向WHO提供关于普及使用Mosquirix的政策建议[22]。该计划将关注儿童死亡率的降低情况以及疫苗的接种情况,包括父母是否按时带其孩子接受4次疫苗接种以及常规使用时疫苗的安全性。该试点计划由WHO负责协调,是一项涉及加纳、肯尼亚和马拉维三国卫生部以及包括PATH和疫苗研发者兼生产商葛兰素史克在内的一系列国内和国际合作伙伴的合作计划。葛兰素史克为此试点计划捐赠了高达1,000万剂疫苗。

去年的另一款新开发的药物也令人振奋:EC于2019年11月对默克公司的**扎伊尔型埃博拉疫苗**(Ervebo)授予有条件批准,这是首款在大型临床试验中进行评价后获得监管机构批准的埃博拉疫苗;1个月后,该疫苗也获得了FDA的有条件批准。在美国生物医学高级研究和发展管理局(BARDA)的资助下,加拿大国家微生物学实验室发现了该疫苗,并与NewLink Genetics和默克公司通过政府与民间合作的形式进行研发。该疫苗已在最近两次西非地区(2013~2016年)和刚果民主共和国(2018~2019年)的埃博拉大爆发中经受了广泛的考验。Ervebo适用于在年满18岁的个体中诱导主动免疫,以预防扎伊尔型埃博拉病毒引起的埃博拉病毒病。该疫苗获批后,Merck即可在德国启动许可剂量的生产工作,预计从2020年第三季度开始生产。Merck还将与WHO、美国政府和Gavi(疫苗联盟)合作,确保持续供应疫苗,以在对刚果目前爆发的疫情开展的国际应对工作时提供支持。之前已批准的另外两款埃博拉疫苗基于I期和II期试验,但仅供应急接种使用。俄罗斯Gamaleya联邦流行病学和微生物学研究中心研发了Gam Evac Combi,这是一款抗埃博拉热的联合载体疫苗,于2015年获批在俄罗斯联邦境内用于医疗实践。2017年,中国国家药品监督管理局批准了由中国人民解放军军事医学科学院生物医学工程研究所和天津康希诺生物股份公司联合研发的Ad5-EBOV疫苗。

2019年9月,Bavarian Nordic公司的**MVA-BN天花疫苗**(Jynneos)获得FDA的上市批准,用于确定在具有天花或猴痘感染高风险的年满18岁成人中进行天花和猴痘的预防。该公司获得了优先审评凭券和批准。虽然该疫苗自2013年以来已在欧盟上市用于预防天花,但猴痘在美国为新增适应症,可能为其带来了新的商机;Jynneos是全球首款猴痘疫苗。Jynneos正在供应给美国政府,供其纳入国家战略储备。

同样在9月,印度药物控制中心批准了一种由Zydus Cadila公司与WHO合作研发的两种单克隆抗体组成的鸡尾酒式新药**Twinrab**。该药获批与狂犬病疫苗联合使用,用于狂犬病病毒暴露后的预防,避免出现狂犬病病毒感染。

丹麦疫苗公司AJ Vaccines于2017年接管了Statens Serum Institute的疫苗业务,并于去年在丹麦获得脊髓灰质炎灭活疫苗Picovax(**IPV-AI-SSI**)的上市批准。该疫苗由1型、2型和3型灭活脊髓灰质炎病毒组成,根据专有配方技术制成,允许使用较低剂量的活性物质;适用于≥6周龄婴儿的疫苗初种和婴儿、儿童、青少年和成人的疫苗再次接种。AJ Vaccines获得丹麦上市批准为通过WHO资格预审做了准备,使得其可在2020~2024年间向联合国机构最多提供1亿剂Picovax。虽然脊髓灰质炎在具备有效国家免疫接种计划的工业化国家已基本根除,但该疾病仍在3个国家(阿富汗、尼日利亚和巴基斯坦)流行;此外,还有13个国家被视为"爆发国家",即那些本地脊髓灰质炎野生病毒已得到遏制但正在经历再次感染的国家,引起再次感染的两个途径为:通过从另一国家输入野生病毒或疫苗衍生的脊髓灰质炎病毒,或疫苗衍生的脊髓灰质炎病毒在本国出现和传播[23]。

2019年12月下旬,北京科兴生物公司宣布,中国NMPA已批准了该公司的**水痘减毒活疫苗**并签发了产品许可证,其适应症为预防1～12岁儿童出现水痘-带状疱疹病毒(水痘)感染。该疫苗是继2019年6月中国新版疫苗管理法获得通过后,中国政府批准的首款疫苗产品。中国在发生了一系列疫苗安全问题后实施了该法律,该法律要求对疫苗的生产、研究和分装进行更严格的管理[24]。

人乳头瘤病毒(HPV)是一种已知的致癌物,与几乎所有宫颈癌的发生有关;也是阴茎、阴道/外阴、肛门和口咽部位癌症的主要风险因素。HPV占全球恶性肿瘤总负荷的5%以上,其中近1/3的恶性肿瘤由感染性病原体所致。2006年,首款HPV疫苗(Merck公司的 Gardasil)上市,随后又有两种上市。许多国家在免疫接种计划中纳入HPV疫苗后,宫颈癌发病率和死亡率显著下降;但是,在发展中国家,如中国,HPV疫苗接种仍未得到普及应用,因为对于普通大众而言,进口疫苗过于昂贵[25]。因此,国内研发的**针对HPV-16和HPV-18 L1衣壳蛋白的双价HPV病毒样颗粒(VLP)疫苗**馨可宁(厦门万泰沧海生物技术有限公司开发)于12月31日在中国获批,这属于一项重大进展。该疫苗适用于女童和9～45岁的女性接种。2012年,在37个中国城市进行的筛查研究中发现,HPV的患病率为18.4%(南昌)～31.9%(海口)[26]。

癌症治疗药物

大多数前列腺癌在早期具有雄激素依赖性,因此雄激素剥夺治疗(ADT)是首选的一线治疗方法,包括GnRH激动剂、抗雄激素或手术去势。前列腺癌经过上述激素疗法治疗一段时间后,可能会进展为雄激素非依赖性(又称去势抵抗性)状态,即使没有雄激素的刺激,肿瘤仍会继续生长和转移,因此必须调整治疗方案。去年,美国批准并上市了一种新一代的雄激素受体抑制剂,用于治疗非转移性去势抵抗性前列腺癌。**darolutamide**(Nubeqa;拜耳/Orion)。FDA基于评价darolutamide联合ADT疗法的III期ARAMIS试验批准了该药物;该试验表明,主要终点无转移生存得到显著改善,中位无转移生存期为40.4个月,而安慰剂联合ADT为18.4个月[27]。

2019年5月,FDA经过优先审评,批准诺华公司的磷脂酰肌醇-3激酶a(PI3Kα)抑制剂**alpelisib**(Piqray)联合氟维司群治疗激素受体阳性、HER2阴性(HR+/HER2-)、携带*PIK3CA*突变的晚期或转移性乳腺癌且在接受内分泌治疗方案期间或之后仍出现进展的绝经后女性和男性患者,患者的诊断基于FDA批准的一种检测方法。该药的获批基于III期试验SOLAR-1的结果,该研究发现:与氟维司群单药治疗相比,alpelisib联合氟维司群治疗后,携带PIK3CA突变的HR+/HER2-晚期乳腺癌患者的中位无进展生存期(mPFS)几乎翻倍(mPFS 11.0个月vs.5.7个月)(NCT02437318)[28]。Alpelisib在预先设定的亚组,包括既往接受细胞周期蛋白依赖性激酶4/6(CDK4/6)抑制剂治疗的患者中获得了一致的PFS结果。在接受氟维司群治疗的携带PIK3CA突变患者中加用alpelisib时,ORR增加1倍以上(ORR = 35.7% vs. 16.2%)。Alpelisib与其伴随诊断检测试剂(Qiagen's therascreen PIK3CA RGQ PCR Kit)同时获批;alpelisib是FDA肿瘤卓越中心实时肿瘤审评(RTOR)试点计划批准的首个联合疗法[29]。获批后不久,alpelisib即在美国上市。

由日本第一三共发现并随后与阿斯利康进行共同开发和商业化的抗体-偶联物(ADC)**trastuzumab deruxtecan**(Enhertu),于2019年12月底(比PDUFA提前4个月)获得FDA的加速批准。ADC由人源化抗HER2抗体组成,通过四肽连接拓扑异构酶I抑制剂,适用于治疗既往至少接受过2种基于抗HER2方案治疗的不可切除或转移性HER2阳性乳腺癌成人患者。FDA基于DESTINY-Breast01(NCT03248492)研究中184例患者的疗效结果(缓解率和缓解持续时间)对该药进行了加速审评,另外,此前也先后授予了该产品快速通道和突破性疗法资格。该适应症能否获得完全批准取决于验证性临床是否可以证明其临床获益。

首创新药泛FGFR抑制剂**erdafitinib**(Balversa;Janssen)于去年在美国获批并几乎立即上市,适用于治疗携带易感的FGFR3或FGFR2基因突变以及在既往接受至少一种含铂化疗期间或之后出现进展的成人局部晚期或转移性尿路上皮癌患者。Erdafitinib是FDA批准的首个口服泛FGFR激酶抑制剂,可与4种FGFR(FGFR-1~FGFR-4)结合,从而减少细胞信号传导和细胞凋亡(图7)。Erdafitinib还与RET、CSF-1受体(CSF-1R)、PDGFR-α和PDGFR-β、Fms相关酪氨酸激酶4(FLT4)、KIT和VEGFR-2结合,显示出杀灭肿瘤细胞的其他抗肿瘤机制。此外,erdafitinib是尿路上皮癌患者的首个口服治疗药物。

2019年底,FDA加速批准了治疗尿路上皮癌的第二款新药**enfortumab vedotin**(Padcev;Astellas/Seattle Genetics),这是一种ADC,由靶向细胞粘附分子nectin-4的全人源单克隆抗体和微管破坏剂monomethyl auristatin E(MMAE)组成,抗体和MMAE通过缬氨酸瓜氨酸可裂解连接子与偶联。ADC可在血流中保持稳定,但内化到表达nectin-4的肿瘤细胞后则会释放MMAE,从而具有靶向杀灭细胞的作用。在一项enfortumab vedotin的早期临床试验中,经检测发现,97%的膀胱癌标本

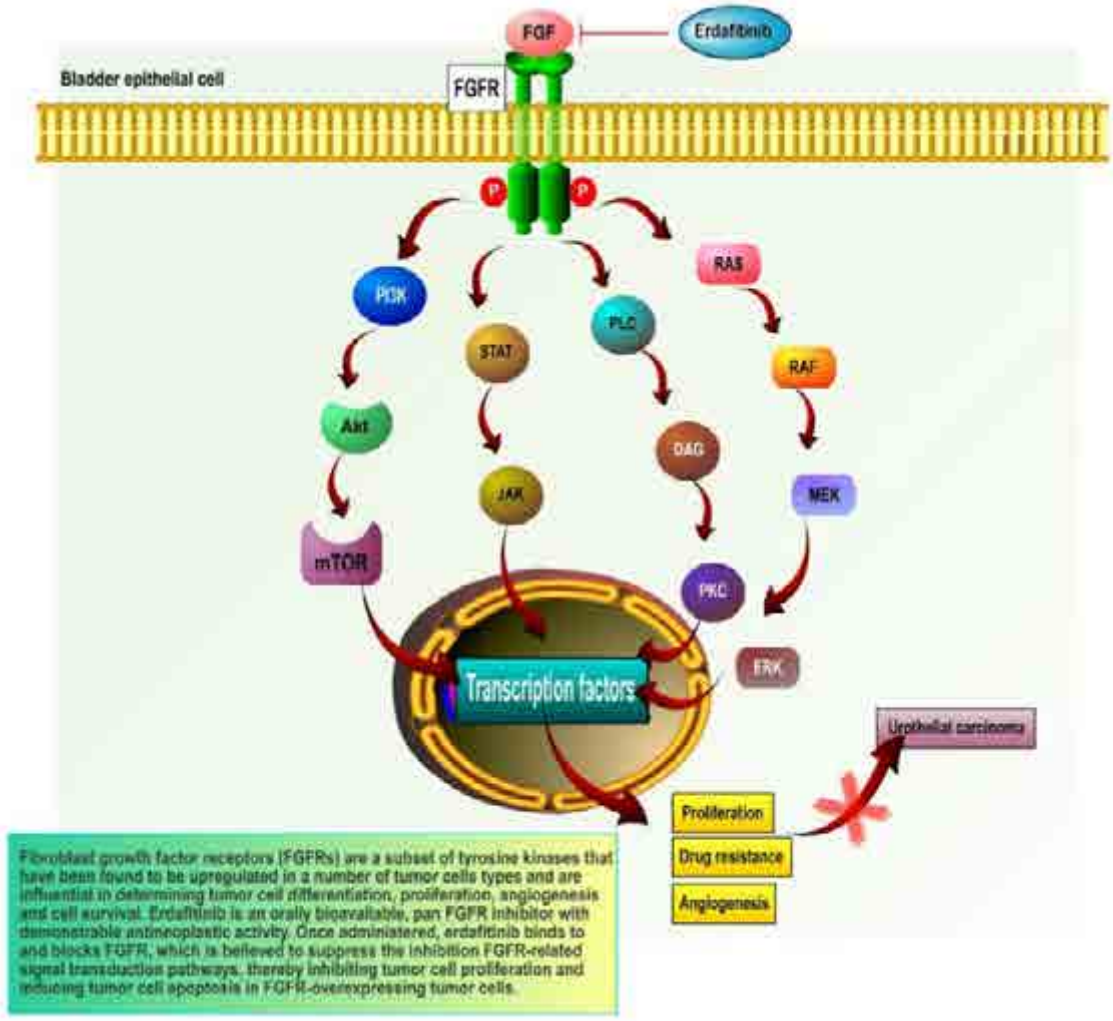

图7. 成纤维细胞生长因子受体(FGFR)是酪氨酸激酶家族中的一个亚群,已发现其在很多类型的肿瘤细胞中的表达上调,并可调节肿瘤细胞的分化、增殖、血管生成和细胞生存。Erdafitinib是一种口服的具有生物活性的泛FGFR抑制剂,具有明显的抗肿瘤活性。Erdafitinib在给药后可与FGFR结合并阻断FGFR,这一作用机制被认为可抑制FGFR相关信号传导通路,从而在FGFR过表达的肿瘤细胞中抑制肿瘤细胞增殖并诱导肿瘤细胞凋亡。

显著表达nectin-4,证实了该靶点普遍存在于膀胱癌中。FDA批准enfortumab vedotin用于治疗既往接受过PD-1/PD-L1抑制剂和在术前/术后或在局部晚期或出现转移后接受过铂类化疗的成人局部晚期或转移性尿路上皮癌患者。Seattle Genetics公司估计,在美国每年诊断为转移性尿路上皮癌的2万例患者中,将有2,000至3,000例患者适合接受该药物作为三线治疗。FDA基于一项入组了125例患者的单臂II期多中心关键性试验EV-201获得的治疗应答率,通过加速审评批准了该药物[30]。该适应症能否获得完全批准取决于验证性临床是否可以证明其临床获益。

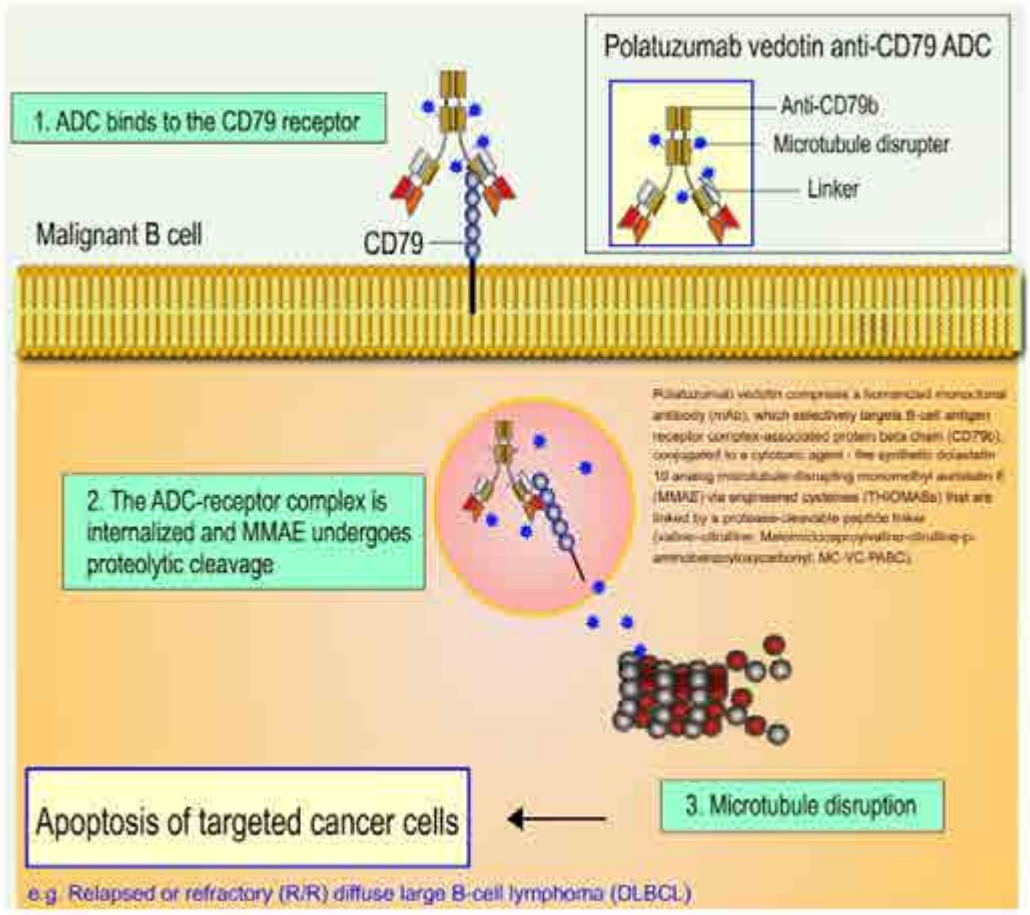

图8. Polatuzumab vedotin是一种抗体-药物偶联物(ADC),由靶向CD79b的单克隆抗体(MAb)和monomethyl auristatin E(MMAE)组成,前者通过蛋白酶可裂解肽连接子与后者偶联。该药物适用于与苯达莫司汀加利妥昔单抗联合使用,治疗既往至少接受过两种治疗的成人复发/难治性弥漫性大B细胞淋巴瘤患者。该ADC靶向在大多数B细胞中均有特异性表达的CD79b蛋白。该ADC药物可与CD79b结合,并通过递送微管破坏剂MMAE破坏这些B细胞,同时对正常细胞的毒性极小。

2019年夏,FDA加速批准了另一款新型ADC:**polatuzumab vedotin**(Polivy;基因泰克)。该药物由抗CD79b单克隆抗体与MMAE组成,两者通过蛋白酶可裂解肽连接子偶联。该药适用于与苯达莫司汀+利妥昔单抗联合用药治疗既往至少接受过2种治疗的成人复发或难治性弥漫性大B细胞淋巴瘤患者。该药在美国已获得孤儿药认定。Polatuzumab vedotin是首款CD79b蛋白(在大多数B细胞中均有特异性表达)靶向药物(图8)。该药物可与CD79b结合,并通过递送抗肿瘤药物MMAE破坏这些B细胞,同时对正常细胞的毒性作用极小。Polatuzumab vedotin获批后不久即在美国上市。去年,Polivy还获得了欧盟的有条件批准,该药物在欧盟获得PRIME称号和孤儿药资格,同时还被认定为高级治疗药物产品。

骨髓纤维化被视为一种慢性白血病,是一种不常见的血液系统恶性肿瘤,患者的骨髓会逐渐被纤维瘢痕组织替代。骨髓纤维化可能是原发性疾病,也可能继发于自身免疫性疾病或其他骨髓肿瘤。约50%的原发性骨髓纤维化患者携带*JAK2*基因突变;骨髓纤维化的首个特异性治疗药物是JAK2抑制剂芦可替尼,已于2011年上市。去年,具有双重作用机制的JAK2/FLT3抑制剂**fedratinib**(Inrebic;Celgene)在美国获批上市,增加了该罕见病的治疗选择。Fedratinib适用于治疗伴有中危-2或高危的原发性或继发性(真性红细胞增多症后或原发性血小板增多症后)成人骨髓纤维化患者。该药物因这个适应症在美国被认定为孤儿药。

2019年6月，日本MHLW批准了口服FLT3抑制剂**奎扎替尼**（Vanflyta；第一三共），用于治疗成人复发/难治性FLT3-ITD急性髓性白血病（AML），患者的诊断基于MHLW批准的一种检测方法。该药物基于全球关键性III期QuANTUM-R研究（NCT02039726）和一项在日本开展的奎扎替尼治疗复发/难治性FLT3-ITD AML患者的II期临床结果获批。QuANTUM-R是第一项评价FLT3抑制剂单药口服给药在复发/难治性FLT3-ITD AML患者中疗效的随机III期试验，结果表明，与化疗相比，奎扎替尼可延长该病患者的总生存期（OS 6.2个月vs.4.7个月）[31]。奎扎替尼在日本被认定为孤儿药，已于2019年10月上市。

2019年11月，中国NMPA批准了**甲磺酸氟马替尼**（Hausen Xin Fu），该药物由江苏豪森药业开发，适用于治疗携带费城染色体（Ph+）突变的慢性髓系白血病。该药获得了优先审评资格。甲磺酸氟马替尼是一种酪氨酸蛋白激酶ABL1抑制剂，可抑制Bcr-ABL1的活性和肿瘤细胞增殖。

核输出蛋白-1（XPO1，CRM1）是一种核输出转运受体，负责从细胞核中转运蛋白，包括肿瘤抑制蛋白。肿瘤抑制蛋白的核输出转运是肿瘤细胞避免凋亡和细胞死亡的重要机制。XPO1过表达会导致无法准确定位肿瘤细胞，造成预后不良。美国FDA于去年夏季加速批准了First in Class药物XPO1受体拮抗剂**selinexor**（Xpovio；Karyopharm）（图9），用于治疗既往至少接受过4种治疗方案且产生耐药的成人复发/难治性多发性骨髓瘤患者。Selinexor因该适应症在美国被认定为孤儿药。

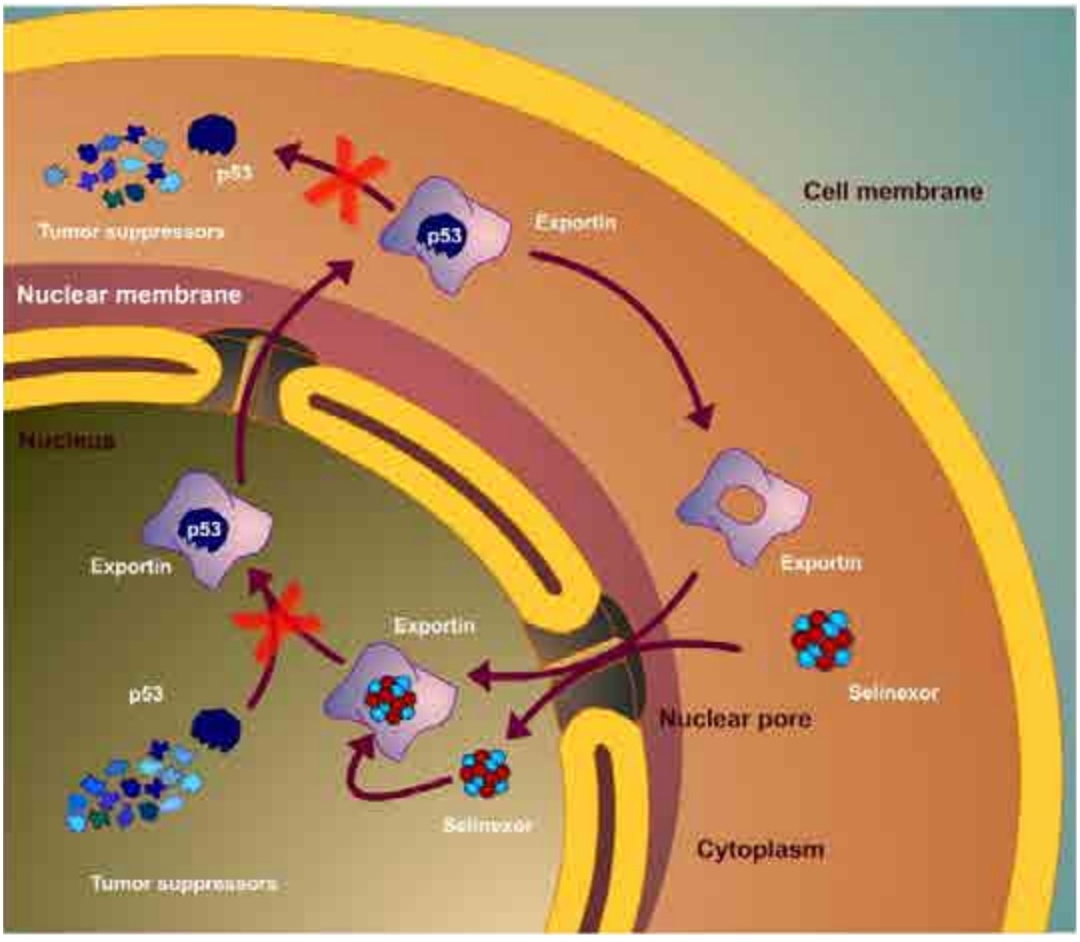

图9. 核输出蛋白-1（XPO1，CRM1）是一种核输出转运受体，负责从细胞核中转运蛋白，包括肿瘤抑制蛋白。肿瘤抑制蛋白的出核转运是肿瘤细胞避免凋亡和细胞死亡的重要机制。XPO1过表达会导致无法准确定位肿瘤细胞，提示预后不良。XPO1拮抗剂selinexor获批用于治疗复发/难治性多发性骨髓瘤。

个体化抗肿瘤药物**恩曲替尼**(Rozlytrek;Chugai/罗氏)于2019年6月在日本首次获批,不久后在美国获批并上市。恩曲替尼是一种酪氨酸激酶抑制剂,可阻断ROS1(原癌基因c-Ros-1)和TRK(神经营养因子受体)家族成员。该药物在美国的适应症为伴有神经营养性酪氨酸激酶受体(NTRK)基因融合但无已知获得性耐药突变、存在转移性疾病或手术切除可能导致病情加重以及治疗后出现进展或目前尚无满意替代疗法的年满12岁的儿童和成人实体瘤。NTRK1/2/3基因与其他基因发生融合后会导致伴有NTRK融合的恶性肿瘤,导致TRK蛋白(TRKA/TRKB/TRKC)改变,进而激活与某些类型恶性肿瘤细胞增殖相关的信号传导通路。NTRK基因融合与肿瘤类型无关,已在多种实体瘤,包括乳腺癌、胆管癌、结直肠癌、妇科恶性肿瘤、神经内分泌肿瘤、非小细胞肺癌、唾液腺癌、胰腺癌、肉瘤和甲状腺癌中检测到NTRK基因融合。恩曲替尼在美国的适应症也包括伴有ROS1基因融合的成人转移性非小细胞肺癌患者。该药物因这两种适应症均被认定为孤儿药。

中国公司百济神州研发的Bruton酪氨酸激酶抑制剂**泽布替尼**(Brukinsa)获得了FDA加速审评,去年11月获批后旋即上市。该药物适用于治疗既往至少接受过一次治疗的成人套细胞淋巴瘤(MCL)患者。该药获批基于两项单臂试验的疗效评价结果,主要终点为独立审查委员会根据2014 Lugano分类法评估的ORR。泽布替尼在两项试验中的ORR均达到了84%。在一项泽布替尼治疗复发/难治性MCL患者的多中心II期试验(NCT03206970)中,ORR为84%,包括59%的CR(需FDG-PET扫描确认),24%的PR。在本研究中,中位缓解持续时间(DOR)为19.5个月,研究期间的中位随访时间为18.4个月。在另一项全球I/II期试验(NCT02343120)中,ORR达84%,包括22%的CR(无需FDG-PET扫描确认)和62%的部分缓解。在该项研究中,中位DOR为18.5个月,研究期间的中位随访时间为18.8个月。泽布替尼在中国也已报产,处于审评状态。

母细胞性浆细胞样树突状细胞肿瘤(BPDCN)是一种侵袭性和罕见的骨髓和血液系统疾病,可累及包括淋巴结和皮肤在内多个器官。该病通常表现为白血病或进展为急性白血病。这种疾病更常见于男性和60岁以上的患者。2018年年底,美国FDA批准了BPDCN的首个治疗药物:靶向CD123的细胞毒素**tagraxofusp**(Elzonris;Stemline Therapeutics)。CD123是识别BPDCN的一个关键标志物,并且是该疾病和多种其他恶性肿瘤治疗干预的靶标。Tagraxofusp于2019年初上市。

免疫检查点抑制剂是一类数量不断增加的肿瘤免疫药物,能够在高选择的亚组患者(包括恶性淋巴瘤患者)中恢复对肿瘤的免疫功能[32]。2019年新推出了数个免疫检查点抑制剂,均在中国上市。抗PD-1单抗**信迪利单抗**(Tyvyt;信达/礼来)在2018年年底获批后,于2019年2月上市,其适应症为复发/难治性经典型霍奇金淋巴瘤(cHL)。数月后,江苏恒瑞的抗PD-1单抗**卡瑞利珠单抗**获批上市。**卡瑞利珠单抗**适应症是作为接受过二线全身化疗的复发/难治性cHL患者的三线治疗;2019年12月,百济神州的人源化抗PD-1单克隆抗体**替雷利珠单抗**获批用于同一适应症。此外,抗PD-1单抗**特瑞普利单抗**(Tuoyi;上海君实生物)也已上市,用于治疗常规全身治疗失败的局部晚期或转移性黑色素瘤患者。

Nanobiotix公司的放疗增强剂**NBTXR-3**(Hensify)于4月获得欧盟的CE标志认证,用于联合放疗治疗局部晚期软组织肉瘤。该药物是一种晶体状的二氧化铪纳米颗粒的水性混悬液,用于在患者接受首次标准放疗前直接注射至肿瘤中。Hensify可在暴露于电离辐射时增强辐射的局部和肿瘤内杀伤效应。该方法可增加递送至肿瘤的X线剂量,而健康组织受到的辐射剂量不变。通过物理方法杀灭原发灶的肿瘤细胞,而对于所有的转移灶则需要通过免疫系统激活和免疫原性细胞杀灭的进行破坏。

眼科药物

继去年3月份获得FDA批准后,Aerie Pharmaceuticals公司的新型固定剂量复方制剂Rocklatan滴眼液(**甲磺酸奈他地尔/拉坦前列素**)于去年5月在美国上市。该药物适用于降低开角型青光眼或高眼压患者的眼内压升高(IOP)。奈他地尔是一种Rho激酶(ROCK)抑制剂,而拉坦前列素是一种前列腺素类似物;两种成分作用机制互补,协同作用,其降低IOP的疗效优于其中任一单药治疗。奈他地尔的作用机制为恢复经小梁网的房水外流,而拉坦前列素则通过一种称为葡萄膜巩膜通道的次要机制增加房水外流。

眼部血管生成定义为眼部现有血管结构中生成异常的新血管,是老年性黄斑变性(AMD)患者眼部发病的重要原因。血管生成抑制剂尤其适用于治疗湿性AMD,其特征为脉络膜异常新生血管形成。去年,诺华公司开发的一种新型血管生成抑制剂**brolucizumab**(Beovu)在美国获批上市,用于治疗湿性AMD。Brolucizumab是一种靶向VEGF-A的人源化单克隆单链抗体Fv片段(scFv)。该项批准基于III期HAWK和HARRIER试验(NCT02307682和NCT02434328)结果,这两项试验是长达96周的前瞻性、随机、双盲、多中心研究,旨在比较湿性AMD患者玻璃体内注射brolucizumab 6 mg(HAWK和HARRIER)和3 mg(仅HAWK)与已上市的血管生成抑制剂阿柏西普的疗效和安全性(33)。在这两项试验进行的第1年(第48周)与aflibercept

进行对比,在最佳矫正视力的平均改变方面,brolucizumab显示出非劣效性。在两项试验中,约30%的患者在研究第1年时的视力相对基线时在视力表上至少增加了15个字母。在HAWK和HARRIER研究中,早在第16周和第1年时,brolucizumab已显示出中央视网膜厚度显著减少的疗效,而且只有极少数的患者出现视网膜内和/或视网膜下积液。在给药期后,符合标准的患者可以立即维持3个月的给药间隔。研究第1年时,有一半以上的患者可维持3个月的给药间隔(HAWK为56%,HARRIER为51%)。研究中的其余患者则以2个月给药方案接受治疗。Brolucizumab的总体安全性特征与阿柏西普相似。

Dextenza(**地塞米松泪点塞**)是Ocular theraptix公司开发的一种新型抗炎作用的糖皮质激素眼内给药制剂,去年在美国上市用于治疗眼科手术后的眼部炎症和疼痛。Dextenza是一种不含防腐剂的泪小管内插入物,可通过泪点插入下泪小管中。一次插入可释放0.4 mg剂量的地塞米松,药效最长可维持30天。因此,Dextenza有可能取代目前的一种复杂的滴眼液给药方案,即根据目前的标准治疗,需要局部使用眼用类固醇滴眼液滴眼多达70余次。

代谢疾病药物

骨质疏松症是一种年龄相关性很强的疾病,由骨重建生理过程中的不平衡所致。长期以来,骨质疏松症的主要治疗药物始终是雌激素、双膦酸盐和抗RANKL抗体狄诺塞单抗,这些药物均为减少骨吸收,从而减缓骨流失。但在合成代谢药物领域的新药较少,即促进新骨形成的药物。去年,一种具有合成代谢活性的first-in-class新药在日本获批上市,即抗硬化蛋白单克隆抗体**romosozumab**(Evenity;UCB/Amgen Astellas BioPharma)(图10)。骨硬化蛋白是一种

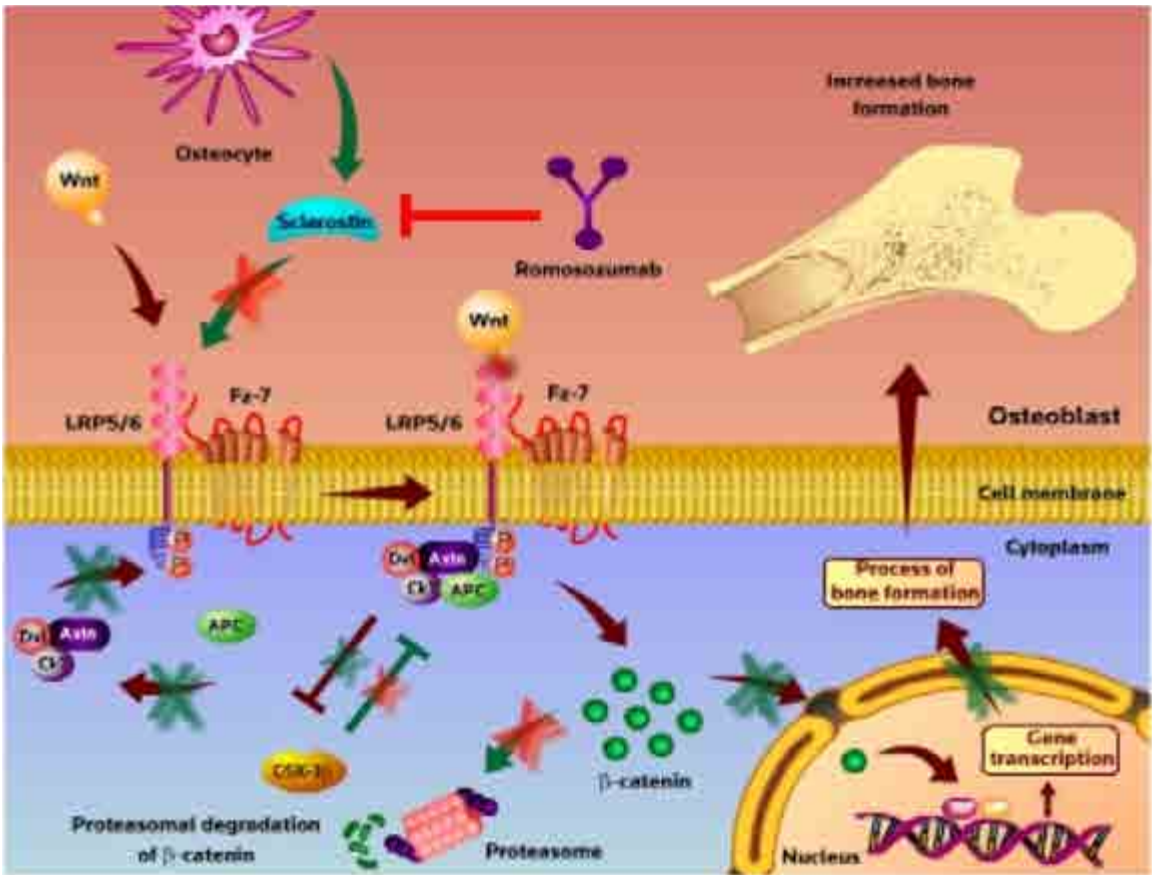

图10. 骨硬化蛋白是一种骨形态发生蛋白拮抗剂,可抑制骨祖细胞分化并降低成骨细胞活性。骨硬化蛋白由埋在骨基质中的骨细胞产生的*SOST*基因表达,是骨形成的强效抑制剂。成骨细胞被埋入矿化骨基质后,转变为骨细胞,并开始表达控制骨形成和磷酸盐代谢的硬化蛋白。抗硬化蛋白人源化单克隆抗体romosozumab能增强成骨细胞功能,同时促进骨形成和抑制骨吸收。

骨形态发生蛋白拮抗剂,可抑制骨祖细胞分化并降低成骨细胞活性。骨硬化蛋白由埋在骨基质中的骨细胞产生的*SOST*基因表达,是骨形成的强效抑制剂。成骨细胞被埋入矿化骨基质后,转变为骨细胞,并开始表达控制骨形成和磷酸盐代谢的硬化蛋白。Romosozumab和其他抑制骨硬化蛋白的药物均可增强成骨细胞功能,从而同时促进骨形成和抑制骨吸收。Romosozumab在日本的适应症为存在骨折高风险的男性和绝经后女性的骨质疏松症。2019年下半年,romosozumab在美国获批上市,用于治疗存在骨折高风险的绝经后女性,或其他现有骨质疏松症治疗失败或不耐受的骨质疏松症患者。

急性肝卟啉症(AHP)是一类极其罕见的遗传性疾病,以可能危及生命的发作为特征;对于一些患者而言,慢性的临床表现对日常功能和生活质量会带来不利影响。AHP分为四种类型:急性间歇性卟啉症、遗传性粪卟啉症、混合型卟啉症和ALA脱水酶缺乏性卟啉症。每种类型的AHP的病因均为遗传缺陷导致肝脏血红素生物合成通路的某种酶缺乏所致。去年,FDA批准Alnylam Pharmaceuticals公司的givosiran(Givlaari)用于治疗成人AHP,该药是一种靶向5-氨基乙酰丙酸合酶1(ALAS1)的小干扰RNA(siRNA)。该药物经优先审评后,基于一项在94例AHP患者的III期ENVISION研究(NCT03338816)的结果,于11月获批。在一项关键性随机双盲安慰剂对照的多国研究中,AHP患者接受givosiran治疗后,卟啉症的发作次数相较安慰剂治疗组患者减少70%。同样,该药物治疗还可以减少静脉输注血红素的用量,而且尿氨基乙酰丙酸和尿卟胆原的水平也有所下降。与治疗相关的最常见不良反应为恶心(27%)和注射部位的反应(25%)。

2019年5月,Ionis Pharmaceuticals及其全资子公司Akcea Therapeutics获得了volanesorsen(Waylivra)在欧盟有条件的上市许可,该药适用于作为基因检测确认家族性乳糜微粒血症(FCS)且胰腺炎风险较高的成人患者的饮食辅助治疗,这些患者对饮食限制和降脂治疗的应答不足。FCS是一种罕见的常染色体隐性遗传病,由脂蛋白脂肪酶突变引起,进而导致血浆中乳糜微粒蓄积和高甘油三酯血症(34)。在高甘油三酯血症的并发症中,急性胰腺炎是最为严重的一种。Volanesorsen是一种反义寡核苷酸,旨在减少载脂蛋白C-III(ApoC-III)的生成,而载脂蛋白C-III是一种调节血浆甘油三酯的蛋白。作为有条件上市许可的一部分,Akcea和Ionis公司基于临床试验登记将进行一项非干预性的许可后安全性研究(PASS)。临床III期APPROACH研究(NCT02211209)是迄今为止针对FCS患者进行的最大规模的研究;在研究中,与安慰剂相比,反义药物治疗导致具有临床意义和统计学意义的血甘油三酯水平降低。对有复发性胰腺炎病史的患者的分析显示,与安慰剂治疗患者相比,接受volanesorsen治疗的患者中胰腺炎发作率显著降低。APPROACH试验中最常见的不良事件是注射部位反应和血小板水平降低。由于FCS是一种尚无有效治疗方案的罕见病,volanesorsen的研发获得了多个监管项目的支持,包括欧盟和美国的孤儿药资格认定以及英国突破性创新药物(PIM)资格认定。该产品于2019年8月在德国和法国上市。

2019年上市新药完整清单详见表III。

展望 2020

虽然2020年新年刚过,但FDA和其他监管机构又开始为新的一年而忙碌了。根据Cortellis早期药物研发情报和Cortellis综合性竞争情报的分析,我们期待以下药物和生物制品将会是明年本系列文章的讨论内容。

AR-101(Palforzia;Aimmune Therapeutics)是一种由花生衍生物的口服免疫治疗药物,有望成为首个获批用于花生过敏脱敏治疗药物。去年9月,FDA过敏产品咨询委员会建议批准该药品用于4-17岁儿童。生物制品许可申请(BLA)的审评目标日期为2020年1月下旬。

Horizon Therapeutics公司的**teprotumumab**是一种针对人胰岛素样生长因子1受体(IGF-1R)的人源化单克隆抗体,将成为活动性甲状腺眼病(又称Graves眼眶病)的首款治疗药物。2019年12月,FDA皮肤和眼科药物咨询委员会一致投票支持批准该药物上市。FDA已于2020年1月中旬批准teprotumumab,早于PDUFA目标日期(3月8日)。

预计FDA将在今年批准Sunovion公司上市**dasotraline**,一种新型多巴胺和去甲肾上腺素再摄取抑制剂(DNRI),用于治疗中度至重度暴食症(BED)患者,BED是一种严重的心理疾病且治疗方案有限。BED特征为反复和持续的暴食,其定义为在短时间内摄入大量食物,发作期间感觉失控,之后有强烈羞愧感、内疚感和窘迫感。

去年11月,罗氏宣布FDA已接受**diplrisam**新药申请NDA,并授予其优先审评资格,该药是一种试验性运动神经元生存基因-2(SMN-2)剪接修饰剂,用于治疗SMA。Risdiplam可增加并维持CNS和身体外周组织中的SMN蛋白水平。FDA预计将于2020年5月24日前作出批准决定。在此期间,罗氏计划针对合格的1型SMA患者开展一项全球患者同情用药项目。

EMA正在审查Hansa Biopharma公司的**imlifidase**的上市许可申请(MAA),该药的适应症为肾移植患者术前的脱敏治疗。Hansa Biopharma于2019年12月22日提交了对第120天问题的回复,审评过程正在按计划进行。该公司表示,预计CHMP将于2020年第二季度给出意见,随后欧盟委员会可能于2020年夏季做出决定。

有关这些药物和其他2020年预测的概述详见表IV。

披露

本文作者均为科睿唯安公司雇员。

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表 III. 2019 年新产品简介

商品名（国家）[1]	公司	活性成分	适应症
Piqray (US)	诺华	Alpelisib，片剂，50 mg、150 mg、200 mg	联合氟维司群治疗激素受体阳性、HER2 阴性（HR+/HER2-）、携带 PIK3CA 突变的绝经后女性和男性晚期或转移性乳腺癌患者
Katerzia (US)	Azurity	苯磺酸氨氯地平口服混悬剂，1 mg/mL	单药或与其他降压药和抗心绞痛药物联合使用，用于： · 降低年满 6 岁的儿童和成人高血压患者的血压 · 冠心病（包括慢性稳定型心绞痛；血管痉挛性心绞痛；无心力衰竭或射血分数 <40% 的冠心病患者）
Otezla (US)	新基生物	Apremilast，片剂，10 mg、20 mg、30 mg	治疗白塞病患者的口腔溃疡 *
Stemirac (JP)	Nipro	在自体人血清中扩增的自体人骨髓来源的间充质干细胞	治疗脊髓损伤
Collategene (JP)	AnGes/ 田边三菱	Beperminogene perplasmid，肌肉注射，4 mg	改善对标准药物治疗应答不足且难以接受血运重建的慢性动脉闭塞（闭塞性动脉硬化症和 Buerger 病）患者的溃疡程度
Vyleesi (US)	Palatin Technologies/ AMAG Pharmaceuticals	Bremelanotide，皮下注射液，用预充式自动注射笔注射，1.75 mg/0.3 mL	治疗绝经前女性出现的获得性、全身性性欲减退障碍
Zulresso (US)	Sage Therapeutics	Brexanolone，注射剂，100 mg/20 mL（5 mg/mL）单剂量小瓶	治疗产后抑郁症
Beovu (US)	诺华	Brolucizumab，注射液，用预充式注射器注射，0.165 mL（6 mg/0.05 mL）	治疗湿性年龄相关性黄斑变性
Breztri Aerosphere (JP)	阿斯利康	布地奈德 / 格隆铵 / 富马酸福莫特罗 ***，定量吸入器，每揿递送 160 μg/9 μg/5 μg 剂量	缓解慢性阻塞性肺疾病症状
艾瑞卡 (CN)	江苏恒瑞	卡瑞利珠单抗，注射剂，200 mg	作为复发性 / 难治性经典型霍奇金淋巴瘤的三线治疗
Invokana (US)	田边三菱 / 杨森	卡格列净，片剂，100 mg、300 mg	降低成人 2 型糖尿病和糖尿病肾病白蛋白尿患者发生终末期肾病、血清肌酐翻倍、心血管死亡和因心力衰竭住院的风险 *
Nubeqa (US)	拜耳 /Orion	Darolutamide，片剂，300 mg	用于治疗非转移性去势抵抗型前列腺癌患者
Dextenza (US)	Ocular Therapeutix	地塞米松，眼内（泪小管内）用药，0.4 mg***	治疗眼科手术后眼部炎症和疼痛
Dovato (US)	ViiV Healthca re	多替拉韦 / 拉米夫定 **，片剂，50 mg/300 mg	治疗无抗逆转录病毒治疗史且对多替拉韦或拉米夫定无已知耐药性的成人 HIV-1 感染患者

表 III. 2019 年新产品简介（续）

商品名（国家）[1]	公司	活性成分	适应症
Slynd (US)	Exeltis USA	屈螺酮，片剂，4 mg	供育龄期女性避孕用
Dupixent (US)	Regeneron/ 赛诺菲	Dupilumab，注射剂，300 mg/2 mL 注射液，预充式注射器注射	与其他药物联合使用治疗病情控制不佳的成人慢性鼻窦炎伴鼻息肉 *
Soliris (US)	Alexion	Eculizumab 单抗，注射液，300 mg/30 mL，单剂量小瓶	治疗抗水通道蛋白 -4（AQP4）抗体阳性成年患者的视神经脊髓炎谱系障碍 *
Trikafta (US)	Vertex	Elexacaftor/tezacaftor/ivacaftor**，片剂，含 elexacaftor 100 mg/ tezacaftor 50 mg/ivacaftor 75 mg 的固定剂量复方制剂；与片剂共同包装，ivacaftor 150 mg	治疗年满 12 岁 CFTR 基因中至少携带 1 个 F508del 突变拷贝的患者的囊性纤维化
Gamifant (US)	Novlmmune/Sobi	Emapalumab，输注液，10 mg/2 mL、50 mg/10 mL	治疗原发性噬血细胞性淋巴组织细胞增生症的成人和儿童（新生儿和更大的儿童）
Rozlytrek (US)	Chugai/ 罗氏	Entrectinib，胶囊，100 mg、200 mg	· 治疗实体肿瘤有 NTRK 基因融合但无已知获得性耐药突变，转移性或手术切除可能导致严重发病率、治疗后进展或无满意替代疗法的 12 岁及以上儿童和成人患者 · 治疗伴 ROS1 基因融合的转移性非小细胞肺癌成人患者
Balversa (US)	杨森	Erdafitinib，片剂，3 mg、4 mg、5 mg	治疗携带易感 FGFR3 或 FGFR2 基因变异且在既往接受至少一线含铂化疗期间或之后发生进展的局部晚期或转移性尿路上皮癌的成人患者
Minnebro (JP)	Exelixis/ 第一三共	Esaxerenone，片剂，1.25 mg、2.5 mg、5 mg	高血压治疗
Spravato (US)	杨森	盐酸艾司氯胺酮，鼻喷剂 ***，28 mg	与成人口服抗抑郁药联合治疗难治性抑郁症患者 *
Bijuva (US)	TherapeuticsMD	17β- 雌二醇 / 孕酮 **，胶囊，1 mg/100 mg	治疗保留有子宫的女性因更年期引起的中度至重度血管舒缩症状
Orkedia (JP)	Kyowa Kirin	Evocalcet，片剂，1 mg、2 mg	治疗不能接受甲状旁腺切除术或甲状旁腺切除术后复发的甲状旁腺癌或原发性甲状旁腺功能亢进患者的高钙血症 *
Inrebic (US)	新基生物	Fedratinib，胶囊，100 mg	治疗成人中危 -2 级或高危原发性或继发性（真性红细胞增多症后或原发性血小板增多症后）骨髓纤维化患者
Baqsimi (US)	礼来	胰高血糖素，单剂量鼻内给药装置 *** 含干粉，3 mg	治疗年满 4 岁糖尿病患者的严重低血糖
Gvoke (US)	Xeris Pharmaceuticals	胰高血糖素，单剂量预充式 HypoPen 自动注射器 ***，0.5 mg/0.1 mL、1.0 mg/0.2 mL；单剂量预充式注射器，0.5 mg/0.1 mL、1.0 mg/0.2 mL	治疗年满 2 岁儿童和成年糖尿病患者的严重低血糖

表 III. 2019 年新产品简介（续）

商品名（国家）[1]	公司	活性成分	适应症
Vyondys 53 (US)	Sarepta Therapeutics	Golodirsen，注射剂，100 mg/2 mL（50 mg/mL）单剂量小瓶	治疗已证实携带适合 53 号外显子跳跃的基因突变的杜氏肌营养不良患者
甘露特钠胶囊 (CN)	上海绿谷制药	GV-971，胶囊	治疗轻度至中度阿尔茨海默病
Duobrii (US)	Bausch Health	Halobetasol propionate/ 他扎罗汀 **，洗液，0.01%/0.045%	成人斑块状银屑病的局部治疗
Asceniv (US)	ADMA Biologies	免疫球蛋白静脉注射制剂（human-slra），静脉注射液，10%	治疗成人和青少年（12 ～ 17 岁）原发性体液免疫缺陷
Xembify (US)	Grifols	免疫球蛋白皮下注射（human-klhw），皮下注射液，20%	治疗年满 2 岁患者的原发性体液免疫缺陷
Taltz (US)	礼来	Ixekizumab，注射液，用单剂量预充式自动注射器注射，80 mg/mL；注射液，用单剂量预充式注射器注射，80 mg/mL	治疗成人活动性强直性脊柱炎患者 *
Xenleta (US)	Nabriva Therapeutics	Lefamulin，片剂，600 mg；注射剂瓶，150 mg/15 mL	治疗由敏感微生物引起的成人社区获得性细菌性肺炎患者
Inbrija (US)	Acorda Therapeutics	左旋多巴，胶囊型干粉吸入剂 ***，含 42 mg 左旋多巴，与 Inbrija 吸入器同时使用	卡比多巴 / 左旋多巴治疗帕金森病患者的“关闭期”发作间歇治疗
Reblozyl (US)	Acceleron/ 新基生物	Luspatercept，冻干粉末，单次使用小瓶装，25 mg 和 75 mg，用于复溶和皮下注射	治疗需定期输注红细胞的成人 β- 地中海贫血患者的贫血
Tarlige (JP)	第一三共	苯磺酸米罗加巴林，片剂，2.5 mg、5 mg、10 mg、15 mg	治疗周围神经痛
Jynneos (US)	Bavarian Nordic	MVA-BN 天花疫苗，皮下注射混悬液，一次性小瓶装，0.5 mL	预防确定为高危的年满 18 岁成人出现猴痘病 *
Efleira (RU)	Biocad	Netakimab，皮下注射液，60 mg/mL	治疗中度至重度斑块状银屑病
Rocklatan (US)	Aerie Pharmaceuticals	Netarsudil mesylate/ 拉坦前列素 ***，滴眼液，0.2 mg/mL（0.02%）netarsudil/0.05 mg/mL（0.005%）拉坦前列素	降低开角型青光眼或高眼压患者的眼内压升高
Ofev (US)	Boehringer Ingelheim	Nintedanib，胶囊，100 mg、150 mg	减缓系统性硬化症相关性间质性肺病患者的肺功能下降速度 *
Nuzyra (US)	Paratek	Omadacycline，冻干粉，100 mg，单次给药小瓶装，用于复溶和在静脉输注前进一步稀释；片剂，150 mg	治疗敏感微生物引起下列感染的成年患者：社区获得性细菌性肺炎；急性皮肤及皮肤结构感染
Zolgensma (US)	AveXis (Novartis)	Onasemnogene abeparvovec，静脉输注混悬液，一次性小瓶装，5.5 mL 或 8.3 mL，含标称浓度 2.0 × 1013 载体基因组（vg）/mL	治疗＜ 2 岁儿童 SMN1 基因双等位基因突变的脊髓性肌萎缩症患者

表 III. 2019 年新产品简介（续）

商品名（国家）[1]	公司	活性成分	适应症
Smyraf (JP)	Astellas	Peficitinib hydrobromide，片剂，50 mg、100 mg	在常规治疗疗效不佳的患者中，治疗类风湿性关节炎，包括预防关节结构损伤
Turalio (US)	Plexxikon/ 第一三共	Pexidartinib hydrochloride，胶囊，200 mg	治疗病情严重或功能受限且无法通过手术改善的成人症状性腱鞘巨细胞瘤患者
Polivy (US)	Genentech	Polatuzumab vedotin，冻干粉一次性小瓶装，140 mg	联合苯达莫司汀加利妥昔单抗治疗成人复发性或难治性弥漫性大 B 细胞淋巴瘤患者
Fulaimei (CN)	Hansoh Pharma	聚乙二醇 loxenatide，皮下注射液，用预充式注射笔或注射器，长效，0.1mg/0.5 mL 和 0.2 mg/0.5 mL	治疗成人 2 型糖尿病
(US)	TB Alliance/Mylan	Pretomanid，片剂，200 mg	作为贝达喹啉和利奈唑胺联合用药方案的一部分，治疗成人广泛耐药（XDR）、治疗不耐受或无反应的多药耐药（MDR）结核患者
Vanflyta (JP)	第一三共	Quizartinib，片剂，17.7 mg、26.5 mg	治疗日本厚生劳动福利省（MHLW）批准的检测发现的成人复发性 / 难治性 FLT3-ITD 急性髓系白血病患者
Ultomiris (US)	Alexion	Ravulizumab，静脉注射液，单剂量小瓶装，300 mg/30 mL（10 mg/mL）	· 治疗成人阵发性夜间血红蛋白尿患者 · 治疗成人和≥ 1 个月儿童非典型溶血性尿毒症综合征患者，抑制补体介导的血栓性微血管病
Relumina (JP)	武田 /Aska	Relugolix，片剂，40 mg	缓解子宫肌瘤症状
Remo (IN)	Glenmark/Avolynt	Remogliflozin etabonate，片剂，100 mg	治疗成人 2 型糖尿病
Aemcolo (US)	Cosmo Pharmaceuticals/ RedHill Biopharma	利福霉素，结肠缓释片 ***，194 mg	治疗成人非侵袭性大肠埃希菌菌株引起的旅行者腹泻
Skyrizi (US, GB)	AbbVie/Boehringer Ingelheim	Risankizumab，皮下注射液，用单剂量预充式注射器注射，75 mg/0.83 mL	治疗成人中度至重度斑块状银屑病患者
Evenity (JP)	UCB/Amgen Astellas BioPharma	Romosozumab，皮下注射液，用预充式注射器注射，105 mg/1.17 mL	治疗骨折高风险男性和绝经后女性的骨质疏松症
Besremi (AT, DE)	PharmaEssentia/AOP Orphan	Ropeginterferon α-2b，预充式注射笔，250μg/ 0.5 mL、500 μg/0.5 mL	单药治疗成人无症状性脾肿大的真性红细胞增多症
爱瑞卓 (CN)	FibroGen/AstraZeneca	罗沙司他，胶囊，50 mg	治疗慢性肾病导致的透析依赖性贫血
Mosquirix (MW)	GlaxoSmithKline	RTS，S/AS01E，注射用混悬液的粉末和混悬液；复溶后，1 剂（0.5 mL）含 25 mg RTS，SI，2 剂含 AS01E 佐剂	预防 2 岁以下儿童出现疟疾

表 III. 2019 年新产品简介（续）

商品名（国家）[1]	公司	活性成分	适应症
Jakafi (US)	Incyte	磷酸芦可替尼，片剂，5 mg、10 mg、15 mg、20 mg、25 mg	治疗成人和年满 12 岁儿童类固醇难治性急性移植物抗宿主病患者 *
Seysara (US)	Paratek/Almirall	Sarecycline hydrochloride，片剂，相当于 60 mg、100 mg 和 150 mg sarecycline base	治疗年满 9 岁的中度至重度非结节性寻常型痤疮患者的炎性病变
Annovera（美国）	Population Council/ TherapeuticsMD	醋酸孕酮（SA）/ 炔雌醇（EE）**，含有 103 mg SA 和 17.4 mg EE 的硅胶阴道避孕环，平均释放 0.15 mg/dSA 和 0.013 mg/dEE	供育龄期女性避孕用
Xpovio (US)	Karyopharm	Selinexor，片剂，20 mg	与地塞米松联合用于治疗至少接受过 4 种既往治疗且对几种其他形式的治疗耐药的成人复发性 / 难治性多发性骨髓瘤患者
Rybelsus (US)	诺和诺德	索马鲁肽，片剂，7 mg 和 14 mg***	作为饮食控制和运动的辅助治疗，以改善成人 2 型糖尿病血糖
Tyvyt (CN)	信达生物 / 礼来	信迪利单抗，静脉注射，100 mg/10 mL	治疗复发性 / 难治性经典型霍奇金淋巴瘤患者
Mayzent (US)	诺华	Siponimod fumarate，片剂，0.25 mg 和 2 mg	治疗成人复发型多发性硬化患者，包括临床孤立综合征、复发 - 缓解型疾病和活动性继发性进展型疾病
Lokelma (DK, FI, NO,SE)	阿斯利康	环硅酸钠锆，口服混悬液，5 g 和 10 g	治疗成人高钾血症
Sunosi (US)	Jazz Pharmaceuticals	Solriamfetol hydrochloride，片剂，75 和 150 mg	提高与成人发作性睡病或阻塞性睡眠呼吸暂停相关的日间过度嗜睡患者的醒觉状态
Elzonris (US)	Stemline Therapeutics	Tagraxofusp，单剂量小瓶装溶液，1 mL 含 1000μg tagraxofusp	治疗成人和≥ 2 岁儿童患者的母细胞性浆细胞样树突状细胞肿瘤
(CN)	天济医药	Tapinarof，乳膏	治疗成人中度稳定型寻常型银屑病
K-CAB (KR)	RaQualia/ CJ HealthCare	Tegoprazan，片剂，50 mg	治疗胃食管反流病，包括糜烂性食管炎和非糜烂性反流病
Tuoyi (CN)	上海君实生物	特瑞普利单抗，小瓶装，240 mg	治疗常规全身治疗失败的局部晚期或转移性黑色素瘤患者
Itulazax (DE)	ALK-Abell	树花粉舌下免疫治疗（SLIT），舌下片剂，12 SQ-Bet 标准化白桦花粉变应原提取物（疣皮桦）	治疗由桦木同源树家族花粉引起的成年中度至重度过敏性鼻炎和 / 或结膜炎患者
Trecondi (DE)	Medac	Treosulfan，小瓶装静脉注射液用粉末，50 mg/mL	联合氟达拉滨作为恶性和非恶性疾病成人患者以及≥ 1 个月儿童恶性疾病患者接受异基因造血干细胞移植前的预处理治疗的一部分 *
Aklief (US)	Galderma	Trifarotene，乳剂，0.005%	年满 9 岁的寻常型痤疮患者的外用治疗

表 III. 2019 年新产品简介（续）

商品名（国家）[1]	公司	活性成分	适应症
Esperoct (DE, CH)	诺和诺德	Turoctocogαpegol，注射用粉剂和溶剂，500 IU、1000 IU、1500 IU、2000 IU 和 3000 IU	治疗和预防年满 12 岁血友病 A（先天性因子 VIII 缺乏）患者出血
Rinvoq (US)	AbbVie	Upadacitinib tartrate，片剂，缓释，15 mg	治疗甲氨蝶呤疗效不佳或治疗不耐受的成人中重度活动性类风湿性关节炎患者
Waylivra (DE, FR)	Akcea Therapeutics（Ionis Pharmaceuticals）	Volanesorsen，注射液，285 mg	在经基因检测确诊的成人家族性乳糜微粒血症和胰腺炎高危患者（饮食控制和降脂治疗效果不佳）中，作为辅助治疗
Oxbryta (US)	Global Blood Therapeutics	Voxelotor，片剂，500 mg	治疗年满 12 岁儿童和成人的镰状细胞病
Brukinsa (US)	百济神州	泽布替尼，胶囊，80 mg	治疗既往接受过至少一种治疗的成人套细胞淋巴瘤患者

1. 国家代码为世界知识产权组织使用的缩写。

*:新适应症。

**:新联合用药。

***:新剂型。

表 IV. 2020 年批准及候选药物批准情况

产品名称	机构	国家 / 地区	适应症	状态 / 备注
Abicipar pegol	Allergan/Molecular Partners	美国，欧盟	治疗新生血管性（湿性）年龄相关性黄斑变性患者	预计美国的 PDUFA 目标日期是 2020 年年中；预计欧盟于 2020 年下半年批准
Ad26.ZEBOV（rHAd26），联合 MVA-BN Filo	杨森	欧盟	作为异源性加强免疫疫苗方案，用于预防扎伊尔型埃博拉病毒引起的埃博拉病毒病	于 2019 年 11 月提交每种疫苗的 MAA（加速评估）
Alalevonadifloxacin mesylate	Wockhardt	印度	对于 ABSSSI，包括糖尿病足感染和并发菌血症	于 2020 年 1 月在印度获批
AR-101（Palforzia）	Aimmune Therapeutics	美国，欧盟	4 ～ 17 岁儿童和青少年花生过敏脱敏	美国于 2020 年 1 月作出获批；欧盟于 2020 年下半年作出决定
Avapritinib	Blueprint Medicines	美国	携带 PDGFRA 外显子 18 突变（包括 *PDGFRAD842V* 突变）的无法切除或转移性 GIST	于 2020 年 1 月在美国获批；欧盟正在审查 MAA。
Belantamab mafodotin	GlaxoSmithKline	美国	治疗既往治疗（包括免疫调节剂、蛋白酶体抑制剂和抗 CD38 抗体）后复发或耐药的多发性骨髓瘤患者	于 2019 年 12 月提交 BLA
Bempedoic acid 和 bempedoic acid/ 依折麦布	Esperion Therapeutics	美国，欧盟	治疗使用目前可用的疗法但仍需额外降低低密度脂蛋白胆固醇（LDL-C）水平升高的患者	预计于 2020 年上半年获批
Berotralstat hydrochloride	BioCryst	美国	预防遗传性血管性水肿发作	于 2019 年 12 月提交 NDA
BP-101（Libicore）	Ivix	俄罗斯联邦	治疗机能减退性女性性欲障碍	于 2019 年 9 月提交申请
Cabotegravir 和 Cabotegravir/ 利匹韦林	ViiV Healthcare	美国，欧盟	开始注射治疗前，联合利匹韦林，对病毒载量受抑制的成人 HIV-1 感染者进行导入治疗	于 2019 年 4 月（美国）和 2019 年 7 月（欧盟）进行申请备案。
Chiglitazar	Chipscreen Biosciences	中国	2 型糖尿病	于 2019 年 9 月受理申请
Daprodustat	GlaxoSmithKline	日本	治疗 CKD 相关性贫血	于 2019 年 8 月日本进行申请备案
Dasotraline hydrochloride	Sunovion	美国	治疗中度至重度暴食症患者	PDUFA 日期是 2020 年 5 月 14 日

表 IV. 2020 年批准及候选药物批准情况（续）

产品名称	机构	国家 / 地区	适应症	状态 / 备注
Delgocitinib	Japan Tobacco (JT) Torii	日本	特应性皮炎	于 2020 年 1 月获批
Dotinurad	Fuji Yakuhin/Mochida	日本	治疗高尿酸血症（伴或不伴痛风）	于 2020 年 1 月获批
Eflapegrastim	Spectrum Pharmaceuticals	美国	治疗化疗引起的中性粒细胞减少症	PDUFA 日期是 2020 年 10 月 24 日
Eptinezumab	Alder Biopharmaceuticals	美国	预防慢性和发作性偏头痛；输注；静脉注射	PDUFA 日期是 2020 年 2 月 21 日
Fenfluramine hydrochloride	Zogenix	美国，欧盟	治疗 Dravet 综合征相关性癫痫发作	预计于 2020 年第一季度获得批准
Filgotinib	Galapagos/ 吉列德	美国、欧盟、日本	类风湿性关节炎	于 2019 年 8 月（欧盟）、2019 年 10 月（日本）和 2019 年 12 月（美国）进行申请备案
Flortaucipir F 18	礼来	美国	用于阿尔茨海默病患者的 tau 成像	
Fostemsavir	ViiV Healthcare	美国，欧盟	与其他抗逆转录病毒药物联合用于治疗因耐药、不耐受或安全性考虑而无法制定抑制方案、接受过多次治疗的多药耐药感染的成人 HIV-1 患者	于 2019 年 12 月在美国进行 NDA 备案；于 2020 年 1 月在欧盟进行 MAA 备案
HSK-3486	Haisco Pharmaceutical Group	中国	内镜诊断性检查前的全身麻醉和镇静诱导	于 2019 年 8 月申请获得优先审评资格
Imlifidase	Hansa Biopharma	欧盟	肾移植术前患者脱敏	预计于 2020 年夏季做出决定
Inebilizumab	Viela Bio	美国	治疗 NMO 和 NMOSD	PDUFA 日期是 2020 年 6 月 11 日
Isatuximab	Sanofi	美国、欧盟、日本	多发性骨髓瘤	PDUFA 日期是 2020 年 4 月 30 日（美国）；欧盟和日本正在审评申请
左氧氟沙星精氨酸盐	Wockhardt	印度	对于 ABSSSI，包括糖尿病足感染和并发菌血症	于 2020 年 1 月在印度获批
Lisocabtagene maraleucel	新基生物	美国	治疗既往至少接受过 2 种治疗的成人复发性 / 难治性 LBCL 患者	于 2019 年 12 月提交 BLA

表 IV. 2020 年批准及候选药物批准情况（续）

产品名称	机构	国家 / 地区	适应症	状态 / 备注
Lonafarnib	Eiger BioPharma-ceuticals/Progeria Research Foundation	美国	治疗早衰和早老样核纤层蛋白病	于 2019 年 12 月开始滚动提交，预计于 2020 年第一季度完成
LY-900014 (Ultrarapid lispro)	礼来	美国、欧盟、日本	1 型和 2 型糖尿病	于 2019 年第一季度提交申请
Margetuximab	MacroGenics	美国	与化疗联合治疗转移性 HER2 阳性乳腺癌患者	于 2019 年 12 月提交 BLA
Nadofaragene firadenovec	FKD Therapies	美国	治疗高级别卡介苗（BCG）治疗无反应性非肌层浸润型膀胱癌患者	BLA 于 2019 年 11 月获得优先审评资格
Orelabrutinib	诺诚健华	中国	治疗复发性 / 难治性慢性淋巴细胞白血病 / 小淋巴细胞淋巴瘤患者	于 11 月 19 日在中国受理备案，于 2020 年 1 月获得优先审评资格
Osilodrostat	Recordati	欧盟	成人内源性柯兴综合征	于 2020 年 1 月获批
OTL-200	Orchard Therapeutics	欧盟	异染性脑白质营养不良	于 2019 年 11 月进行 MAA 备案，进行加速评估
Ozanimod	新基生物	美国，欧盟	治疗复发型多发性硬化症	美国 PDUFA 日期是 2020 年 3 月 25 日；预计欧盟于 2020 年上半年做出决定
Pemigatinib	Incyte	美国，欧盟	治疗既往经治的伴 FGFR2 融合或重排的局部晚期或转移性胆管癌患者	PDUFA 日期是 2020 年 5 月 30 日（美国）；欧盟正在审评 MAA。
PPE（Viaskin Peanut）	DBV Technologies	美国	治疗 4 ～ 11 岁儿童的花生过敏	PDUFA 目标日期是 2020 年 8 月 5 日
REGN-3470-3471-3479（atoltivimab/odesivimab/maftivimab）	再生元	美国	埃博拉病毒感染	于 2019 年 9 月开始滚动提交
瑞马唑仑	PAION、Mundipharma（日本）、宜昌人福药业有限责任公司（中国）、Hana Pharm（韩国）、Cosmo Pharmaceuticals（美国）	日本、美国、中国、韩国、欧盟	全身麻醉（日本、韩国）；手术镇静（美国、中国、欧盟）	日本于 2020 年 1 月批准全身麻醉；美国的 PDUFA 日期是 2020 年 4 月 5 日；于 2018 年 11 月、2019 年 12 月和 2019 年 11 月分别在中国、韩国和欧盟进行申请备案
Rimegepant	BioHaven Pharmaceutical	美国	治疗急性偏头痛	PDUFA 目标日期是 2020 年第一季度

表 IV. 2020 年批准及候选药物批准情况（续）

产品名称	机构	国家 / 地区	适应症	状态 / 备注
Ripretinib	Deciphera	美国	治疗既往接受过抗肿瘤治疗（包括伊马替尼、舒尼替尼和瑞戈非尼）的晚期 GIST 患者	于 2019 年 12 月进行 NDA 备案
Risdiplam	Roche	美国	脊髓性肌萎缩症	PDUFA 日期是 2020 年 5 月 24 日
Sacituzumab govitecan	Immunomedics	美国	治疗既往接受过至少两种转移性疾病治疗的三阴性转移性乳腺癌患者	PDUFA 目标日期是 2020 年 6 月 2 日
Satralizumab	Chugai Pharmaceutical/Roche	日本、欧盟、美国	治疗 NMO 和 NMOSD	于 2019 年 8 月（欧盟）、2019 年 10 月（美国）、2019 年 11 月（日本）提交申请
Selumetinib sulfate	阿斯利康	美国	治疗患有 1 型神经纤维瘤病和症状性、无法手术切除的丛状神经纤维瘤的年满 3 岁的儿童患者	PDUFA 目标日期是 2020 年第二季度
Somapacitan	诺和诺德	美国，欧盟	治疗成人生长激素缺乏症	于 2019 年 9 月提交申请
Surufatinib	Hutchison China MediTech (Chi-Med)	中国	治疗晚期非胰腺神经内分泌肿瘤	于 2019 年 12 月申请获得获优先审评资格
Tafasitamab	MorphoSys	美国	联合来那度胺治疗后复发的或耐药性弥漫性 LBCL	于 2019 年 12 月提交申请
Tazemetostat	Epizyme	美国	治疗不适合根治性手术的转移性或局部晚期上皮样肉瘤患者；治疗既往接受过至少二线全身治疗的伴或不伴 EZH2 激活突变的复发性或难治性滤泡性淋巴瘤患者	2020 年 1 月获批用于上皮样肉瘤；于 2019 年 12 月提交滤泡性淋巴瘤 NDA
Teprotumumab	Horizon Therapeutics	美国	治疗 Graves 眼眶病（活动性甲状腺眼病）	于 2020 年 1 月获批
TetraMen-T	赛诺菲	美国，欧盟	预防≥ 2 岁人群出现流行性脑脊髓膜炎	PDUFA 日期是 2020 年 4 月 25 日（美国）；MAA 于 2019 年 10 月在欧盟提交
Tirabrutinib hydrochloride	Ono	日本	治疗 Waldenstrom 巨球蛋白血症和淋巴浆细胞淋巴瘤；治疗复发性或难治性原发性中枢神经系统淋巴瘤	于 2019 年 8 月和 11 月提交单独申请

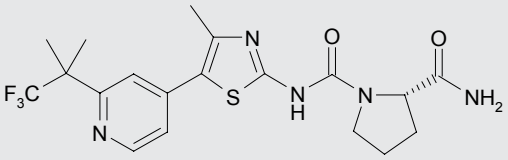
表 IV. 2020 年批准及候选药物批准情况（续）

产品名称	机构	国家 / 地区	适应症	状态 / 备注
Triheptanoin	Ultragenyx	美国	治疗长链脂肪酸氧化障碍，包括肉碱棕榈酰转移酶、极长链酰基辅酶 A 脱氢酶症和长链 3- 羟基酰基辅酶 A 脱氢酶缺乏症	PDUFA 目标日期是 2020 年 7 月 31 日
Tucatinib	Array BioPharma/ Seattle Genetics	美国	与曲妥珠单抗和卡培他滨联合用药，用于治疗局部晚期不可手术切除或转移性（包括脑转移患者），在新辅助治疗、辅助治疗或转移背景中，已单独或联合接受至少三种既往 HER2 靶向药物治疗的 HER2 阳性乳腺癌患者	于 2019 年 12 月提交 NDA
Vadadustat	Mitsubishi Tanabe Pharma	日本	治疗继发于 CKD 的肾性贫血患者	于 2019 年 7 月在日本提交申请
Valoctocogene roxaparvovec	BioMarin	美国，欧盟	治疗成人血友病 A 患者	于 2019 年年底提交申请
Veverimer	Tricida	美国	治疗 CKD 患者的代谢性酸中毒	PDUFA 日期是 2020 年 8 月 22 日
Viloxazine hydrochloride	Supernus	美国	注意力缺陷多动障碍	于 2019 年 11 月进行 NDA 备案
Viltolarsen	Nippon Shinyaku	美国、日本	杜氏肌营养不良症	于 2019 年 10 月在美国完成滚动提交；于 2019 年 11 月日本受理申请
Yimitasvir	HEC Pharm	中国	丙型肝炎病毒感染	于 2019 年 11 月申请获得优先审评资格

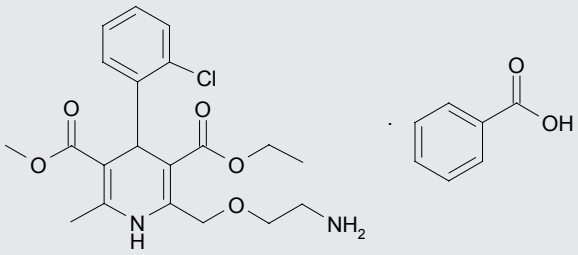
ABSSSI:急性细菌性皮肤及皮肤结构感染;BLA:生物制品许可申请;CKD:慢性肾脏病;GIST:胃肠道间质瘤;LBCL:大 B 细胞淋巴瘤;MAA:上市许可申请;NDA:新药申请;NMO:视神经脊髓炎;NMOSD:视神经脊髓炎谱系疾病;PDUFA:处方药申报者付费法案。

*来源 : Cortellis 药物早期研发情报和 Cortellis 综合性竞争情报。*截至 2020 年 1 月 24 日的最新信息。

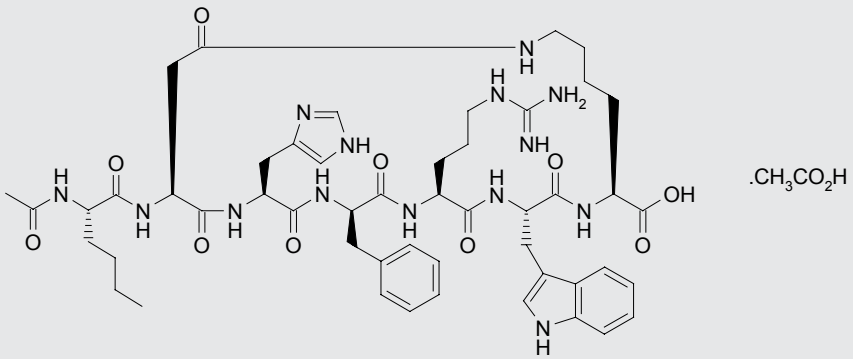
2019 年上市的 NCE 的化学结构



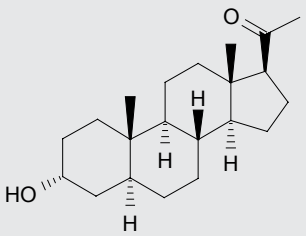
Alpelisib



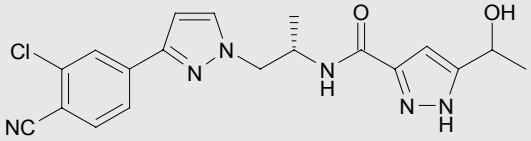
Amlodipine benzoate



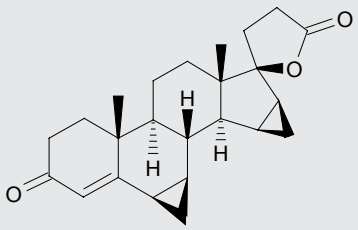
Bremelanotide



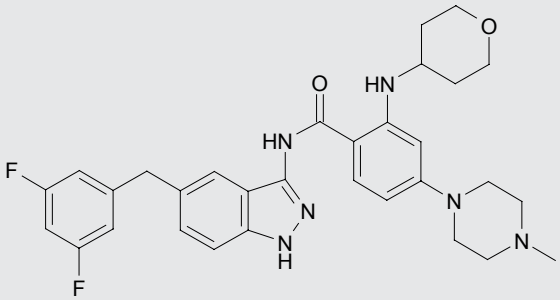
Brexanolone



Darolutamide



Drospirenone



Entrectinib

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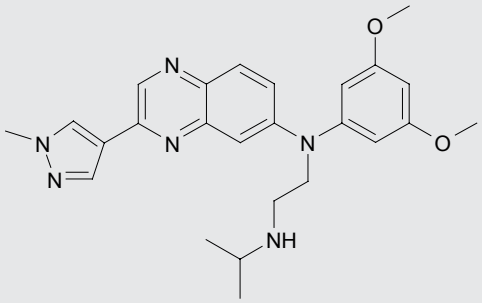
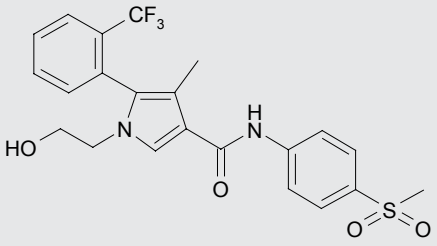
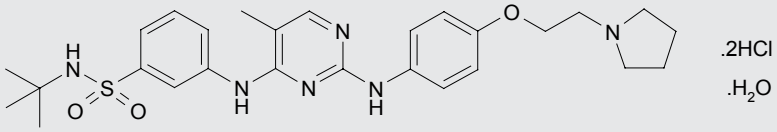


Erdafitinib

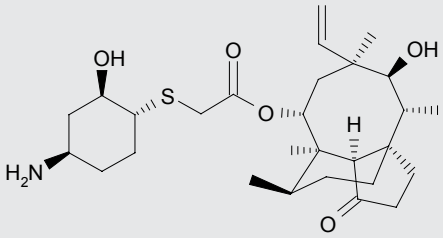


Esaxerenone

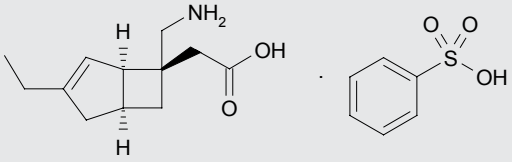


.2HCl
.H_2O

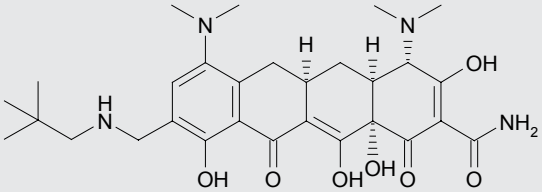
Fedratinib hydrochloride



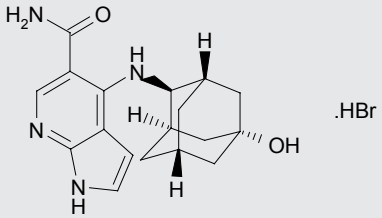
Lefamulin



Mirogabalin besylate

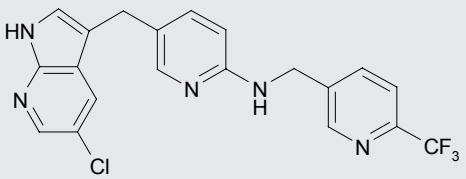


Omadacycline



.HBr

Peficitinib hydrobromide



.HCl

Pexidartinib hydrochloride

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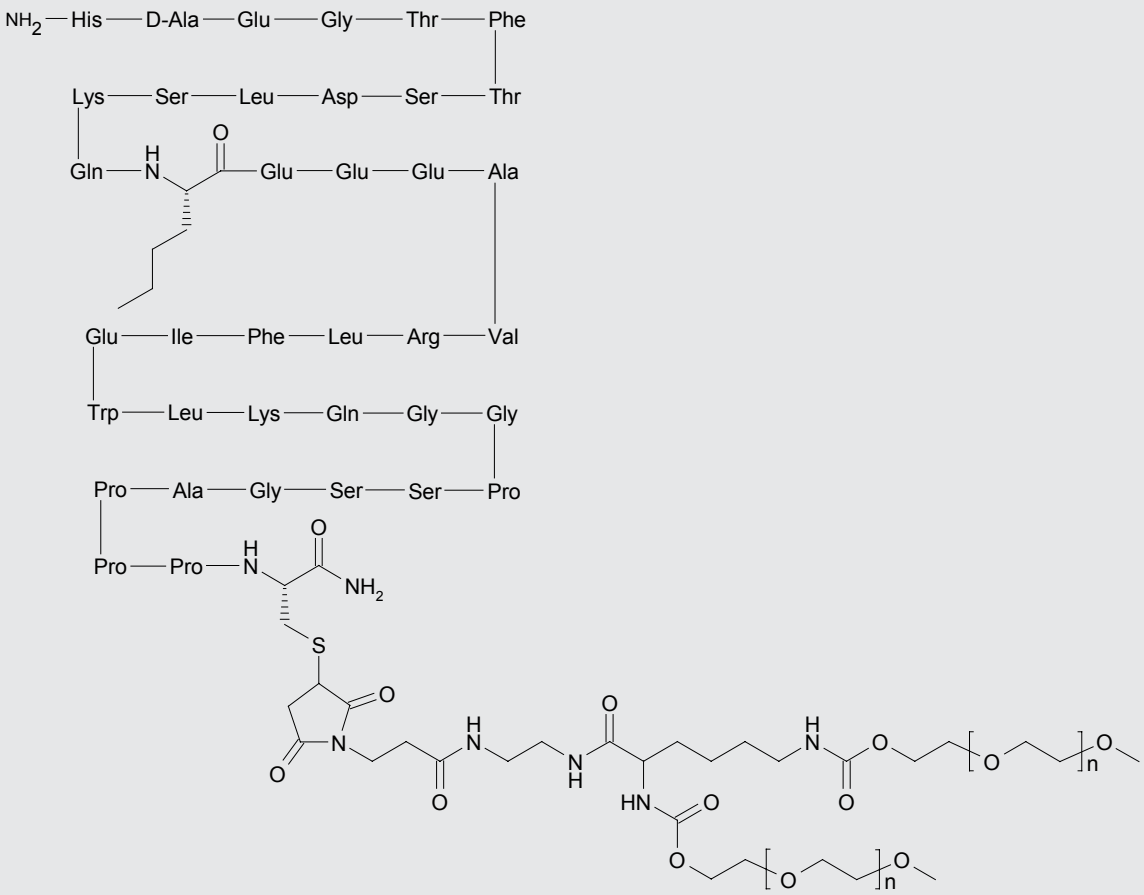
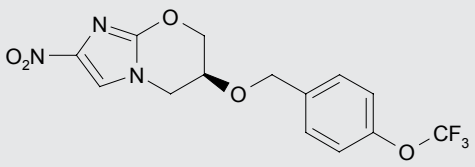
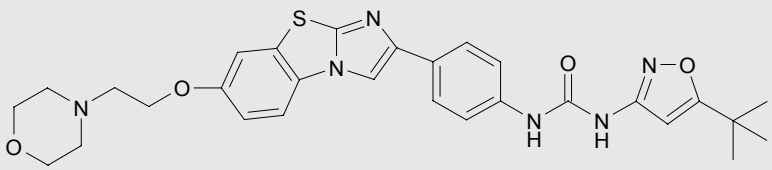


Polyethylene glycol loxenatide

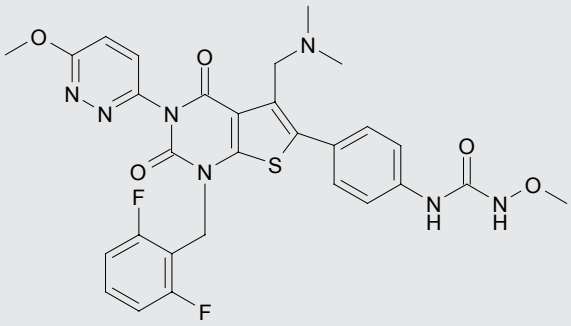


Pretomanid

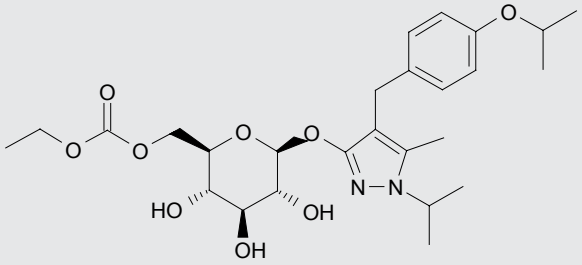


Quizartinib

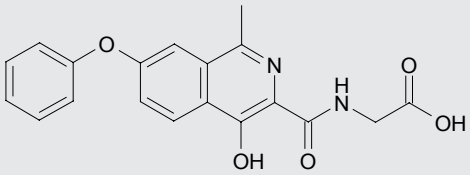
2019 年上市的 NCE 的化学结构



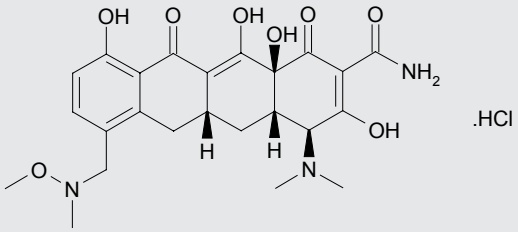
Relugolix



Remogliflozin etabonate

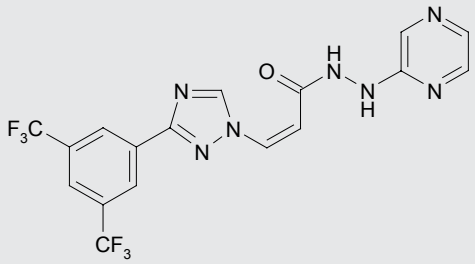


Roxadustat

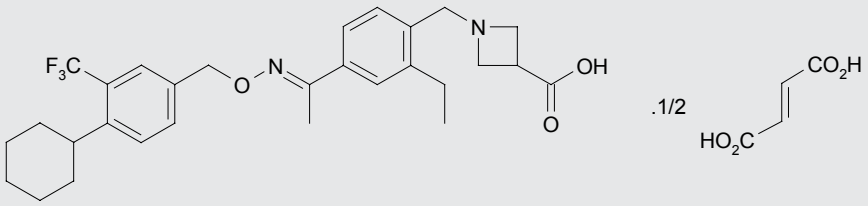


.HCl

Sarecycline hydrochloride



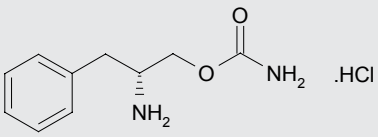
Selinexor



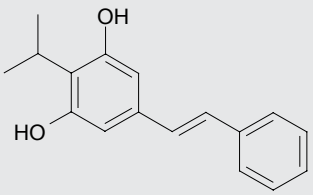
.1/2

Siponimod fumarate

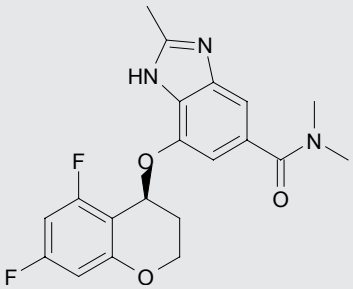
2019 年上市的 NCE 的化学结构



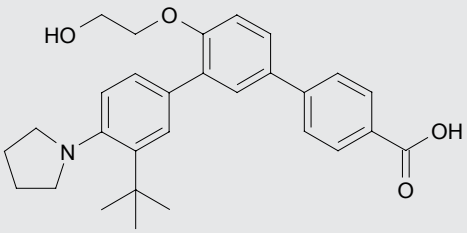
Solriamfetol hydrochloride



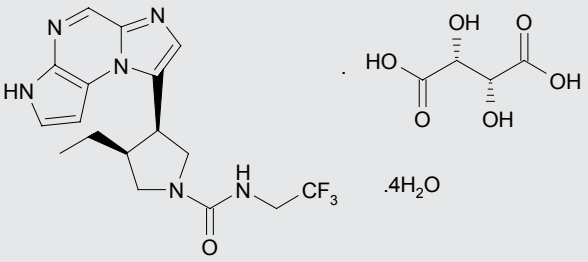
Tapinarof



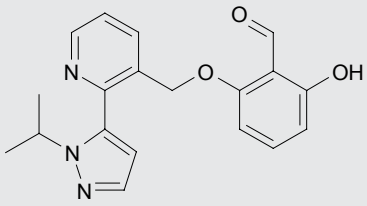
Tegoprazan



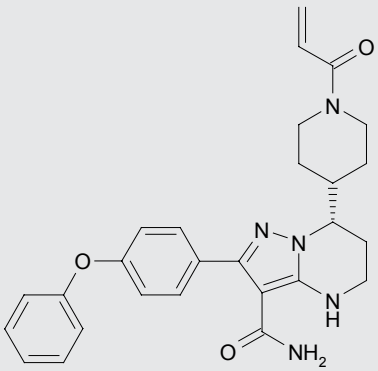
Trifarotene



Upadacitinib tartrate



Voxelotor



Zanubrutinib

科睿唯安生命科学与制药产品与解决方案

Cortellis™
A Clarivate Analytics solution

产品与解决方案	主要内容	特点	适用的专业人员	帮助您
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Cortellis Clinical Trials Intelligence 全球临床试验情报数据库 02	**专业临床试验情报数据库，加速临床试验开发决策，提供循证医学证据** • 包含药物、生物制品、医疗设备、生物标记物等相关的临床试验数据。所有信息均经人工审阅，并与Cortellis信息平台上的其他药物情报数据库完美整合，以支持您做出最佳决策 • 340,000+项全球临床试验，390,000+个临床试验相关的新闻发布，超过2,540,000+全文抽提的文献论文，117,000+份会议摘要和9,500+份会议报告	• 信息来源广泛 • 深度专业标引 • 直观可视化分析 • 动态跟踪提醒	• 临床研究 • 产品组合管理 • 注册法规 • 市场部 • 医学部 • 情报信息等	• 获取临床试验竞争情报 • 临床试验方案设计：患者筛选、方案制定以及临床终点的选择等 • 制定临床开发策略 • 探索临床科学数据 • 专业化推广
Cortellis Regulatory Intelligence 全球药政法规情报数据库 03	**全球药政法规情报数据库，提升国际化竞争优势，降低监管风险** • 包括从1885年至今、近80个国家/地区，220,000+份药品注册情报 • 全球模块：比较不同国家的药政注册要求 • 药政注册情报报告：追踪药政注册变更，比较竞争产品，为监管审查、沟通会议做好充分准备 • 监管信息汇总：了解不同国家/地区申请提交路线和特定国家药政注册需求 • 原始文件汇编：浏览最新/历史存档的药政注册文件	• 完整收录全球药物监管信息 • 无可比拟的文件对比功能，及时跟踪法规变更 • 独一无二的解释性文件（英语），由专家团队撰写，按国家/地区阐述重要过程和趋势 • 按国家/地区订阅，根据商务拓展计划选择相应区域信息 • 来自专家团队的卓越支持和培训	• 注册法规 • 法规情报信息 • 研发 • 临床研究 • 生产质量 • 供应链等	• 及时跟踪变化，获取最新药政信息，降低监管风险 • 节约时间和成本，获得竞争优势
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BioWorld Science 药物新闻 08	**每周一至周五动态更新的药物新闻及Email 跟踪提醒** • 精选最新、最重要的药物研发新闻在线发布，并以简明扼要的方式发送提醒邮件，帮助您快速锁定重要新闻事件。同时可以设定检索条件（新闻发生时间、药品名称、专利号、公司名称、机构名称、治疗领域类别、化合物类型、信息源等），跟踪研究相关内容	• 回溯至1996年 • 精选的重要药物新闻 • 准确信息，包括化学结构式 • 每年超过300个重要会议的最新药物进展 • Email跟踪提醒	• 业务发展 • 研发 • 情报信息等	• 从海量信息中总结摘要报告 • 从全球会议中获取新闻信息 • 获知在研药物最新进展（进入临床前最具前景的化合物、先导化合物和最新作用机制），并通过简洁表格形式收到更新提醒
BioWorld 生物制药行业系列资讯 09	**每日提供的生物制药行业权威系列资讯，包括BioWorld Today, BioWorld Asia, BioWorld Insight** • 专注于创新药相关的商务、科学及监管信息，帮助客户第一时间了解行业重大事件。客观传递新闻、专业报道与分析评论 • 包括：药物开发信息（从早期发现到最终上市），新兴、成熟生物技术公司、特色制药公司以及大型制药公司的最新报道，公司之间战略合作、收并购信息，资金筹集信息，行业重大科学突破，全球药政法规最新变更等	• 每日第一时间Email推送信息，同时可在线检索	• 业务发展& 合作授权 • 注册法规 • 临床研究 • 风险投资、券商及行业咨询	• 第一时间获取行业重大新闻
MetaCore 整合性系统生物学平台 10	**整合性系统生物学平台，集成分子生物学、系统生物学知识库以及高通量组学实验数据分析软件于一身** • 分析功能主要用于芯片、代谢、SAGE、蛋白质组学、siRNA、microRNA和筛选工作的数据进行功能性分析。2,000,000+总的相互作用，其中包括蛋白质-蛋白质（~900,000），化合物-蛋白质（~800,000），化合物-化合物（10,000+），RNA-蛋白质（~200,000）等相互作用。并定义了方向和机制, 1,500+个经典范式通路, 38,000+多个代谢反应, 860,000+个化合物, 5,000+个内源化合物, 9,000+个药物	• 同行评审、人工验证 • 收录全面、准确的信号通路、相互作用信息 • 支持所有组学数据分析功能	• 生物研究 • 生物信息 • 生物标记物 • 临床前研究 • 医疗领域 • 转化研究	• 分析高通量筛选试验数据，找出与之相关的重要通路图、网络关系、疾病，并排序列出 • 针对研究，通过疾病、组织、功能过程和亚细胞定位过滤功能，找到相关的网络关系图
MetaDrug 小分子药物活性/ 毒理预测平台 11	**全球领先的系统药理学平台。整合大量小分子化合物的生物学信息，为化合物预测和分析算法开发的多角度一站式信息平台** • 全部信息均经人工审阅。对化合物靶点、代谢产物、药代动力学特征、治疗效果和副作用进行预测。70+个QSAR模型，160+种代谢规则，用于代谢产物预测，约1,000个经典范式通路图，涵盖近200,000 个人类、小鼠、大鼠代谢和信号通路（基于文献报道的一致性），1,200,000+个蛋白与蛋白、DNA、RNA、代谢产物、外源物相互作用，几千种疾病生物标记物，近700,000个化合物	• 最大的药物相关靶标库，覆盖近6,000个人类蛋白 • 针对每个化合物，整合其已有信息，并预测其未知特性 • 化合物预测利用目前最完善的MetaCore相互作用网络 • 具有组学数据分析功能	• 药物研发 • 先导化合物确认及优化 • 靶标发现 • 疾病领域研究 • 化合物筛选 • 化学信息学和药物化学 • 药代动力学研究 • 毒性评估	• 预测小分子化合物潜在靶点 • 找出影响相关的生物学通路 • 预测适应症 • 发现药效预测的生物标记物 • 预测代谢产物、药代动力学特征和副作用
Drug Research Advisor 靶点成药性评估工具 12	• 数据源由Integrity数据库和组学数据库（MetaCore/MetaDrug）提供；收录大量靶点、疾病和药物信息。 • 是基于人工智能并交互呈现、可视化分析的靶点探索和评估工具，快速实现“探索-筛选-评级-评估”的靶点发现工作流程； • 按疾病领域筛选first-in-class靶点和相对成熟靶点，并给出排序； • 探索在同一靶点通路或靶点家族中是否还存在具有成药性更好、竞争较小、成功性较大的靶点； • 汇总单一靶点的相关信息，包含疾病关联度、药物、生物学知识、通路、试验数据、竞争情报。	• 人工智能 • 每日更新 • 直观可视化分析 • 关联Integrity和MetaCore/MetaDrug	• 研发 • 业务发展 • 项目合作 • 知识产权 • 产品组合管理 • 情报信息等	• 掌握早期靶标发展格局 • 全面了解药物、靶标和疾病的联系 • 跟踪所关注治疗领域的热点机制和最新靶标动态 • 探索靶点成药性级别 • 指导挑选靶点和治疗领域
OFF-X 药物安全信息平台 13	• OFF-X应用范围广泛， 通过整合/关联关键药物安全信息，建立从早期靶点发现到临床应用的安全信息平台 • 提供药物研发中与药物和靶点相关的综合临床前毒性和临床不良事件信息，包括first-in-class及新验证的靶点 • 通过检索靶点在数据库中获得相关的安全信息，同时也可以通过检索药物不良事件识别相关的靶点、获知相关药物的化学结构 • OFF-X可根据新药的药理学特征，预测其潜在的安全性问题 • 可帮助研发机构和科学家降低项目风险、加速药物研发、提高研发效率	• 每日更新 • 直观可视化分析 • 通过靶点、药物或不良事件进行检索 • 信息相互关联，分类细致，可以快速锁定关键信息。 • 链接信息来源 • 动态跟踪提醒	• 早期研究 • 临床开发 • 项目合作 • 知识产权 • 产品组合管理 • 情报信息等	• 随时了解对您所研发药物有影响的关键安全信息 • 识别新靶点的安全风险 • 建立脱靶效应的假设，并指导验证性实验计划的制定 • 挖掘药物临床前毒理信息用以指导临床研究 • 发现靶点与药物安全性之间的直接机理联系 • 了解竞品的安全性信息 • 监测特定类别药物的监管信息
Cortellis Drug Timeline and Success Rate 药物研发时程及注册成功率预测 14	**全球第一运用AI预测药物研发及注册成功率** • 多市场预测：美欧日三地进入临床即开始预测 • 适应症个别预测：提供针对每个适应症的预测结果 • 实时数据：机器学习基于Cortellis 15年的数据建立模型，持续跟踪最新药物发展动态，使用15+以上特征计算并及时提供预测结果 • 适用18+治疗领域、2,200+适应症	• 实时数据 • 直观可视化 • 动态更新	• 战略规划 • 业务发展 • 项目合作 • 产品组合管理 • 投资组合管理	• 评估及监控竞争对手 • 项目合作筛选 • 对标同类型项目研发时程及策略调整自身产品组合 • 投资项目评估及投资组合筛选

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Clarivate Analytics

Review Article

The year's new drugs & biologics 2019

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Contents

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Summary

Highlights of our annual review of new approvals and launches on global drug markets include the approval and launch of Trikafta, the most widely applicable treatment to date for cystic fibrosis; approval of the first Ebola vaccine for general (rather than emergency) use; the pilot rollout in three African countries of the world's first malaria vaccine; approval of a new treatment option for multidrug-resistant bacterial infections; and the approval and launch in China of the first new drug to treat Alzheimer's disease in more than a decade. Several new immune checkpoint inhibitors and antibody–drug conjugates were approved for cancer indications, confirming continued industry enthusiasm for cancer immunotherapy. The most notable trend of 2019 was the granting by the Food and Drug Administration (FDA) of a record number of accelerated approvals, many of which were issued several months ahead of the expected action date.

Key words: New drug launches – New drug approvals – Line extensions – New formulations – New indications – New combinations – Orphan drugs – First-in-class drugs – Accelerated approval

Introduction

Inaugurated 32 years ago, this annual review article provides the opportunity to present from both a historical and a research perspective those molecular entities and biological drugs that were launched or approved in various countries for the first time during the year just ended.

Fifty-six new molecular entities and biologics were introduced in their first markets worldwide in 2019 (see Table I). In addition, 24 significant new line extensions—a label used in this publication to refer to new combinations, new formulations and new indications for previously marketed drugs—were rolled out worldwide during the year. Another

Table I. *New drugs & biologics by therapeutic category, launched in 2009-2019*.*

Therapeutics	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Central nervous system	7	4	5	2	4	3	4	7	6	6	8
Respiratory	2	1	1	2	1	5	3	1	1	2	1
Cardiovascular	1	1	1	1	2	1	1	2	0	1	3
Renal–urologic	2	0	2	1	0	2	1	1	0	1	1
Hematologic	3	1	3	2	1	7	7	4	2	7	6
Gastrointestinal	1	1	0	1	4	1	4	1	4	2	1
Endocrine drugs	3	2	1	4	4	6	3	1	3	4	5
Dermatologic	1	0	1	2	1	1	2	4	3	3	5
Anti-infective	1	2	6	0	5	11	5	5	6	10	3
Musculoskeletal	3	0	1	2	0	1	1	1	3	1	3
Immunologic	17	5	4	5	11	2	5	10	8	5	4
Cancer	6	7	7	10	12	10	14	5	18	18	13
Ophthalmic	1	1	2	0	1	2	0	1	2	3	1
Metabolic drugs	3	4	2	2	7	3	5	4	4	5	2
Poisoning & drug abuse	0	0	0	1	1	0	0	1	0	0	0
Mouth & dental	0	0	0	0	1	0	0	0	0	0	0
Diagnostic agents	0	0	0	1	1	3	0	2	1	1	0
Total	**51**	**29**	**36**	**36**	**56**	**58**	**55**	**50**	**61**	**69**	**56**

*Does not include line extensions.

26 new products, including both novel drugs and biologics and new line extensions, were approved, although we were unable to verify that they had been launched before December 31, 2019.

The most active therapeutic group was again oncolytic agents, with 13 new products introduced, followed by central nervous system (CNS) agents with 8.

Nine first-in-class agents were launched for the first time in 2019, among them new treatments for Alzheimer's disease (AD), hemophilia and hypoactive sexual desire disorder, as well as several first-in-class cancer therapeutics.

Again in 2019, the U.S. was the most active market for new drugs, accounting for 56% of global new launches (Fig. 1). The U.S. Food and Drug Administration (FDA) has been aggressively accelerating the process for approving new drugs. In 2017, U.S. researchers found that FDA review times (2011–2015) were on average 60 days shorter than at the European Medicines Agency (EMA) (1); since then, the U.S. regulatory body has picked up its pace even further. The agency is fast tracking and accelerating the approval of more drugs and rejecting fewer, leading some to accuse it of being a partner to the industry that it is tasked with regulating. Also notable is the consistent increase in new drugs and biologics emerging from China's domestic pharma industry. Seven of last year's first launches were reported in that country, accounting for 12% of the global total.

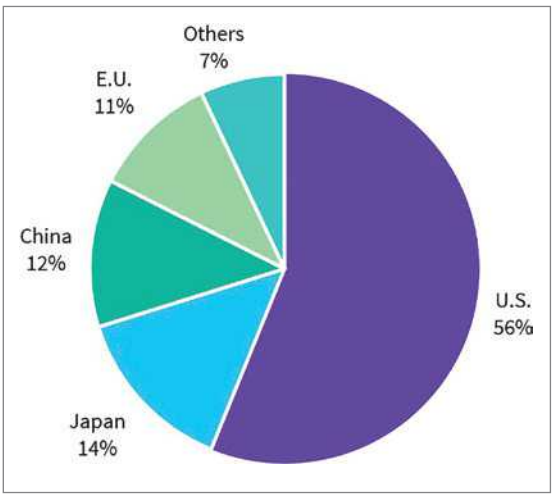

Figure 1. Distribution of new drug launches by country, 2019.

Regulatory agencies—primarily the FDA, although programs are also being established in other markets—can expedite the development and review processes and provide incentives to drug companies via a growing number of special designations. The first such program authorized by the U.S. Congress was the 1983 Orphan Drug Act, conceived and introduced to spur investigation into treatments for rare diseases. This was followed in 1988 by "fast track" designation, designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill unmet medical needs. This was followed in 1992 by the Prescription Drug User Fee Act (PDUFA), which included "accelerated approval" and "priority review" programs (and, not incidentally, first required drug companies to pay fees to the regulatory agency). In 1997, the PDUFA goal for review times was lowered from a year to 10 months. In 2012, Congress added the "breakthrough therapy," designation, which enabled the FDA to waive normal procedures and requirements for drugs deemed to demonstrate a substantial improvement over available treatments. Approximately three-quarters of new drugs in the U.S. receive some type of expedited review at this time (2). In the European Union, the priority medicines (PRIME) program, now in its third year, focuses on medicines that may offer a major therapeutic advantage over existing treatments or benefit patients without treatment options. Between March 2014 and August 2016, the EMA ran a pilot project to assess the Adaptive Pathways approach, a scientific concept for drug development and data generation which allows for early and progressive patient access to new medicines in areas of high medical need. The EMA has also implemented an "accelerated assessment" program, which provides for faster review (150 vs. 210 days) of drugs that are able to address unmet medical needs. In Japan, the Sakigake designation system was established in 2015 to promote access to innovative drugs, devices and regenerative medicines. Modeling the success of the U.S.'s pioneering orphan drug program, many other countries have set up similar programs over the years.

The two categories of disease that have benefitted most from these programs are cancer and rare diseases. A study by *The Wall Street Journal* found that the majority of cancer drugs approved from 2015-2018

Table II. *Drug development in an age of exceptionality: special regulatory status/designations granted to 2019 newly launched products*.*

Drug name	Indication	Orphan drug	Breakthrough therapy	Accelerated approval	Fast track	Priority review	Real-time oncology	QIDP	Rare pediatric disease	Sakigake
Alpelisib	$HR^+/HER2^-$, *PIK3CA*-mutated, advanced or metastatic breast cancer					X	X			
Apremilast	Behçet's disease	X								
Beperminogene perplasmid	Chronic arterial occlusion (arteriosclerosis obliterans and Buerger's disease)				X					
Brexanolone	Postpartum depression		X			X				
Dupilumab	Chronic rhinosinusitis with nasal polyposis					X				
Eculizumab	Neuromyelitis optica spectrum disorder	X								
Elexacaftor/tezacaftor/ivacaftor	Cystic fibrosis	X				X				
Emapalumab	Primary hemophagocytic lymphohistiocytosis	X	X			X			X	
Entrectinib	Solid tumors with *NTRK* gene fusion	X	X							
	ROS1 fusion-positive non-small cell lung cancer	X								
Erdafitinib	Urothelial carcinoma		X							
Esketamine hydrochloride	Treatment-resistant depression		X							
Evocalcet	Hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism	X								
Fedratinib	Myelofibrosis	X								
Golodirsen	Duchenne muscular dystrophy	X		X	X	X				
Lefamulin	Community-acquired bacterial pneumonia				X	X		X		
Luspatercept	β-Thalassemia	X			X	X				
Nintedanib	Systemic sclerosis-associated interstitial lung disease	X	X			X				

(Continued)

Table II. *Drug development in an age of exceptionality: special regulatory status/designations granted to 2019 newly launched products*. (Cont.)*

Drug name	Indication	Orphan drug	Breakthrough therapy	Accelerated approval	Fast track	Priority review	Real-time oncology	QIDP	Rare pediatric disease	Sakigake
Omadacycline	Community-acquired bacterial pneumonia and acute skin and skin structure infections				X			X		
Onasemnogene abeparvovec	Spinal muscular atrophy	X	X							
Pexidartinib hydrochloride	Tenosynovial giant cell tumor	X	X							
Polatuzumab vedotin	Diffuse large B-cell lymphoma	X		X						
Pretomanid	Extensively drug-resistant and multidrug-resistant tuberculosis	X			X			X		
Quizartinib	Acute myeloid leukemia	X								
Ravulizumab	Paroxysmal nocturnal hemoglobinuria	X				X				
	Atypical hemolytic uremic syndrome	X								
Rifamycin	Travelers' diarrhea				X			X		
Ropeginterferon alfa-2b	Polycythemia vera	X								
Ruxolitinib phosphate	Graft-versus-host disease	X	X			X				
Selinexor	Multiple myeloma	X		X	X					
Solriamfetol hydrochloride	Narcolepsy	X								
Stemirac	Spinal cord injury									X
Tagraxofusp	Blastic plasmacytoid dendritic cell neoplasm	X								
Treosulfan	Conditioning treatment prior to allogeneic hematopoietic stem cell transplantation	X								
Volanesorsen	Familial chylomicronemia syndrome	X								
Voxelotor	Sickle cell disease	X	X	X	X	X			X	
Zanubrutinib	Mantle cell lymphoma		X	X						

QIDP, Qualified Infectious Disease Product.
*Designations apply only to the indication and country of launch. This table includes line extensions.

were fast tracked, and that just 19% had proof upon approval that their use translated into significant increases in overall survival (2). Postmarketing studies, which are required by the agency in order for a drug to be granted full approval, do not always confirm the results of smaller studies using surrogate endpoints upon which accelerated approval was based (3).

All told, roughly half of all new drugs, biologics and line extensions introduced worldwide in 2019 had been granted at least one special designation in the country of launch, as shown in Table II.

Agents for Analgesia & Anesthesia

Neuropathic pain encompasses a heterogeneous group of chronic conditions that cannot be explained by a single etiology or anatomical lesion. It evolves in the wake of a variety of causative etiologies and underlying mechanisms; representative neuropathic pain syndromes include postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, central pain syndromes, phantom limb pain and Guillain–Barré syndrome. All neuropathic pain states are characterized by hyperexcitability that may vary in type and degree, depending upon a combination of factors derived from the patient and the underlying neurological condition. In 2019, the voltage-dependent calcium channel subunit α-2/δ-1 ligand **mirogabalin besylate** (Tarlige; Daiichi Sankyo) was approved and launched in Japan for the treatment of peripheral neuropathic pain (PNP), including diabetic PNP and postherpetic neuralgia.

Lasmiditan hydrochloride (Reyvow; Lilly), an oral 5-HT_{1F} receptor agonist, belongs to a new class known as neurally acting antimigraine agents (NAAMAs). NAAMAs were designed to deliver efficacy in migraine without the vasoconstrictor activity associated with previous generations of antimigraine drugs. Lasmiditan selectively targets 5-HT_{1F} receptors expressed in the trigeminal nerve pathway. In October 2019, it was approved by the U.S. FDA for the acute treatment of migraine, with or without aura, in adults. Following Drug Enforcement Administration (DEA) review, Lilly anticipates launching the drug in early 2020.

As highlighted in last year's edition of this publication (4), calcitonin gene-related peptide (CGRP) is a promising new target for antimigraine drugs. The 37-amino acid vasodilatory neuropeptide is distributed widely throughout the central and peripheral nervous systems and the cardiovascular system, where it exerts a range of biological effects and physiological functions that are critical in the pathophysiology of migraine, including both neuromodulation and vasodilation. Three anti-CGRP receptor monoclonal antibodies (MAbs) were introduced in 2018, all indicated for migraine prophylaxis and administered via injection. In 2019, the FDA approved the first orally active small-molecule drug acting on CGRP: **ubrogepant** (Ubrelvy), indicated for the acute treatment of migraine, with or without aura, in adults. Ubrogepant was discovered by Merck & Co. and licensed in 2015 to Allergan for development and commercialization worldwide. Launch is planned for the first half of 2020.

Jiangsu Hengrui's **remimazolam tosylate**, a benzodiazepine and γ-aminobutyric acid ($GABA_A$) BZ site receptor agonist, was approved in late December in China, where it is indicated for sedation in patients undergoing diagnostic upper gastrointestinal endoscopy.

Psychopharmacologic Drugs

According to the World Health Organization (WHO), depression affects more than 300 million people of all ages worldwide, equivalent to 4.4% of the global population. In spite of this prevalence, treatment is often ineffective or only partially effective, or is associated with intolerable side effects. For decades, depression has been treated with tricyclic antidepressants, monoamine oxidase inhibitors or neurotransmitter reuptake inhibitors. Last year saw the introduction of two new antidepressants with novel mechanisms of action (5). Both were granted breakthrough therapy designation, and both are approved for medically supervised administration only.

A new intranasal spray formulation of the *N*-methyl-D-aspartate (NMDA) receptor antagonist **esketamine hydrochloride** (Spravato; Janssen) was approved by the FDA and introduced last year in the U.S. for use, in conjunction with an oral antidepressant, for the treatment of adults with treatment-resistant depression (defined as failure to respond to any two antidepressants). This is a new indication for

esketamine, which has been marketed since 1997 as an intravenous general anesthetic. In clinical trials enrolling more than 1,700 patients with treatment-resistant depression, esketamine administered by the intranasal route at subanesthetic doses, given in combination with a newly initiated oral antidepressant, was associated with reduction of depressive symptoms and delayed time to relapse of symptoms. Of note, at least one member of the Psychiatric Drugs Advisory Committee, who was not present at the meeting due to a U.S. government shutdown, argued that this treatment effect was not significant (6). Moreover, esketamine can cause serious side effects, including sedation, dissociation, and suicidal ideation and behavior (5). In late December, the European Commission (EC) issued its own approval for esketamine, administered in combination with a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor, for adults living with treatment-resistant major depressive disorder.

Allopregnanolone is a positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors that has been studied as a potential antidepressant. **Brexanolone** (Zulresso; Sage Therapeutics), an intravenous formulation of allopregnanolone, was approved and launched last year in the U.S. as the first and only treatment specifically indicated for postpartum depression. The most common medical complication of childbirth, postpartum depression affects approximately 400,000 women each year in the U.S. Brexanolone is formulated using Ligand's Captisol, a chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. The drug is administered by continuous intravenous infusion for 2.5 days under the supervision of healthcare providers in sites of care that have been certified under the Zulresso Risk Evaluation and Mitigation Strategy (REMS) program.

A great deal has been achieved in the treatment of schizophrenia in recent decades, especially with respect to the treatment of positive symptoms by targeting dopamine D_2 receptors. However, the disease has a range of other symptoms which severely affect quality of life and which require other strategies or additional targets. Last year saw the first approval of a new drug designed to fill this gap: Intra-Cellular Therapies' **lumateperone tosylate** (Caplyta). Lumateperone acts synergistically via multiple systems, thus representing a unique approach for the therapeutic management of a range of neuropsychiatric disorders. It possesses a potent antagonistic activity at serotonin 5-HT_{2A} receptors and also binds to dopamine (D_1 as well as D_2) receptors, with partial agonism at presynaptic D_2 receptors and postsynaptic antagonism. Further, preclinical data demonstrated that lumateperone uniquely acts as an indirect modulator of glutamatergic phosphoprotein, with D_1-dependent augmentation of both NMDA and AMPA activity via the mammalian target of rapamycin (mTOR) pathway, mechanisms thought to predict potent and rapid antidepressant effects (7). The efficacy of lumateperone was demonstrated in two placebo-controlled trials, which confirmed a statistically significant separation from placebo on the primary endpoint, the Positive and Negative Syndrome Scale total score. The drug will be launched in 2020.

In March, the FDA approved Jazz Pharmaceuticals' dual-acting dopamine and norepinephrine reuptake inhibitor **solriamfetol hydrochloride** (Sunosi) to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). Approval was based on data from the TONES (Treatment of Obstructive sleep apnea and Narcolepsy Excessive Sleepiness) phase III program, which included four randomized, placebo-controlled studies that demonstrated the superiority of solriamfetol relative to placebo. In 12-week studies, approximately 68-74% of people taking solriamfetol at 75 mg and 78-90% of those taking the drug at 150 mg reported improvement in their overall clinical condition, as assessed by the Patient Global Impression of Change scale. At week 12, 150 mg of solriamfetol for narcolepsy patients and all doses for OSA patients demonstrated improvements in wakefulness compared with placebo as assessed in test sessions 1 (approximately 1 hour after dosing) through 5 (approximately 9 hours after dosing) of the maintenance of wakefulness test. The most common adverse reactions (incidence ≥ 5% and higher than placebo) reported in both the narcolepsy and OSA study populations were headache, nausea, decreased appetite and anxiety. The drug was launched in July, following a final scheduling decision by the U.S. DEA. Solriamfetol was also

approved in Europe in January 2020 for the same indication.

In December, the FDA approved a second new treatment for a sleep disorder: the dual orexin receptor antagonist **lemborexant** (Dayvigo; Eisai), indicated for the treatment of adults with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to orexin receptors OX_1 and OX_2 is thought to suppress the wake drive. Lemborexant binds to OX_1 and OX_2 receptors and acts as a competitive antagonist with stronger inhibition effect toward OX_2. Lemborexant is only the second orexin antagonist to emerge from the pipeline, following the 2014 introduction of suvorexant. It will be available in the U.S. following DEA scheduling, which was expected to occur within 90 days of approval.

Neurologic Drugs

The pivotal role of the intestinal microbiome in human health and disease has become increasingly apparent in recent years. The microbiome—defined as the genetic material of all commensal microorganisms residing in the gut, respiratory tract, skin and elsewhere in the human organism—has been known for some time to function as a signaling hub, integrating environmental stimuli with host genetic and immune signals to regulate the host's metabolic and immune functions, as well as orchestrating its response to infection. More recently, alterations to the gut microbiome have also been implicated in neurological disorders such as AD through a multiplicity of interactions (8). In November 2019, China's National Medical Products Administration (NMPA) granted conditional approval for **GV-971** (Oligomannate), a first-in-class treatment for AD thought to act by reconditioning dysbiosis of the gut microbiome (Fig. 2). The product is a mixture of acidic linear oligosaccharides isolated from brown algae. It was developed by Shanghai Green Valley Pharmaceuticals and is indicated for the treatment of mild to moderate AD and for improving cognitive function. In a phase III trial in Chinese patients with mild to moderate AD, GV-971 was shown to statistically improve cognitive function as early as 4 weeks after treatment initiation, with sustained benefits at each follow-up visit throughout the 36-week study. The mean difference between the active and placebo groups in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog12) scores was 2.54. GV-971 was safe and well tolerated. The conditional approval in China requires further evaluation of the mechanism of action, safety and efficacy of GV-971. A multicenter global phase III clinical trial with sites in the U.S., Europe and Asia is planned to begin in early 2020 to support global regulatory filing of the product, expected within 5 years. GV-971 was launched in China in late December.

Acorda Therapeutics' Inbrija, a new inhalation formulation of the standard antiparkinsonian drug **levodopa**, was introduced in the U.S. last year for the intermittent treatment of "off" episodes in people with Parkinson's disease treated with carbidopa/levodopa. "Off" episodes are characterized by the return of motor and nonmotor symptoms between regular doses of antiparkinsonian drugs; these typically become progressively worse as the disease progresses. Later in the year, Inbrija was also approved in the European Union.

Cenobamate (Xcopri), a novel anticonvulsant discovered and developed by Korean company SK Biopharmaceuticals, was approved in November by the U.S. FDA, indicated for the treatment of partial-onset seizures in adults. While the precise mechanism by which cenobamate exerts its therapeutic effect is unknown, the drug is believed to reduce repetitive neuronal firing by inhibiting voltage-gated sodium currents. It is also a positive allosteric modulator of $GABA_A$ receptors. Launch of cenobamate is expected in the second quarter of 2020, following scheduling review by the DEA.

The second-generation sphingosine-1-phosphate (S1P) receptor modulator **siponimod fumarate** (Mayzent; Novartis) was approved and launched last spring in the U.S. for the treatment of adults with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing–remitting disease and active secondary progressive multiple sclerosis (SPMS). Later in the year, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for siponimod

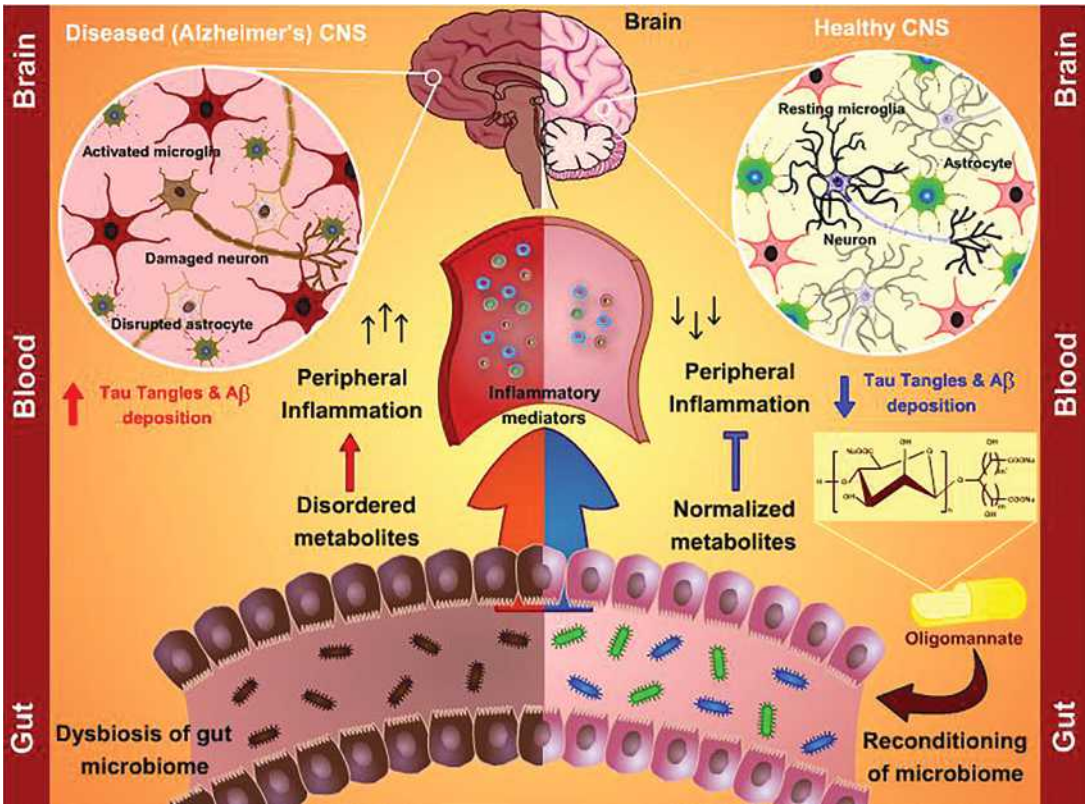

Figure 2. Oligomannate (GV-971), a first-in-class agent, is a seaweed-based drug intended to treat Alzheimer's disease. This drug is administered orally and has the ability to restore the gut microbiome to a state of symbiosis, thereby reducing peripheral and central inflammation. This in turn regulates the central nervous system (CNS), decreases deposition of amyloid protein and tau hyperphosphorylation, and improves cognitive function.

for the treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity (i.e., gadolinium-enhancing T1 lesions or active, new or enlarging, T2 lesions). Approval in Europe for this indication took place in January 2020.

Stemirac (STR-01), a novel cell therapy discovered at Sapporo Medical University and developed by Nipro, was approved and launched last year in Japan for the treatment of spinal cord injury. Stemirac consists of autologous human bone marrow-derived mesenchymal stem cells expanded in autologous human serum. The cell therapy was designated as a target product under the country's 2015 Sakigake designation system.

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neurodegenerative disorder, predominantly with onset in childhood, that affects motor neurons in the spinal cord and brainstem. SMA is found worldwide, with an estimated incidence of 1 in 11,000 live births and a carrier frequency of 1 in 50. Approximately 95% of SMA subtypes involve mutations in the survival motor neuron 1 gene (*SMN1*). Until just 2 years ago, supportive care was the only treatment available for SMA; in 2017, the disease-modifying therapy nusinersen was introduced, radically improving the treatment landscape for type I SMA. In 2019, prospects for patients improved further with the U.S. approval and launch of **onasemnogene abeparvovec** (Zolgensma), an

adeno-associated virus vector-based gene therapy developed by the Novartis subsidiary AveXis. Zolgensma is indicated for the treatment of pediatric patients less than 2 years of age with SMA with biallelic mutations in the *SMN1* gene. It is designed to address the genetic root cause of SMA by providing a functional copy of the human *SMN* gene, potentially halting disease progression through sustained SMN protein expression following a single, one-time intravenous infusion. The potentially curative nature of the therapy was used to justify its record-breaking price tag of USD 2.1 million. The product has orphan drug status and breakthrough therapy designation in the U.S.

In 2016, in spite of a negative recommendation from the Peripheral and Central Nervous System Advisory Committee, the FDA granted accelerated approval of Sarepta Therapeutics' first-in-class exon-skipping agent eteplirsen for the treatment of Duchenne muscular dystrophy (DMD) in patients with a specific mutation (9). Three years later, again in spite of a negative opinion (complete response letter) issued by the agency itself just months earlier, the FDA approved Sarepta's second exon-skipping antisense agent, **golodirsen** (Vyondys 53), indicated for the treatment of DMD in patients with a confirmed mutation amenable to exon 53 skipping. According to the FDA, only about 8% of DMD patients have this mutation; as such, golodirsen has orphan drug status. The exon-skipping strategy is based on the discovery that internally deleted dystrophins may retain part of their functionality; hence, if the disrupted open-reading frame could be restored, the production of at least partially functioning dystrophin could be resumed. Echoing the case of eteplirsen, accelerated approval of golodirsen was based on the surrogate endpoint of an increase in dystrophin production in the skeletal muscle observed in some patients treated with the drug. The agency concluded that the data submitted by Sarepta demonstrated an increase in dystrophin production "that is reasonably likely to predict clinical benefit in patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 53 skipping" (10), although clinical benefit of the drug, including improved motor function, has not been established. In making this decision, the FDA said it had also considered the potential risks associated with the drug (infections and renal toxicity), as well as the life-threatening and debilitating nature of the disease and the lack of available therapy. Sarepta announced that commercial distribution of golodirsen would begin immediately. Continued approval of the drug may be contingent upon verification of a clinical benefit in confirmatory trials.

Neuromyelitis optica spectrum disorder (NMOSD), also known as Devic disease, is a chronic, relapsing autoimmune inflammatory disorder affecting the brain and spinal cord, and characterized by unilateral or bilateral attacks of optic neuritis and/or myelitis. NMOSD is a rare disorder, with a prevalence of 1-10 per 100,000 population worldwide, according to the U.S. National Organization for Rare Disorders (NORD) (11). Its etiology is unknown, but in approximately two-third of cases, patients have antibodies to aquaporin-4 (AQP4-IgG) as well as complement-mediated damage to the CNS. It is typically treated with immunosuppressants or prednisone. Last summer, the FDA approved a new treatment option for patients with NMOSD: Alexion's complement inhibitor **eculizumab** (Soliris). This is a new indication for the anti-C5 MAb, which was previously launched for paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and myasthenia gravis. It was immediately made available for the new indication, for which it has orphan drug status, in the U.S. Eculizumab is under regulatory review for NMOSD in Japan.

Respiratory Drugs

Allergen-specific immunotherapy is an increasingly popular option for the treatment of patients with confirmed sensitivity to one or a few allergens. Itulazax, a novel **tree pollen sublingual immunotherapy** (SLIT) from ALK-Abelló, was approved last year in the E.U. (17 countries) and launched for the first time in Germany. The sublingual tablet vaccine is indicated for the treatment of adult patients with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from the birch homologous family of trees—which includes birch, alder, beech, hazel, hornbeam and oak—and whose symptoms cannot be adequately controlled with symptom-relieving medication. In contrast with subcutaneous immunotherapy, which can cause adverse reactions

and must be administered by a doctor, SLIT is well tolerated and can be taken by the patient at home.

In December, Glenmark Pharmaceuticals announced receipt of marketing authorization from Australia's Therapeutic Goods Administration (TGA) for the fixed-dose combination product Ryaltris (**olopatadine hydrochloride/mometasone furoate**), indicated for the treatment of allergic rhinitis and rhinoconjunctivitis in patients over age 12. The fixed-dose nasal spray delivers the antihistamine olopatadine and the corticosteroid mometasone furoate in a single administration. It will be marketed in Australia, which has one of the world's highest indices of allergic rhinitis—nearly 20%—, by Seqirus.

The anti-interleukin-4 (IL-4) receptor MAb **dupilumab** (Dupixent; Regeneron/Sanofi), marketed since 2017 for atopic dermatitis and since 2018 for asthma, was approved and launched in 2019 for a third indication: treatment, in combination with other agents, of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled. Prior to the introduction of dupilumab, the only treatment option for CRSwNP was intranasal or short-course systemic corticosteroids. Following a priority review, the U.S. FDA approved the new indication for dupilumab on the basis of two pivotal trials—the 24-week SINUS-24 and 52-week SINUS-52 studies—that evaluated dupilumab 300 mg every 2 weeks plus standard-of-care mometasone furoate nasal spray (MFNS) compared to placebo injection plus MFNS (ClinicalTrials.gov Identifiers NCT02912468 and NCT02898454). In these trials, dupilumab significantly improved key disease measures and met all primary and secondary endpoints: the treatment reduced polyp size, sinus opacification and severity of symptoms, and was well tolerated. This new indication was also approved later in the year by the EMA.

Breztri Aerosphere (**budesonide/glycopyrronium bromide/formoterol fumarate**), a triple combination therapy developed by AstraZeneca subsidiary Pearl Therapeutics, was approved and launched last year in Japan for the relief of symptoms of chronic obstructive pulmonary disease (COPD). A single inhalation of Breztri delivers the inhaled corticosteroid budesonide, the long-acting muscarinic agonist glycopyrronium bromide and the long-acting β_2-agonist formoterol fumarate via a pressurized metered-dose inhaler that uses Aerosphere delivery technology. Triple combination therapy is increasingly used to treat COPD, which affects more than 5 million people in Japan; Breztri Aerosphere is the first such product to be approved in that country. Applications for approval are under review in the E.U. and China; in the U.S., the FDA issued a complete response letter in October.

The cystic fibrosis transmembrane regulator (CFTR) protein is embedded in the membranes of several cell types in the body and plays a pivotal role in the pathogenesis of cystic fibrosis (CF). CFTR levels are highest in the epithelial cells lining the internal surfaces of the pancreas, sweat glands, salivary glands, intestines and reproductive organs, as well as in the submucosal glands of the airways—precisely the organs and tissues that are most affected in patients with CF. The most straightforward role of CFTR involves its function as a cAMP-regulated chloride channel, facilitating the flow of chloride ions in both directions. In addition to serving as a chloride channel itself, CFTR also acts as a channel regulator, influencing the function of other chloride channels and of sodium channels located nearby on the cell membrane. The discovery of a new class of drugs targeting the defective CFTR protein marked a new era in the treatment of CF. The first drug in this class, ivacaftor (Kalydeco), was launched in 2012 and transformed the outlook for a subset of CF patients with certain specific *CFTR* mutations. Ivacaftor-containing two-drug combinations (Orkambi and Symdeko) provided additional options for a wider population of CF patients. The first ivacaftor-containing three-drug combination, Trikafta (**elexacaftor/ivacaftor/tezacaftor**), was approved by the FDA in October 2019 (just 3 months after the new drug application [NDA] was filed), and was launched almost immediately. Trikafta is indicated for the treatment of patients aged 12 years and older who have at least one copy of the F508del mutation in the *CFTR* gene, regardless of their second mutation. This means that approximately 90% of all CF patients are eligible for treatment with the combination.

In September, the FDA approved the triple kinase (vascular endothelial growth factor receptor [VEGFR], fibroblast growth factor receptor [FGFR]

and platelet-derived growth factor receptor [PDGFR]) inhibitor **nintedanib** (Ofev; Boehringer Ingelheim) for a new indication: to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease. It is the first FDA-approved treatment for this rare lung condition, and has both orphan drug status and breakthrough therapy designation in the U.S. Approval, which followed a priority review, was supported by a randomized, double-blind, placebo-controlled trial of 576 patients aged 20-79 years with the disease (NCT02597933). Patients received treatment for 52 weeks, with some patients treated for up to 100 weeks. The primary test for efficacy measured the forced vital capacity and showed that those patients who took nintedanib had less lung function decline than those on placebo (12). The overall safety profile observed in the active treatment group was consistent with the known safety profile of the therapy. The most frequent serious adverse event reported in patients treated with nintedanib was pneumonia (2.8% vs. 0.3% placebo). Adverse reactions leading to permanent dose reduction were reported in 34% of nintedanib-treated patients compared to 4% of placebo-treated patients; diarrhea was the most frequent such adverse reaction in the active treatment group. Nintedanib was approved in 2014 for adult patients with idiopathic pulmonary fibrosis and in 2015 for non-small cell lung cancer.

Cardiovascular Drugs

Azurity's Katerzia (**amlodipine benzoate**) was approved and launched last year in the U.S. This novel salt of the established calcium channel blocker is the first and only amlodipine oral suspension. It can be used alone or in combination with other antihypertensive and antianginal agents, and is indicated for the treatment of hypertension in adults and pediatric patients and for coronary artery disease in adults. Katerzia offers a safe and effective, ready-to-use oral suspension for children 6 years of age and older who require or prefer an oral liquid option of amlodipine.

Daiichi Sankyo's **esaxerenone** (Minnebro), a nonsteroidal, selective mineralocorticoid receptor blocker identified during a research collaboration with Exelixis, was launched last year in Japan. It is indicated for the treatment of essential hypertension, and is only the third drug in this class. Mineralocorticoids are involved in the regulation of electrolyte and water balance. They affect ion transport in epithelial cells and renal tubules, causing retention of sodium and loss of potassium.

In March, AnGes obtained conditional approval from the Japanese Ministry of Health, Labour and Welfare (MHLW) for **beperminogene perplasmid** (DNA plasmid encoding the hepatocyte growth factor gene [*HGF*]) to treat patients with critical limb ischemia (CLI). Beperminogene perplasmid, the first gene therapy product to be approved in Japan, is indicated for the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger's disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization. Approval was sought based on results from a randomized, placebo-controlled phase III trial and investigator-led study conducted in Japan. Under the conditions of the approval, AnGes will conduct a confirmatory study for all patients who receive the treatment under this conditional approval and will submit an application to lift the conditions within 5 years. AnGes has granted to Mitsubishi Tanabe Pharma the marketing rights to beperminogene perplasmid in Japan and the U.S. for treating peripheral arterial diseases, including CLI. Mitsubishi Tanabe launched the product under the brand name Collategene in September.

Renal–Urologic Drugs

Following approval in the E.U. almost a year earlier, AstraZeneca's phosphate-binding agent **sodium zirconium cyclosilicate** (Lokelma) was launched for the first time in the Scandinavian countries in early 2019. The drug is indicated for the treatment of hyperkalemia, a serious condition characterized by elevated potassium levels in the blood associated with cardiovascular, renal and metabolic diseases. The risk of hyperkalemia increases significantly for patients with chronic kidney disease (CKD) and for those who take common medications for heart failure, such as renin–angiotensin–aldosterone system (RAAS) inhibitors. To help prevent the recurrence of hyperkalemia, RAAS-inhibitor therapy is often modified or discontinued, which

can compromise cardio-renal outcomes and increase the risk of death. Regulatory approval was supported by data from three double-blind, placebo-controlled trials and one open-label trial, in which patients with hyperkalemia were treated for up to 12 months. In these trials, the median time to achieving normal potassium levels in the blood for patients receiving Lokelma was 2.2 hours, with 98% achieving normal levels within 48 hours from baseline. Lokelma demonstrated sustained potassium control for up to 1 year.

Hematologic Agents

The first-in-class hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor **roxadustat** (Airuizhuo) was launched for the first time last year in China (Fig. 3). HIF-PH inhibitors are a novel category of orally active erythropoietic agents that work by stabilizing the HIF complex and stimulating endogenous production of erythropoietin. Roxadustat is indicated for the treatment of anemia in patients with CKD who are dialysis-dependent, whether they use hemodialysis or peritoneal dialysis. The drug was developed

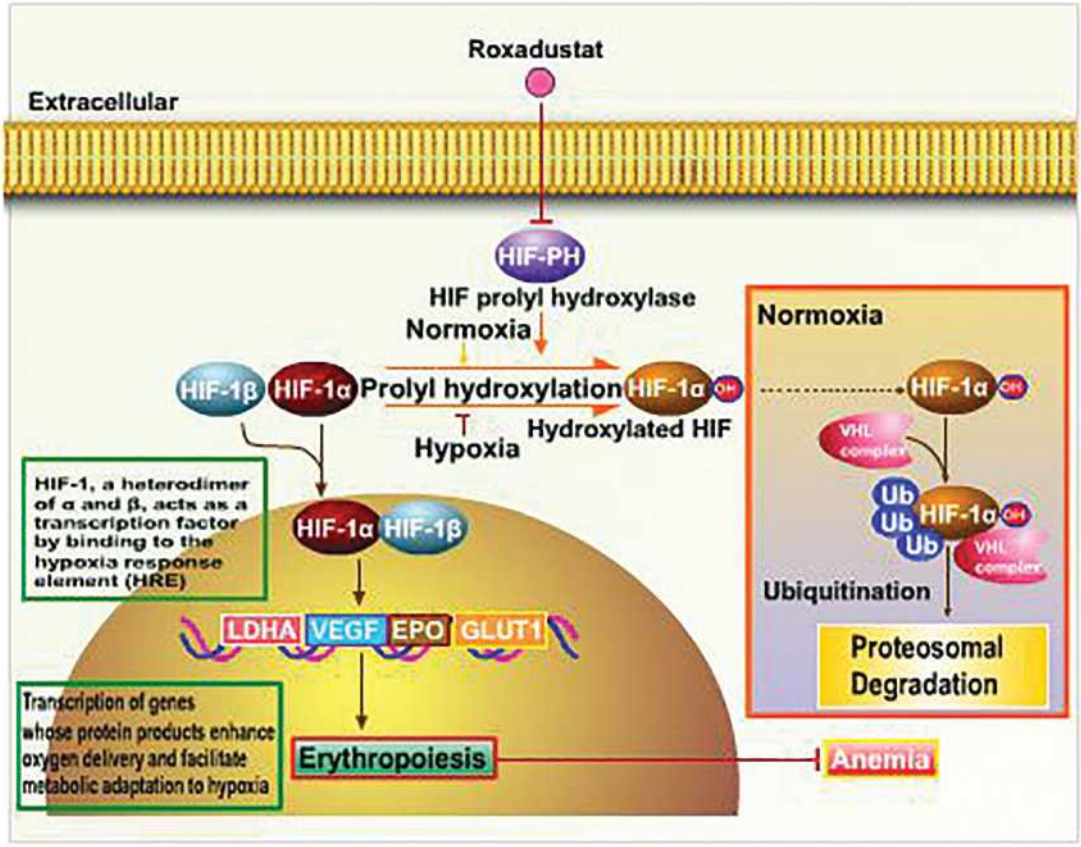

Figure 3. Hypoxia-inducible factor (HIF) regulates expression of the erythropoietin gene (*EPO*) in the kidney and liver. Oxygen-dependent degradation of HIF-1α is mediated by prolyl hydroxylation, and this process in turn suppresses *EPO* expression in liver and kidneys. The HIF stabilizer roxadustat, which acts by inhibiting HIF prolyl hydroxylases (PHs), is designed to stabilize and upregulate *EPO* gene transcription, thereby stimulating endogenous erythropoiesis and reversing anemia.

by FibroGen and is licensed to AstraZeneca for the Chinese market.

In June 2019, the EC granted conditional marketing authorization for bluebird bio's **betibeglogene darolentivec** (Zynteglo), a gene therapy for patients age 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β^0/β^0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. The one-time gene therapy is based on autologous $CD34^+$ cells encoding $\beta^{A\text{-}T87Q}$-globin gene, and addresses the underlying genetic cause of TDT, offering eligible patients the potential to achieve lifelong independence from transfusion. Betibeglogene darolentivec was developed under the EMA's PRIME program; it was also selected for the agency's Adaptive Pathways pilot program. In late October, the EMA approved a refined manufacturing process for Zynteglo, paving the way for the company to begin treating patients in early 2020.

In November, the FDA approved **luspatercept** (Reblozyl; Acceleron Pharma/Celgene) for the treatment of anemia in adult patients with β-thalassemia who require regular red blood cell (RBC) transfusions. Luspatercept is a first-in-class transforming growth factor β (TGF-β)-inhibiting erythroid maturation agent, representing a new class of therapy which works by regulating late-stage RBC maturation to help patients reduce their RBC transfusion burden (Fig. 4). Following a priority review, approval was based on results from the pivotal, randomized,

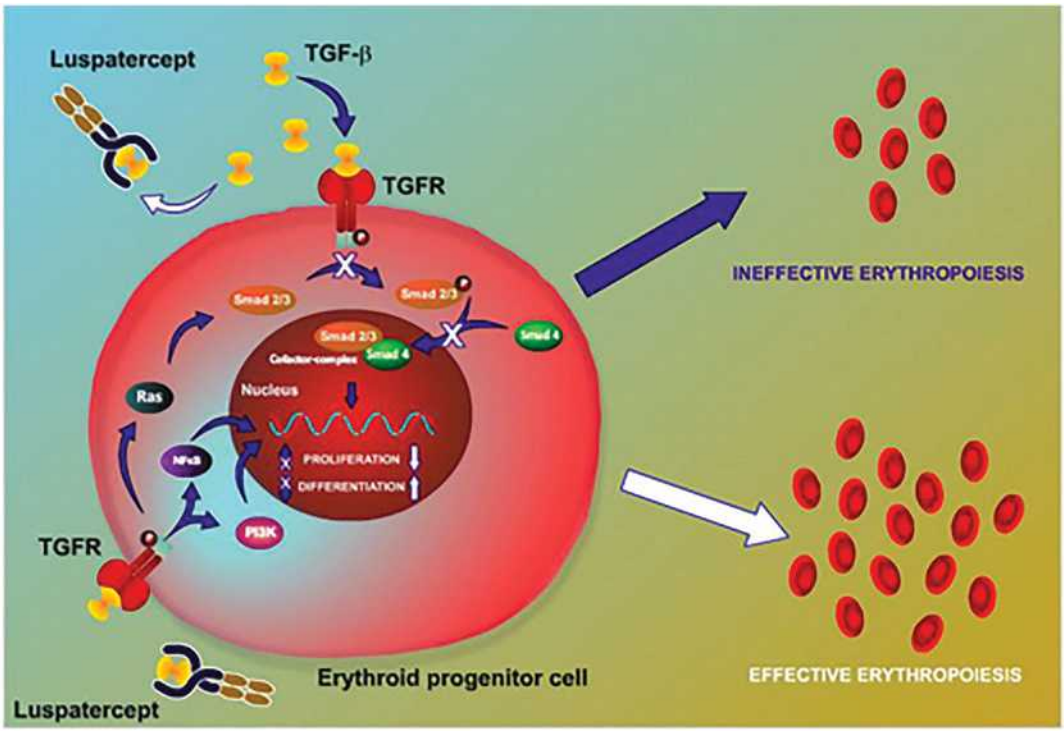

Figure 4. Luspatercept is a first-in-class erythroid maturation agent in development for serious blood disorders associated with ineffective erythropoiesis. The drug binds several transforming growth factor β (TGF-β) superfamily ligands, thereby diminishing Smad2/3 signaling. This, in turn, decreases proliferation and promotes differentiation of late-stage erythroid precursors and restores the production of red blood cells.

double-blind, placebo-controlled, multicenter phase III BELIEVE study (NCT02604433), which evaluated luspatercept for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions (defined as 6-20 RBC units per 24 weeks, with no transfusion-free period greater than 35 days during that period). The trial achieved a clinically meaningful and statistically significant improvement on the primary endpoint. In the luspatercept arm, 21.4% of patients achieved a 33% or greater reduction from baseline in RBC transfusion burden (with a reduction of at least 2 units) during weeks 13-24 after randomization, compared with 4.5% in the placebo arm. The study also met key secondary endpoints, including transfusion burden reduction of at least 33% (with a reduction of at least 2 units), during weeks 37-48, which was achieved in 19.6% of patients in the luspatercept arm and 3.6% in the placebo arm. Other efficacy endpoints included transfusion burden reduction of at least 50% (with a reduction of at least 2 units) during weeks 13-24 and weeks 37-48. A 50% or greater reduction in transfusion burden was observed in 7.6% of patients receiving luspatercept versus 1.8% of patients in the placebo arm at weeks 13-24, and 10.3% of patients versus 0.9% of patients at weeks 37-48, respectively. The drug, which has orphan drug status, was launched in the U.S. within a week of approval.

Coagulation factor replacement therapy with recombinant factor VIII (rFVIII), administered on demand to stop bleeds or prophylactically to prevent bleeding episodes, is the backbone of therapy for patients with congenital hemophilia A. One major drawback to existing coagulation factor concentrate formulations is the need for frequent (often daily) administration, so that many patients eventually require placement of a central venous access device. These devices may lead to significant adverse events such as infection and thrombosis, representing a serious limitation, particularly in the treatment of pediatric patients. The development of longer-acting rFVIII formulations has thus become an important objective. Last year one such biologic was approved in several countries, including the U.S., E.U, Canada and Japan: Novo Nordisk's glycopegylated rFVIII, **turoctocog alfa pegol** (Esperoct). It was launched in its first markets, Germany and Switzerland, in the third quarter, indicated for the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital FVIII deficiency). Although the product had been granted orphan drug status in the E.U. in 2012, this designation was withdrawn in May 2019 by request of Novo Nordisk at the time of granting of marketing authorization.

Polycythemia vera (PV) is a rare blood disease in which the body makes too many RBCs. This causes the blood to be thicker and form blood clots more easily than normal, and increases the risk of stroke and myocardial infarction. In February, the EC approved PharmaEssentia's **ropeginterferon alfa-2b** (Besremi) as monotherapy for the treatment of adults with PV without symptomatic splenomegaly. Besremi is the first and only approved therapy that can be used in PV patients regardless of previous hydroxyurea exposure. The approval is applicable to all 28 European Union member states plus Iceland, Norway and Liechtenstein, and the marketing authorization holder for Besremi in Europe is AOP Orphan Pharmaceuticals. The first product launches took place in Austria and Germany.

Sickle cell disease (SCD) is a chronic, lifelong inherited hematologic disorder affecting RBCs. Because of a genetic mutation, people with SCD have RBCs containing an abnormal type of hemoglobin known as hemoglobin S (HbS). Under conditions of low oxygen tension, these RBCs polymerize and become sickle- or crescent-shaped, making it difficult for them to pass through small blood vessels. The sickle cells also show an increased propensity to stick to one another and to vascular endothelial cells. Patients with SCD suffer from debilitating episodes of vaso-occlusive crises (VOCs), which occur when the rigid, adhesive and inflexible RBCs block blood vessels, resulting in excruciating pain. Sickle cell crises can lead to organ damage, stroke, pulmonary complications and other adverse outcomes, including acute chest syndrome, which may be potentially fatal and is the leading cause of death in this patient population. As reported here last year (4), 2018 saw the introduction of the first new SCD treatment in 50 years. In 2019, two additional new treatment options were approved.

SCD is associated with chronic inflammation, causing higher levels of cell adhesion proteins, including P-selectin; these also contribute to make blood

vessels and blood cells stickier and more prone to multicellular interactions in the bloodstream. This environment can lead to painful and potentially life-threatening VOCs. Novartis' **crizanlizumab** (Adakveo), a novel targeted therapy for SCD, was approved by the FDA in November, 2 months ahead of its PDUFA date. Crizanlizumab is a MAb that binds to P-selectin. The approval was supported by results of the 52-week, randomized, placebo-controlled SUSTAIN trial, which showed that crizanlizumab significantly lowered the median annual rate of VOCs by 45% compared with placebo (1.63 vs. 2.98). Furthermore, it reduced the median number of hospitalization days per year by 42% (4 vs. 6.87 days, respectively) (13).

Later in the same month, and also well ahead of the PDUFA date, the FDA granted accelerated approval to another first-in-class agent for SCD: the antisickling agent **voxelotor** (Oxbryta; Global Blood Therapeutics [GBT]). Voxelotor, a hemoglobin polymerization inhibitor, is a direct antisickling agent (Fig. 5) with demonstrated benefit in animal

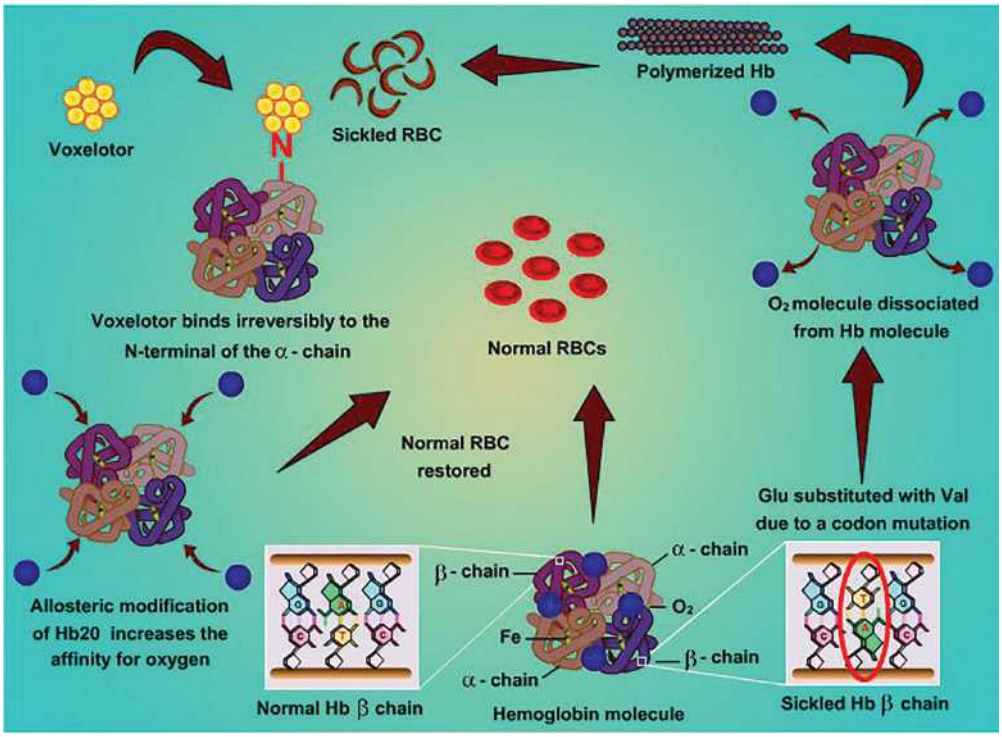

Figure 5. Sickle hemoglobin (HbS) polymerization is the causal factor for sickle cell disease. The substitution of glutamate (Glu) with valine (Val), associated with a codon mutation in the β-chain of the Hb molecule reduces the affinity for the O_2 molecule leading to its dissociation. This, in turn, causes the formation of abnormal, sickle-shaped red blood cells (RBCs) that aggregate and block blood vessels throughout the body. Voxelotor, a first-in-class novel molecule, binds irreversibly with the N-terminal Val of the α-chain of Hb, leading to an allosteric modification of Hb20, which increases the affinity for oxygen. Oxygenated HbS does not polymerize. By directly blocking HbS polymerization, voxelotor reverses the affinity of HbS for the O_2 molecule thereby restoring normal blood flow.

models as well as in patients with SCD. By increasing the oxygen affinity of hemoglobin, voxelotor prevents HbS polymerization and the sickling of RBCs. Approval was based on data from the phase III study HOPE (NCT03036813), which enrolled 274 patients aged 12 years and older with SCD. The study showed that after 24 weeks of treatment, 51% of patients receiving voxelotor achieved a > 1 g/dL increase in hemoglobin (a surrogate endpoint) compared with 6.5% receiving placebo (14). The study did not, however, show a decrease in the rate of VOCs. The most common adverse reactions occurring in 10% or more of patients treated with voxelotor with a difference of > 3% compared with placebo were headache (26% vs. 22%), diarrhea (20% vs. 10%), abdominal pain (19% vs. 13%), nausea (17% vs. 10%), fatigue (14% vs. 10%), rash (14% vs. 10%) and pyrexia (12% vs. 7%). As a condition of accelerated approval, GBT will continue to study voxelotor in the HOPE-KIDS 2 study, a postapproval confirmatory study using transcranial doppler flow velocity to demonstrate a decrease in stroke risk in children aged 2-15 years. The drug was launched in December.

In the early days of 2019, the anti-complement 5 (C5) MAb **ravulizumab** (Ultomiris; Alexion) was launched in the U.S. for the treatment of adult patients with PNH. This ultra-rare, debilitating blood disorder is characterized by hemolysis, the destruction of RBCs by the complement system. PNH affects men and women of all races, backgrounds and ages, with an average age of onset in the early 30s. Symptoms include fatigue, difficulty swallowing, shortness of breath, abdominal pain, erectile dysfunction, dark-colored urine and anemia. The most serious consequence of chronic hemolysis is thrombosis, which can occur in blood vessels throughout the body, damaging vital organs and potentially causing premature death. The FDA granted this application priority review designation, and ravulizumab also received orphan drug status. Later in the year, ravulizumab was approved for PNH in the European Union and Japan.

In October, the FDA approved a second indication for **ravulizumab**: for the treatment of adults and pediatric patients 1 month of age and older with aHUS, to inhibit complement-mediated thrombotic microangiopathy. aHUS is a rare disease that causes abnormal blood clots to form in small blood vessels in the kidneys. These clots, if they block or restrict blood flow, can cause serious medical problems including hemolytic anemia, thrombocytopenia and kidney failure. aHUS can occur at any age and is often caused by a combination of environmental and genetic factors (15). Ravulizumab also has orphan drug status for this second indication, and was rolled out immediately to the aHUS community.

Gastrointestinal Drugs

Proton pump (H^+/K^+-ATPase) inhibitors (PPIs) are widely used for the treatment of gastric ulcer and gastroesophageal reflux disease (GERD). They are generally considered to be safe, although long-term usage can lead to an increased risk of bone fracture as these agents can interfere with calcium absorption. In an effort to overcome the shortcomings of existing PPIs, a newer-generation class of compounds known as potassium-competitive acid blockers (P-CABs) has been developed and evaluated in clinical trials. P-CABs inhibit H^+/K^+-ATPase in a potassium-competitive and reversible manner, with higher pKa values and improved stability at low pH. These properties endow the P-CABs with improved pharmacokinetic properties, as manifested by a less variable onset of action, reduced acid liability, prolonged efficacy over the 24-hour period and more consistent efficacy across a wide range of patient profiles. Last year, CJ HealthCare launched the P-CAB **tegoprazan** (K-CAB) in the Republic of Korea. The drug is indicated for the treatment of GERD, including both erosive esophagitis and nonerosive reflux disease.

In November, the FDA approved RedHill Biopharma's triple combination Talicia (**omeprazole magnesium/amoxicillin/rifabutin**) for the treatment of *Helicobacter pylori* infection in adults. Talicia is the only rifabutin-based therapy approved for the treatment of *H. pylori* infection and is designed to address the high resistance of *H. pylori* bacteria to current clarithromycin-based standard-of-care therapies. RedHill expects to launch Talicia in the U.S. in the first quarter of 2020.

Aemcolo, a novel formulation of **rifamycin** developed by Cosmo Pharmaceuticals and licensed to RedHill Biopharma for sale and marketing, was launched in the U.S. for the new indication of travelers' diarrhea

in adults. Aemcolo is a delayed-release tablet formulation of the minimally absorbed antibiotic that is delivered to the colon. It is specifically indicated for travelers' diarrhea caused by noninvasive strains of *Escherichia coli*; in order to avoid the development of drug-resistant bacteria, Aemcolo should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. The FDA granted qualified infectious disease product (QIDP) and fast track designations for Aemcolo.

Ardelyx's **tenapanor** (Ibsrela) was approved in September for the treatment of irritable bowel syndrome with constipation in adults. Tenapanor is a minimally absorbed small molecule that acts locally in the gastrointestinal tract by inhibiting the sodium/hydrogen exchanger 3 (NHE-3). The apical membrane protein NHE-3 is highly expressed in the intestine and colon, where it regulates salt and water absorption in the gut. Abnormally high intestinal absorption of sodium is one mechanism that contributes to constipation via reduced water content in feces. NHE-3 inhibitors help normalize or augment the intestinal fluid content by decreasing sodium absorption throughout the gastrointestinal tract, thereby restoring normal hydration of the intestinal contents, accelerating stool transit and relieving pain. Ardelyx is currently in discussions with potential strategic partners to market Ibsrela in the United States.

Endocrine Drugs

Among the insulin secretagogue class of antidiabetic drugs, incretin mimetics represent an important and growing treatment option. Last year, Hansoh Pharma launched the long-acting glucagon-like peptide 1 (GLP-1) receptor agonist **polyethylene glycol loxenatide** (Fulaimei) in China, a country where nearly 10% of the population suffers diabetes. The drug is indicated as monotherapy or in combination with metformin, in addition to diet and exercise, to improve the blood glucose control in adult patients with type 2 diabetes (T2D).

Another GLP-1 agonist, Novo Nordisk's **semaglutide**, was introduced in the U.S. last year in a new tablet formulation called Rybelsus; the active ingredient had previously been approved in an injectable formulation (Ozempic). Rybelsus is the first GLP-1 receptor agonist that can be taken orally, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. FDA approval was based on the results from 10 PIONEER trials, which included 9,543 adults with T2D. Rybelsus lowered blood sugar more effectively than sitagliptin and empagliflozin. Treatment with Rybelsus resulted in up to a 4.4-kg reduction in body weight. Rybelsus demonstrated a safe and well-tolerated profile across the PIONEER program, with the most common adverse event being mild to moderate nausea that diminished over time.

Although they have been on the market for less than a decade, sodium/glucose cotransporter (SGLT) inhibitors have become well established as oral antidiabetic agents for the treatment of T2D. SGLT inhibitors continued to make the news in 2019, with the approval and launch in India of Remo (**remogliflozin etabonate**) and the approval of the combination product Remo-M (**remogliflozin etabonate/metformin**), both from Glenmark Pharmaceuticals, as well as the approval in the E.U. of **sotagliflozin** (Zynquista; Lexicon).

AstraZeneca's Qternmet XR, a triple combination incorporating the SGLT inhibitor **dapagliflozin**, the dipeptidyl peptidase 4 (DPP IV) inhibitor **saxagliptin** and the insulin sensitizer **metformin**, was approved by the FDA last May for the treatment of adults with T2D. The combination was approved in November in the E.U., where it will be marketed under the name Qtrilmet; it is indicated to improve glycemic control in adults with T2D when metformin with or without a sulfonylurea and either saxagliptin or dapagliflozin does not provide adequate glycemic control, or when T2D patients are already being treated with metformin, saxagliptin and dapagliflozin.

In related news, and on the basis of its favorable effect on cardiovascular disease in diabetes patients, the FDA approved a new indication for the marketed SGLT inhibitor **canagliflozin** (Invokana; Mitsubishi Tanabe/Janssen): to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death and hospitalization for heart failure in adults with T2D mellitus and diabetic nephropathy with albuminuria. The new indication is based on results from the phase III CREDENCE study in patients with T2D and diabetic kidney disease, which was stopped early when it met the prespecified criteria for efficacy (NCT02065791). In the randomized,

double-blind, event-driven, placebo-controlled, parallel-group, two-arm, multicenter study, the SGLT inhibitor demonstrated a 30% reduction in the risk of the primary composite endpoint (end-stage kidney disease, doubling of serum creatinine and renal or cardiovascular death). Results also showed canagliflozin reduced the risk of secondary cardiovascular endpoints, including a 39% reduction in the risk of hospitalization for heart failure. Overall, adverse events and serious adverse events were similar but numerically lower in the canagliflozin group compared with placebo. The rates of diabetic ketoacidosis and genital mycotic infections were numerically higher with the study drug, as observed in other clinical trials. Additionally, there was no imbalance in lower limb amputation or bone fracture in this trial and no new safety signals were identified (16).

Hypoglycemia, defined as blood sugar level of less than 54 mg/dL, is a potentially dangerous consequence of exercise, alcohol consumption or prolonged fasting, as well as of poor or overly intensive glucose control, and is most common in diabetes patients treated with insulin. Symptoms range from dizziness, anxiety and confusion to coordination problems, blurred vision, loss of consciousness and seizures. Chronic hypoglycemia can have severe negative effects on cognitive ability and brain microanatomy, particularly in children with type 1 diabetes, and severe hypoglycemia can be life-threatening. Mild episodes of hypoglycemia may be reversed by intake of oral carbohydrates (candy, fruit juice, soda or glucose tablets), while more severe episodes may require the administration of glucagon by intramuscular injection. The year 2019 saw the introduction of two new glucagon formulations for the treatment of hypoglycemia, greatly facilitating the treatment of hypoglycemia. In July, the FDA approved Lilly's **Baqsimi**, a single-dose intranasal device delivering glucagon dry powder. It is indicated for the treatment of severe hypoglycemia in patients with diabetes aged 4 years and older, and was launched in August. The following month, the FDA approved Xeris Pharmaceuticals' **Gvoke**, a single-dose prefilled syringe or HypoPen autoinjector device for the treatment of patients aged 2 and older. Gvoke was launched in November.

In April 2019, TherapeuticsMD announced the commercial launch of Bijuva (**17β-estradiol/progesterone**), the first and only FDA-approved bio-identical combination hormone therapy delivering estradiol and progesterone in a single, oral capsule. The product is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus. Approval was based on the Bijuva clinical development program that included the pivotal phase III Replenish Trial (NCT01942668), which evaluated the safety and efficacy of Bijuva in generally healthy, postmenopausal women with a uterus for the treatment of moderate to severe hot flashes (17). Bijuva resulted in a statistically significant reduction from baseline in both the frequency and severity of hot flashes compared with placebo, while reducing the risks to the endometrium. The most common adverse reactions reported were breast tenderness, headache, vaginal bleeding, vaginal discharge and pelvic pain. There were no clinically significant changes in lipid, coagulation or glucose parameters as compared to placebo, and no unexpected safety signals were seen.

Drospirenone (Slynd; Exeltis USA), the first progestin-only oral contraceptive agent, was approved by the FDA in May for pregnancy prevention. The novel estrogen-free contraceptive is supplied as a 24-active plus 4-inactive tablet dosing regimen. Significantly, it allows a 24-hour missed pill window. This not only can mean favorable safety and efficacy, but an improved bleeding profile and contraceptive efficacy for up to 24 hours in the event of a delayed or missed dose. Slynd was launched in the U.S. in September.

The Population Council's Annovera (**segesterone acetate/ethinyl estradiol vaginal system**) was launched last year in the U.S., where it is the first long-acting prescription birth control that is patient-controlled, procedure-free and reversible. Annovera is a small, soft flexible ring that prevents ovulation for an entire year (13 cycles) and can be inserted and removed by a woman at her discretion in repeated 4-week cycles. This technology combines low doses of a novel progestin, segesterone acetate, with the widely used estrogen ethinyl estradiol. The approval was based in part on data from 17 clinical trials, including two pivotal phase III safety and efficacy trials. The phase III program enrolled a total of 2,308 women across 27 study sites in the U.S., Latin America, Europe and Australia. Women in

the trials were between 18 and 40 years of age and were instructed to use the system over 13 menstrual cycles, or 1 full year. The data show that Annovera is 97.3% effective in preventing pregnancy when used as directed. Annovera offers a similar risk profile to those of other combined hormonal contraceptives, and carries a boxed warning related to increased cardiovascular risk when used while smoking. Annovera is licensed to TherapeuticsMD for marketing in the U.S.

In the summer of 2019, the U.S. FDA approved **bremelanotide** (Vyleesi; Palatin Technologies/AMAG Pharmaceuticals), a first-in-class melanocortin MC_3/MC_4 receptor agonist (Fig. 6), indicated to treat acquired, generalized hypoactive sexual desire disorder in premenopausal women. The

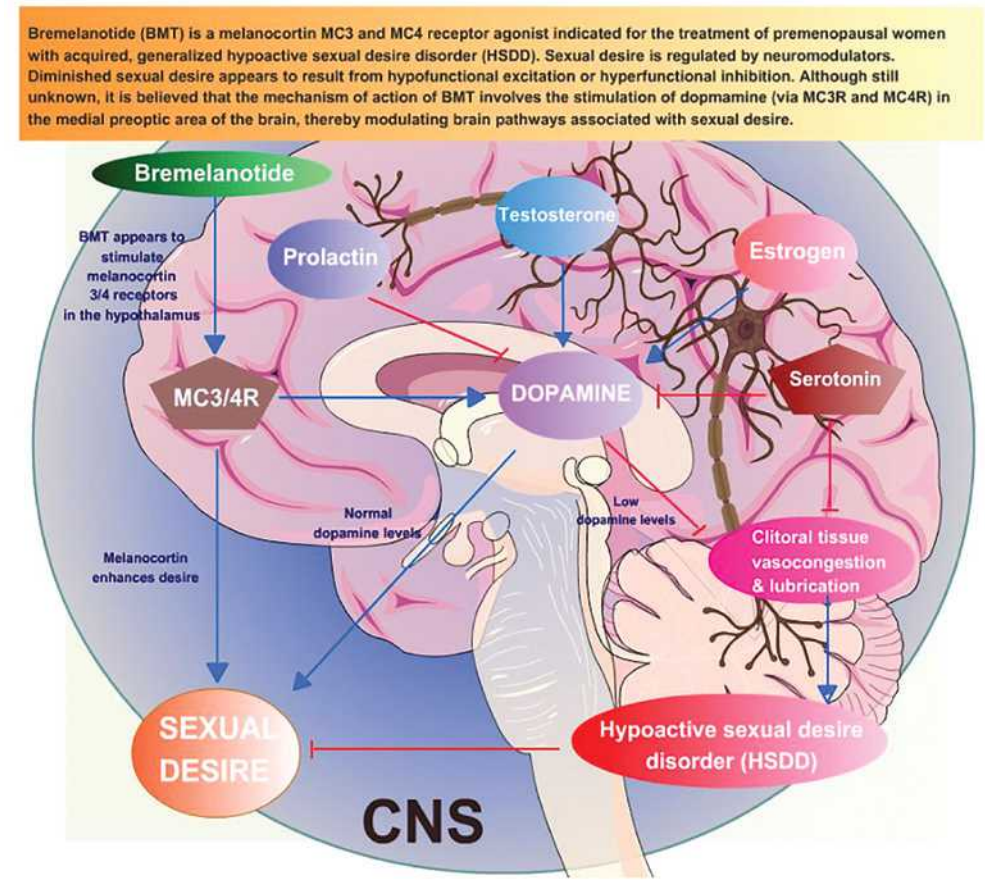

Figure 6. Bremelanotide (BMT) is a melanocortin MC_3 and MC_4 receptor agonist indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder. Sexual desire is regulated by neuromodulators. Diminished sexual desire appears to result from hypofunctional excitation or hyperfunctional inhibition. Although still unknown, it is believed that the mechanism of action of bremelanotide involves the stimulation of dopamine (via MC_3 and MC_4) in the medial preoptic area of the brain, thereby modulating brain pathways associated with sexual desire.

drug is self-administered by autoinjector at least 45 minutes before anticipated sexual activity. The approval was based upon data from approximately 1,200 women in two pivotal, double-blind, placebo-controlled phase III trials (RECONNECT). In the two identical trials, bremelanotide met the prespecified coprimary efficacy endpoints of improvement in desire and reduction in distress as measured by validated patient-reported outcome instruments, with a favorable safety profile. Upon completion of the trials, women had the option to continue in a voluntary open-label safety extension study for an additional 12 months. Nearly 80% of patients who completed the phase III trials elected to remain in the open-label portion of the study, wherein all patients received the active drug. Bremelanotide was launched in late August.

Takeda's gonadotropin-releasing hormone (GnRH) receptor antagonist **relugolix** (Relumina) was approved and launched last year in Japan for the symptomatic relief of uterine fibroids. Takeda filed an application for approval in February 2018, based on the Japanese phase III clinical trials (TAK-385/CCT-002 study and 3008 study) in patients with uterine fibroids. In May 2018, the company licensed exclusive Japanese marketing rights for this indication to Aska.

Evocalcet (Orkedia; Kyowa Kirin), an oral calcium-sensing receptor (CaSR) agonist first approved in 2018 for the treatment of secondary hyperparathyroidism, was approved and launched in Japan in late 2019 for a new and related indication: treatment of hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy. This action was labeled a "partial change approval" by Japan's MHLW, and was based on the results of a phase III trial. Evocalcet has orphan drug status in Japan for this new indication.

Dermatologic Drugs

In January 2019, Almirall launched the once-daily, oral, narrow-spectrum tetracycline-derived antibiotic **sarecycline hydrochloride** (Seysara) in the U.S., where it is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients age 9 years and older. Sarecycline exhibits antibacterial activity against important skin/soft tissue pathogens with targeted activity against *Cutibacterium acnes*, an anaerobic Gram-positive bacterium linked with acne lesions (18). It also exerts anti-inflammatory effects, as do other tetracyclines used in the treatment of acne vulgaris. In contrast with broad-spectrum tetracyclines, sarecycline is less potent against aerobic Gram-negative bacilli and anaerobic bacteria associated with endogenous intestinal microbial flora. This provides it with a more specific antibacterial spectrum and lower chances of adverse off-target antibacterial effects, thus making it a promising choice of treatment over others in its class. It has demonstrated less propensity to resistance than other tetracyclines, and is active against tetracycline-resistant *Staphylococcus aureus* as well as erythromycin- and clindamycin-resistant *C. acnes* strains. Sarecycline was discovered by Paratek and licensed to Allergan, which subsequently divested its U.S. medical dermatology portfolio to Almirall.

Galderma's **trifarotene** (Aklief) was approved and launched last year in the U.S. for the topical treatment of acne in patients aged 9 years and older. Trifarotene is the only topical retinoid that selectively targets retinoic acid receptor γ (RAR-γ), the most common RAR found in the skin, and is the first new retinoid approved by the FDA for the treatment of acne in more than 20 years.

The IL-17 family has six known members (IL-17A-F); IL-17A is the principal T-helper 17 (Th17) cell effector cytokine. Activation of the Th17/IL-17 response has been implicated in various autoimmune disorders, including psoriasis, and several biologics targeting the cytokine are marketed as antipsoriatic agents. The most recent addition to the anti-IL-17A MAb family is **netakimab** (Efleira; Biocad), which was approved and launched for the first time last year in Russia for the treatment of moderate to severe plaque psoriasis.

IL-23 works upstream of IL-17, and its inhibition results in effective inhibition of the downstream cytokine, while requiring less frequent dosing. **Risankizumab** (Skyrizi), an IL-23-directed humanized MAb codeveloped by Boehringer Ingelheim and AbbVie, was launched by the latter in the U.S. and U.K. for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Risankizumab was also launched in Japan,

where it is indicated for the treatment of psoriatic arthritis and plaque, pustular or erythrodermic psoriasis in adult patients who have an inadequate response to conventional therapies. The introduction of agents targeting the IL-17/IL-23 signaling pathway has revolutionized the treatment of psoriasis.

Duobrii, a fixed-dose combination of **halobetasol propionate and tazarotene** developed by Bausch Health (formerly Valeant), was launched in the U.S. in 2019 as a topical treatment for adults with plaque psoriasis. Duobrii is the first and only topical lotion that contains a unique combination of halobetasol propionate, a corticosteroid, and tazarotene, a retinoid. When used separately to treat plaque psoriasis, the duration of use of halobetasol propionate is limited by FDA labeling constraints to 2-4 weeks, and the use of tazarotene can be limited due to tolerability concerns. Duobrii, in contrast, has been used successfully for up to 52 weeks in safety studies.

Tapinarof is a naturally derived topical anti-inflammatory agent that acts as an aryl hydrocarbon receptor (AhR) agonist. In May 2019, the drug was approved in China for the treatment of moderate stable psoriasis vulgaris in adults. It was launched for this indication by Tianji Pharma, a subsidiary of Guanhao Biotech, in July.

Behçet's disease is a rare, chronic, relapsing, idiopathic autoimmune disorder that causes small blood vessels around the body to become inflamed, known as vasculitis. The symptoms—which vary depending on the body part affected—include recurrent oral and/or genital ulcerations, other skin lesions, uveitis and ocular lesions that may lead to blindness. The treatment of Behçet's disease is generally empiric, with a goal of controlling symptoms, suppressing the inflammatory process and preventing organ damage. Various anti-inflammatory and immunosuppressive agents have been used as the main therapeutic modalities, although none effectively controls all symptoms. On the basis of its anti-inflammatory activity in other indications, the small-molecule phosphodiesterase 4 (PDE4) inhibitor **apremilast** was evaluated for the treatment of oral ulcers in patients with Behçet's. By inhibiting PDE4, apremilast boosts levels of intracellular cyclic AMP, particularly in immune cells. This leads to decreases in levels of proinflammatory cytokines (tumor necrosis factor α [TNF-α], IL-23 and interferon γ [IFN-γ]), together with elevations in those of anti-inflammatory cytokines such as IL-10. Last year, on the basis of results obtained in the randomized, placebo-controlled, double-blind phase III RELIEF study, apremilast (Otezla; Celgene) was approved and launched in the U.S. for the treatment of oral ulcers in patients with Behçet's disease. The product has orphan drug status for this new indication. Apremilast has been marketed since 2014 for the treatment of psoriasis and psoriatic arthritis.

Anti-infective Therapy

For decades, experts have voiced concerns about the lack of new antibacterial agents with which to face the increasingly urgent threat of multidrug resistance. It was a promising development last year, therefore, when several new anti-infective drugs and drug combinations were approved by regulatory agencies around the world.

Pleuromutilin antibiotics interfere with bacterial protein synthesis via a specific interaction with the 23S rRNA of the 50S bacterial ribosome subunit. They have a distinct antibacterial profile and show no cross-resistance with any other class of antibiotics (19). In August 2019, the U.S. FDA approved oral and intravenous formulations of the pleuromutilin antibiotic **lefamulin** (Xenleta; Nabriva Therapeutics) for the treatment of community-acquired bacterial pneumonia (CABP) in adults. Lefamulin thus became the first intravenous and oral antibiotic with a novel mechanism of action to be approved by the FDA in nearly 2 decades. Both the intravenous and oral formulations of lefamulin had been granted QIDP and fast track designation by the FDA. As part of the former, lefamulin underwent priority review; the drug was launched in September.

In June, the FDA approved Merck & Co.'s new combination antibacterial Recarbrio (**imipenem/cilastatin sodium/relebactam**) for patients age 18 years and older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infection (cUTI), including pyelonephritis, caused by the susceptible Gram-negative microorganisms *Enterobacter cloacae, E. coli, Klebsiella aerogenes, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Recarbrio is also indicated in patients

age 18 years or older who have limited or no alternative treatment options, for the treatment of complicated intra-abdominal infections caused by the susceptible Gram-negative microorganisms *Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides stercoris, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Citrobacter freundii, E. cloacae, E. coli, Fusobacterium nucleatum, K. aerogenes, Klebsiella oxytoca, K. pneumoniae, Parabacteroides distasonis* and *P. aeruginosa*. Approval of these indications, under priority review, is based on limited clinical safety and efficacy data for Recarbrio. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Recarbrio and other antibacterial drugs, Recarbrio should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. In mid-December, the EMA's CHMP adopted a positive opinion recommending approval of Recarbrio for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

In mid-November, the FDA approved Shionogi's **cefiderocol** (Fetroja) for patients age 18 years and older who have limited or no alternative treatment options, for the treatment of cUTI, including pyelonephritis, caused by *E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *P. aeruginosa* and *E. cloacae* complex. A member of the cephalosporin class, cefiderocol functions as a siderophore and binds to extracellular free ferric iron. In addition to passive diffusion via porin channels, cefiderocol is actively transported across the outer cell membrane of bacteria into the periplasmic space using a siderophore iron uptake mechanism. The drug exerts bactericidal action by inhibiting cell wall biosynthesis through binding to penicillin-binding proteins. Cefiderocol was designated a QIDP by the FDA, receiving fast track designation and priority review. Of note, an increase in all-cause mortality was observed in patients treated with cefiderocol as compared with best available therapy in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595); for this reason, the drug is reserved for use in patients with limited or no other treatment options. Shionogi anticipates making cefiderocol commercially available in early 2020.

Following a late 2018 approval, the novel tetracycline antibiotic **omadacycline** (Nuzyra; Paratek) was launched in the U.S. in early 2019, indicated for the treatment of adult patients with acute bacterial skin and skin structure infections and CABP caused by susceptible microorganisms. Omadacycline was granted fast track and QIDP designations in the U.S. for both of these indications. Paratek had also filed in the E.U. for approval of omadacycline for these indications; however, in October 2019, following an EMA request for an additional clinical study in patients with CABP, the company decided to withdraw both applications in order to later pursue a concurrent approval.

The quinolone antibacterial agent **lascufloxacin hydrochloride** (Lasvic; Kyorin) was approved by Japan's MHLW last year for the treatment of respiratory and ear, nose and throat infections. It is indicated for use in pharyngitis, stomatitis, tonsillitis, acute bronchitis, pneumonia, secondary infection of chronic respiratory disease, middle ear infection and sinusitis. It is suitable for treating infections caused by susceptible strains of *Staphylococcus, Streptococcus, Pneumococcus, Moraxella (Branhamella) catarrhalis, Klebsiella, Enterobacter, Haemophilus influenzae, Legionella pneumophila, Prevotella* and *Mycoplasma pneumoniae*.

Dovato, a fixed-dose combination of the HIV integrase inhibitor **dolutegravir** and the reverse transcriptase inhibitor **lamivudine**, was approved last year in the U.S., E.U. and Canada for the treatment of HIV-1 infection in treatment-naive adults with no known resistance to either agent. The combination product was developed by ViiV Healthcare with the aim of simplifying anti-HIV treatment regimens, and was introduced in the U.S., its first market, in April 2019.

African trypanosomiasis, commonly known as sleeping sickness, is caused by the parasite *Trypanosoma brucei gambiense*, which is transmitted to humans by the bite of infected tsetse flies. Without prompt diagnosis and treatment, sleeping sickness is usually fatal, as the parasites invade the CNS. In 2019, the antitrypanosomal medication **fexinidazole** (Fexinidazole Winthrop) was approved in the Democratic Republic of the Congo (DRC) and the European Union (in the latter case, for use outside the E.U.), becoming the first all-oral treatment

for this neglected tropical disease. In July, the WHO added fexinidazole to the Essential Medicines Lists for adults and children, for the treatment of the first and second stages (hemolymphatic and neurologic phases, respectively) of sleeping sickness. Fexinidazole development was driven by Drugs for Neglected Diseases initiative (DNDi) using a new model for drug development that ultimately involved 15 governmental, private industry and civil society partners, including Sanofi as the main pharma partner.

Pretomanid, a small-molecule inhibitor of cell wall biosynthesis, was approved last August by the FDA for use, as part of an oral combination regimen with bedaquiline and linezolid (BPaL regimen), for the treatment of adults with pulmonary, extensively drug-resistant tuberculosis (XDR-TB) and treatment-intolerant or nonresponsive multidrug-resistant tuberculosis (MDR-TB). Pretomanid was added to the Stop TB Partnership's Global Drug Facility product catalog in October, just 2 months after receiving approval, making the treatment available in 150 countries and territories. Pretomanid was first identified by Pathogenesis and was licensed to the Global Alliance for TB Drug Development (TB Alliance) for development, with a commitment to make it available royalty-free in endemic countries. In 2019, TB Alliance signed a license and collaboration agreement granting rights to Mylan to commercialize pretomanid, as part of the BPaL regimen, for the treatment of XDR-TB and MDR-TB. Pretomanid has been granted orphan drug, fast track and QIDP designations in the U.S.

Therapy of Musculoskeletal & Connective Tissue Diseases

The Janus kinases (JAK1, JAK2, JAK3 and Tyk2) are associated with different receptors for cytokines that are relevant in arthritis, including IL-6, IFN-γ, IL-12, IL-15 and IL-23. For this reason, JAK inhibitors have been investigated extensively as potential disease-modifying antirheumatic drugs, culminating in the first-in-class agent tofacitinib in 2012. Last year saw the introduction of two new JAK inhibitors for the treatment of rheumatoid arthritis: **peficitinib hydrobromide** (Smyraf; Astellas) in Japan and **upadacitinib tartrate** (Rinvoq; AbbVie) in the U.S.

The IL-23/IL-17 axis, described above (see Dermatologic Drugs section), regulates acquired immunity as well as proinflammatory and allergic responses, and has been identified as an important inflammatory pathway in ankylosing spondylitis (AS). In 2019, the anti-IL-17A MAb **ixekizumab** (Taltz; Lilly) was approved and launched for the treatment of adults with active AS, also known as radiographic axial spondylarthritis. This is a new indication for ixekizumab, which was previously launched for psoriasis, plaque psoriasis and psoriatic arthritis.

In August, Daiichi Sankyo announced that the FDA had approved **pexidartinib** (Turalio) as the first and only treatment for adult patients with symptomatic tenosynovial giant cell tumor (TGCT), a group of rare nonmalignant tumors that affect small and large joints. Researchers have determined that a minority of the cells that make up a TGCT carry a specific chromosomal translocation in specific regions on chromosomes 1 and 2. Cells containing this translocation overproduce colony-stimulating factor 1 (CSF-1) (20), and thus attract other cells expressing a CSF-1 receptor (CSF 1R), such as macrophages. These other cells make up the bulk of a TGCT, and most likely cause the inflammatory changes associated with these tumors. Pexidartinib, a small-molecule CSF-1R inhibitor, was discovered by Plexxicon, which was acquired by Daiichi in 2011, but continues to function as an independent unit. Pexidartinib is indicated for use in patients with TGCT that is associated with severe morbidity or functional limitations and is not amenable to improvement with surgery. Because of risk of hepatotoxicity, the drug will be available only through the Turalio REMS Program, and can only be prescribed by certified healthcare providers. Given the rarity of TGCT (incidence 1.8 people per 1 million population in the U.S.), pexidartinib has been awarded orphan drug and breakthrough therapy status.

Immunomodulators & Agents for Immunization

Hemophagocytic lymphohistiocytosis (HLH) is an ultra-rare, rapidly progressive and often fatal syndrome of hyperinflammation in which massive overexpression of IFN-γ is thought to drive immune system hyperactivation, ultimately leading to organ

failure. Both primary (familial) and secondary (acquired) forms exist. Primary HLH is a rare disease, with an incidence of approximately 1:50,000 births per year worldwide, according to the Immune Deficiency Foundation (21). In late 2018, the FDA approved **emapalumab** (Gamifant), a MAb that binds to and neutralizes IFN-γ, as the first new treatment for HLH in nearly a quarter of a century. Prior to this agent, standard therapy for HLH consisted of steroids, chemotherapy and hematopoietic stem cell transplant. Emapalumab was discovered and developed by NovImmune and is marketed by Sobi; the product was launched during the first quarter of 2019. Emapalumab has orphan drug status, breakthrough therapy designation and rare pediatric disease designation in the U.S., and was granted priority review by the FDA.

Asceniv (**immune globulin intravenous, human-slra**), is a plasma-derived, polyclonal, intravenous immune globulin from ADMA Biologics. The product, which was approved by the FDA in April 2019, is indicated for the treatment of primary humoral immunodeficiency (PI) or primary immune deficiency disease in adults and adolescents (12-17 years of age). PI includes but is not limited to the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott–Aldrich syndrome and severe combined immunodeficiencies (SCID). Following optimization of the manufacturing process, Asceniv was launched in the U.S., its first market, in October.

Grifols obtained FDA approval last summer for Xembify (**immune globulin subcutaneous, human-klhw**), a subcutaneous immune globulin that is also indicated for the treatment of PI, including but not limited to congenital agammaglobulinemia, CVID, X-linked agammaglobulinemia, Wiskott–Aldrich syndrome and SCID. The product, which is indicated for use in patients 2 years of age and older, was launched in mid-December.

The JAK inhibitor **ruxolitinib phosphate** (Jakafi; Incyte) was approved and launched last year in the U.S. for a new indication: the treatment of steroid-refractory acute graft-versus-host disease (GvHD) in adult and pediatric patients aged 12 years and older. Approval, under priority review, was based on data from REACH1, an open-label, single-arm, multicenter study of ruxolitinib in combination with corticosteroids in patients with steroid-refractory grade II-IV acute GvHD (NCT02953678). Of the 71 patients recruited into REACH1, 49 patients were refractory to steroids alone, 12 patients had received two or more prior anti-GvHD therapies and 10 patients did not otherwise meet the FDA definition of steroid-refractory. Efficacy was evaluated on the basis of day 28 overall response rate (ORR), defined as a complete response (CR), very good partial response or partial response as per the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria. The day 28 ORR in the 49 patients refractory to steroids alone was 57% with a CR rate of 31%. The most frequently reported adverse reactions among all 71 study participants were infections (55%) and edema (51%), and the most common laboratory abnormalities were anemia (75%), thrombocytopenia (75%) and neutropenia (58%). Ruxolitinib was previously launched for the treatment of myelofibrosis (2011) and PV (2014). It has orphan drug status and breakthrough therapy designation for the GvHD indication.

Medac's DNA alkylating agent **treosulfan**, long marketed for the treatment of ovarian cancer, was approved last year in the E.U. for a new indication: in combination with fludarabine, as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in adult patients with malignant and nonmalignant diseases, and in pediatric patients with malignant diseases. In comparison with other conditioning regimens, the treosulfan-based regimen is associated with reduced toxicity while maintaining a high level of intensity and antileukemic effect. Marketed for the new indication as Trecondi, the product was introduced in Germany in the third quarter. It has orphan drug status for this indication in the E.U. as well as the U.S.

In 2019, 4 years after receiving a positive scientific opinion from the CHMP, the WHO announced the rollout of the **RTS,S/AS01E malaria vaccine** Mosquirix in Malawi in a landmark pilot program, culminating 30 years of vaccine development. Malawi was the first of three African countries in which the vaccine was made available for administration to children up to 2 years of age; Ghana and Kenya introduced the vaccine shortly thereafter.

The pilot program will enroll approximately 360,000 children. Designed to generate evidence and experience to inform WHO policy recommendations on the broader use of Mosquirix (22), the program will look at reductions in child deaths; vaccine uptake, including whether parents bring their children on time for the four required doses; and vaccine safety in the context of routine use. The WHO-coordinated pilot program is a collaborative effort with ministries of health in Ghana, Kenya and Malawi and a range of in-country and international partners, including PATH and GlaxoSmithKline, the vaccine developer and manufacturer; the latter is donating up to 10 million vaccine doses for this pilot.

In another exciting development last year, the EC in November granted conditional approval for Merck & Co.'s **Ebola Zaire Vaccine** (Ervebo), the first Ebola vaccine to be approved by any regulatory agency following evaluation in large clinical trials; the FDA followed suit a month later. The vaccine was discovered at Canada's National Microbiology Laboratory with funding from the U.S. government's Biomedical Advanced Research and Development Authority (BARDA), and was developed through a public–private partnership with NewLink Genetics and Merck. It has been tested extensively in the last two major Ebola outbreaks in West Africa (2013-2016) and the DRC (2018-2019). Ervebo is indicated for active immunization of individuals age 18 years or older, to protect against Ebola virus disease caused by Zaire Ebola virus. The approval allows Merck to initiate manufacturing in Germany of licensed doses, which are expected to be available from Q3 2020. Merck is also working with the WHO, the U.S. government and Gavi, the Vaccine Alliance, to ensure uninterrupted access of its vaccine in support of international response efforts in the ongoing outbreak in the DRC. Two other Ebola vaccines had previously been approved, on the basis of phase I and phase II testing, albeit for emergency use only. Russia's Gamaleya Federal Research Centre for Epidemiology and Microbiology developed Gam Evac Combi, a combined vector vaccine against Ebola fever that was authorized for use in medical practice within the territory of the Russian Federation in 2015. In 2017, the China FDA approved Ad5-EBOV, a vaccine codeveloped by the Institute of Biomedical Engineering, Academy of Military Medical Sciences and Tianjin CanSino Biotechnology.

In September 2019, Bavarian Nordic received marketing approval from the FDA of its **MVA-BN orthopox vaccine** (Jynneos), indicated for the prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for smallpox or monkeypox infection. The company was awarded a Priority Review Voucher along with the approval. Although the vaccine has been available in the E.U. since 2013 for prevention of smallpox, the additional indication of monkeypox in the U.S. is new and provides additional commercial opportunities: Jynneos is the world's first monkeypox vaccine. Jynneos is being supplied to the U.S. government for inclusion in the Strategic National Stockpile.

Also in September, the Drug Controller General of India approved **Twinrab**, a cocktail of two MAbs developed by Zydus Cadila in partnership with the WHO. The product was approved for postexposure prophylaxis against rabies virus infection, in combination with a rabies vaccine.

Danish vaccine company AJ Vaccines, which took over the Statens Serum Institute vaccine business in 2017, obtained marketing approval in Denmark last year for the inactivated poliomyelitis vaccine Picovax (**IPV-AI-SSI**). The vaccine consists of inactivated poliovirus type 1, 2 and 3, and is based on a proprietary formulation technology that allows a lower dose of active substances. It is indicated for primary vaccination of infants from age 6 weeks and revaccination of infants, children, adolescents and adults. The Danish marketing approval paves the way for WHO prequalification, which will enable AJ Vaccines to deliver up to 100 million doses of Picovax to UN agencies from 2020-2024. Although polio has largely been eradicated in industrialized nations with effective national immunization programs, the disease remains endemic in three countries (Afghanistan, Nigeria and Pakistan); moreover, 13 others are considered "outbreak countries", i.e., those that have stopped indigenous wild poliovirus but are experiencing re-infection, either through the importation of wild or vaccine-derived poliovirus from another country, or the emergence and circulation of vaccine-derived poliovirus (23).

In late December, Sinovac announced that the China NMPA had approved and issued a product license for

the company's **live-attenuated varicella vaccine**, indicated to prevent varicella zoster virus (chickenpox) infection in children aged 1 to 12 years old. This is the first vaccine product approved by the Chinese government after the passage in June 2019 of the country's new vaccine management law. The law, which requires stricter management of the production, research and distribution of vaccines, was implemented in the wake of a series of safety scandals (24).

Human papillomavirus (HPV), a known carcinogen, is implicated in the development of virtually all cervical cancers; it is also an important risk factor for penile, vaginal/vulvar, anal and oropharyngeal cancers. HPV is responsible for more than 5% of the global cancer burden overall, including almost one-third of cancers attributable to an infectious agent. The first HPV vaccine (Merck & Co.'s Gardasil) was introduced in 2006, and two others soon followed. The inclusion of HPV vaccines in many national immunization programs has resulted in significant reductions in cervical cancer morbidity and mortality in those countries; however, HPV vaccination is still not widely practiced in developing countries such as China, where imported vaccines are too expensive for the general public (25). Thus the December 31 approval in China of Cecolin (Xiamen Innovax Biotech), a domestically developed **bivalent HPV virus-like particle (VLP) vaccine against HPV-16 and HPV-18 L1 capsid proteins**, is a significant development. The vaccine is indicated for use in girls and women aged 9-45 years. In a 2012 screening study conducted in 37 Chinese cities, the prevalence of HPV ranged from 18.4% in Nanchang to 31.9% in Haikou (26).

Treatment of Cancer

Most prostate cancers initially depend upon androgens for sustenance, and androgen deprivation therapy (ADT) is the first-line treatment of choice, consisting of GnRH agonists, antiandrogens or surgical castration. After a period of response to hormonal manipulation as described, tumors may progress to an androgen-independent (or castration-resistant) state, in which tumor growth and metastasis continue even in the absence of hormonal stimulation, necessitating modification of the treatment regimen. Last year saw the U.S. approval and launch of a next-generation androgen receptor inhibitor indicated for the treatment of patients with nonmetastatic castration-resistant prostate cancer: **darolutamide** (Nubeqa; Bayer/Orion). The FDA approval was based on the phase III ARAMIS trial evaluating darolutamide plus ADT, which demonstrated a highly significant improvement in the primary efficacy endpoint of metastasis-free survival, with a median of 40.4 months versus 18.4 months for placebo plus ADT (27).

In May, following a priority review, the FDA approved Novartis' phosphatidylinositol 3-kinase α (PI3Kα) inhibitor **alpelisib** (Piqray) in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative ($HR^+/HER2^-$), *PIK3CA*-mutated, advanced or metastatic breast cancer, as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Approval was based on results of the phase III trial SOLAR-1, which showed alpelisib plus fulvestrant nearly doubled median progression-free survival (PFS) compared with fulvestrant alone in $HR^+/HER2^-$ advanced breast cancer patients with a *PIK3CA* mutation (median PFS 11.0 vs. 5.7 months) (NCT02437318) (28). Alpelisib provided consistent PFS results across prespecified subgroups, including among patients previously treated with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. The ORR was more than doubled when alpelisib was added to fulvestrant in patients with a *PIK3CA* mutation (ORR = 35.7% vs. 16.2% for fulvestrant alone). Approved together with its companion diagnostic test (Qiagen's therascreen PIK3CA RGQ PCR Kit), alpelisib was the first combination product approved under the FDA Oncology Center of Excellence's real-time oncology review (RTOR) pilot program (29). The U.S. launch of alpelisib took place shortly after approval.

The antibody–drug conjugate (ADC) **trastuzumab deruxtecan** (Enhertu), discovered by Daiichi Sankyo and licensed to AstraZeneca for codevelopment and commercialization, received accelerated approval from the FDA in the waning days of December 2019, 4 months ahead of the PDUFA date. The ADC is comprised of a humanized anti-HER2 antibody attached to a topoisomerase I inhibitor

payload by a tetrapeptide linker. It is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. In addition to the accelerated approval, which was based on efficacy results (tumor response rate and duration of response) in 184 patients in the DESTINY-Breast01 (NCT03248492) study, the FDA previously bestowed fast track and breakthrough therapy status to the product. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The first-in-class pan-FGFR inhibitor **erdafitinib** (Balversa; Janssen) was approved and almost immediately launched last year in the U.S., where it is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible *FGFR3* or *FGFR2* genetic alterations and that has progressed during or following at least one line of prior platinum-containing chemotherapy. Erdafitinib is the first FDA-approved oral pan-FGFR kinase inhibitor that binds to four FGFRs (FGFR-1 to -4), leading to decreased cell signaling and cellular apoptosis (Fig. 7). Erdafitinib also binds to RET, CSF-1 receptor (CSF-1R), PDGFR-α and PDGFR-β, Fms-related tyrosine kinase 4 (FLT4), KIT and VEGFR-2, exhibiting additional antitumor mechanisms that result in cell kill. Moreover, erdafitinib is the first oral treatment option for patients with urothelial carcinoma.

In late 2019, the FDA granted accelerated approval for a second new treatment option for urothelial carcinoma: **enfortumab vedotin** (Padcev; Astellas/Seattle Genetics), an ADC composed of a fully human MAb targeting the cell adhesion molecule nectin-4 conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a valine-citrulline cleavable linker. The ADC is designed to be stable in the bloodstream but to release MMAE upon internalization into nectin-4-expressing tumor cells, resulting in a targeted cell-killing effect. In an early clinical trial of enfortumab vedotin, 97% of bladder tumor samples tested were found to markedly express nectin-4, confirming the ubiquity of this target in bladder carcinoma. The FDA approved enfortumab vedotin for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) inhibitor and a platinum-containing chemotherapy before or after surgery, or in a locally advanced or metastatic setting. Seattle Genetics estimates that of the 20,000 patients diagnosed with metastatic urothelial cancer each year in the U.S., between 2,000 and 3,000 would be eligible for treatment in this third-line setting. The ADC was approved under the FDA's Accelerated Approval Program on the basis of tumor response rate in the pivotal trial EV-201, a single-arm phase II multicenter trial that enrolled 125 patients (30). Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

In the summer of 2019, the FDA granted accelerated approval to another novel ADC: **polatuzumab vedotin** (Polivy; Genentech). The agent comprises an anti-CD79b MAb conjugated to MMAE via a protease-cleavable peptide linker. It is indicated for use in combination with bendamustine plus rituximab, for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma who have received at least two prior therapies, and has orphan drug status in the U.S. Polatuzumab vedotin is a first-in-class agent targeted to the CD79b protein, which is expressed specifically in the majority of B cells (Fig. 8). It binds to CD79b and destroys these B cells through the delivery of the anticancer agent MMAE, while having a minimal effect on normal cells. Polatuzumab vedotin was introduced in the U.S. shortly after approval. The ADC was also granted conditional approval last year in the E.U., where it has PRIME designation and orphan drug status, and where it is designated an Advanced Therapy Medicinal Product.

Myelofibrosis, considered a form of chronic leukemia, is an uncommon hematologic cancer in which the bone marrow is progressively replaced by fibrous scar tissue. It may exist as a primary disorder, or secondary to an autoimmune disease or other bone marrow cancer. Approximately 50% of patients with primary myelofibrosis have a mutation in the *JAK2* gene; the first specific treatment for myelofibrosis was ruxolitinib, a JAK2 inhibitor that was launched in 2011. Last year, the dual-acting JAK2/FLT3 inhibitor **fedratinib** (Inrebic; Celgene) was approved and launched in the U.S.,

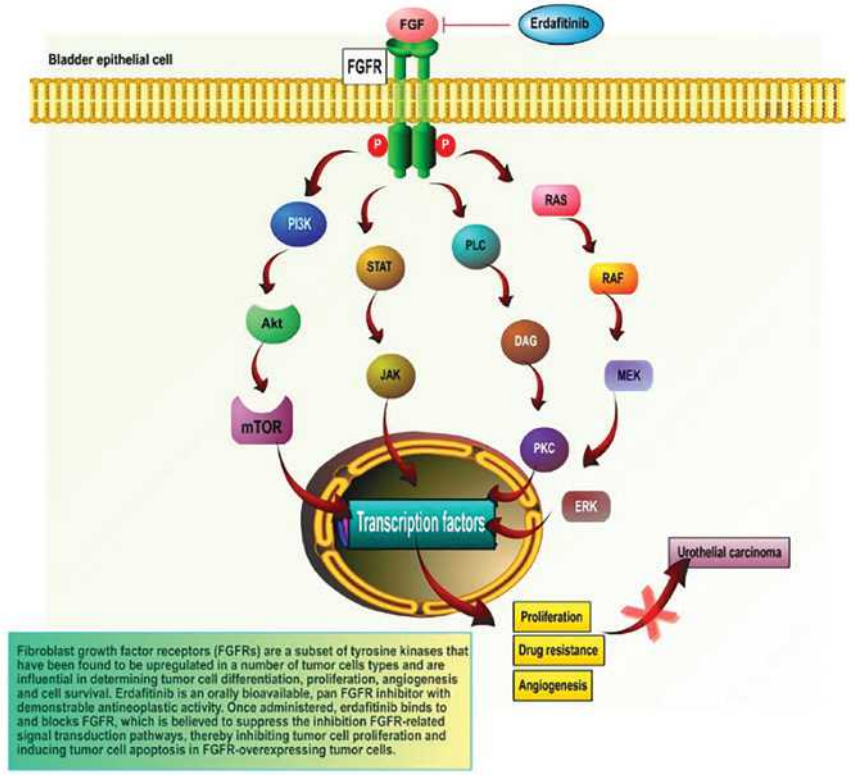

Figure 7. Fibroblast growth factor receptors (FGFRs) are a subset of tyrosine kinases that have been found to be upregulated in a number of tumor cell types and are influential in determining tumor cell differentiation, proliferation, angiogenesis and cell survival. Erdafitinib is an orally bioavailable, pan-FGFR inhibitor with demonstrable antineoplastic activity. Once administered, erdafitinib binds to and blocks FGFR, which is believed to suppress the inhibition of FGFR-related signal transduction pathways, thereby inhibiting tumor cell proliferation and inducing tumor cell apoptosis in FGFR-overexpressing tumor cells.

increasing the therapeutic options for this rare condition. Fedratinib is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-PV or post-essential thrombocythemia) myelofibrosis. It has orphan drug status in the U.S. for this indication.

In June, Japan's MHLW approved the oral FLT3 inhibitor **quizartinib** (Vanflyta; Daiichi Sankyo) for the treatment of adult patients with relapsed/refractory FLT3-ITD acute myeloid leukemia (AML), as detected by an MHLW-approved test. The marketing authorization was based on the results from the global pivotal phase III QuANTUM-R study (NCT02039726) and a phase II study of quizartinib in Japan in patients with relapsed/refractory FLT3-ITD AML. QuANTUM-R was the first randomized phase III trial to demonstrate that an FLT3 inhibitor, given as an oral, single agent, prolonged overall survival compared with

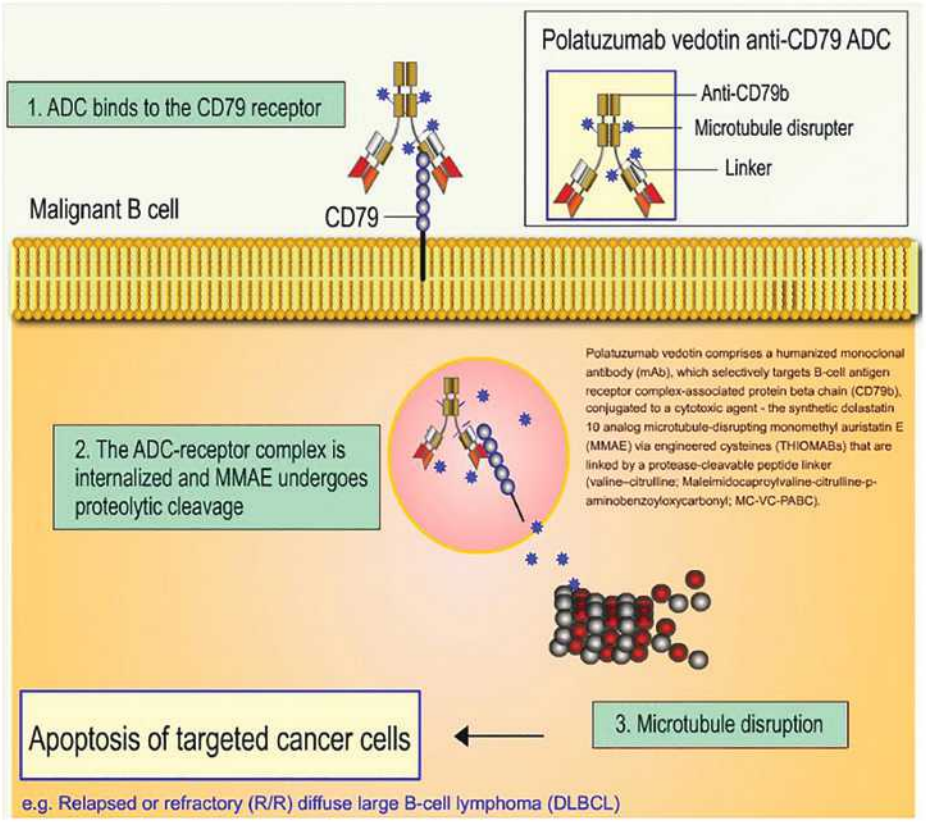

Figure 8. Polatuzumab vedotin is an antibody–drug conjugate (ADC) which consists of an anti-CD79b monoclonal antibody (MAb) conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker. It is indicated for use in combination with bendamustine plus rituximab, for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma who have received at least two prior therapies. The MAb is targeted to the CD79b protein, which is expressed specifically in the majority of B cells. The ADC binds to CD79b and destroys these B cells through the delivery of the antimicrotubule agent MMAE, while having a minimal effect on normal cells.

chemotherapy (OS 6.2 months vs. 4.7 months) in patients with relapsed/refractory FLT3-ITD AML (31). The drug, which has orphan drug status in Japan, was launched in October.

In November 2019, China's NMPA approved **flumatinib mesylate** (Hausen Xin Fu), developed by Jiangsu Hansoh and indicated for the treatment of chronic myeloid leukemia with Philadelphia chromosome-positive (Ph^+) mutation. The product received priority review. Flumatinib mesylate is a tyrosine-protein kinase ABL1 inhibitor that inhibits the activity of Bcr-Abl1 and the proliferation of tumor cells.

Exportin-1 (XPO1, CRM1) is a nuclear export receptor that is responsible for transporting proteins,

including tumor suppressor proteins, out of the nucleus. Nuclear export of tumor suppressor proteins is an important mechanism by which cancer cells avoid apoptosis and cell death. Overexpression of XPO1 leads to improper localization of cellular substrates and imparts poor prognosis. Last summer, the U.S. FDA granted accelerated approval to the first-in-class XPO1 receptor antagonist **selinexor** (Xpovio; Karyopharm) (Fig. 9), indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is resistant to several other forms of treatment. Selinexor has orphan drug status in the U.S. for this indication.

The personalized antitumor medicine **entrectinib** (Rozlytrek; Chugai/Roche) was approved in Japan for the first time in June, and was approved and launched in the U.S. shortly thereafter. Entrectinib is a tyrosine kinase inhibitor that blocks the ROS1 (proto-oncogene c-Ros-1) and TRK (neurotrophin receptor) family. It is indicated in the U.S. for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine kinase receptor (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy. NTRK fusion-positive cancer occurs when the *NTRK1/2/3* genes fuse with other genes, resulting in altered TRK proteins (TRKA/TRKB/TRKC) that can activate signaling pathways involved in proliferation of certain types of cancer. NTRK gene fusions are tumor-agnostic and have been identified in a broad range of solid tumor types, including breast, cholangiocarcinoma, colorectal, gynecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers. Entrectinib is also indicated in the U.S. for treatment of adults with *ROS1* fusion-positive, metastatic non-small cell lung cancer. It has orphan drug status for both indications.

The Bruton tyrosine kinase inhibitor **zanubrutinib** (Brukinsa), developed by Chinese company BeiGene, was granted accelerated approval by the FDA and launched almost immediately last November. The drug is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The approval was based on efficacy results from two single-arm trials, with independent review committee-assessed ORR per 2014 Lugano Classification as the primary endpoint. Across both trials, zanubrutinib achieved an ORR of 84%. In the multicenter phase II trial of zanubrutinib in patients with relapsed or refractory MCL (NCT03206970), the ORR was 84%, including 59% CR (FDG-PET scan required) and 24% partial response. In this study, the median duration of response (DOR) was 19.5 months and median follow-up time on study was 18.4 months. In the global phase I/II trial (NCT02343120), the ORR was 84%, including 22% CR (FDG-PET scan not required) and 62% partial response. In this study, the median DOR was 18.5 months and median follow-up time on study was 18.8 months. Zanubrutinib is also undergoing regulatory review in China.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive and rare disease of the bone marrow and blood that can affect multiple organs, including the lymph nodes and the skin. It often presents as leukemia or evolves into acute leukemia. The disease is more common in men than women and in patients aged 60 years and older. In late 2018, the U.S. FDA approved the first treatment for BPDCN: the CD123-directed cytotoxin **tagraxofusp** (Elzonris; Stemline Therapeutics). CD123 is a key marker in identifying BPDCN and was identified as a target for therapeutic intervention in this and a variety of other cancers. Tagraxofusp was launched in early 2019.

Immune checkpoint inhibitors are a growing class of immuno-oncology agents that are capable of restoring tumor immunity in a subset of carefully selected patients (32), including patients with lymphoid malignancies. Several new members of this class were added to the therapeutic armamentarium in 2019, all in China. Following a late 2018 approval, the anti-PD-1 MAb **sintilimab** (Tyvyt; Innovent Biologics/Lilly) was launched in February, indicated for the treatment of patients with relapsed or refractory classical Hodgkin's lymphoma (cHL). A few months later, Jiangsu Hengrui's anti-PD-1 MAb **camrelizumab** was approved and launched. Camrelizumab is indicated as third-line treatment for recurrent or refractory cHL in patients who have received second-line systemic chemotherapy; in

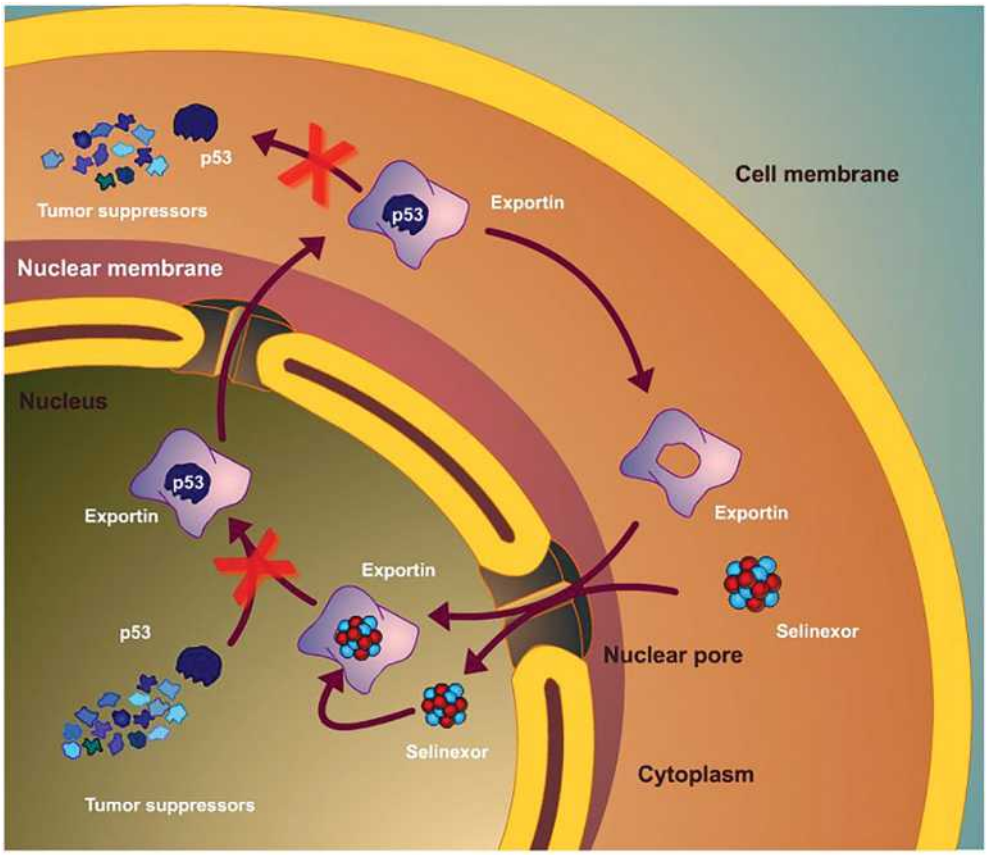

Figure 9. Exportin-1 (XPO1, CRM1) is a nuclear export receptor that is responsible for exporting proteins, including tumor suppressor proteins, out of the nucleus. Nuclear export of tumor suppressor proteins is an important mechanism by which cancer cells avoid apoptosis and cell death. Overexpression of XPO1 leads to improper localization of cellular substrates and imparts poor prognosis. The XPO1 antagonist selinexor is approved for the treatment of relapsed or refractory multiple myeloma.

December, BeiGene's humanized anti-PD-1 MAb **tislelizumab** was approved for the same indication. Finally, the anti-PD-1 MAb **toripalimab** (Tuoyi; Shanghai Junshi Biosciences) was launched for the treatment of locally advanced or metastatic melanoma in patients who have failed routine systemic treatment.

Nanobiotix's radioenhancing agent **NBTXR-3** (Hensify) was granted CE Mark approval by the EC in April for the treatment, in combination with concurrent radiation therapy, of locally advanced soft-tissue sarcoma. The product is an aqueous suspension of crystalline hafnium oxide nanoparticles designed for injection directly into a tumor prior to a patient's

first standard radiotherapy treatment. When exposed to ionizing radiation, Hensify amplifies the localized, intratumor killing effect of that radiation. The dose of X-ray delivered to the tumor is magnified, while the dose passing through healthy tissues remains unchanged. The primary tumor is killed via physical cell death, whereas any metastases are destroyed via activation of the immune system and immunogenic cell death.

Ophthalmic Drugs

Following FDA approval in March, Rocklatan (**netarsudil mesylate/latanoprost**), a new fixed-dose combination from Aerie Pharmaceuticals, was launched in the U.S. last May. It is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Netarsudil is a Rho kinase (ROCK) inhibitor and latanoprost is a prostaglandin analogue; the two components work via complementary mechanisms of action to reduce IOP more effectively than either drug alone. Netarsudil works by restoring outflow through the trabecular meshwork, while latanoprost increases fluid outflow through a secondary mechanism known as the uveoscleral pathway.

Ocular angiogenesis, the abnormal formation of new blood vessels from the existing vasculature of the eye, is an important cause of ocular morbidity in patients with age-related macular degeneration (AMD). Angiogenesis inhibitors are especially appropriate for treating wet AMD, which is characterized by aberrant neovascularization. A new angiogenesis inhibitor, Novartis' **brolucizumab** (Beovu), was approved and launched in the U.S. last year for the treatment of wet AMD. Brolucizumab is a humanized monoclonal single-chain antibody Fv fragment (scFv) targeting VEGF-A. Approval was based on findings from the phase III HAWK and HARRIER trials (NCT02307682 and NCT02434328), which were 96-week, prospective, randomized, double-masked, multicenter studies designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and 3 mg (HAWK only) versus the marketed angiogenesis inhibitor aflibercept in patients with wet AMD (33). In the trials, brolucizumab demonstrated noninferiority versus aflibercept in mean change in best corrected visual acuity at year 1 (week 48). In both trials, approximately 30% of patients gained at least 15 letters at year 1. In HAWK and HARRIER, brolucizumab showed greater reduction in central subfield thickness as early as week 16 and at year 1, and fewer patients had intraretinal and/or subretinal fluid. Eligible patients could be maintained on a 3-month dosing interval immediately after the loading phase. At year 1, over half of the patients were maintained on the 3-month dosing interval (56% in HAWK and 51% in HARRIER). The remaining patients in the study were treated on a 2-month dosing schedule. Brolucizumab exhibited an overall safety profile comparable to that of aflibercept.

Dextenza (**dexamethasone punctum plug**), a novel intraocular formulation of the anti-inflammatory glucocorticoid developed by Ocular Therapeutix, was launched last year in the U.S. for the treatment of ocular inflammation and pain following ophthalmic surgery. Dextenza is a preservative-free ophthalmic insert that is inserted in the lower lacrimal punctum and into the canaliculus. A single insert releases a 0.4-mg dose of dexamethasone for up to 30 days following insertion. As such, Dextenza has the potential to replace a complex eye drop regimen that, under the current standard of care, requires up to 70 topical ocular steroid drops.

Metabolic Drugs

Osteoporosis is a largely age-related disorder caused by an imbalance in the physiological process of bone remodeling. Its treatment has long been dominated by estrogens, bisphosphonates and the anti-RANKL antibody denosumab, all of which act by decreasing bone resorption, hence slowing bone loss. Less success has been achieved in the field of anabolic agents, i.e., those that promote the formation of new bone. Last year saw the approval and launch in Japan of a first-in-class agent with anabolic activity: the anti-sclerostin MAb **romosozumab** (Evenity; UCB/Amgen Astellas BioPharma) (Fig. 10). Sclerostin is a bone morphogenetic protein antagonist that inhibits the differentiation of osteoprogenitor cells and reduces osteoblast activity. Sclerostin is the product of the *SOST* gene that is produced in osteocytes buried in the bone and is a powerful inhibitor of bone formation. As osteoblasts become embedded

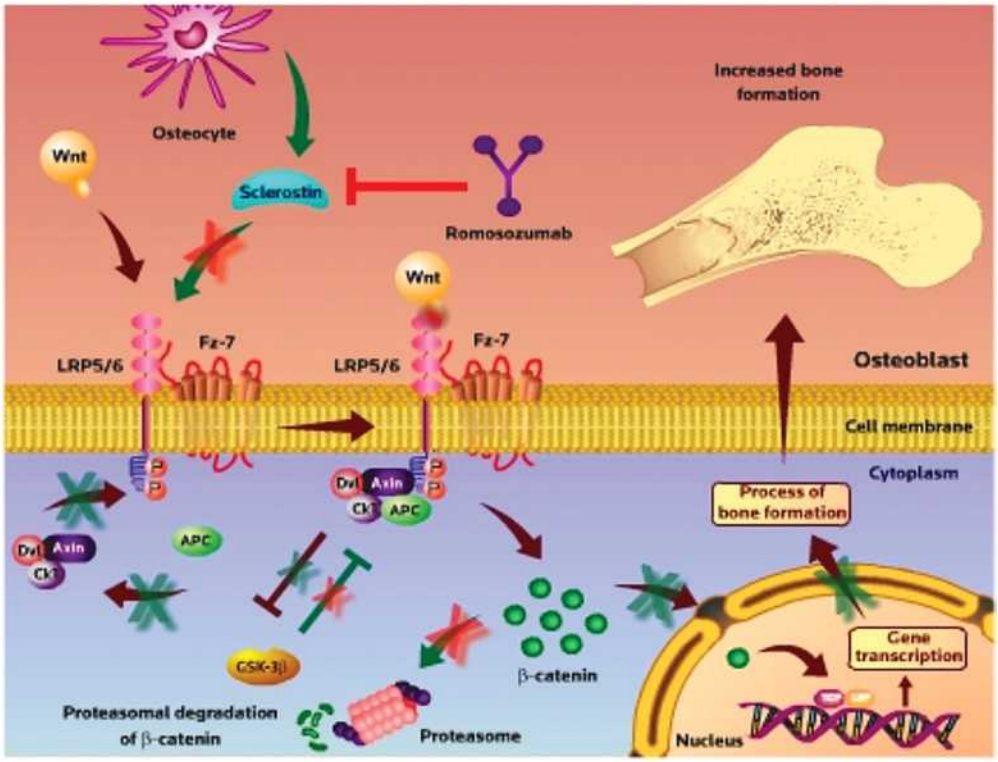

Figure 10. Sclerostin is a bone morphogenetic protein antagonist that inhibits the differentiation of osteoprogenitor cells and reduces osteoblast activity. Sclerostin is the product of the *SOST* gene that is produced in osteocytes buried in the bone and is a powerful inhibitor of bone formation. As osteoblasts become embedded in the mineralized matrix, they transform into osteocytes and begin expressing sclerostin, which controls bone formation and phosphate metabolism. The anti-sclerostin humanized monoclonal antibody romosozumab enhances osteoblast function, leading to simultaneous enhancement of bone formation and suppression of bone resorption.

in the mineralized matrix, they transform into osteocytes and begin expressing sclerostin, which controls bone formation and phosphate metabolism. Romosozumab and other agents that inhibit sclerostin enhance osteoblast function, leading to simultaneous enhancement of bone formation and suppression of bone resorption. Romosozumab is indicated in Japan for the treatment of osteoporosis in men and postmenopausal women at high risk of fracture. Later in 2019, romosozumab was approved and launched in the U.S., where it is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, or in patients who have failed or are intolerant to other available osteoporosis therapies.

Acute hepatic porphyria (AHP) is a family of ultra-rare genetic diseases characterized by potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily

functioning and quality of life. AHP is comprised of four types: acute intermittent porphyria, hereditary coproporphyria, variegate porphyria and ALA dehydratase-deficiency porphyria. Each type of AHP results from a genetic defect leading to deficiency in one of the enzymes in the heme biosynthesis pathway in the liver. Last year, the FDA approved Alnylam Pharmaceuticals' **givosiran** (Givlaari), a small interfering RNA (siRNA) targeting 5-amino levulinic acid synthase 1 (ALAS1), for the treatment of adults with AHP. The November approval, which followed a priority review, was based on results from the phase III ENVISION study in 94 patients with AHP (NCT03338816). In the pivotal, randomized, double-blind, placebo-controlled, multinational study, patients with AHP on givosiran experienced 70% fewer porphyria attacks than patients on placebo. Treatment with the agent also led to similar reductions in intravenous hemin use, as well as reductions in urinary aminolevulinic acid and urinary porphobilinogen. The most common adverse reactions associated with the treatment were nausea (27%) and injection-site reactions (25%).

In May 2019, Ionis Pharmaceuticals and its wholly owned subsidiary Akcea Therapeutics received conditional marketing authorization in the European Union for **volanesorsen** (Waylivra), indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride-lowering therapy has been inadequate. FCS is a rare autosomal recessive disorder caused by mutations in lipoprotein lipase, which leads to the accumulation of chylomicrons in plasma and hypertriglyceridemia (34). Among the complications produced by elevated triglycerides, the most serious is acute pancreatitis. Volanesorsen is an antisense oligonucleotide designed to reduce the production of apolipoprotein C-III (ApoC-III), a protein that regulates plasma triglycerides. As part of the conditional marketing authorization, Akcea and Ionis will conduct a noninterventional postauthorization safety study (PASS) based on a registry. In the phase III APPROACH study (NCT02211209), the largest study ever conducted in patients with FCS, treatment with the antisense drug led to clinically and statistically meaningful reduction in triglycerides compared with placebo over the study period. An analysis of patients with a history of recurrent pancreatitis events showed a significant reduction in pancreatitis attacks in volanesorsen-treated patients compared with those receiving placebo. The most common adverse events in the APPROACH trial were injection-site reactions and reductions in platelet levels. As a rare disease without effective treatment options, the development of volanesorsen was supported by several regulatory programs, including orphan drug designation in the E.U. and U.S. and Promising Innovative Medicine (PIM) designation in the U.K. The product was launched in Germany and France in August.

For a full list of all drugs launched in 2019, see Table III.

Looking Ahead to 2020

Just weeks into the new year, 2020 is already shaping up to be another busy year at the FDA and other regulatory agencies. On the basis of an analysis of *Cortellis Drug Discovery Intelligence* and *Cortellis Competitive Intelligence* data, these are a few of the drugs and biologics that we expect to see discussed in next year's edition of this article.

AR-101 (Palforzia; Aimmune Therapeutics), a peanut-derived oral immunotherapy, is on track to become the first approved desensitizing treatment for peanut allergy. Last September, the FDA's Allergenic Products Advisory Committee recommended approval of the product for use in children aged 4-17 years. The biologics license application (BLA) has a review action date of late January 2020.

Horizon Therapeutics' **teprotumumab**, a human monoclonal antibody directed against the human insulin-like growth factor 1 receptor (IGF-1R), will become the first treatment for patients with active thyroid eye disease, also known as Graves' orbitopathy. In December 2019, the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted unanimously in support of approval. The FDA approved teprotumumab in mid-January, 2020, well ahead of the PDUFA action date of March 8.

Sunovion expects to get approval from the FDA this year to market **dasotraline**, a novel dopamine and norepinephrine reuptake inhibitor (DNRI), for the treatment of patients with moderate to severe binge

eating disorder (BED), a serious mental health condition with limited treatment options. BED is characterized by recurrent and persistent episodes of binge eating, defined as consuming large quantities of food in a short period of time, perception of loss of control during the episode, and intense feelings of shame, guilt and embarrassment afterwards.

Last November, Roche announced that the FDA had accepted the NDA and granted priority review for **risdiplam**, an investigational survival motor neuron-2 (SMN-2) splicing modifier for the treatment of SMA. Risdiplam is designed to increase and sustain SMN protein levels both throughout the CNS and peripheral tissues of the body. The FDA is expected to make a decision on approval by May 24, 2020. In the meantime, the company plans to run a global compassionate use program for eligible patients with type 1 SMA.

The EMA is reviewing a marketing authorization application (MAA) for Hansa Biopharma's **imlifidase**, indicated as desensitization therapy for patients undergoing kidney transplantation. Hansa Biopharma submitted responses to the Day 120 questions on December 22, 2019, and the review process is on track. An opinion from the CHMP is expected in the second quarter of 2020, according to the company, followed by a potential decision by the EC during the summer 2020.

For an overview of these and other 2020 predictions, see Table IV.

Disclosures

The authors are employees of Clarivate Analytics

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Table III. *New product intros 2019.*

Trade name (country)[1]	Company	Active ingredient	Indication
Piqray (US)	Novartis	Alpelisib, tablets, 50, 150 & 200 mg	In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative ($HR^+/HER2^-$), *PIK3CA*-mutated, advanced or metastatic breast cancer
Katerzia (US)	Azurity	Amlodipine benzoate, oral suspension, 1 mg/mL	Used alone or in combination with other antihypertensive and antianginal agents for the treatment of: • Hypertension in adults and children 6 years and older, to lower blood pressure • Coronary artery disease (includes chronic stable angina; vasospastic angina; coronary artery disease in patients without heart failure or injection fraction < 40%)
Otezla (US)	Celgene	Apremilast, tablets, 10, 20 & 30 mg	Treatment of oral ulcers in patients with Behçet's disease*
Stemirac (JP)	Nipro	Autologous human bone marrow-derived mesenchymal stem cells expanded in autologous human serum	Treatment of spinal cord injury
Collategene (JP)	AnGes/Mitsubishi Tanabe	Beperminogene perplasmid, i.m. injections, 4 mg	For the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger's disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization
Vyleesi (US)	Palatin Technologies/ AMAG Pharmaceuticals	Bremelanotide, solution for s.c. injection in prefilled autoinjector pen, 1.75 mg/0.3 mL	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder
Zulresso (US)	Sage Therapeutics	Brexanolone, injections, 100 mg/20 mL (5 mg/mL) in single-dose vials	Treatment of postpartum depression
Beovu (US)	Novartis	Brolucizumab, solution for injection in prefilled syringe, 0.165 mL (6 mg/0.05 mL)	Treatment of wet age-related macular degeneration

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Breztri Aerosphere (JP)	AstraZeneca	Budesonide/glycopyrronium bromide/ formoterol fumarate***, metered-dose inhaler delivering 160 µg/9 µg/5 µg per inhalation	To relieve symptoms of chronic obstructive pulmonary disease
(CN)	Jiangsu Hengrui	Camrelizumab, injections, 200 mg	Third-line treatment for recurrent or refractory classical Hodgkin's lymphoma
Invokana (US)	Mitsubishi Tanabe/ Janssen	Canagliflozin, tablets, 100 & 300 mg	To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with albuminuria*
Nubeqa (US)	Bayer/Orion	Darolutamide, tablets, 300 mg	Treatment of patients with nonmetastatic castration-resistant prostate cancer
Dextenza (US)	Ocular Therapeutix	Dexamethasone, intraocular (intracanalicular) insert, 0.4 mg***	Treatment of ocular inflammation and pain following ophthalmic surgery
Dovato (US)	ViiV Healthcare	Dolutegravir/lamivudine**, tablets, 50 mg/ 300 mg	Treatment of HIV-1 infection in adults with no antiretroviral treatment history and with no known resistance to either dolutegravir or lamivudine
Slynd (US)	Exeltis USA	Drospirenone, tablets, 4 mg	For use by females of reproductive potential to prevent pregnancy
Dupixent (US)	Regeneron/Sanofi	Dupilumab, injections, 300 mg/2 mL solution in prefilled syringe	For use with other medicines to treat chronic rhinosinusitis with nasal polyposis in adults whose disease is not controlled*
Soliris (US)	Alexion	Eculizumab, injections, 300 mg/30 mL in single-dose vials	Treatment of neuromyelitis optica spectrum disorder in adult patients who are anti-aquaporin-4 (AQP4) antibody-positive*
Trikafta (US)	Vertex	Elexacaftor/tezacaftor/ivacaftor**, tablets, fixed-dose combination containing elexacaftor 100 mg/tezacaftor 50 mg/ ivacaftor 75 mg; co-packaged with tablets, ivacaftor 150 mg	Treatment of cystic fibrosis in patients aged 12 years and older who have at least one copy of the F508del mutation in the *CFTR* gene

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Gamifant (US)	NovImmune/Sobi	Emapalumab, infusion, 10 mg/2 mL & 50 mg/10 mL	Treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis
Rozlytrek (US)	Chugai/Roche	Entrectinib, capsules, 100 & 200 mg	• Treatment of adult and pediatric patients 12 years of age and older with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy • Treatment of adults with *ROS1* fusion-positive, metastatic non-small cell lung cancer
Balversa (US)	Janssen	Erdafitinib, tablets, 3, 4 & 5 mg	Treatment of adult patients with locally advanced or metastatic urothelial carcinoma that has susceptible *FGFR3* or *FGFR2* genetic alterations and progressed during or following at least one line of prior platinum-containing chemotherapy
Minnebro (JP)	Exelixis/Daiichi Sankyo	Esaxerenone, tablets, 1.25, 2.5 & 5 mg	Treatment of hypertension
Spravato (US)	Janssen	Esketamine hydrochloride, nasal spray***, 28 mg	In conjunction with an oral antidepressant, for treatment of adults with treatment-resistant depression*
Bijuva (US)	TherapeuticsMD	17β-Estradiol/progesterone**, capsules, 1 mg/100 mg	Treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus
Orkedia (JP)	Kyowa Kirin	Evocalcet, tablets, 1 & 2 mg	Treatment of hypercalcemia in patients with parathyroid carcinoma or primary hyperparathyroidism who are unable to undergo parathyroidectomy or relapse after parathyroidectomy*

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Inrebic (US)	Celgene	Fedratinib, capsules, 100 mg	Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis
Baqsimi (US)	Lilly	Glucagon, single-dose intranasal device*** containing dry powder, 3 mg	Treatment of severe hypoglycemia in patients with diabetes ages 4 years and older
Gvoke (US)	Xeris Pharmaceuticals	Glucagon, single-dose prefilled HypoPen autoinjector***, 0.5 mg/0.1 mL & 1.0 mg/0.2 mL; single-dose prefilled syringe, 0.5 mg/0.1 mL & 1.0 mg/0.2 mL	Treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and older
Vyondys 53 (US)	Sarepta Therapeutics	Golodirsen, injections, 100 mg/2 mL (50 mg/mL) in single-dose vials	Treatment of Duchenne muscular dystrophy in patients with a confirmed mutation amenable to exon 53 skipping
Oligomannate (CN)	Shanghai Green Valley Pharmaceuticals	GV-971, capsules	Treatment of mild to moderate Alzheimer's disease
Duobrii (US)	Bausch Health	Halobetasol propionate/tazarotene**, lotion, 0.01%/0.045%	Topical treatment of plaque psoriasis in adults
Asceniv (US)	ADMA Biologics	Immune globulin intravenous, human-slra, liquid for intravenous injection, 10%	Treatment of primary humoral immunodeficiency in adults and adolescents (12 to 17 years of age)
Xembify (US)	Grifols	Immune globulin subcutaneous, human-klhw, solution for subcutaneous injection, 20%	Treatment of primary humoral immunodeficiency in patients 2 years of age and older
Taltz (US)	Lilly	Ixekizumab, solution in single-dose prefilled autoinjector, 80 mg/mL; solution in single-dose prefilled syringe, 80 mg/mL	Treatment of adults with active ankylosing spondylitis*
Xenleta (US)	Nabriva Therapeutics	Lefamulin, tablets, 600 mg; vials for injection, 150 mg/15 mL	Treatment of adults with community-acquired bacterial pneumonia caused by susceptible microorganisms
Inbrija (US)	Acorda Therapeutics	Levodopa, inhalation powder in capsules*** containing 42 mg levodopa for use with the Inbrija inhaler	Intermittent treatment of "off" episodes in patients with Parkinson's disease treated with carbidopa/levodopa

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Reblozyl (US)	Acceleron/Celgene	Luspatercept, lyophilized powder in single-use vials, 25 & 75 mg, for reconstitution and subcutaneous injection	Treatment of anemia in adult patients with β-thalassemia who require regular red blood cell transfusions
Tarlige (JP)	Daiichi Sankyo	Mirogabalin besylate, tablets, 2.5, 5, 10 & 15 mg	Treatment of peripheral neuropathic pain
Jynneos (US)	Bavarian Nordic	MVA-BN orthopox vaccine, suspension for subcutaneous injection in single-use vials, 0.5 mL	Prevention of monkeypox disease in adults 18 years of age and older determined to be at high risk*
Efleira (RU)	Biocad	Netakimab, subcutaneous injections, 60 mg/mL	Treatment of moderate to severe plaque psoriasis
Rocklatan (US)	Aerie Pharmaceuticals	Netarsudil mesylate/latanoprost***, ophthalmic solution, 0.2 mg/mL (0.02%) netarsudil/0.05 mg/mL (0.005%) latanoprost	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Ofev (US)	Boehringer Ingelheim	Nintedanib, capsules, 100 & 150 mg	To slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease*
Nuzyra (US)	Paratek	Omadacycline, lyophilized powder, 100 mg in single-dose vials for reconstitution and further dilution before i.v. infusion; tablets, 150 mg	Treatment of adult patients with the following infections caused by susceptible microorganisms: community-acquired bacterial pneumonia; acute skin and skin structure infections
Zolgensma (US)	AveXis (Novartis)	Onasemnogene abeparvovec, suspension for intravenous infusion in single-use vials, 5.5 mL or 8.3 mL, containing a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL	Treatment of pediatric patients < 2 years of age with spinal muscular atrophy with biallelic mutations in the *SMN1* gene
Smyraf (JP)	Astellas	Peficitinib hydrobromide, tablets, 50 & 100 mg	Treatment of rheumatoid arthritis, including prevention of structural joint damage, in patients who have an inadequate response to conventional therapies
Turalio (US)	Plexxikon/Daiichi Sankyo	Pexidartinib hydrochloride, capsules, 200 mg	Treatment of adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Polivy (US)	Genentech	Polatuzumab vedotin, lyophilized powder in single-use vials, 140 mg	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, in combination with bendamustine plus rituximab
Fulaimei (CN)	Hansoh Pharma	Polyethylene glycol loxenatide, prefilled pen or syringe for subcutaneous injection, long-acting, 0.1 and 0.2 mg/0.5 mL	Treatment of type 2 diabetes in adults
(US)	TB Alliance/Mylan	Pretomanid, tablets, 200 mg	As part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary, extensively drug-resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis
Vanflyta (JP)	Daiichi Sankyo	Quizartinib, tablets, 17.7 & 26.5 mg	Treatment of adult patients with relapsed/refractory FLT3-ITD acute myeloid leukemia, as detected by a test approved by Japan's Ministry of Health, Labour and Welfare (MHLW)
Ultomiris (US)	Alexion	Ravulizumab, single-dose vials for i.v. injection, 300 mg/30 mL (10 mg/mL)	• Treatment of adult patients with paroxysmal nocturnal hemoglobinuria • Treatment of adults and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome, to inhibit complement-mediated thrombotic microangiopathy
Relumina (JP)	Takeda/Aska	Relugolix, tablets, 40 mg	Relief of symptoms of uterine fibroids
Remo (IN)	Glenmark/Avolynt	Remogliflozin etabonate, tablets, 100 mg	Treatment of type 2 diabetes in adults
Aemcolo (US)	Cosmo Pharmaceuticals/ RedHill Biopharma	Rifamycin, delayed-colonic release tablets***, 194 mg	Treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in adults
Skyrizi (US, GB)	AbbVie/Boehringer Ingelheim	Risankizumab, single-dose prefilled syringe for s.c. injection, 75 mg/0.83 mL	Treatment of moderate to severe plaque psoriasis in adult patients

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Evenity (JP)	UCB/Amgen Astellas BioPharma	Romosozumab, prefilled syringe for s.c. injection, 105 mg/1.17 mL	Treatment of osteoporosis in men and postmenopausal women at high risk of fracture
Besremi (AT, DE)	PharmaEssentia/AOP Orphan	Ropeginterferon alfa-2b, prefilled pen, 250 µg/0.5 mL & 500 µg/0.5 mL	As monotherapy in adults for the treatment of polycythemia vera without symptomatic splenomegaly
Airuizhuo (CN)	FibroGen/AstraZeneca	Roxadustat, capsules, 50 mg	Treatment of anemia caused by chronic kidney disease in patients who are dialysis-dependent
Mosquirix (MW)	GlaxoSmithKline	RTS,S/AS01E, powder and suspension for suspension for injection; after reconstitution, 1 dose (0.5 mL) contains 25 mg of RTS,S1,2 adjuvanted with AS01E	Prevention of malaria in children up to 2 years of age
Jakafi (US)	Incyte	Ruxolitinib phosphate, tablets, 5, 10, 15, 20 & 25 mg	Treatment of steroid-refractory acute graft-vs-host disease in adults and pediatric patients 12 years and older*
Seysara (US)	Paratek/Almirall	Sarecycline hydrochloride, tablets, equiv. to 60, 100 & 150 mg sarecycline base	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older
Annovera (US)	Population Council/ TherapeuticsMD	Segesterone acetate (SA)/ethinyl estradiol (EE)**, silicone elastomer vaginal system containing 103 mg SA and 17.4 mg EE, which releases on average 0.15 mg/day SA and 0.013 mg/day EE	For use by females of reproductive potential to prevent pregnancy
Xpovio (US)	Karyopharm	Selinexor, tablets, 20 mg	In combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is resistant to several other forms of treatment
Rybelsus (US)	Novo Nordisk	Semaglutide, tablets, 7 & 14 mg***	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Tyvyt (CN)	Innovent Biologics/ Lilly	Sintilimab, intravenous injections, 100 mg/ 10 mL	Treatment of patients with relapsed or refractory classical Hodgkin's lymphoma

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Mayzent (US)	Novartis	Siponimod fumarate, tablets, 0.25 & 2 mg	Treatment of adults with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing–remitting disease and active secondary progressive disease
Lokelma (DK, FI, NO, SE)	AstraZeneca	Sodium zirconium cyclosilicate, oral suspension, 5 & 10 g	Treatment of adults with hyperkalemia
Sunosi (US)	Jazz Pharmaceuticals	Solriamfetol hydrochloride, tablets, 75 & 150 mg	To improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea
Elzonris (US)	Stemline Therapeutics	Tagraxofusp, solution in single-dose vials, 1 mL containing 1000 µg tagraxofusp	Treatment of blastic plasmacytoid dendritic cell neoplasm in adults and in pediatric patients 2 years and older
(CN)	Tianji Pharma	Tapinarof, cream	Treatment of moderate stable psoriasis vulgaris in adults
K-CAB (KR)	RaQualia/ CJ HealthCare	Tegoprazan, tablets, 50 mg	Treatment of gastroesophageal reflux disease, including erosive esophagitis and nonerosive reflux disease
Tuoyi (CN)	Shanghai Junshi Biosciences	Toripalimab, vials, 240 mg	Treatment of locally advanced or metastatic melanoma in patients who have failed routine systemic treatment
Itulazax (DE)	ALK-Abelló	Tree pollen sublingual immunotherapy (SLIT), sublingual tablets, 12 SQ-Bet standardized allergen extract of pollen from white birch (*Betula verrucosa*)	Treatment of adult patients with moderate to severe allergic rhinitis and/or conjunctivitis, induced by pollen from the birch homologous family of trees
Trecondi (DE)	Medac	Treosulfan, powder for solution for i.v. infusion in vials, 50 mg/mL	In combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in adult patients with malignant and nonmalignant diseases and in pediatric patients older than 1 month with malignant diseases*

(Continued)

Table III. *New product intros 2019. (Cont.)*

Trade name (country)[1]	Company	Active ingredient	Indication
Aklief (US)	Galderma	Trifarotene, cream, 0.005%	Topical treatment of acne vulgaris in patients 9 years of age and older
Esperoct (DE, CH)	Novo Nordisk	Turoctocog alfa pegol, powder and solvent for solution for injection, 500, 1000, 1500, 2000 & 3000 IU	Treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A (congenital factor VIII deficiency)
Rinvoq (US)	AbbVie	Upadacitinib tartrate, tablets, extended-release, 15 mg	Treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate
Waylivra (DE, FR)	Akcea Therapeutics (Ionis Pharmaceuticals)	Volanesorsen, solution for injection, 285 mg	As an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome and at high risk for pancreatitis, in whom response to diet and triglyceride-lowering therapy has been inadequate
Oxbryta (US)	Global Blood Therapeutics	Voxelotor, tablets, 500 mg	Treatment of sickle cell disease in adults and children 12 years of age and older
Brukinsa (US)	BeiGene	Zanubrutinib, capsules, 80 mg	Treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy

[1]Country codes are the abbreviations used by the World Intellectual Property Organization.
*New indication.
**New combination.
***New formulation.

Table IV. *Approvals and candidates for approval in 2020.*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Abicipar pegol	Allergan/Molecular Partners	U.S., E.U.	Treatment of patients with neovascular (wet) age-related macular degeneration	Mid-2020 PDUFA date in U.S.; E.U. approval expected in second half 2020
Ad26.ZEBOV (rHAd26), in combination with MVA-BN Filo	Janssen	E.U.	As a heterologous prime–boost vaccine regimen for the prevention of Ebola virus disease caused by Zaire ebolavirus	MAAs for each vaccine submitted in Nov 2019 (accelerated assessment)
Alalevonadifloxacin mesylate	Wockhardt	India	For ABSSSIs, including diabetic foot infections and concurrent bacteremia	Approved in India in Jan 2020
AR-101 (Palforzia)	Aimmune Therapeutics	U.S., E.U.	Peanut allergy desensitization in children and adolescents aged 4 to 17 years	Decision expected in U.S. in Jan 2020; in E.U. in second half of 2020
Avapritinib	Blueprint Medicines	U.S.	Unresectable or metastatic GIST harboring a *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations	Approved in Jan 2020 in US; MAA under review in E.U.
Belantamab mafodotin	GlaxoSmithKline	U.S.	Treatment of patients with relapsed or refractory multiple myeloma whose prior therapy included an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody	BLA submitted in Dec 2019
Bempedoic acid and bempedoic acid/ ezetimibe	Esperion Therapeutics	U.S., E.U.	Treatment of patients with elevated LDL cholesterol (LDL-C) who need additional LDL-C lowering despite the use of currently accessible therapies	Approvals expected in first half of 2020
Berotralstat hydrochloride	BioCryst	U.S.	Prevention of hereditary angioedema attacks	NDA submitted in Dec 2019
BP-101 (Libicore)	Ivix	Russian Federation	Female hypoactive sexual desire disorder	Application submitted in Sept 2019

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Cabotegravir & cabotegravir/ rilpivirine	ViiV Healthcare	U.S., E.U.	Lead-in treatment for HIV-1-infected adults whose viral load is suppressed, in combination with rilpivirine and prior to the commencement of injectable therapy	Applications filed in Apr 2019 (U.S.) and July 2019 (E.U.)
Chiglitazar	Chipscreen Biosciences	China	Type 2 diabetes	Application accepted in Sept 2019
Daprodustat	GlaxoSmithKline	Japan	Treatment of anemia associated with CKD	Application filed in Japan in Aug 2019
Dasotraline hydrochloride	Sunovion	U.S.	Treatment of patients with moderate to severe binge eating disorder	PDUFA date of May 14, 2020
Delgocitinib	Japan Tobacco (JT) Torii	Japan	Atopic dermatitis	Approved in Jan 2020
Dotinurad	Fuji Yakuhin/Mochida	Japan	Treatment of hyperuricemia with or without gout	Approved in Jan 2020
Eflapegrastim	Spectrum Pharmaceuticals	U.S.	Treatment of chemotherapy-induced neutropenia	PDUFA date of Oct 24, 2020
Eptinezumab	Alder Biopharmaceuticals	U.S.	Prevention of chronic and episodic migraine; Infusion; Intravenous	PDUFA date of Feb 21, 2020
Fenfluramine hydrochloride	Zogenix	U.S., E.U.	Treatment of seizures associated with Dravet syndrome	Approvals expected in Q1 2020
Filgotinib	Galapagos/Gilead	U.S., E.U., Japan	Rheumatoid arthritis	Applications filed in Aug 2019 (E.U.), Oct 2019 (Japan) and Dec 2019 (U.S.)
Flortaucipir F 18	Lilly	U.S.	For imaging tau in patients with Alzheimer's disease	
Fostemsavir	ViiV Healthcare	U.S., E.U.	For use in combination with other antiretroviral agents in heavily treatment-experienced adults infected with multidrug-resistant HIV-1 infection who are unable to form a suppressive regimen due to resistance, intolerance or safety considerations	NDA filed in U.S. in Dec 2019; MAA filed in E.U. in Jan 2020

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
HSK-3486	Haisco Pharmaceutical Group	China	Induction of general anesthesia and sedation of patients undergoing endoscopic diagnosis	Application granted priority review in Aug 2019
Imlifidase	Hansa Biopharma	E.U.	For the desensitization of patients prior to kidney transplant	Decision expected during summer of 2020
Inebilizumab	Viela Bio	U.S.	Treatment of NMO and NMOSD	PDUFA date of June 11, 2020
Isatuximab	Sanofi	U.S., E.U., Japan	Multiple myeloma	PDUFA date of Apr 30, 2020 in U.S.; applications also under review in E.U. and Japan
Levonadifloxacin arginine salt	Wockhardt	India	For ABSSSIs, including diabetic foot infections and concurrent bacteremia	Approved in India in Jan 2020
Lisocabtagene maraleucel	Celgene	U.S.	Treatment of adult patients with relapsed or refractory LBCL after at least two prior therapies	BLA submitted in Dec 2019
Lonafarnib	Eiger BioPharmaceuticals/Progeria Research Foundation	U.S.	Treatment of progeria and progeroid laminopathies	Rolling submission started in Dec 2019, expected to complete in Q1 2020
LY-900014 (Ultra-rapid lispro)	Lilly	U.S., E.U., Japan	Type 1 and 2 diabetes	Applications submitted in Q1 2019
Margetuximab	MacroGenics	U.S.	Treatment of patients with metastatic HER2-positive breast cancer in combination with chemotherapy	BLA submitted in Dec 2019
Nadofaragene firadenovec	FKD Therapies	U.S.	Treatment of patients with high-grade Bacillus Calmette–Guérin (BCG)-unresponsive nonmuscle-invasive bladder cancer	BLA accepted for priority review in Nov 2019
Orelabrutinib	InnoCare Pharma	China	Treatment of patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma	Filing accepted in China in Nov 19, granted priority review in Jan 2020
Osilodrostat	Recordati	E.U.	Treatment of endogenous Cushing syndrome in adults	Approved in Jan 2020

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
OTL-200	Orchard Therapeutics	E.U.	Metachromatic leukodystrophy	MAA filed in Nov 2019, accelerated assessment
Ozanimod	Celgene	U.S., E.U.	Treatment of relapsing forms of multiple sclerosis	PDUFA date of Mar 25, 2020 in U.S.; decision expected in E.U. in first half 2020
Pemigatinib	Incyte	U.S., E.U.	Previously treated, locally advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements	PDUFA date of May 30, 2020 in U.S.; MAA under review in E.U.
PPE (Viaskin Peanut)	DBV Technologies	U.S.	Treatment of peanut allergy in children 4 to 11 years of age	PDUFA date of Aug 5, 2020
REGN-3470-3471-3479 (atoltivimab/ odesivimab/ maftivimab)	Regeneron	U.S.	Ebola virus infection	Rolling submission started in Sept 2019
Remimazolam	PAION, Mundipharma (Japan), Yichang Humanwell Pharmaceutical (China), Hana Pharm (South Korea), Cosmo Pharmaceuticals (US)	Japan, U.S., China, South Korea, E.U.	General anesthesia (Japan, South Korea); procedural sedation (U.S., China, E.U.)	Approved in Japan for general anesthesia in Jan 2020; PDUFA date in U.S. is Apr 5, 2020; Applications filed in China, South Korea and E.U. in Nov 2018, Dec 2019 and Nov 2019, respectively
Rimegepant	BioHaven Pharmaceutical	U.S.	Treatment of acute migraine	PDUFA date in Q1 2020
Ripretinib	Deciphera	U.S.	In patients with advanced GIST who have received treatment with prior anticancer therapies, including imatinib, sunitinib and regorafenib	NDA filed in Dec 2019
Risdiplam	Roche	U.S.	Spinal muscular atrophy	PDUFA date of May 24, 2020
Sacituzumab govitecan	Immunomedics	U.S.	Treatment of patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease	PDUFA date of June 2, 2020
Satralizumab	Chugai Pharmaceutical/ Roche	Japan, E.U., U.S.	Treatment of NMO and NMOSD	Applications submitted in Aug 2019 (E.U.), Oct 2019 (U.S.), Nov 2019 (Japan)

(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Selumetinib sulfate	AstraZeneca	U.S.	Treatment of pediatric patients aged 3 years and older with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas	PDUFA date in Q2 2020
Somapacitan	Novo Nordisk	U.S., E.U.	Treatment of adults with growth hormone deficiency	Applications filed in Sept 2019
Surufatinib	Hutchison China MediTech (Chi-Med)	China	Treatment of advanced nonpancreatic neuroendocrine tumors	Application granted priority review in Dec 2019
Tafasitamab	MorphoSys	U.S.	Treatment of relapsed or refractory diffuse LBCL in combination with lenalidomide	Application submitted in Dec 2019
Tazemetostat	Epizyme	U.S.	Treatment of patients with metastatic or locally advanced epithelioid sarcoma not eligible for curative surgery; Treatment of patients with relapsed or refractory follicular lymphoma, both with or without EZH2 activating mutations, who have received at least two prior lines of systemic therapy	Approved for epithelioid sarcoma in Jan 2020; NDA for follicular lymphoma submitted in Dec 2019
Teprotumumab	Horizon Therapeutics	U.S.	Treatment of Graves orbitopathy (active thyroid eye disease)	Approved in Jan 2020
TetraMen-T	Sanofi	U.S., E.U.	Prevention of meningococcal meningitis in persons 2 years of age and older	PDUFA date of Apr 25, 2020 in U.S.; MAA submitted in E.U. in Oct 2019
Tirabrutinib hydrochloride	Ono	Japan	Treatment of Waldenström macroglobulinemia and lymphoplasmacytic lymphoma; treatment of recurrent or refractory primary central nervous system lymphoma	Separate applications submitted in Aug and Nov 2019

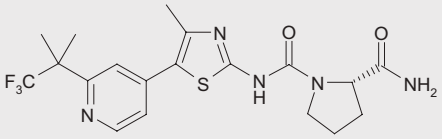
(Continued)

Table IV. *Approvals and candidates for approval in 2020. (Cont.)*

Product name	Organization(s)	Country/ region	Indication	Status/notes
Triheptanoin	Ultragenyx	U.S.	Treatment of long-chain fatty acid oxidation disorders, including carnitine palmitoyltransferase, very long-chain acyl-CoA dehydrogenase and long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiencies	PDUFA date of July 31, 2020
Tucatinib	Array BioPharma/ Seattle Genetics	U.S.	In combination with trastuzumab and capecitabine, for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least three prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant or metastatic setting	NDA submitted in Dec 2019
Vadadustat	Mitsubishi Tanabe Pharma	Japan	Treatment of patients with renal anemia secondary to CKD	Application filed in Japan in July 2019
Valoctocogene roxaparvovec	BioMarin	U.S., E.U.	Treatment of adults with hemophilia A	Applications filed in late 2019
Veverimer	Tricida	U.S.	Treatment of metabolic acidosis in patients with CKD	PDUFA date of Aug 22, 2020
Viloxazine hydrochloride	Supernus	U.S.	Attention deficit hyperactivity disorder	NDA filed in Nov 2019
Viltolarsen	Nippon Shinyaku	U.S., Japan	Duchenne muscular dystrophy	Rolling submission completed in Oct 2019 in U.S.; application accepted in Japan in Nov 2019
Yimitasvir	HEC Pharm	China	Hepatitis C virus infection	Application granted priority review in Nov 2019

ABSSSIs, acute bacterial skin and skin structure infections; BLA, biologics license application; CKD, chronic kidney disease; GIST, gastrointestinal stromal tumor; LBCL, large B-cell lymphoma; MAA, marketing authorization application; NDA, new drug application; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; PDUFA, Prescription Drug User Fee Act.
Source: *Cortellis Drug Discovery Intelligence* and *Cortellis Competitive Intelligence*. Information current as of January 24, 2020.

Chemical structures of NCEs launched in 2019



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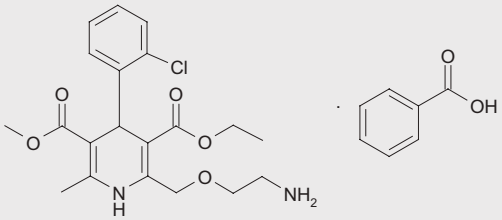

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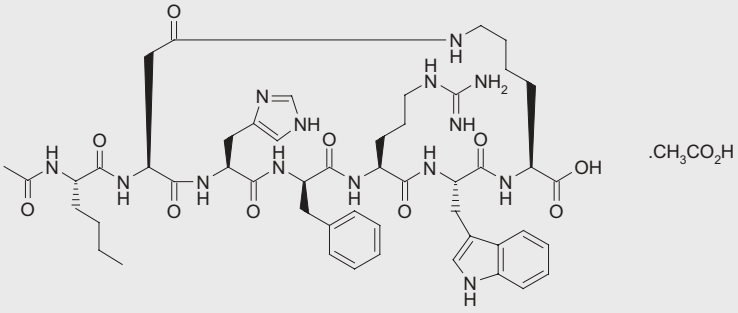

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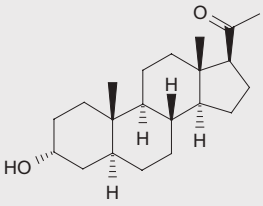

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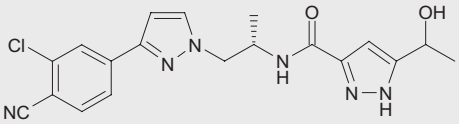

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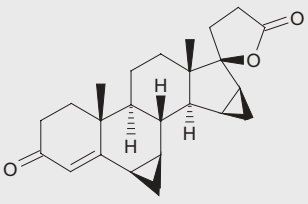

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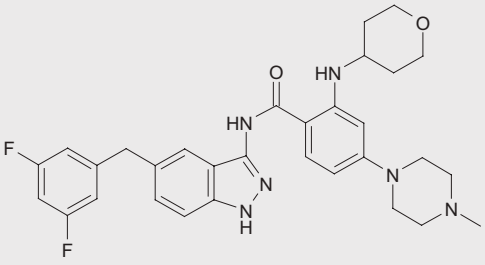
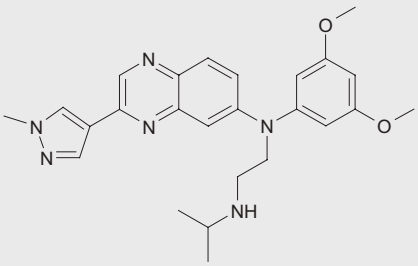


Entrectinib

Chemical structures of NCEs launched in 2019



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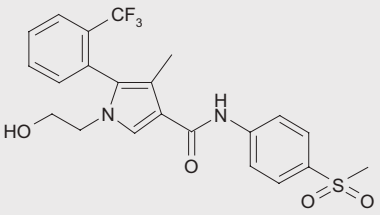
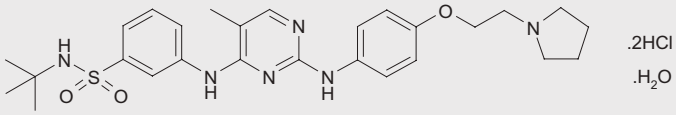
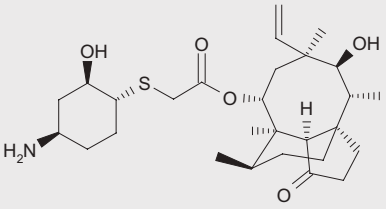


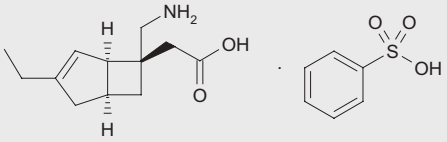
Esaxerenone



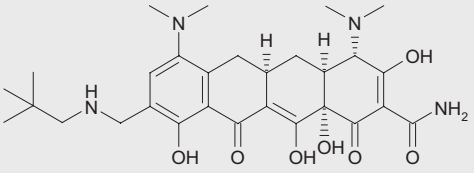
Fedratinib hydrochloride



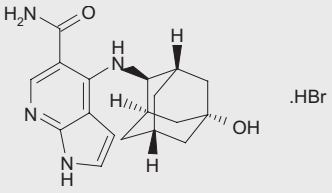
Lefamulin



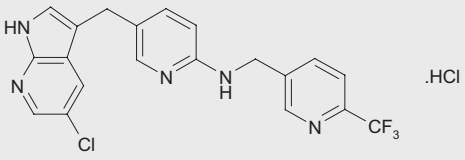
Mirogabalin besylate



Omadacycline

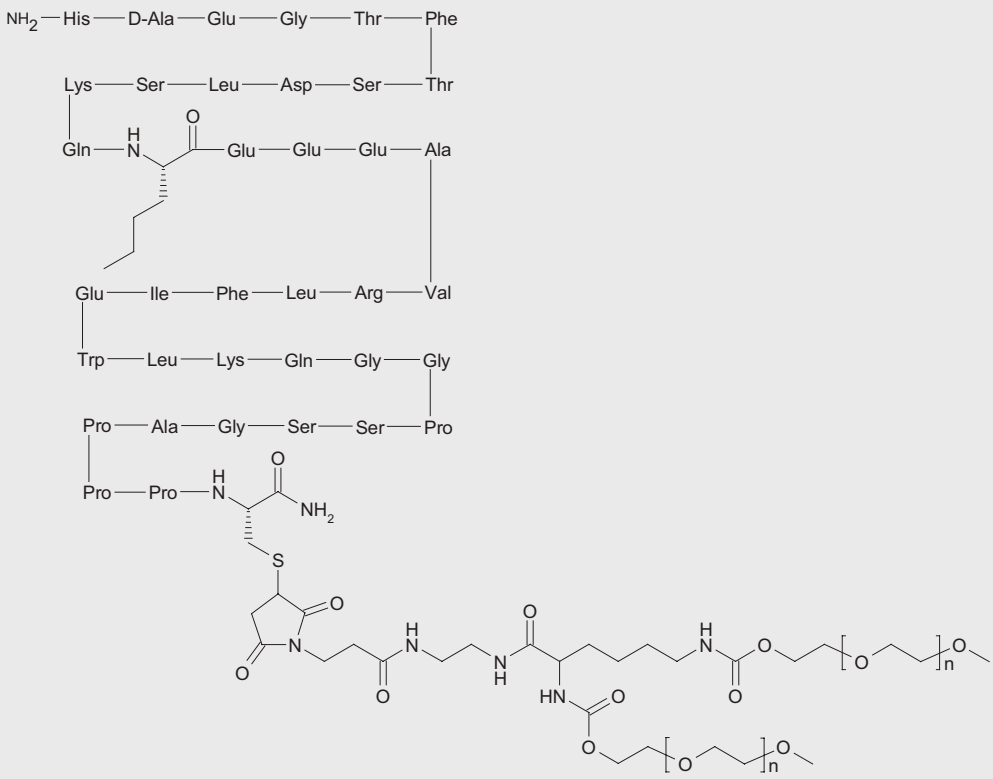


Peficitinib hydrobromide

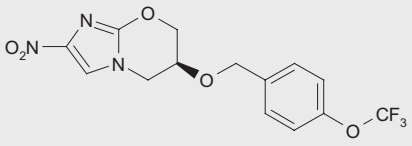


Pexidartinib hydrochloride

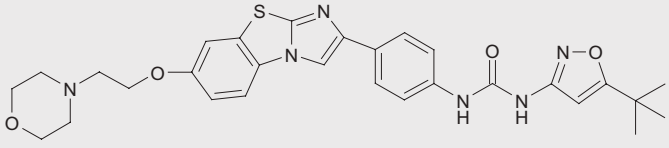
Chemical structures of NCEs launched in 2019



Polyethylene glycol loxenatide

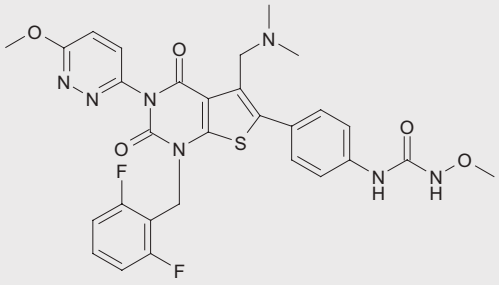


Pretomanid

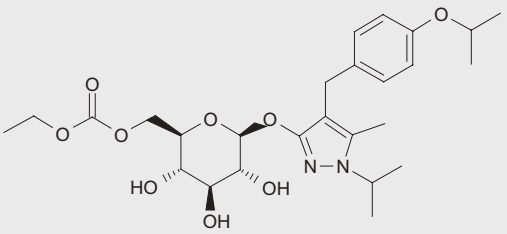


Quizartinib

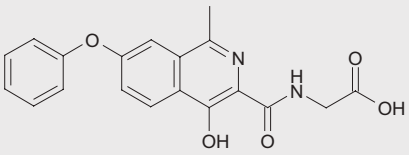
Chemical structures of NCEs launched in 2019



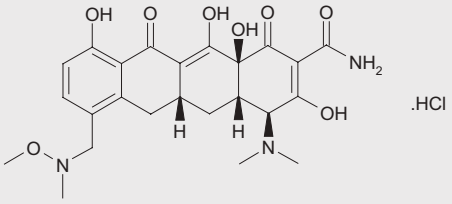
Relugolix



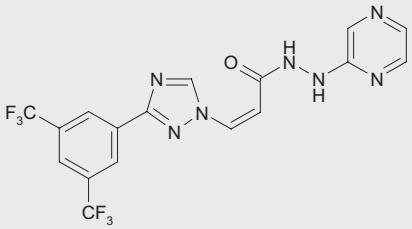
Remogliflozin etabonate



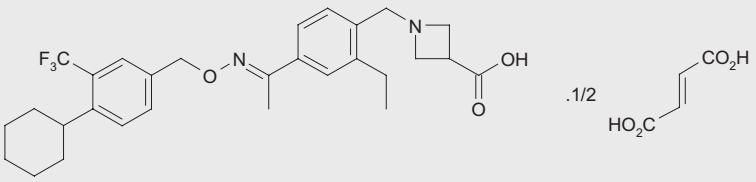
Roxadustat



Sarecycline hydrochloride

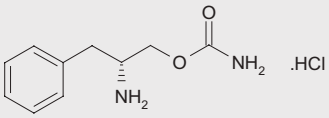


Selinexor

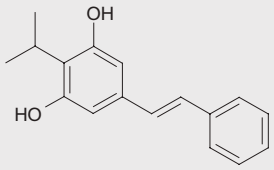


Siponimod fumarate

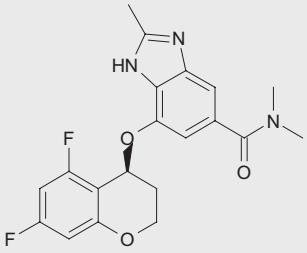
Chemical structures of NCEs launched in 2019



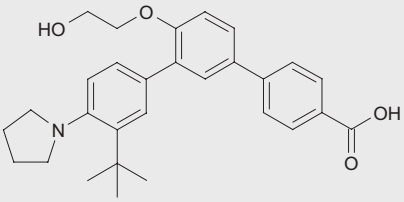
Solriamfetol hydrochloride



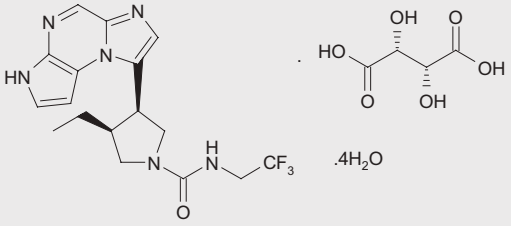
Tapinarof



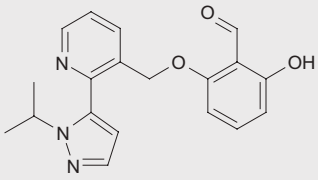
Tegoprazan



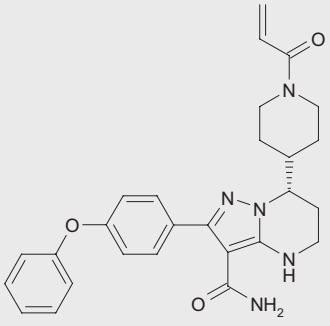
Trifarotene



Upadacitinib tartrate



Voxelotor



Zanubrutinib