R&D DAY

July 09, 2024

HKEX: 13, Nasdaq / AIM:HCM

HUTCHMED

Safe harbor statement & disclaimer

The performance and results of operations of the HUTCHMED Group contained within this presentation are historical in nature, and past performance is no guarantee of future results.

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the U.S. Private Securities Litigation Reform Act of 1995. These forward-looking statements can be identified by words like "will," "expects," "anticipates," "future," "intends," "plans," "believes," "estimates," "pipeline," "could," "potential," "first-in-class," "best-in-class," "designed to," "objective," "guidance," "pursue," or similar terms, or by express or implied discussions regarding potential drug candidates, potential indications for drug candidates or by discussions of strategy, plans, expectations or intentions. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that any of our drug candidates will be approved for sale in any market, that any approvals which are obtained will continue to remain valid and effective , or that the sales of products marketed or otherwise commercialized by HUTCHMED and/or its collaboration partners (collectively, "HUTCHMED Products") will achieve any particular revenue or net income levels. In particular, management's expectations could be affected by, among other things: unexpected regulatory actions or delays or government regulation generally, including, among others; the uncertainties inherent in research and development, including the inability to meet our key study assumptions regarding enrollment rates, timing and availability of subjects meeting a study's inclusion and exclusion criteria and funding requirements, changes to clinical protocols, unexpected adverse events or safety, quality or manufacturing issues; and the inability of a drug candidate to meet the primary or secondary endpoint of a study; the inability of a drug candidate to obtain regulatory approval in different jurisdictions or the utilization, market acceptance and commercial success of HUTCHMED Products after obtaining regulatory approval; the emergence of competing drugs and product candidates that may be superior to, or more cost effective than, HUTCHMED'S Products and drug candidates; the impact of studies (whether conducted by HUTCHMED or others and whether mandated or voluntary) or recommendations and guidelines from governmental authorities and other third parties on the commercial success of HUTCHMED Products and candidates in development; the costs of developing, producing and selling HUTCHMED Products; the ability of HUTCHMED to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; global trends toward health care cost containment, including ongoing pricing pressures; uncertainties regarding actual or potential legal proceedings, including, among others, actual or potential product liability litigation, litigation and investigations regarding sales and marketing practices, intellectual property disputes, and government investigations generally; general economic and industry conditions, including uncertainties regarding the effects of the persistently weak economic and financial environment in many countries and uncertainties regarding future global exchange rates ,. the risk that HUTCHMED's ADSs could be barred from trading in the United States as a result of the Holding Foreign Companies Accountable Act and the rules promulgated thereunder, and the impact of pandemics or other health crises in China or globally. For further discussion of these and other risks, see HUTCHMED's filings with the U.S. Securities and Exchange Commission, on AIM and with The Stock Exchange of Hong Kong Limited. HUTCHMED is providing the information in this presentation as of this date and does not undertake any obligation to update any forward-looking statements as a result of new information, future events or otherwise.

This presentation is intended for investors only. Information concerning pharmaceuticals (including compounds under development) contained within this material is not intended as advertising or medical advice.

Some of the clinical data in this presentation relating to HUTCHMED's products or its investigational drug candidates is from pre-clinical studies or early phase, single-arm clinical trials. When such data or data from later stage trials are presented in relation to other investigational or marketed drug products, the presentation and discussion are not based on head-to-head trials between HUTCHMED's investigational drug candidates and other products unless specified in the trial protocol. HUTCHMED is still conducting pre-clinical studies and clinical trials and, as additional patients are enrolled and evaluated, data on HUTCHMED's investigational drug candidates may change.

In addition, this presentation contains statistical data, third-party clinical data and estimates that HUTCHMED obtained from industry publications and reports generated by third-party market research firms, including Frost & Sullivan, IQVIA, independent market research firms, clinical data of competitors, and other publicly available data. All patient population, market size and market share estimates are based on Frost & Sullivan or QuintilesIMS/IQVIA research, unless otherwise noted. Although HUTCHMED believes that the publications, reports, surveys and third-party clinical data are reliable, HUTCHMED has not independently verified the data and cannot guarantee the accuracy or completeness of such data. You are cautioned not to give undue weight to this data. Such data involves risks and uncertainties and are subject to change based on various factors, including those discussed above.

Nothing in this presentation or in any accompanying management discussion of this presentation constitutes, nor is it intended to constitute or form any part of: (i) an invitation or inducement to engage in any investment activity, whether in the United States, the United Kingdom, Hong Kong or in any other jurisdiction; (ii) any recommendation or advice in respect of any securities of HUTCHMED; or (iii) any offer or an invitation to induce an offer by any person for the sale, purchase or subscription of any securities of HUTCHMED. Information concerning pharmaceuticals (including compounds under development) contained within this material is not intended as advertising or medical advice.

No representation or warranty, express or implied, is made as to, and no reliance should be placed on, the fairness, accuracy, completeness or correctness of the information, or opinions contained herein. Neither HUTCHMED, nor any of HUTCHMED's advisors or representatives shall have any responsibility or liability whatsoever (for negligence or otherwise) for any loss howsoever arising from any use of this presentation or its contents or otherwise arising in connection with this presentation. The information set out herein may be subject to updating, completion, revision, verification and amendment and such information may change materially.

All references to "HUTCHMED" as used throughout this presentation refer to HUTCHMED (China) Limited and its consolidated subsidiaries and joint ventures unless otherwise stated or indicated by context. This presentation should be read in conjunction with HUTCHMED's results for the year ended December 31, 2023 and HUTCHMED's other SEC filings and announcements published in accordance with the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited copies of which are available on HUTCHMED's website (www.hutch-med.com).

Use of Non-GAAP Financial Measures - This presentation includes certain non-GAAP financial measures. Please see the section of the HUTCHMED results announcement titled "Non-GAAP Financial Measures and Reconciliation" for further information relevant to the interpretation of these financial measures and reconciliations of these financial measures to the most comparable GAAP measures.

Agenda

HUTCHMED

Welcome Opening

Weiguo Su
Chief Executive Officer &
Chief Scientific Officer

Sovleplenib :
Our First Potential Novel Medicine in Autoimmune Diseases

Michael Shi
Chief Medical Officer &
Head of R&D

Break

Surufatinib (Sulanda®) :
Potential Novel Treatment for Pancreatic Cancer

HMPL-306 :
For IDH1- and/or IDH2-mutated Relapsed/Refractory Acute Myeloid Leukemia

Closing Remarks

Q&A Session

AMBITION
to mature into a sustainable biopharma from an emerging growth company

VISION
discovering, developing and bringing new innovative medicines to patients worldwide

Fruquintinib

- Over US$50m sales in US in Q1 2024
- Leader in 3L CRC in China with US$107m sales in 2023
- EU approved; under review in Japan

Savolitinib

- US NDA filing for 2L NSCLC MET+ by end 2024
- Launched in China in 2021 with potential expansion into 1L NSCLC MET Exon 14

Surufatinib

- Encouraging results from an investigator-initiated trial for PDAC
- China Phase II/III 1L PDAC trial initiated
- Launched in China in 2021 for advanced NETs with 21% prescription share in 2023

Sovleplenib

- China NDA ITP filed with priority review granted
- Initiated China registration Phase III trial for wAIHA
- International Phase I ITP study enrolling

HMPL-306 (IDH1/2)

- Initiated China Phase III IDH1/2+ r/r AML

Unlocking potential of our 1st, 2nd and 3rd innovative wave

(US$)	1st Wave Surufatinib	2nd Wave Sovleplenib	3rd Wave HMPL-306 IDH1/2 dual-inhibitor
China Market	PDAC Incidence 100k[1] $800m-$1bn Chemo as SOC	ITP Actively treated 250k[2] $500m-$700m Potential #1 Syk inhibitor in China	AML Incidence 20K[5] $100m-$200m No IDH1/2 dual-inhibitor approved globally
Global Market	Incidence 510k[1]	Incidence 57k[3] Prevalence 520k[4]	Incidence 190k[6]

[1] International Agency for Research on Cancer. World Health Organization. Accessed June 28, 2024; [2 IQVIA analysis; [3]] Clarivate,; Immune Thrombocytopenic Purpura Niche & Rare Disease Landscape & Forecast. 2018 Apr
[4] Prevalence estimated based on Rigel presentation and DelveInsight, only considering China and 7MM markets
[5] Lin J et al. IDH1 and IDH2 mutation analysis in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. Ann Hematol. 2012;91(4):519-525. doi:10.1007/s00277-011-1352-7
[6] AbbVie. (2024). Acute myeloid leukemia (AML). AbbVie Science. Retrieved July 1, 2024, from https://www.abbviescience.com/cancer-types/acute-myeloid-leukemia.html

Sovleplenib:
Our First Potential Novel Medicine in Autoimmune Diseases

Potentially global best-in-class and China's first Syk inhibitor

Our 4th self-developed innovative drug

China NDA accepted for ITP with priority review

Sovleplenib

Multi-stage development programs

ESLIM-01	NDA for ITP in China accepted in Jan 2024 with priority review status
ESLIM-02	Initiated registration stage of Phase II/III study for wAIHA in China in May 2024
ITP overseas study	International Phase I ITP study enrolling
More indications	Expand to other indications

ITP market size

Large growing market with limited options

Limited treatment options

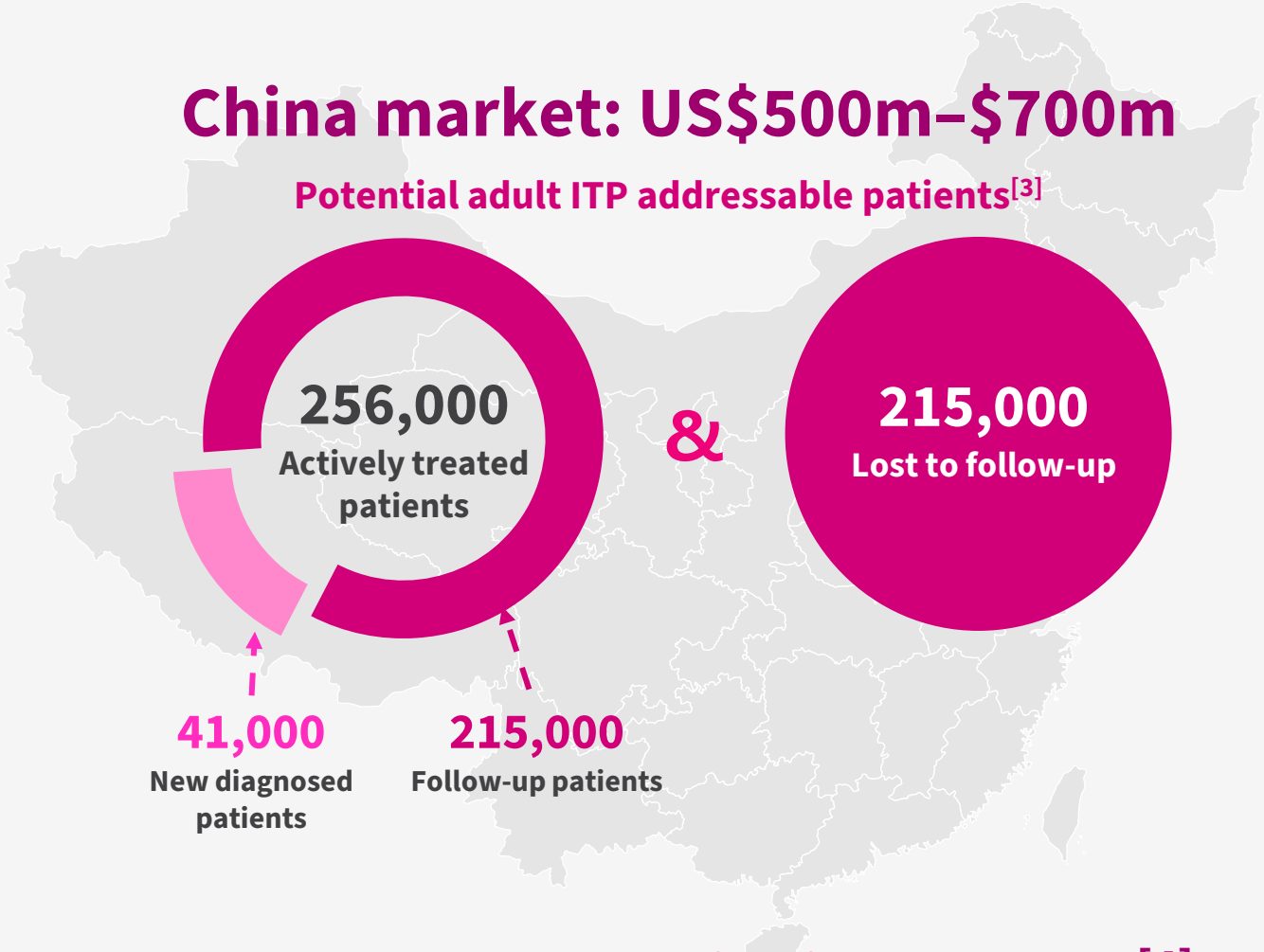
- Many patients do not respond or relapse to treatments like glucocorticoids, and TPO/TPO-RA [1]
- Fostamatinib, the only FDA approved Syk inhibitor, has a limited durable response rate of 18%

Poor quality of life

- ITP negatively effects quality of life due to fatigue, activity restrictions and anxiety [2]

China market: US$500m–$700m

Potential adult ITP addressable patients[3]



Global market: incidence 57k[4]

Prevalence 520K [5]

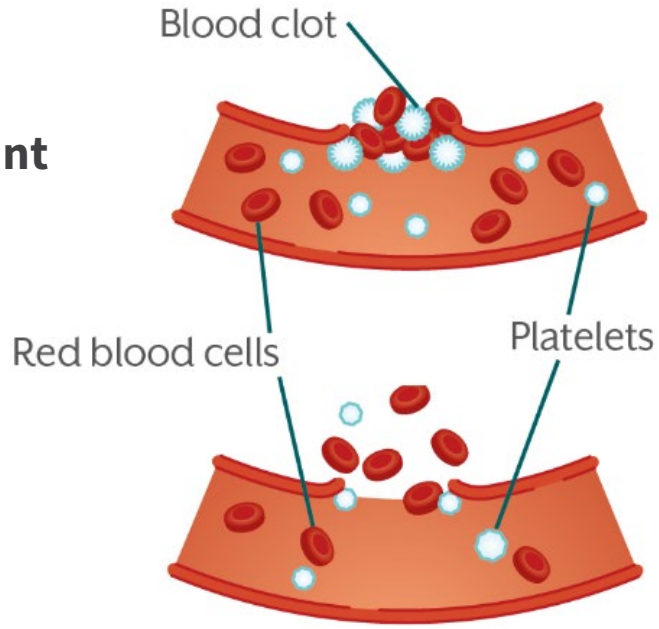
[1] Kim DS. Recent advances in treatments of adult immune thrombocytopenia. Blood Res 2022; 57: 112–19
[2] Mathias SD, Gao SK, Miller KL, et al. Impact of chronic immune thrombocytopenic purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. *Health Qual Life Outcomes* 2008; **6:** 13
[3] IQVIA analysis; [4] Clarivate,; Immune Thrombocytopenic Purpura Niche & Rare Disease Landscape & Forecast. 2018 Apr
[5] Prevalence estimated based on Rigel presentation and DelveInsight, only considering China and 7MM markets

What is immune thrombocytopenia (ITP) ?

ITP can lead to major bleeding and other complications

- An autoimmune disorder, which means that the body's immune system attacks and destroys platelets in the blood
- ITP can slow down the body's ability to make more platelets
- ITP can become chronic, which is when platelet counts are low for a long time

Normal Platelet Count



Low Platelet Count

What happens when you have low platelet counts?

- Tiny reddish-purple spots called petechiae
- Easy bruising

- Bleeding from gums or nose
- Bruising or blood-red spots in the mouth

- Very heavy or long menstrual flow
- Internal bleeding (for example, in the stomach, intestines, or brain)

Current ITP treatment paradigm

Sovleplenib: advancing ITP treatments

Initial diagnosis

Diagnosis

- Platelet count <30 x10^9/L
- +asymptomatic or minor mucocutaneous bleeding

1L treatment

- Glucocorticoid ≤ 6 weeks
- Monitor for side effects and health-related quality of life

50-70% of patients do not experience sustained response post discontinuation [2]

Subsequent treatment: 2L/3L

Based on patient preference:

- TPO/TPO-RA: eltrombopag, romiplostim
- Rituximab and splenectomy

Additional options:

- New TPO-RA: avatrombopag
- Syk inhibitor: fostamatinib

Limited options after failing 2nd line

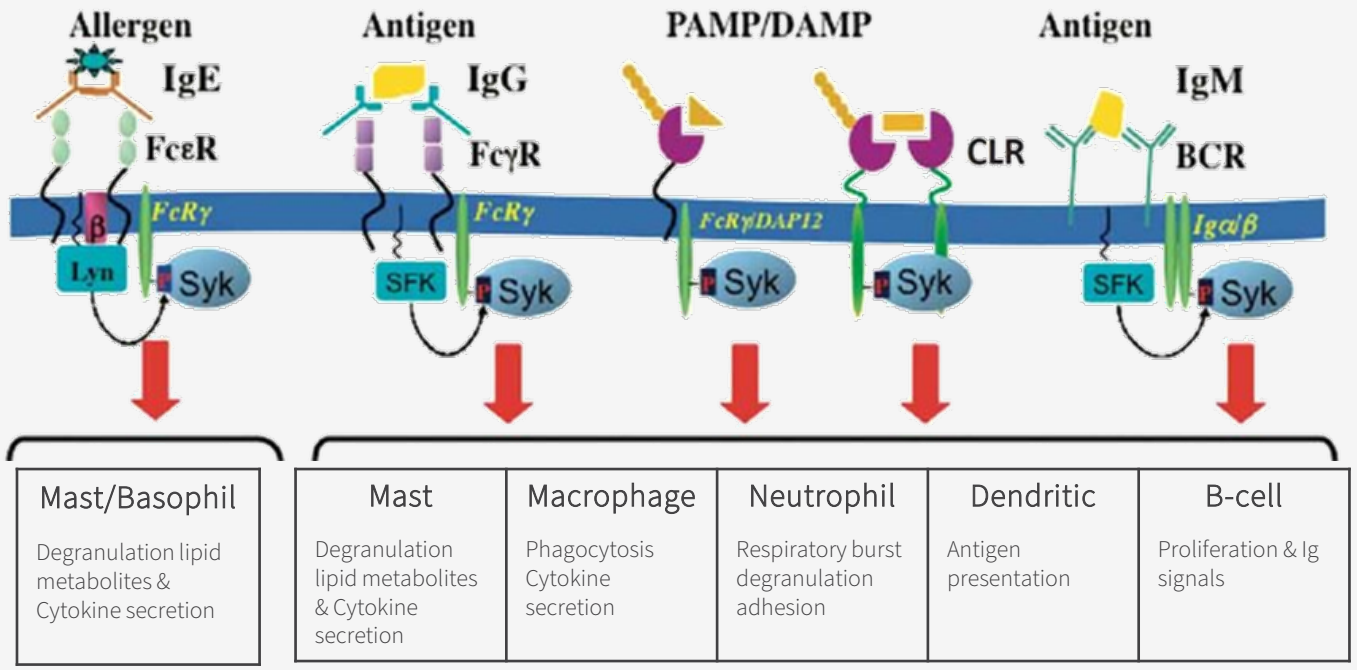
Sovleplenib provides an efficient and safety treatment option for long-term use:

- ✓ Positive ESLIM-01 Phase III results in heavily TPO/TPO-RA treated patients
- ✓ China NDA accepted in January 2024

[1] Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia [published correction appears in Blood Adv. 2020 Jan 28;4(2):252]. Blood Adv. 2019;3(23):3829-3866. doi:10.1182/bloodadvances.2019000966
[2] Cooper N, Ghanima W. Immune Thrombocytopenia. N Engl J Med. 2019;381(10):945-955. doi:10.1056/NEJMcp1810479

Spleen tyrosine kinase (Syk): a promising pathway for immunological diseases

A key signaling component in the activation and proliferation of immune cells

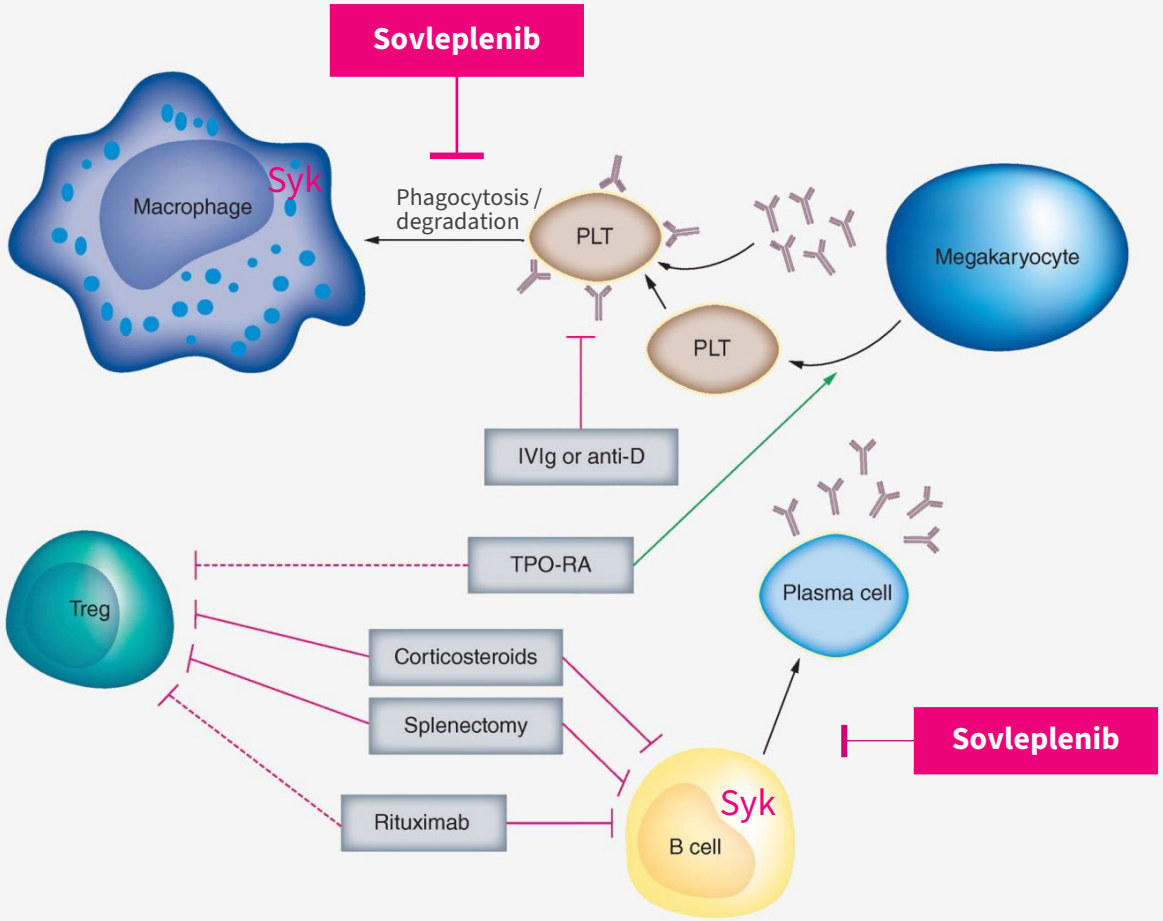


- Cytoplasmic tyrosine kinase
- Ubiquitously expressed in hematopoietic cells critical for immune system
- Key component of Fc receptor and B-cell receptor signaling, and plays a key role in activation and proliferation of macrophages, osteoclast, neutrophils and mast cells
- Platform opportunity for the treatment of autoimmune, inflammatory diseases and hematologic malignancies
- Strong clinical validation in ITP, potential expansion to RA, SLE and NHL

Nichola C. et al. Recent advances in understanding spleen tyrosine kinase (SYK) in human biology and disease, with a focus on fostamatinib. Platelets, 34:1, 2131751, DOI: 10.1080/09537104.2022.2131751

Immune thrombocytopenia (ITP)

Unmet medical needs to be addressed with next-gen Syk inhibitor Sovleplenib (HMPL-523)



Adapted from Newland A, et al. Immunotherapy (2018) 10(1), 9–25

Tackling Root Causes

Current treatments target Treg, magakaryocyte and B cells

- ✓ Long-term efficacy tapers off
- ✓ All patients become refractory and will run out of options

Syk is a validated target for ITP

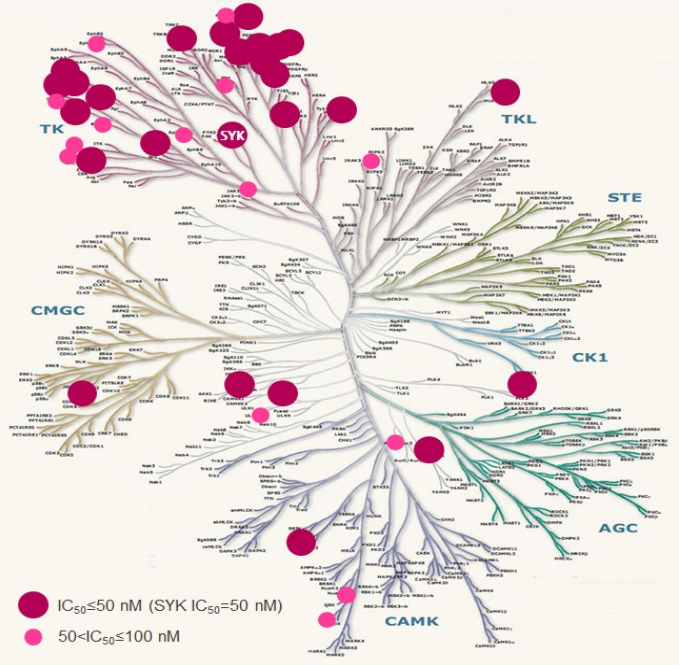
- ✓ Syk offers a different mechanism by targeting both B cells & macrophages
- ✓ Fostamatinib approved in the U.S., Europe and Japan, moderate efficacy, dose limited by tox

Sovleplenib a highly selective Syk inhibitor

Sovleplenib demonstrates higher kinase selectivity to fostamatinib (the only one approved Syk inhibitor in the U.S.)

First-gen

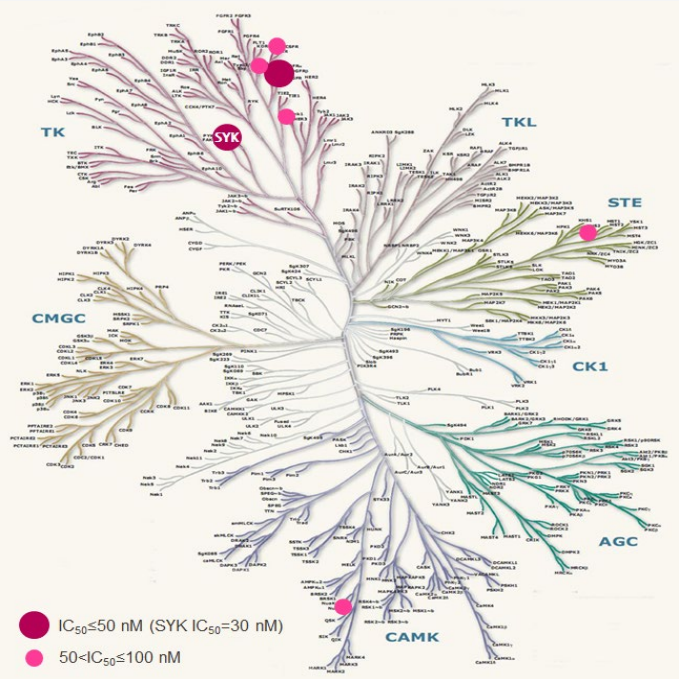
Fostamatinib



Source: Pharmacol Res Perspect. 2015;3(5):e00175. The IC_{50} against 139 kinases tested by Millipore (Now Eurofins) was reported

Next-gen

Sovleplenib



Source: Data on file, HUTCHMED. 287 Kinases were included in the selectivity study which was conducted by Millipore (Now Eurofins)

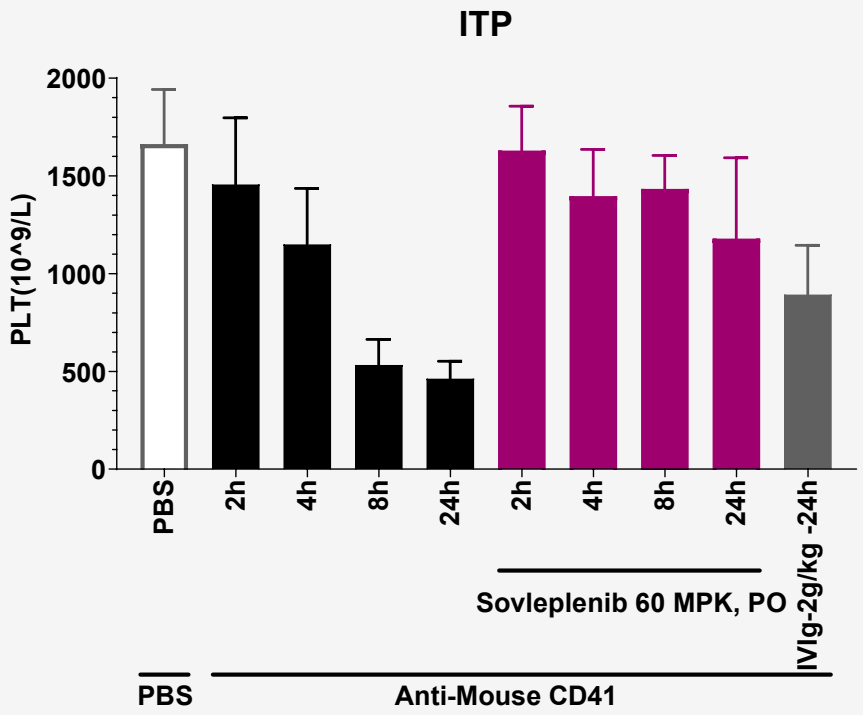
Kinase inhibition	R406 IC_{50} (μM)	Sovleplenib IC_{50} (μM)
Syk	0.054 (1X)	0.025 (1X)
Flt3	0.009 (0.2X)	0.063 (2.5X)
KDR	0.030 (0.6X)	1211 (40X)#
Lyn	0.160 (3.0X)	0.921 (36X)
FGFR2	0.057 (1.1X)	3.214 (129X)
AUR A*	0.219 (4.1X)	3.969 (159X)
Other >200 kinases**	n.a.	<70% inhibition at 3 μM

>100 fold in cell based assays
* Determined at HUTCHMED using z-lyte assay (Invitrogen) or FP (Bellbrook)
** Determined with ^{32}P-ATP incorporation assay by Eurofins

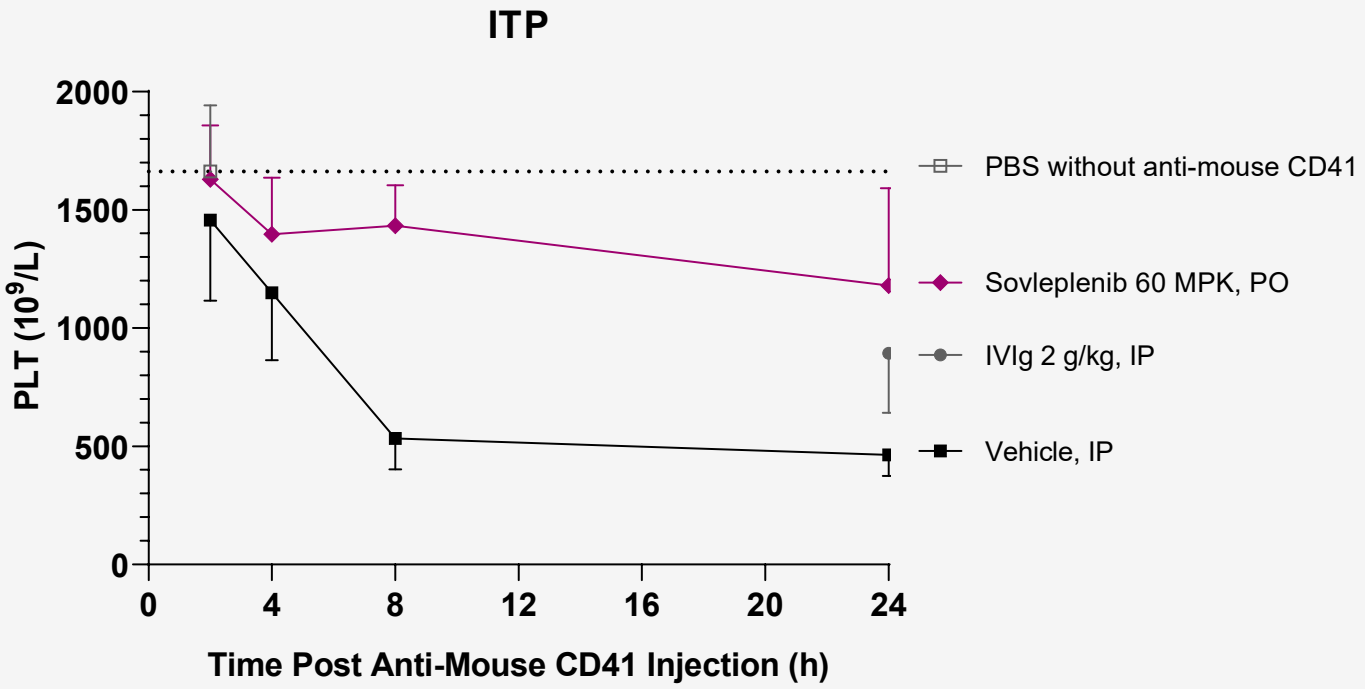
Sovleplenib inhibits only 1 kinase at a lower IC_{50} than Syk, while fostamatinib inhibits at least 24 kinases at an IC_{50} lower than its Syk IC_{50}

Sovleplenib spared off-target activities to improve clinical safety, i.e. KDR activity that leads to hypertension

Sovleplenib *in vivo* efficacy in mouse ITP model



IVIG, intravenous immune globulin,
is a biologic therapeutic for the treatment of ITP



Sovleplenib treatment maintains platelet increase close to normal throughout 24 hours

Source: Yu C., Preclinical Pharmacology Characterization of Sovleplenib (HMPL-523), an Orally Available Syk Inhibitor. *The Journal Of Pharmacology and Experimental Therapeutics* 388:156–170, January 2024

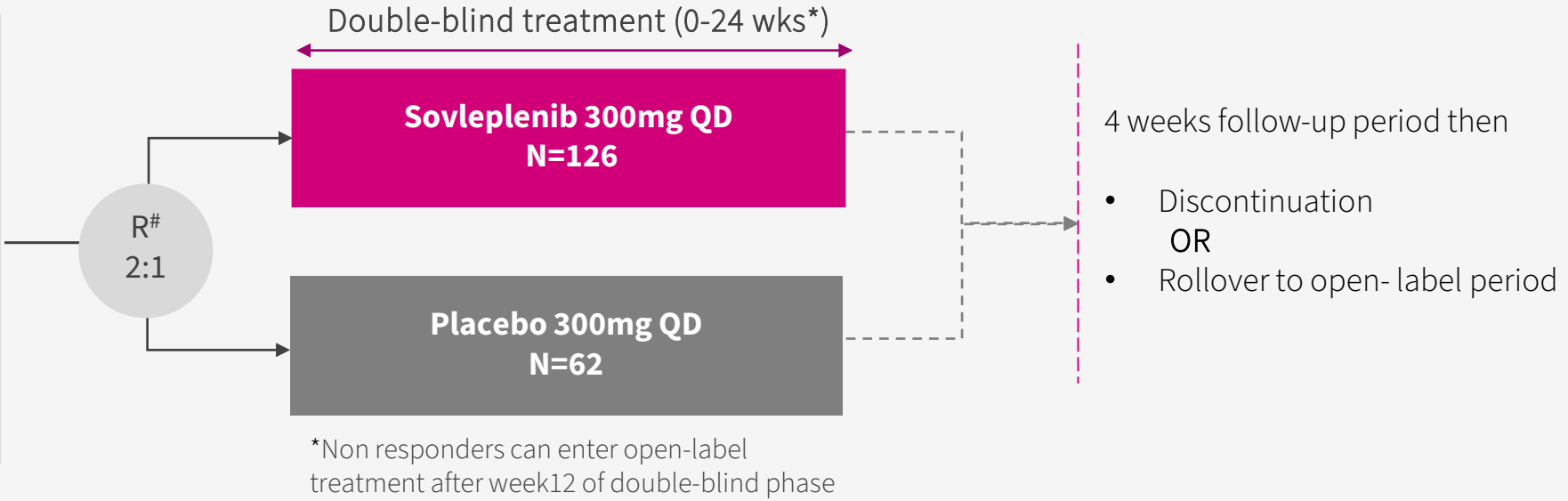
Sovleplenib Phase III ESLIM-01 Study

ESLIM-01 study design

- Randomized, multicenter, double-blind, placebo-controlled Phase III study conducted at 34 sites in China
- Statistical hypothesis: 90% power to test 16% difference (18% vs. 2%)

Patient population:

- Adult primary ITP >12-mo
- Received ≥ 1 prior treatment
- Allowed one maintain concomitant ITP therapy



*Non responders can enter open-label treatment after week12 of double-blind phase

Stratification factor:

- ✓ Baseline platelet counts (15×10^9/L)
- ✓ Concomitant anti-ITP agents
- ✓ Prior splenectomy

Primary endpoint: Durable response rate (platelet counts ≥50×10^9/L at ≥4 of the 6 visits during 14–24 weeks, not impacted by rescue treatment)

Secondary endpoints: Overall response rate, time to response, the reduction of rescue therapy and concomitant anti-ITP agents at baseline, WHO bleeding score, Quality of life based on SF-36

Baseline demographic and characteristics

- All stratification factors were well balanced between the two groups
- Sovleplenib vs. Placebo: imbalance observed in ECOG PS of 1 (21% vs. 13%), TPO/TPO-RA treated (75% vs. 65%), and WHO bleeding scores of 1 (69% vs. 53%)

ITT Set
Enrollment: Sep 2021 to Dec 2022
Data cut-off: 14 Jul 2023

Demographic and baseline characteristics	Sovleplenib, N=126 n (%)	Placebo, N=62 n (%)
Age (years), Median (min, max)	43.5 (18, 72)	42.0 (18, 69)
Female, n (%)	87 (69.0)	37 (60)
Baseline ECOG PS, n (%)		
0	99 (79)	54 (87)
1	27 (21)	8 (13)
Time since first reduction in platelet count to randomization(years), Mean (SD)	7·6 (1.1–36.1)	7·8 (1.1–41.2)
≥ 3 years, n (%)	95 (75)	51 (82)
Baseline Platelet Count, n (%), $<15\times10^9$/L	75 (60)	37 (60)
Lines of prior anti-ITP therapies, Median (min, max)	4 (1, 10)	4 (1, 9)
Previous TPO and/or TPO-RA, n (%)	94 (75)	40 (65)
Prior Splenectomy, n (%)	5 (4.0)	3 (5)
Prior anti-CD20 antibody, n (%)	20 (16)	7(11)
Concomitant Anti-ITP agents at Baseline, n (%)	41 (33)	20 (32)
Baseline WHO bleeding scale scores, n (%)		
0/1	39 (31)/87 (69)	29 (47)/33 (53)

The primary endpoint and platelet related secondary endpoints

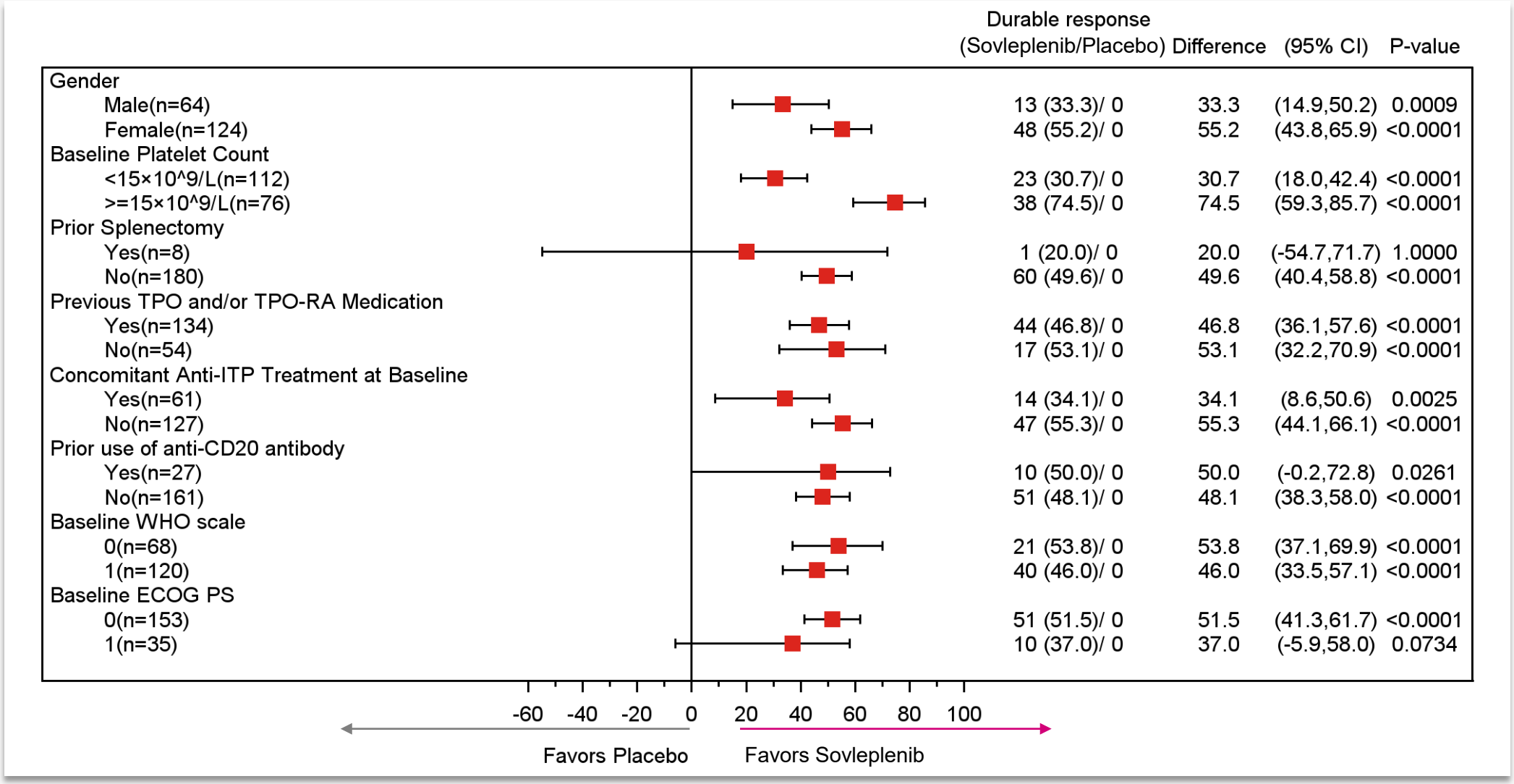
- In the ITT set, Sovleplenib significantly improved durable response rate compared to placebo (48.4% vs 0, p-value < 0.0001)
- The results of all sensitivity analyses were consistent with the primary analysis
- A significantly higher overall response rate was observed with sovleplenib compared with placebo

Endpoint	Definition (analysis set)	Sovleplenib (N=126)	Placebo (N=62)	P value*
Durable response, n (%)	Platelet counts ≥50×10^9/L at ≥ 4 of the 6 visits during 14–24 weeks, not impacted by rescue treatment (126 vs 62)	61 (48.4)	0	<0.0001
Overall response, n (%)	At least one platelet count ≥50×10^9/L , not impacted by rescue treatment in 0–24 weeks (126 vs 62)	89 (71)	10 (16)	<0.0001
	Patients with two consecutive platelet count ≥30×10^9/L and double from the baseline in 0–24 weeks (126 vs 62)	92 (73)	4 (6)	<0.0001
	Platelet count ≥30×10^9/L and increased ≥20×10^9/L from baseline in 0–24 weeks ----for patients with a platelet count of <15×10^9/L at baseline (75 vs 37)	56 (75)	8 (22)	<0.0001

* P value based on CMH test, adjusted for randomization stratification factors.
# Sensitivity Analysis 1 _Stratification Factors from CRF; Sensitivity Analysis 2 _ Per protocol Set

Subgroups of primary endpoint

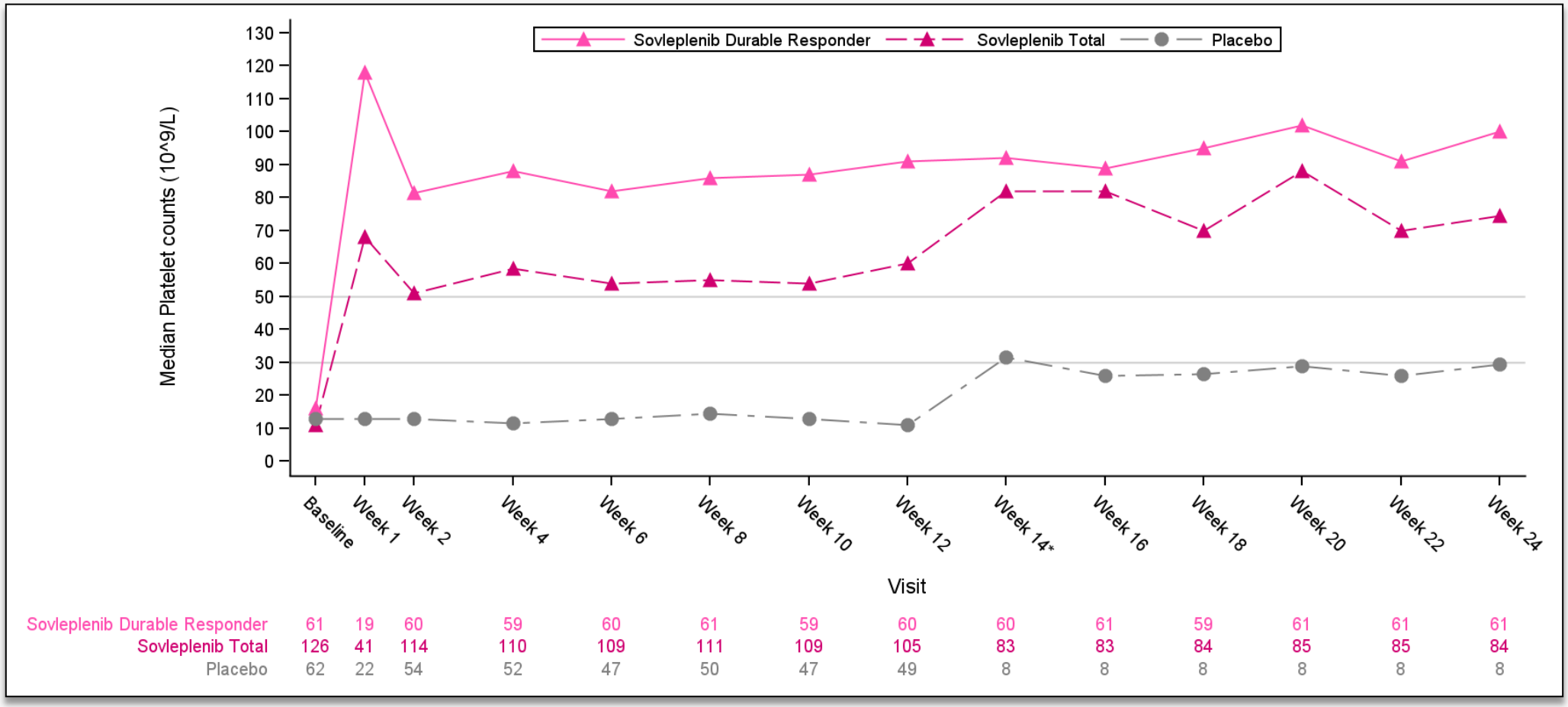
- Consistent benefit of sovleplenib demonstrated across all subgroups



P-value based on Fisher exact test

Efficacy: platelet counts over time

- Fast onset with 8 days to first platelet count ≥ 50 × 10^9/L
- Among the durable responders, 51 of 61 (84%) responded at least 5 of 6 visits and 39 of 61 (64%) at all 6 visits within the week 14-24
- Median duration of response in overall responders were 17.9 weeks in sovleplenib group versus 2.6 weeks in placebo group



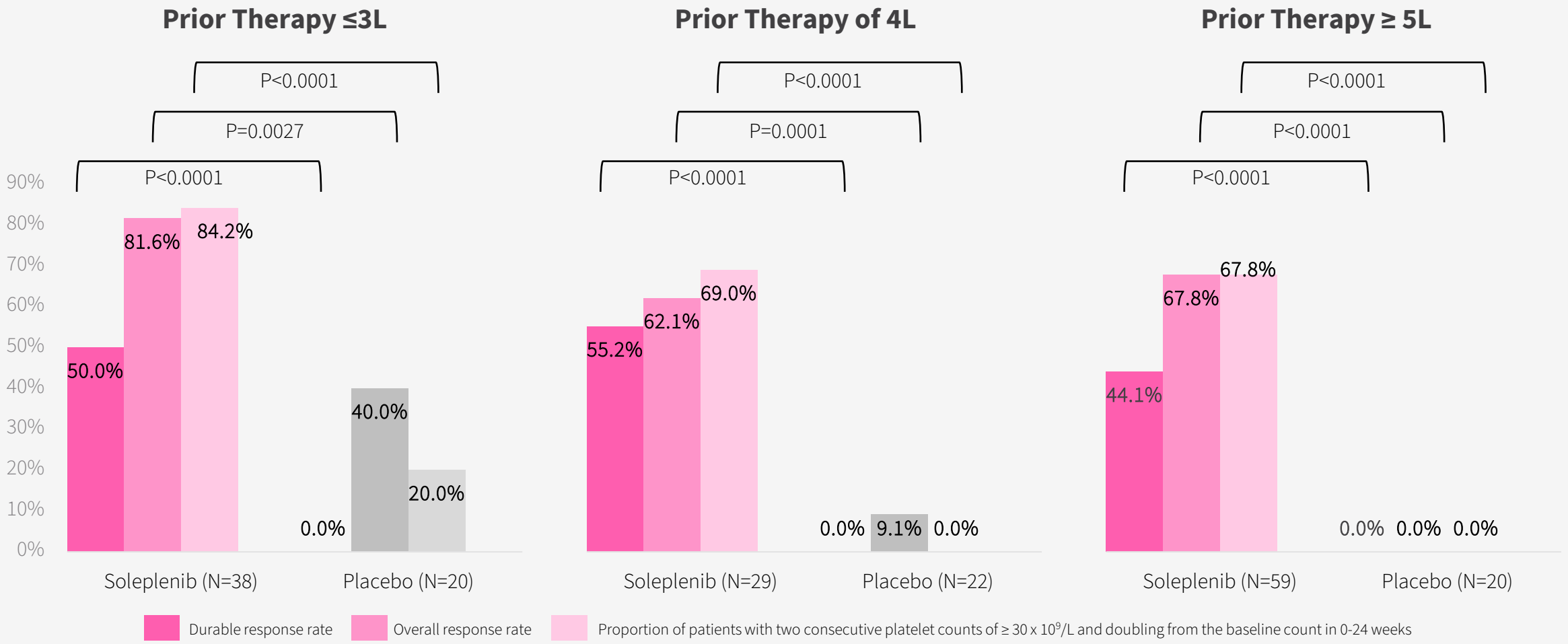
	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14*	Week 16	Week 18	Week 20	Week 22	Week 24
Sovleplenib Durable Responder	61	19	60	59	60	61	59	60	60	61	59	61	61	61
Sovleplenib Total	126	41	114	110	109	111	109	105	83	83	84	85	85	84
Placebo	62	22	54	52	47	50	47	49	8	8	8	8	8	8

*Most of the non-responders ended the double-blind treatment at week 12 due to lack of efficacy.

Consistent Efficacies in patients who had received multiple prior ITP therapies

HUTCHMED

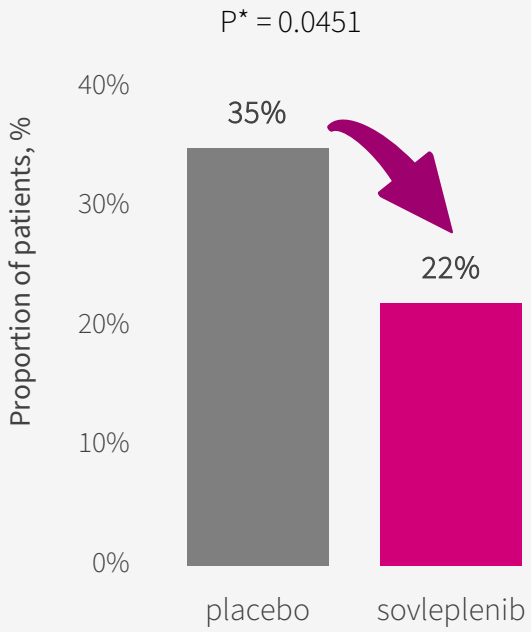
Bar Chart of Subgroup Analysis of Main Efficacy Endpoints in Patients with Prior Therapy Lines



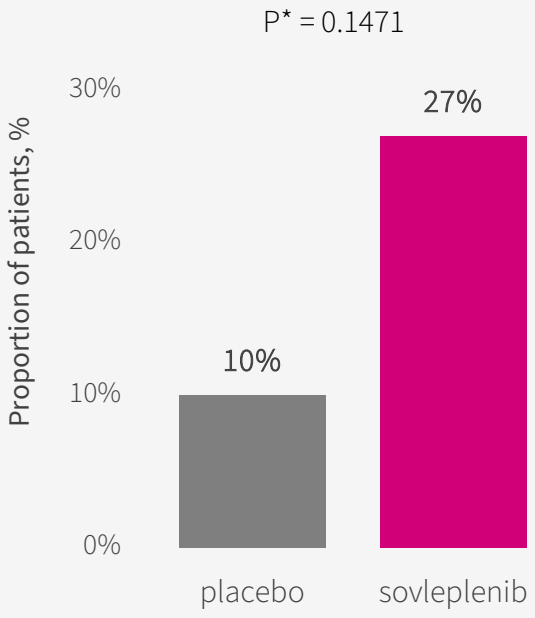
Efficacy: non-platelet related secondary endpoints

- Significantly reduced rescue medication use
- Reduced the baseline concomitant treatments
- Significantly reduced the overall bleeding risk by WHO bleeding score

Rescue therapy

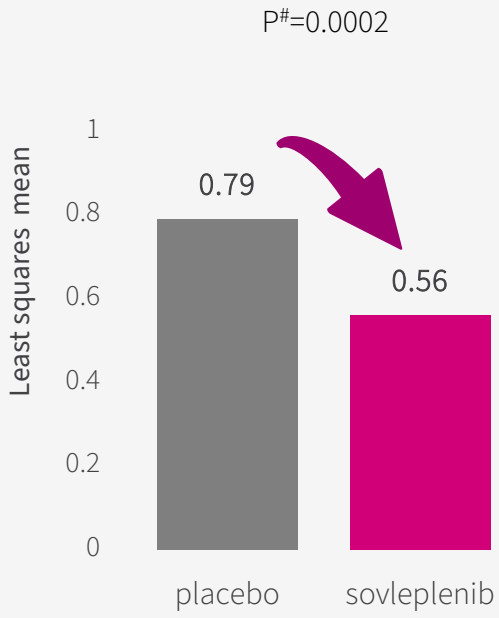


Dose reduction/discontinuation rate of baseline concomitant treatment



2 patients discontinued by themselves before the 1st dose

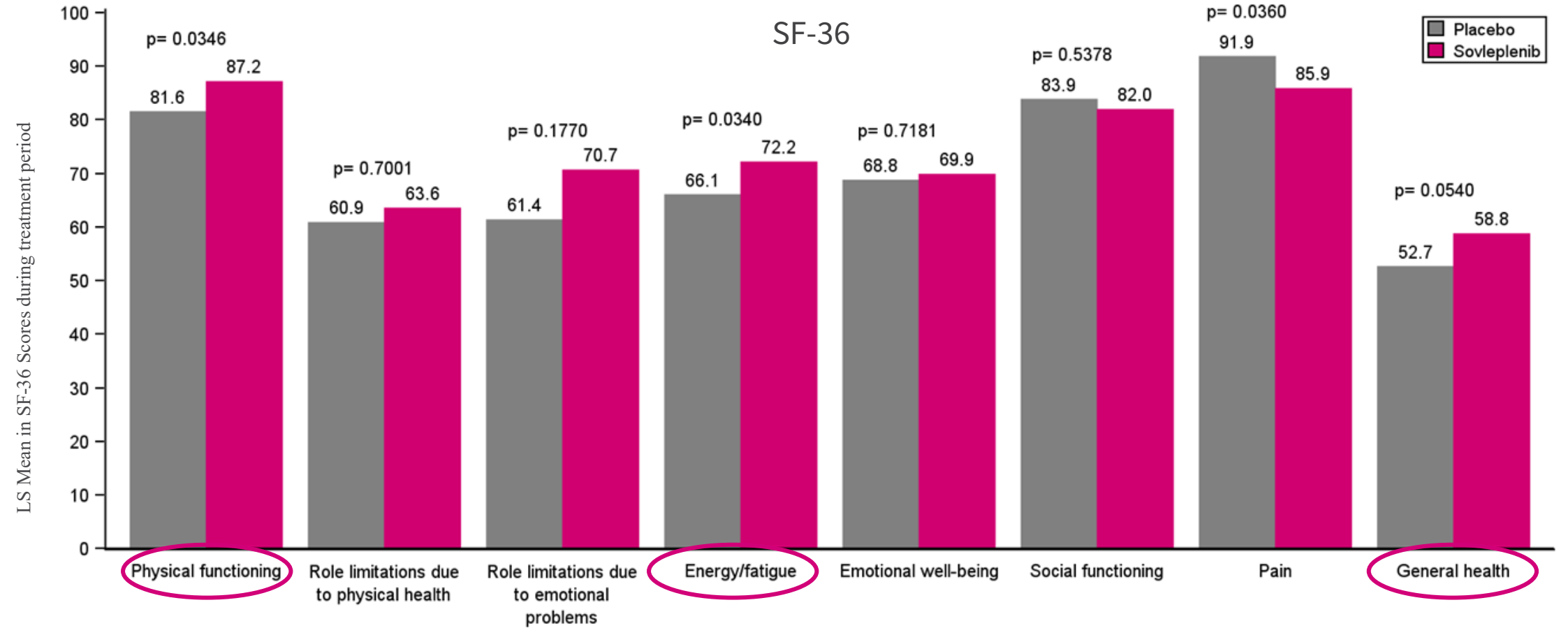
WHO bleeding score



*p-value based on CMH test
#p-value based on ANCOVA model

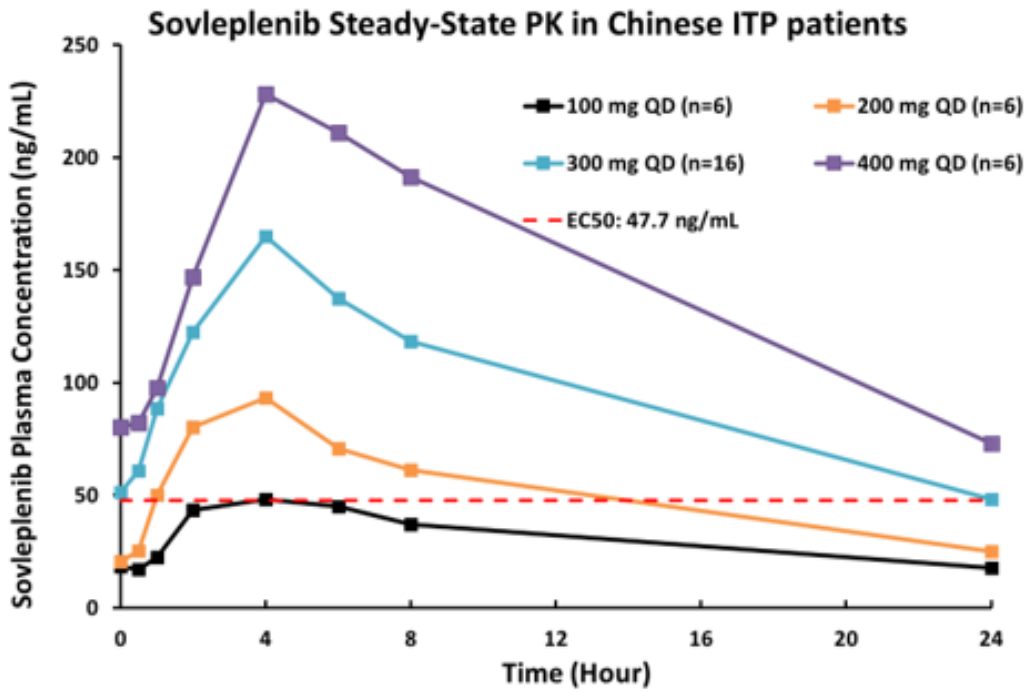
Quality of life

Compared with placebo, Sovleplenib showed an improvement on QoL outcome by SF-36, particularly in physical functioning, energy/fatigue and general health



P-value was based on repeated-measures model

Sustained PK exposure leads to durable target inhibition



- Internal PKPD analysis shows that an sufficient exposure is required for efficacy to maintain C_{trough} above EC_{50} of 47.7 ng/mL
- Sovleplenib 300 mg QD could maintain the drug concentration above EC_{50} throughout 24 hours of the dosing interval
- Fostamatinib 100 mg BID could maintain the drug concentration above EC_{50} for less than 12 hours
- More durable target inhibition by sovleplenib results in a higher clinical response in ITP patients

[1] Lancet Haematol. 2023 Jun;10(6):e406-e418. [2]. Page 69, NDA 209299

Drug exposure and safety summary

- Similar compliance in two groups
- Significant shorter exposure of the placebo group due to lack of efficacy exposure imbalance between the two groups (12.1 weeks vs. 24.1 weeks)
- Similar incidence of TEAEs of any grade, ≥grade 3, and SAE; no fatal cases had occurred

	Sovleplenib N=126	Placebo N=62
Duration of Exposure		
Median (min, max), weeks	24.1 (3.0, 25.9)	12.1 (2.6, 24.4)
≥ 24 weeks, n (%)	86 (68)	8 (13)
Actual Duration of Exposure (weeks)		
Median (min, max)	23.9 (3.0, 25.9)	12.1 (2.6, 24.4)
Compliance (%)		
Mean (SD)	97 (8.9)	99 (2.5)

	Sovleplenib N=126, n (%)	Placebo N=62, n (%)
At least one TEAE	125 (99)	53 (85)
Grade 3	19 (15)	7 (11)
Grade 4	13 (10)	8 (13)
Grade 5	0	0
TEAE having higher toxicity grades (≥3)	32 (25)	15 (24)
Serious TEAE	26 (21)	11 (18)
TEAE leading to study medication discontinuation	4 (3)*	0
TEAE leading to study medication interruption or reduction	15 (12)	3 (5)

TEAE: treatment emergent adverse event
*Four TEAEs led to dose discontinuation: Gr.3 transaminase increased, Gr.3 haemorrhage , Gr.1 weight increased, Gr.1 blood creatinine increased, once respectively.

The most common TEAE (by PT ≥15%)

- The most common TEAEs of sovleplenib included upper respiratory tract infections, COVID-19 infection, and Blood lactate dehydrogenase increased, majority with Grade 1-2
- No thromboembolic events occurred
- Low GI toxicity (nausea 1.6% vs 3.2%, vomit 1.6% vs 1.6%, diarrhea 1.6% vs 0%)

PT terms	Sovleplenib (N=126) n (%)			Placebo (N=62) n (%)		
	All grade	Grade 3	Grade 4	All grade	Grade 3	Grade 4
Upper respiratory tract infections	36 (29)	2 (2)	0	6 (10)	0	0
COVID-19 infection	30 (24)	1 (1)	0	8 (13)	0	0
Blood lactate dehydrogenase increased	30 (24)	0	0	4 (6)	0	0
Haemorrhage subcutaneous	24 (19)	0	0	8 (13)	0	0
Hyperuricaemia	23 (18)	0	0	3 (5)	0	0
Hypokalaemia	23 (18)	0	1 (1)	3 (5)	0	0
Anaemia	23 (18)	2 (2)	1 (1)	8 (13)	4 (6)	0
Rash	22 (17)	1 (1)	0	1 (2)	0	0
Aspartate aminotransferase increased	20 (16)	0	0	1 (2)	0	0
Occult blood positive	20 (16)	0	0	9 (15)	0	0
Alanine aminotransferase increased	19 (15)	3 (2)	0	1 (2)	0	0
Neutrophil count decreased	19 (15)	4 (3)	0	0	0	0

This study was conducted during the COVID-19 pandemic period, and most of the patients in the placebo group have remarkable shorter duration of treatment due to early stop because of lacking of efficacy at week 12

Key takeaways

ESLIM-01 successfully met the primary endpoint and all secondary endpoints, even in heavily treated primary ITP patients

Sovleplenib vs. placebo:

- ✓ Significant and meaningful improvement in durable response: 48% vs 0, $p < 0.0001$
- ✓ Consistent efficacy in previously treated TPO/TPO-RA pts (75% in ESLIM-01)
- ✓ Fast onset with a median of 8 days from baseline to first platelet count ≥50 × 10^9/L
- ✓ Significant improvement of WHO bleeding score and QoL outcome(including fatigue)
- ✓ Sovleplenib is well-tolerated with low GI toxicities, hypertension and no thrombotic events

Sovleplenib is an efficacious and tolerable treatment option for patients with chronic primary ITP

Emerging agents aim to address underlying disease

	Fostamatinib	Efgartigimod	Rilzabrutinib	Cevidoplenib	Lanalumab
Target	Syk	FcRn	BTK	Syk	BAFF
Dosage & administration	Oral 100mg twice daily	IV (10mg/kg) or subcutaneous (1000mg) weekly or every 2 weeks	Oral 400mg twice daily	Oral 400mg twice daily	IV (3mg/kg or 9mg/kg) Once every 4 weeks
Durable response	18% vs. 2%	22% vs. 5%	31%	27%[1]	

Durable response: PLT≥50×10^9/L in minimal 4 of 6 last scheduled visits
[1] secondary efficacy results

Primary chronic ITP landscape

Treatment options in China and outside of China

Sales revenue of TPO, TPO-RA and SYK inhibitor[1]				
Agent	**Available in China?**	**Available ex-China?**	**Approved indications**	**2023 Revenues for all indications (US$)**[2]
TPO-RA treatment increases platelet production				
PROMACTA® (eltrombopag)[3]	✓	✓	ITP + SAA	$2.3 billion
NPLATE® (romiplostim)[3]	✓	✓	ITP + radiation sickness	$1.5 billion
TPIAO® [2]	✓	✗	ITP + CIT	US$580 million
DOPTELET® (avatrombopag)[3]	✓	✓	ITP + CLD	$282 million / $127 million from China distributor Fosun
Hetrombopag[2]	✓	✗	ITP + SAA	Not disclosed
Treatments to decrease platelet destruction				
RITUXAN® (rituximab)[1]	✓	✓	NHL, CLL, RA, GPA, MPA, PV	Not approved for ITP
TAVALISSE® (fostamatinib)[3]	Hainan Pilot Zone	✓	ITP only	$94 million

[1] Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv*. 2019;3(22):3780-3817. doi:10.1182/bloodadvances.2019000812; [2] company reports; [3] USPI.

Limitations of current treatments

Despite the availability of TPO/TPO-RA, significant unmet needs remain for more effective and safer ITP treatments

Adverse effects of current treatments

Eltrombopag

- **Black box:** hepatic decompensation and hepatotoxicity risk
- Drug interaction: >2 hours before or 4 hours after polyvalent cations
- Transaminitis and cataracts are potential side effects[1]

Avatrombopag

- Risk of blood clots[2]
- Headache is the most frequent adverse effect[1]

Romiplostim

- Risk of bone marrow reticulin fiber formation[2]
- Exaggerated pharmacologic effects leading to wide swings in platelet counts and difficulties in dosage adjustment[2]
- Pain after administration (extremity, abdominal, or shoulder pain)[1]

Fostamatinib

- Hypertension (28%), diarrhoea (31%) and nausea (19%) were frequently reported[3]

[1] Ghanima W. et al. Thrombopoietin receptor agonists: ten years later. Haematologica. 2019;104(6):1112–23
[2] Mei H. et al. A multicenter, randomized phase III trial of hetrombopag: a novel thrombopoietin receptor agonist for the treatment of immune thrombocytopenia. Journal of Hematology & Oncology. 2021; 14 (37). doi.org/10.1186/s13045-021-01047-9
[3] Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. Am J Hematol 2018; 93: 921–30

SYK inhibitor:
new option for patients with an increased thrombotic risk

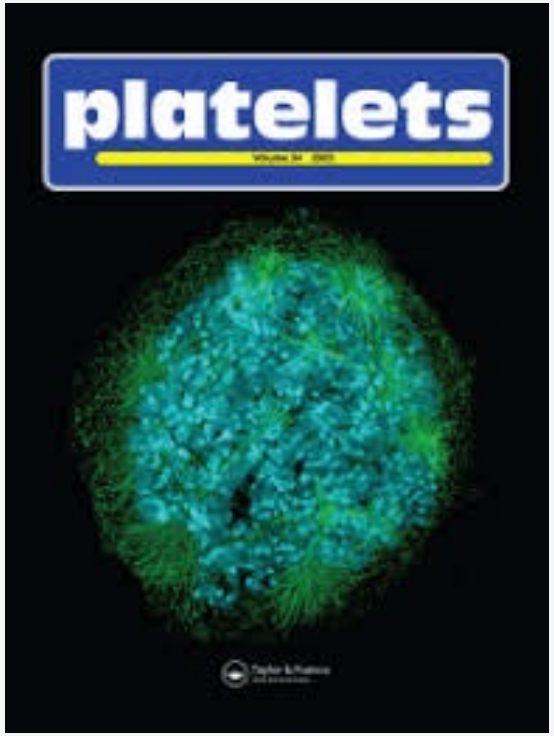
SYK inhibitor may be a drug to consider for patients with an increased thrombotic risk, such as those with coronary artery diseases, diabetes, advanced age or obesity.[1]

Expert opinion: SYK pathways and the future

SYK is an important regulatory molecule of signal transduction pathways involved in the pathogenesis of autoimmune diseases such as ITP, and the SYK-signaling pathway has emerged as a potential target for the treatment of such diseases.

Recent advances in understanding spleen tyrosine kinase (SYK) in human biology and disease, with a focus on fostamatinib

Nichola Cooper, Waleed Ghanima, Quentin A Hill, Phillip LR Nicolson, Vadim Markovtsov & Craig Kessler



[1] Nichola C. et al. Recent advances in understanding spleen tyrosine kinase (SYK) in human biology and disease, with a focus on fostamatinib. Platelets, 34:1, 2131751, DOI: 10.1080/09537104.2022.2131751

Sovleplenib safety observation

Sovleplenib showed:

- lower hypertension, lower GI toxicities (diarrhea, and nausea)
- Less AEs leading to drug discontinued

	Sovleplenib (First 12 weeks)		Fostamatinib[1] (First 12 weeks)	
AESIs[2]	Sovleplenib N=126, n (%)	placebo N=62, n (%)	Fostamatinib N=102, n (%)	placebo N=48, n (%)
Diarrhoea	2 (1.6)	0	32 (31.4)	7 (14.6)
Nausea	2 (1.6)	2 (3.2)	19 (18.6)	4 (8.3)
Hypertension	15 (11.9)	4 (6.5)	28 (27.5)	6 (12.5)
ALT/AST elevation	22 (17.5)	2 (3.2)	14 (13.7)	0
Neutropenia	18 (14.3)	1 (1.6)	7 (6.9)	0
Infection	63 (50.0)	27 (43.5)	31 (30.4)	10 (20.8)
AEs leading to study drug discontinued	4 (3.2)	0	10 (9.8)	4 (8.3)
AEs leading to study drug modification	12 (9.5)	3 (4.8)	Interruptions: (18) Reduction: (9)	(10) (2)

[1] FDA multi-discipline review of fostamatinib, table 70 at page 158 and table 85 at page 173
[2] All AESIs included multiple PTs

No thrombotic events were observed in ESLIM-01 study

- Over target platelet count increased and thromboembolism are potential risks of TPO-RA for ITP. The incidence of thrombosis in ITP treated with avatrombopag is as high as 7%[1]
- The ITP patient population is relatively young, and once thrombosis occurs, it will have a serious impact on the patient 's quality of life

TEAE, n(%)	Sovleplenib ELISM-01 (n=126)	Fostamatinib FIT1 & FIT2 (n=102)[2]	Herombopag China pivotal study (n=339)[3]	Eltrombopag China label (n=466)	Romiplostim China NDA review (n=653)	Avatrombopag US label
Platelet count increased over ULN	1(0.8%)	Not reported	39 (11.5%)	/	Reported as normal ADR	Not reported
Thromboembolic events	0	Not reported	1 case of acute myocardial infarction 1 case of subclavian vein embolism	17 (3.8%)	39 (6.0%)	9 (7%)

[1] DOPTELET® (avatrombopag) FDA label
[2]James Bussel, et al. Am J Hematol. 2018;93:921–930.
[3]Mei et al. J Hematol Oncol (2021) 14:37.

The Lancet Hematology presentation

Efficacy and safety of sovleplenib (HMPL-523) in adult patients with chronic primary immune thrombocytopenia in China (ESLIM-01): a randomised, double-blind, placebo-controlled, phase 3 study

Yu Hu, Xiaofan Liu*, Hu Zhou*, Shujie Wang, Ruibin Huang, Yi Wang, Xin Du, Jing Sun, Zeping Zhou, Zhenyu Yan, Wenming Chen, Wei Wang, Qingchi Liu, Qingshu Zeng, Yuping Gong, Jie Yin, Xuliang Shen, Baodong Ye, Yun Chen, Yajing Xu, Huiping Sun, Yunfeng Cheng, Zhuogang Liu, Chunling Wang, Guolin Yuan, Xiaohui Zhang, Xin Li, Peng Cheng, Xinhong Guo, Zhongxing Jiang, Feng'e Yang, Linhua Yang, Chengwei Luo, Taiwu Xiao, Sisi Fu, Hongyan Yin, Xiaojun Guo, Qian Xu, Songhua Fan, Michael M Shi, Weiguo Su, Heng Mei†, Renchi Yang†*

Summary

Background Sovleplenib, a novel spleen tyrosine kinase (SYK) inhibitor, showed promising safety and activity in patients with primary immune thrombocytopenia in a phase 1b/2 trial. We aimed to evaluate the efficacy and safety of sovleplenib in patients with chronic primary immune thrombocytopenia.

Lancet Haematol 2024
Published Online
June 14, 2024

THE LANCET Haematology

First online: June 14, 2024, at 23:30 UK time

Preliminary marketing strategy

Meet diverse patient needs and treatment scenarios

1 **Capture** previously treated TPO/TPO-RA patients, ensuring continuity of care and improved efficacy

ESLIM-01	**Robust efficacy in 75% heavily pre-treated patients**

2 **Address** the needs of patients with an increased thrombotic risk, such as those with coronary artery diseases, diabetes, advanced age, or obesity

ESLIM-01	**No thrombotic events were observed**

3 **Target** the 2nd line treatment market after glucocorticoids, especially for patients who:

- seek long-term stable platelets
- focus on quality of life and don't want to comprise their lifestyle

ESLIM-01	**Improvement in physical functioning and fatigue**

4 **Employ** a combination therapy strategy together with glucocorticoids

ESLIM-01	**32% concomitant anti-ITP treatment**

International ITP development

- Phase Ib study (U.S., EU and Australia): dose escalation & dose optimization
- ClinicalTrials.gov Identifier: NCT06291415
- Open to enrollment

Potential future development in

- 2L+ ITP post-TPO-RA or TPO-RA naïve
- 1L ITP patients who are not candidates for glucocorticoids treatment (elderly, diabetic, etc)
- Combination with SOC in earlier line ITP
- Secondary ITP

Sovleplenib for Warm Autoimmune Hemolytic Anemia (wAIHA)

No disease-targeted therapies approved

wAIHA demographics

No disease-targeted therapies approved, despite the unmet medical need that exists for these patients

AIHA Incidence:
0.8-3.0/100,000[1]

AIHA Prevalence:
9.5-17/100,000[2] [3]

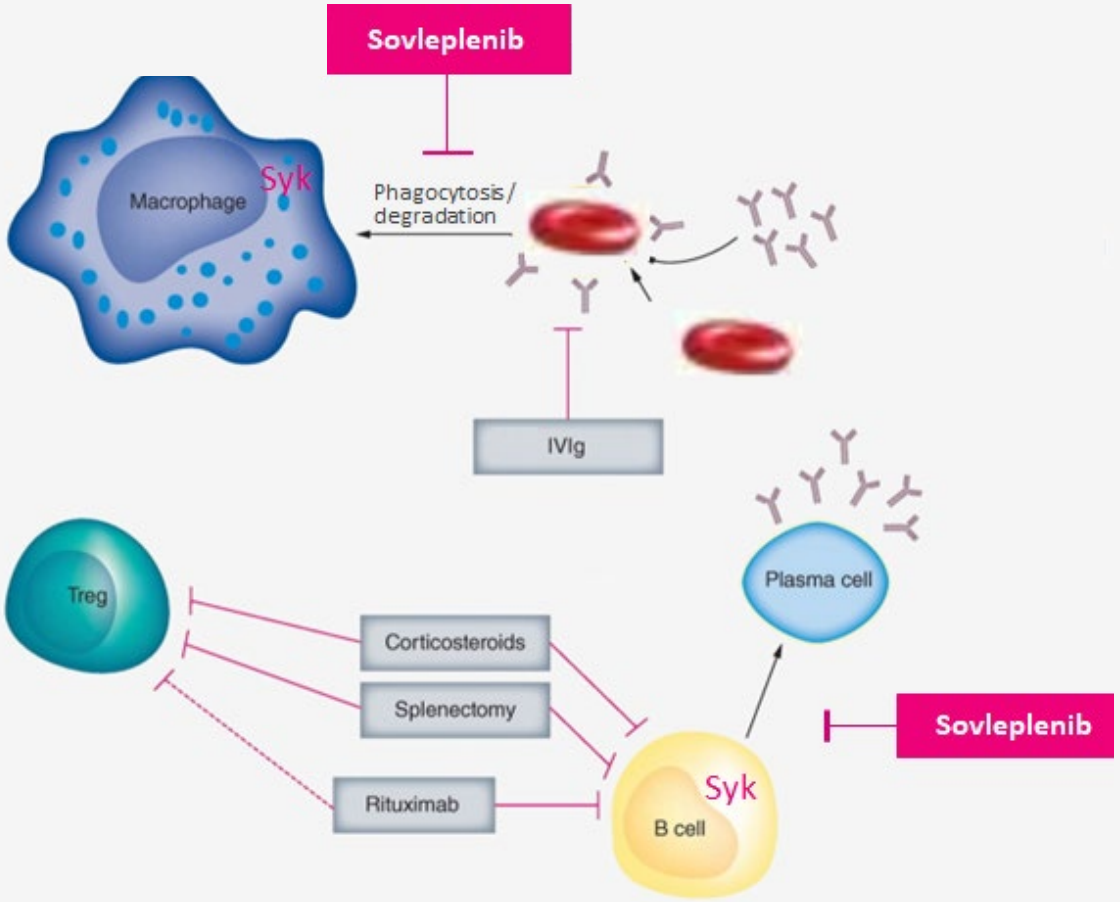
wAIHA represents
75-80% of AIHA case[4]

Death rate: 8% - 11%[5]

[1] Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. J Autoimmun. 2007; 29 (1):1-9. doi: 10.1016/j.jaut.2007.05.002.
[2] Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: new insights based on a single-center experience with 60 patients. Am J Hematol. 2014; 89 (9):E150-5. doi: 10.1002/ajh.23767.
[3] Hansen D.L., Möller S., Andersen K., Gaist D., Frederiksen H. Increasing Incidence and Prevalence of Acquired Hemolytic Anemias in Denmark, 1980–2016. Clin. Epidemiol. 2020;12:497–508. doi: 10.2147/CLEP.S250250
[4] Gehrs BC, Friedberg RC. Autoimmune haemolytic anemia. Am J Hematol. 2002; 69:258–271. doi: 10.1002/ajh.10062.
[5] Cotran Ramzi S, Kumar Vinay, Fausto Nelson, Nelso Fausto, Robbins Stanley L, Abbas Abul K. Robbins and Cotran pathologic basis of disease. St. Louis, Mo: Elsevier Saunders; 2005. p. 637.

What is warm autoimmune hemolytic anemia (wAIHA)?

No FDA-approved therapy for wAIHA yet, significant unmet medical needs exist



wAIHA is an autoimmune disorder characterized by increased destruction of red blood cell (RBC) by autoantibodies at body temperature, leading to hemolysis and anemia

- It is the most prevalent form of AIHA, accounting for ~80% cases of AIHA in adults
- It is associated with significant morbidity and mortality

No FDA approved therapy yet, high unmet medical needs exist

- Corticosteroids are the standard 1L treatment, but majority patients are refractory or experience relapses
- Off-label use of rituximab for 2L wAIHA has been recommended in many countries as an alternative to splenectomy; however, there is no universal consensus on the recommended dose (375 mg/m2 vs 100mg fixed dose), and it has a late onset of effects (4-6 weeks). In addition, relapses are common

Syk is a potential target for wAIHA

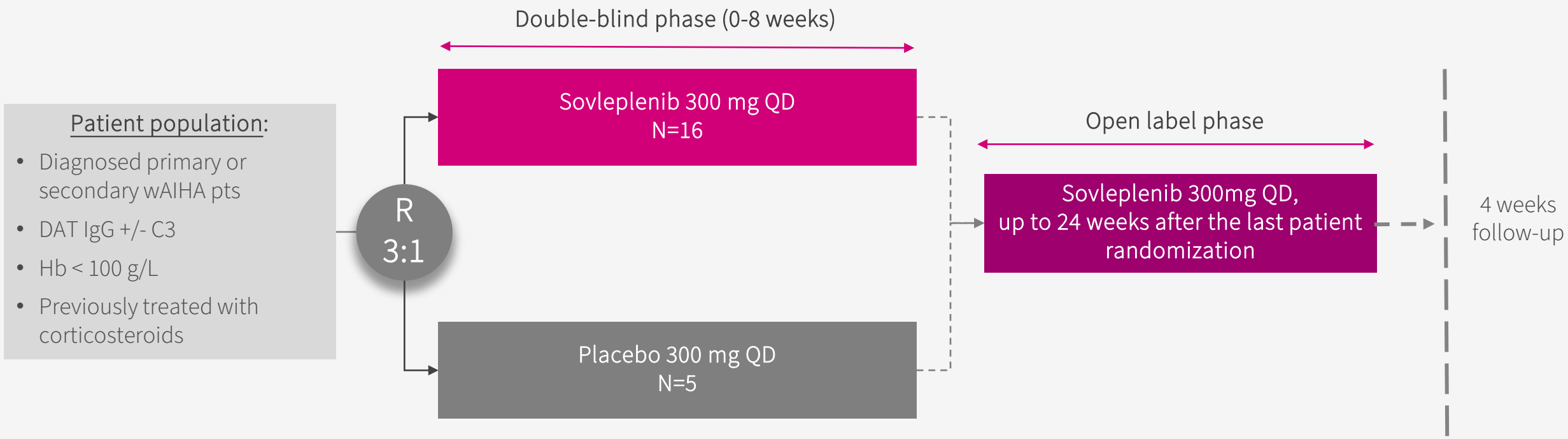
- RBC phagocytosis is dependent on Syk signaling through Fc receptors in macrophages
- Syk is also involved in B-cell receptor signaling pathway that lead to the development of antibody-secreting plasma cells
- Positive Phase II sovleplenib in wAIHA leading to launch of Phase III in China

Sovleplenib is a high selective, potent, oral Syk inhibitor, increased RBC counts dose dependently in an anti-Ly76 induced anemia mouse model

[1] J Pharmacol Exp Ther. 2024 Jan 2;388(1):156-170. doi: 10.1124/jpet.123.001752. PMID: 37918855

Phase II study design

- Study design: a randomized, double-blind, placebo-controlled, Phase II study
- Primary endpoint: overall response rate within 24 weeks



Overall response defined as Hb ≥ 100 g/L and increase from baseline of at least 20 g/L, not impacted by rescue therapy.
wAIHA = warm autoimmune hemolytic anemia; QD = once daily.

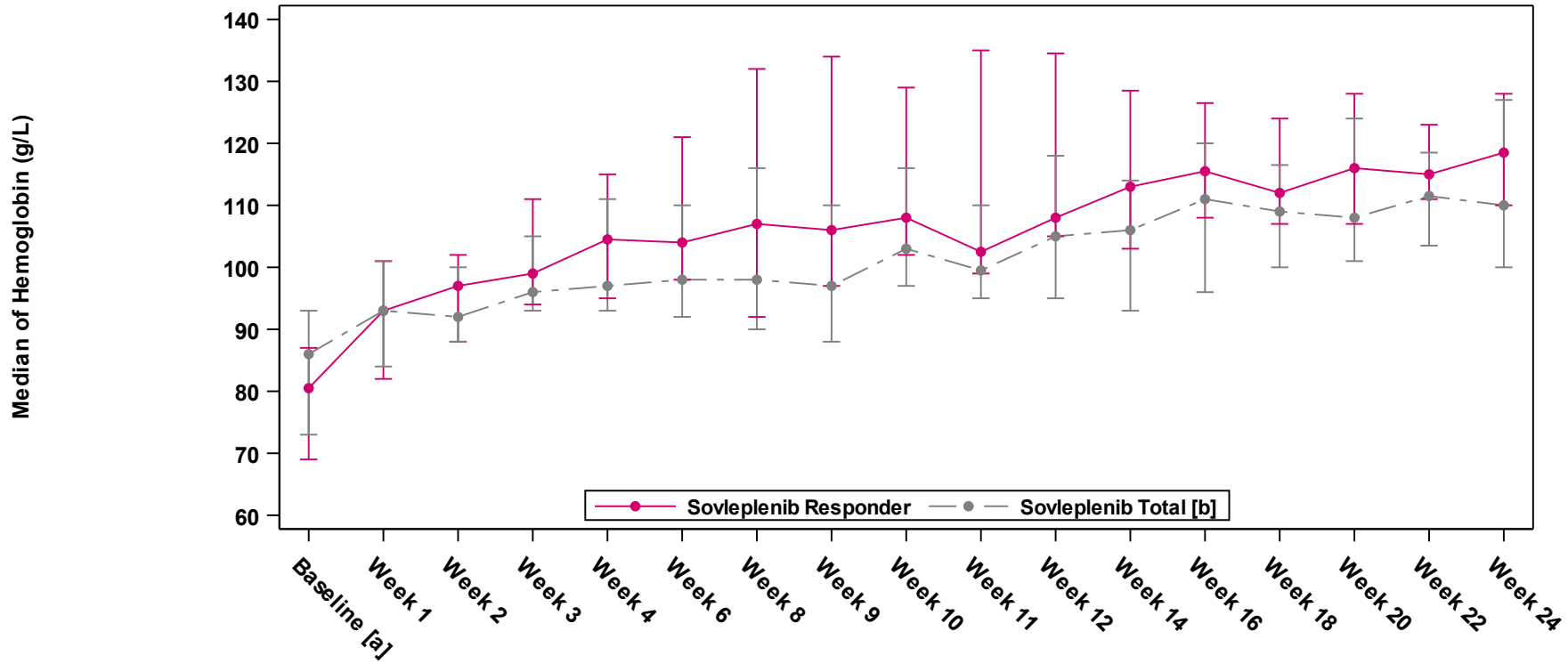
Primary endpoint and hemoglobin related second endpoint

- Sovleplenib achieved an overall response of 66.7% and durable response of 47.6% in wAIHA patients by 24 weeks
- Patients crossed over from placebo also achieved a similar high response as in all patients

Efficacy	Definition	Week 0-8 (Double blind)		Week 8-24 (Open label)	Week 0-24 (Double blind + Open label)
		Sovleplenib (n=16)	Placebo (n=5)	Cross-over from placebo (n=5)	All sovleplenib (n=21)
Overall response, n (%)	Hb ≥100 g/L with an increase of ≥20 g/L from baseline	7 (43.8)	0	3 (60.0)	14 (66.7)
Durable response, n (%)	Hb ≥ 100 g/L with an increase of ≥20 g/L from baseline on 3 consecutive visits with at least 7 days interval	3 (18.8)	0	2 (40.0)	10 (47.6)

DB: double-blind; OL: open label

Hemoglobin level over time



	Baseline [a]	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 9	Week 10	Week 11	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24
Sovleplenib Responder	14	14	14	14	14	14	13	10	13	10	12	12	12	11	11	11	10
Sovleplenib Total [b]	21	21	21	21	21	21	19	16	19	16	18	17	17	16	16	16	14

- Median onset time of Hb response:
  - 4.9 weeks for sovleplenib (0-24wks) to first Hb level ≥100 g/L with an increase of ≥20 g/L from baseline
  - 4.1 weeks for sovleplenib (0-24wks) to first Hb ≥15g/L of increase from baseline
- Sovleplenib achieved stable response during 0-24 weeks:
  - 71.4% (10/14) of responders demonstrated durable response that was sustained through 24 week treatment period

[a] Baseline is defined as the first intake of sovleplenib;
[b] Sovleplenib total includes 5 patients crossed from placebo group to open label sovleplenib at week 8.

Sovleplenib was efficacious regardless of prior anti-CD20 therapies

Efficacy by 24 weeks	Definition	Anti-CD20 naïve (n=13)	Prior anti-CD20 treated (n=8)
Overall response, n (%)	Hb ≥100 g/L with an increase of ≥20 g/L from baseline	9 (69.2)	5 (62.5)
Durable response, n (%)	Hb ≥ 100 g/L with an increase of ≥20 g/L from baseline on 3 consecutive visits with at least 7 days interval	7 (53.8)	3 (37.5)

Key takeaways

POC trial demonstrated encouraging results:

Sovleplenib vs. placebo:

- ✓ Overall response of 66.7% and durable response of 47.6% in wAIHA patients by 24 weeks
- ✓ Patients crossed over from placebo also achieved a similar high response as in all patients
- ✓ A rapid and sustained improvement in hemoglobin levels, with a median onset time of 4.1 to 4.9 weeks to first Hb level ≥100 g/L
- ✓ A stable response maintained over a 24-week treatment period, showing 71.4% durable response of responders

Randomized phase III ESLIM-02 in wAIHA initiated

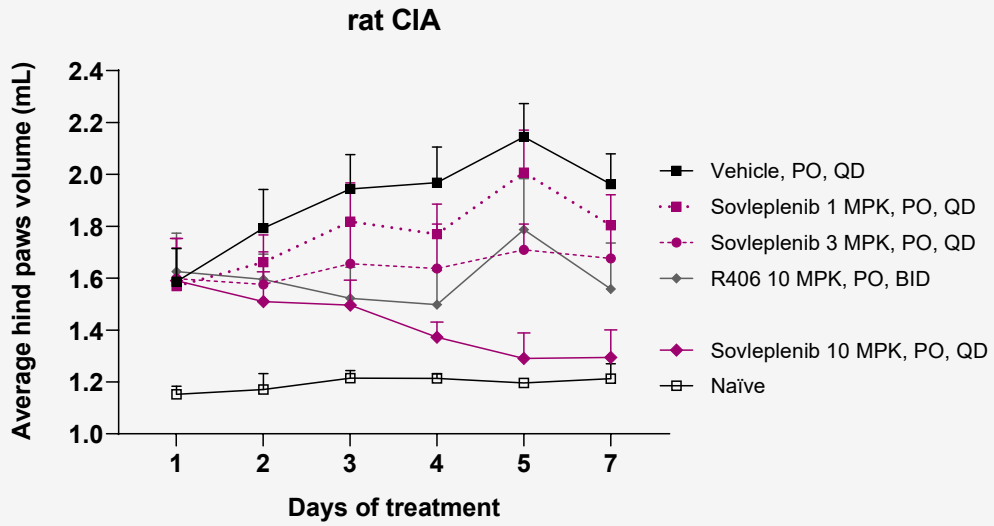
More Autoimmune Disease Opportunities

Aiming for high clinical impact and disease modification

Effect observed in multiple peripheral tissues in several preclinical models

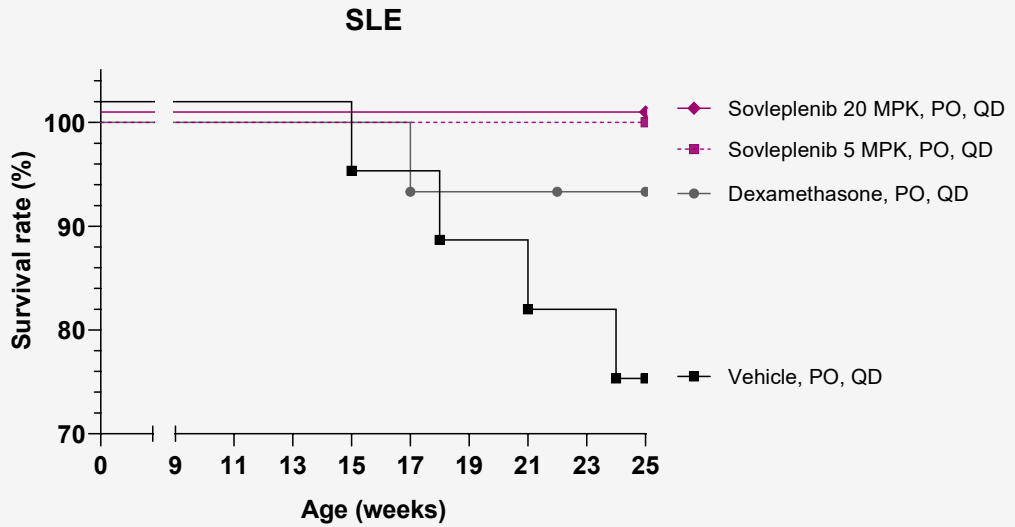
Sovleplenib in a rat CIA model

- Sovleplenib can reverse the joint damage to normal in a rat collagen induced arthritis model



Sovleplenib in a murine lupus model

- Sovleplenib ameliorated kidney and skin lesions in lupus prone MRL/lpr mice
- Sovleplenib demonstrated significant survival beneficial effects in murine lupus model



. 2024 Jan 2;388(1):156-170. doi: 10.1124/jpet.123.001752

Strong foundation to inform broad development

Patient friendly properties

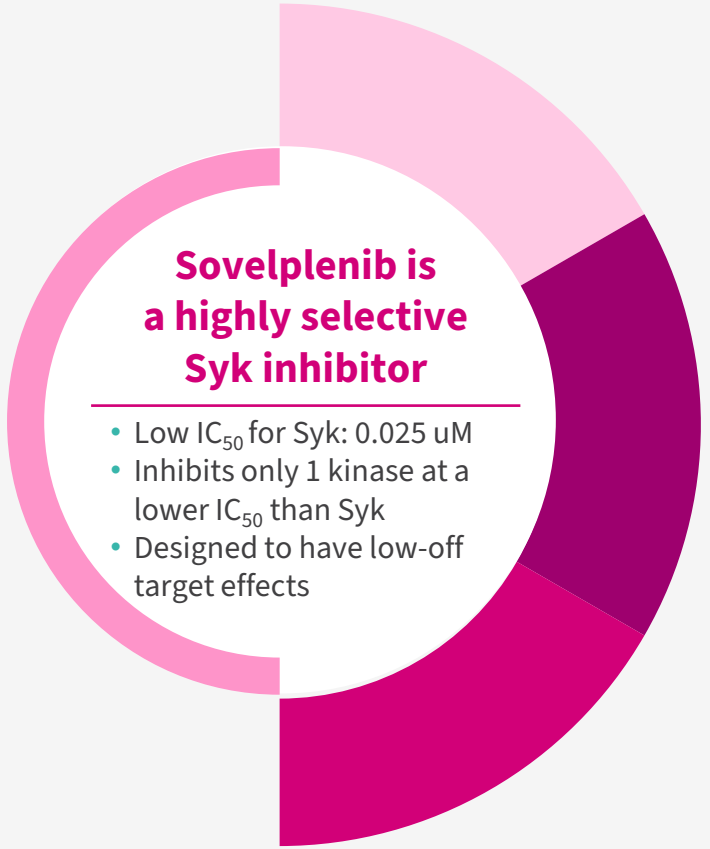
- Suitable for once daily oral dosing with unaffected absorption food
- Not a prodrug

Effect in preclinical models

- Anti-CD41 induced ITP
- Anti-Ly76 induced anemia ► AIHA
- Collagen induced arthritis ► RA
- SLE
- NHL

Additive effect with BTKi

- Seen in preclinical models of NHL
- Response in BTKi-refractory NHL patients



Healthy volunteers

- Australia, China, US
- Extensive clinical pharmacology characterization
- Clear PK-PD correlation
- Low food effect & DDI

Autoimmune / inflammatory diseases

- Evidence of clinically significant activity in two autoimmune diseases: ITP and wAIHA
- IND cleared in the US for ITP

Hematologic malignancies

- Australia, China, US+EU
- Preliminary anti-tumor activities observed in multiple settings
- RP2D established globally

BREAK FOR 5 MINUTES

Surufatinib (SULANDA®) for Pancreatic Ductal Adenocarcinoma (PDAC)

New potential indication with sizeable market potential and global opportunities

Ongoing sales in neuroendocrine tumors

Surufatinib

Multi-stage development programs

SULANDA®	Launched in China in 2021 and ranked the 2nd brand in NET market
IIT in first-line PDAC	Reported encouraging early results at ASCO 2023 of an IIT of surufatinib for PDAC in combination with a PD-1 antibody and chemotherapy
Phase II/III trial	Initiated Phase II/III trial for treatment-naïve PDAC in China

PDAC Demographics and market potential

Significant unmet needs highlight growing demand for effective treatments

Hard to treat

Immunologically cold tumor, lacks sufficient mutations for the immune system to recognize tumor-specific antigens

Limited treatment efficacy

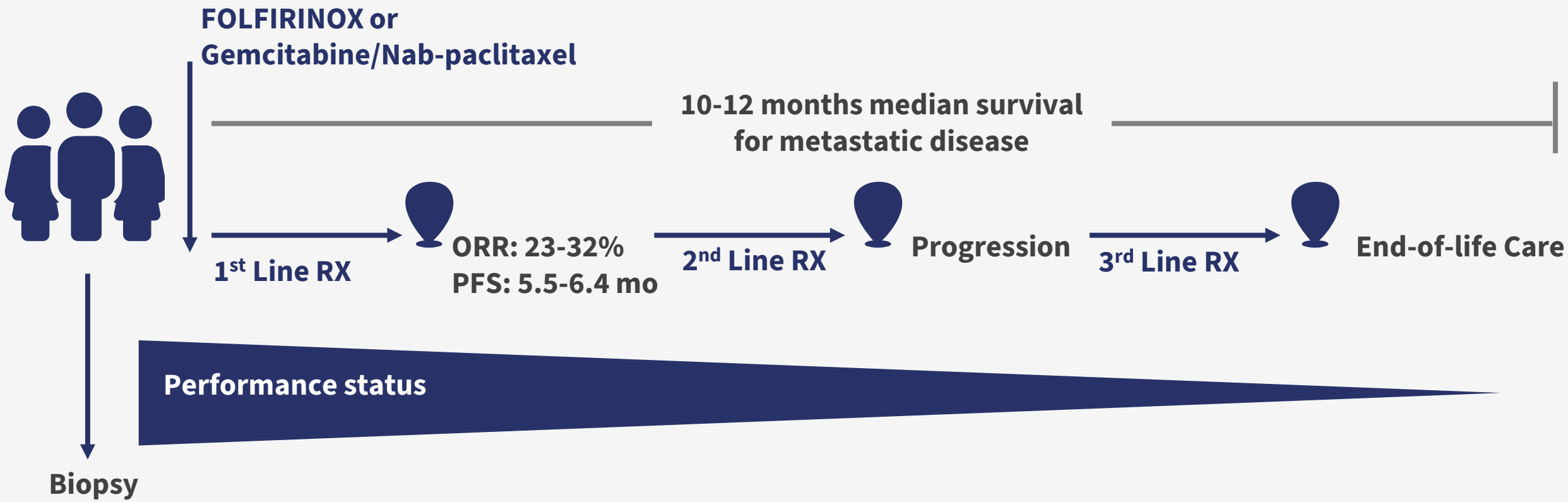
chemotherapy, surgery, and radiation have not significantly improved patient outcomes; surgery eligible only in 10-20% of patients [2]

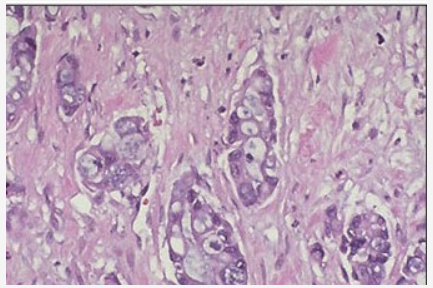
Low survival rate

average five-year survival rate <13%[1]

[1] Pancreatic Cancer Action Network. Accessed June 28, 2024
[2] Sumit S. et al. Current and Future Therapies for Pancreatic Ductal Adenocarcinoma. Cancers (Basel) 2022 May; 14 (10): 2417

Pancreatic cancer is a deadly disease





Complex and challenging biology

- Late presentation at advanced stage of disease
- Dense, fibrotic, and immunosuppressive stroma
- Relative resistance to chemotherapy and immunotherapy

PDAC, a huge unmet medical need

- First-line SOC[2]: chemotherapy such as FOLFIRINOX or gemcitabine combined with albumin-bound paclitaxel.
- No other viable treatment options beyond chemotherapy for PDAC patients.
- Recent failed late-stage trials of immunotherapy combined with chemotherapy [1] : new approach needed
- Complex immunosuppressive tumor microenvironment insulating the tumor against an effective cytotoxic immune response

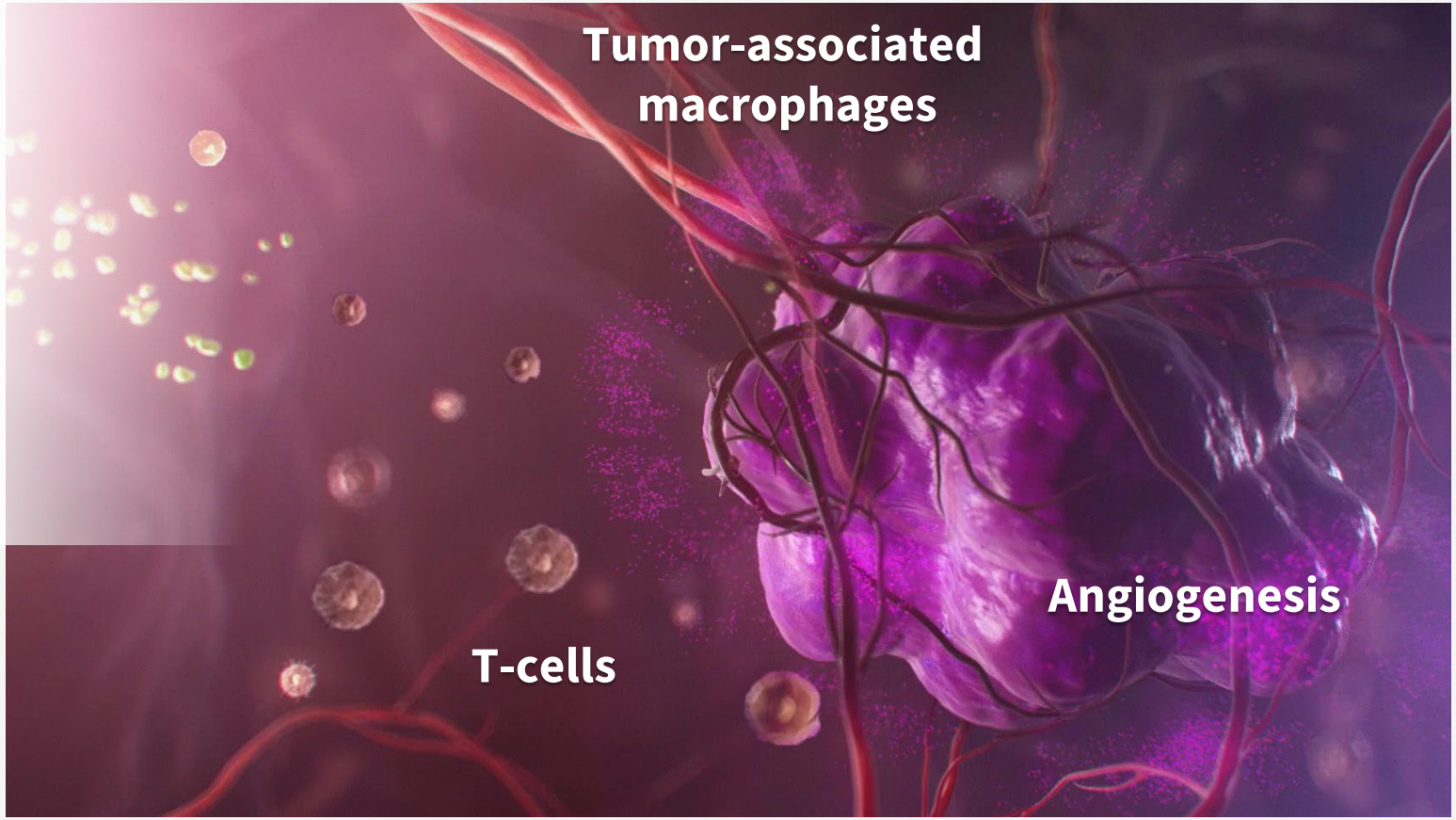
First-line chemotherapy regimens in pancreatic cancer[2]

	FOLFIRINOX		**Gemcitabine/nab-paclitaxel**	
	PRODIGE4-ACCORD11		MPACT	
Trial Details	Randomized, Phase II/III, primary endpoint: OS		Randomized, Phase III, primary endpoint: OS	
No of patients	342		861	
Treatment	FOLFIRINOX	Gemcitabine	Gemcitabine/nab-paclitaxel	Gemcitabine
ORR, %	31.6	9.4	23	7
mPFS, mo (95% CI)	6.4 (5.5 to 7.2)	3.3 (2.2 to 3.6)	5.5 (4.4 to 5.5)	3.7 (3.2 to 3.6)
mOS, mo (95% CI)	11.1 (9 to 13.1)	6.8 (5.5 to 7.6)	8.5 (7.89 to 9.53)	6.7 (6.01 to 7.23)
Neutropenia, %	45.7	21	38	27
Thrombocytopenia, %	9.1	3.6	13	9
Receipt of growth factors, %	42.5	5.3	26	15
Neuropathy, %	9	0	17	1
Diarrhea, %	12.7	1.8	6	1

[1] Wainberg. Clin Cancer Res. 2020;26:4814; Renouf. ESMO 2020. Abstract LBA65; [2] Andre A, et al. Advances in Systemic Therapy for Advanced Pancreas Cancer. ASCO 2024

Surufatinib MOA

Surufatinib has unique angio-immuno kinase profile and mechanism of action



Mechanism of Action

- Anti-angiogenesis: cut off **blood flow to tumor** (VEGFR/FGFR)
- Immunotherapy: inhibit expression of **tumor-associated macrophages** which cloak cancer cells from **T-cell attack** (CSF-1R)

Preclinical Rationale of Surufatinib for PDAC in combination with PD-1 and AG

HUTCHMED

AG treatment creates an immunosuppressive tumor microenvironment

AG treated PDAC patients[1]

M2 type macrophages ↑

CSF-1R ↑ in tumor cells

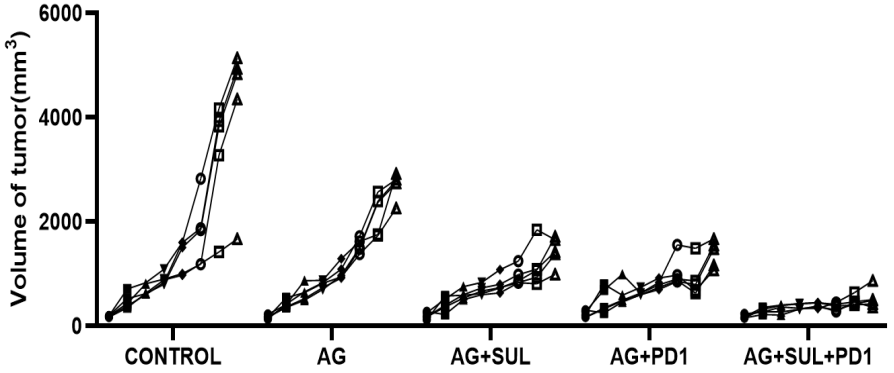
AG treated PDAC mouse xenograft model [1]

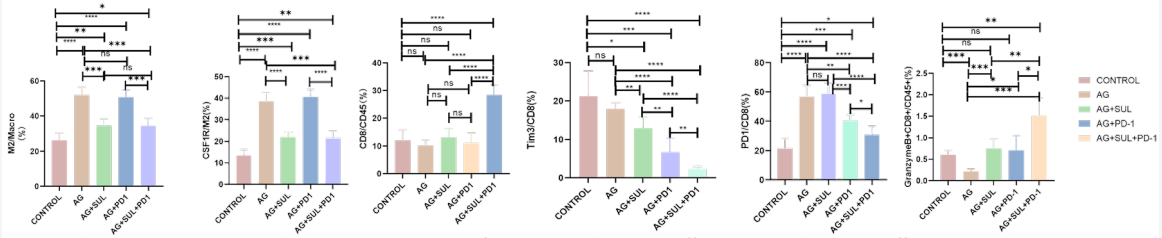
PD-1 ↑ in $CD8^+$ T cells

PD-L1 ↑ in tumor cells

Surufatinib+PD-1 combined with AG

- Combination therapy of surufatinib, PD-1 and AG inhibit tumor cell growth, and improve tumor immune microenvironment[1]



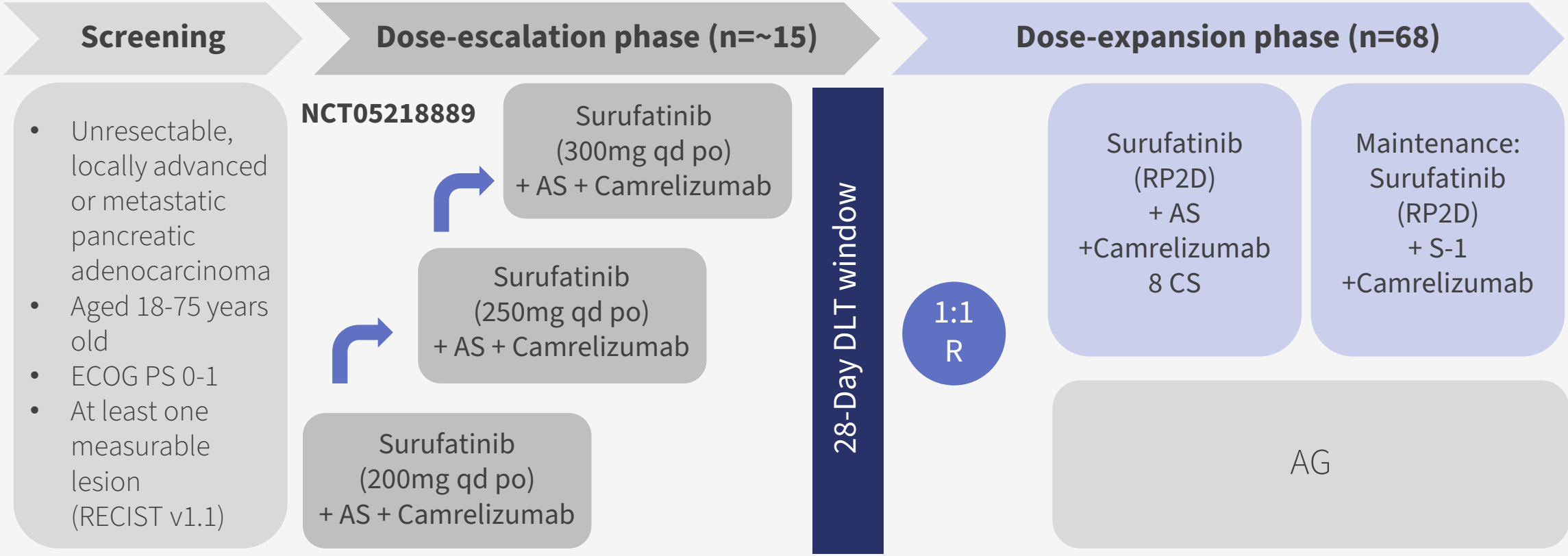


M2/Macro | CSF1R/M2 | CD8+T and CD4+T cells /CD45+cells | Tim3/CD8+T cells | PD1/CD8+T cells | GranzymeB+CD8 + / CD45+cells

[1] Cancer Res 2023; 83 (7_Suppl): Abstract: 2781

ASCO GI IIT Data

HUTCHMED



Primary endpoints

Dose-limiting toxicities (DLTs)
Recommended phase 2 dose (RP2D)
Overall response rate (ORR)
(RECIST v1.1)

Secondary endpoints

Progression-free survival (PFS)
Disease control rate (DCR)
Overall survival (OS)
Safety and tolerability

Anti-PD-1 antibody

Camrelizumab: 200mg, I.V., D1, Q3W

AS

nab-paclitaxel: 125mg/m^2, I.V., D1, D8, Q3W
S-1: 40mg, bid, D1-14, Q3W

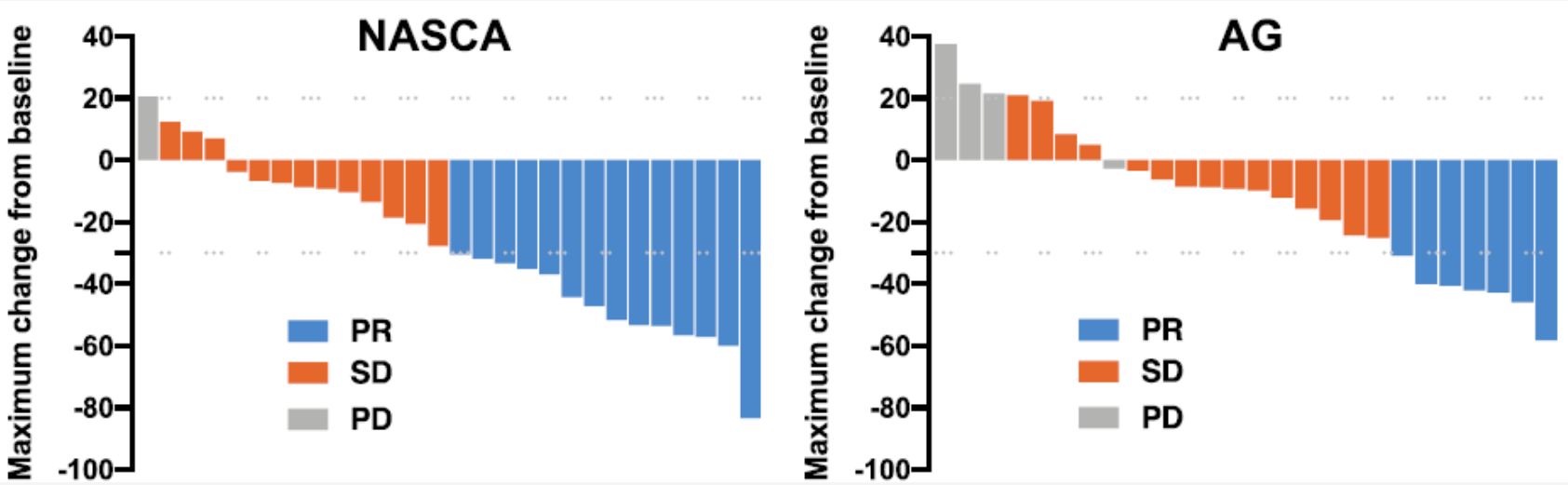
AG

nab-paclitaxel: 125mg/m^2, I.V., D1, D8, Q3W
gemcitabine: 1000/m^2, I.V., D1, D8, Q3W

ASCO GI IIT Data

- Preliminary data shows that surufatinib in combination with AG and camrelizumab has higher clinical activity than AG regimen in first-line treatment of mPDAC, with a manageable safety profile
- Higher immune cell infiltration was observed in NASCA group
- ORR: NASCA 50.0% vs. AG 26.9%

Maximum change from baseline in NASCA and AG group

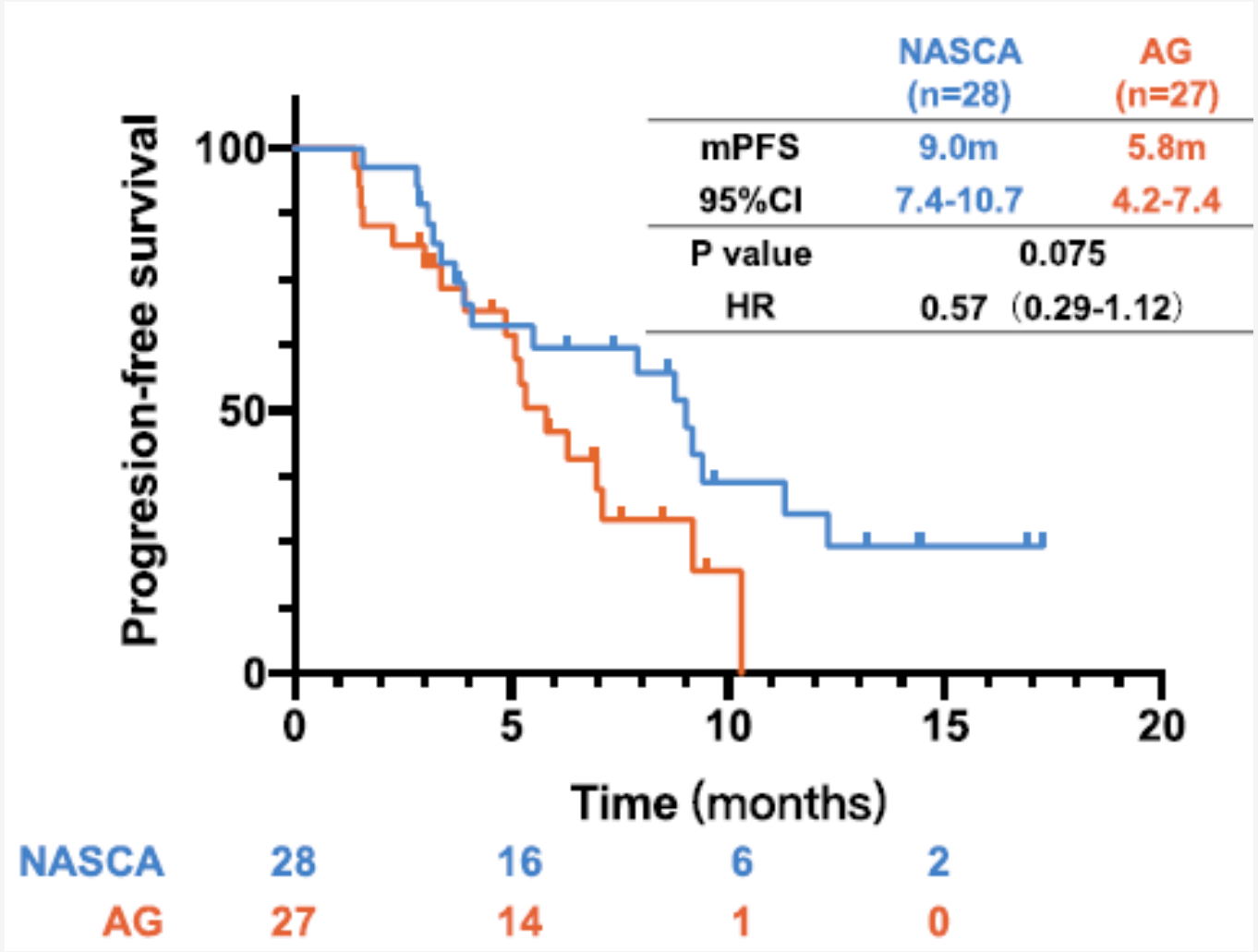


2024 ASCO GI #671

ASCO GI IIT Data

mPFS and mOS achieved 9.0mo and 13.3mo respectively

PFS of NASCA and AG group

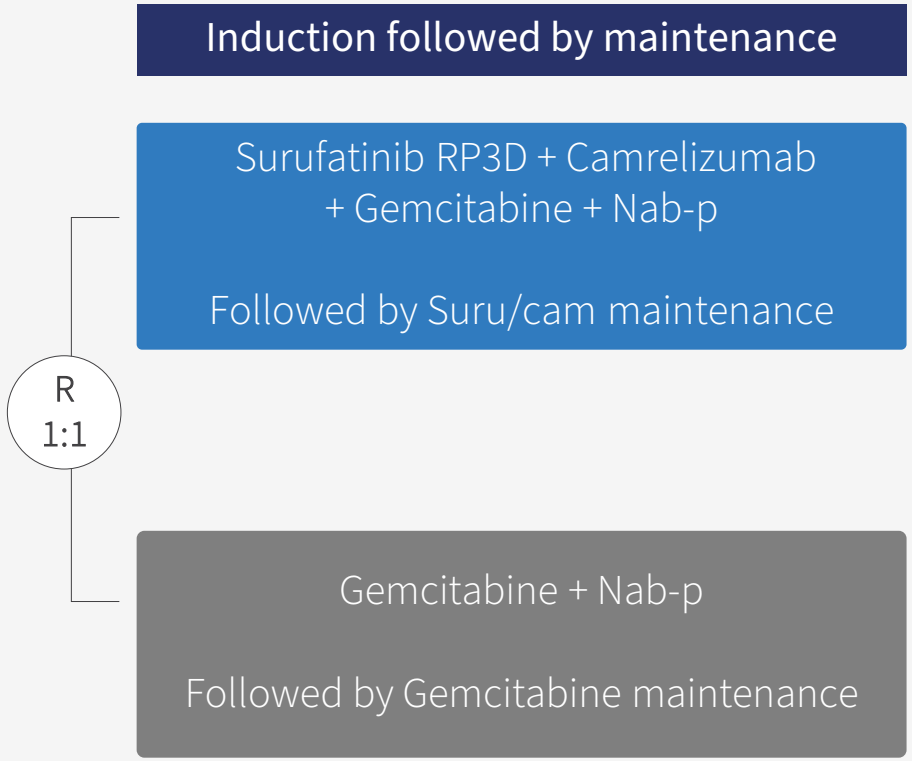


Current Chemotherapy
PFS：~3-6mo
OS：~7-11mo

2024 ASCO GI #671

Phase II/III Seamless Study Design of Surufatinib Combined with Camrelizumab and AG in First-line Treatment of Metastatic Pancreatic Cancer

Multicenter, randomized, open-label, Phase II/III registration study



Phase II
Primary endpoint: ORR
Secondary endpoint: PFS

Phase III
Primary endpoint: OS

HMPL-306 for IDH1/2-mutated Relapsed/Refractory Acute Myeloid Leukemia (AML)

Our third-wave portfolio entering Phase III registration trial

AML demographics and market potential

Unmet medical needs with limited treatment choices

China market

Incidence 20K[1]

US$100m-$200m

Global Market

Incidence 190k[2]

IDH1/2 mutations

~15-25% of AML patients [3]

Nearly 25% of AML patients fail to achieve remission after treatment [4]

No dual inhibitor targeting both IDH1 and IDH2 mutants has been approved

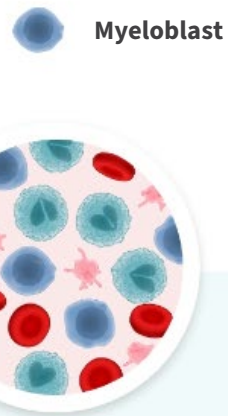
- One IDH1 inhibitor in China
- Two IDH1 inhibitor and 1 IDH2 inhibitor in the U.S.

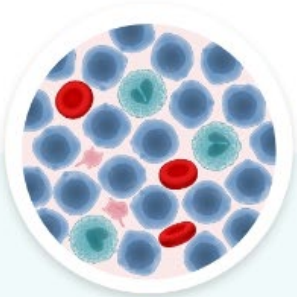
[1] Lin J et al. IDH1 and IDH2 mutation analysis in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. Ann Hematol. 2012;91(4):519-525. doi:10.1007/s00277-011-1352-7.
[2] AbbVie. (2024). Acute myeloid leukemia (AML). AbbVie Science. Retrieved July 1, 2024, from https://www.abbviescience.com/cancer-types/acute-myeloid-leukemia.html
[3] Guillermo Bravo et al. The role of IDH mutations in acute myeloid leukemia. Future Oncology 2018 (14) 10: 979-993
[4] Mianmian Gu et al. The prevalence, risk factors, and prognostic value of anxiety and depression in refractory or relapsed acute myeloid leukemia patients of North China. Medicine 98(50):p e18196, Dec 2019

What is acute myeloid leukemia (AML)?

HUTCHMED

A type of blood cancer that originates in bone marrow, where immature cells, called myeloid cells, are born





NORMAL BLOOD COUNT

Normally, immature myeloid cells develop into:

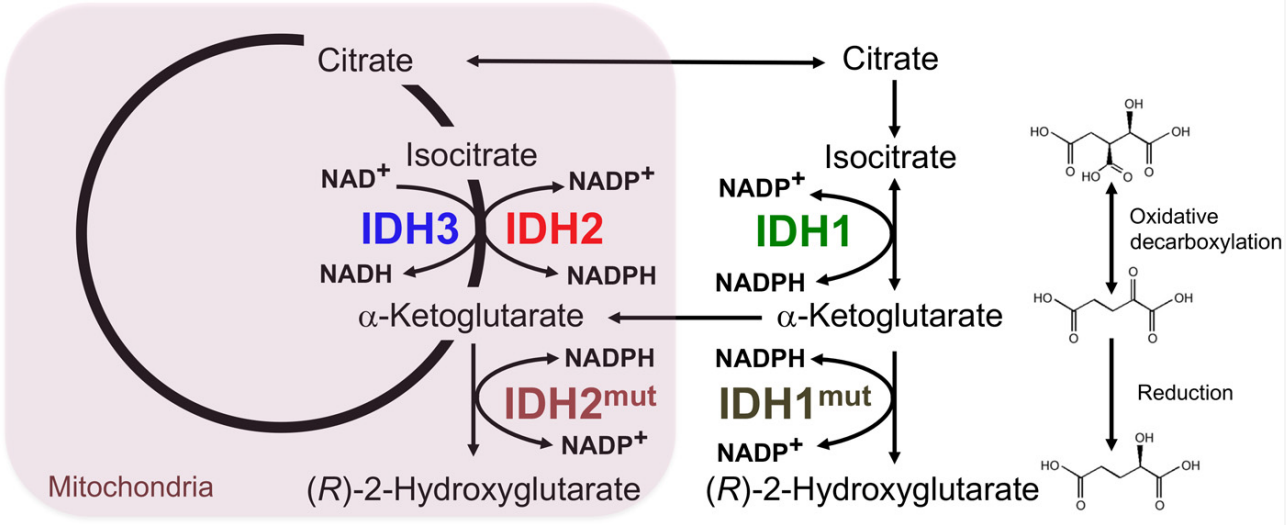
- Red blood cells that carry oxygen throughout the body
- White blood cells that fight infections
- Platelets that help the blood clot

BLOOD COUNT WITH AML

With AML, immature myeloid cells cannot develop into normal blood cells and instead turn into cancer cells, called leukemic myeloblasts (immature blood cells), that grow and divide rapidly, crowding healthy cells and disrupting proper cell function.

This results in symptoms associated with AML, such as: weakness, fever, infection, paleness and bleeding

Isocitrate Dehydrogenase (IDH) MOA



- IDH catalyzes oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) during cellular metabolism[1]
- Mutated IDH produces carcinogenic metabolite (*R*)-2-hydroxyglutaronic acid (2-HG) in both solid tumors and hematologic malignancies
- Accumulation of 2-HG causes DNA hyper-methylation and promotes tumorigenesis, progression and epigenetic dysregulation
- IDH1/2 mutations have been identified as oncogenes and drug targets for cancer
- IDH1-mutant and IDH2-mutant isoform switch is a resistant mechanism to drugs targeting IDH1 or IDH2 only [2]

[1] Sci. Adv. 2019; 5 : eaaw4543
[2] Blood Adv. 2020 May 12;4(9):1894-1905; . Cancer Discov 2018 Dec;8(12):1540-1547

IDH1/2 mutations in various cancers

	Tumor	% IDH Mutation			
		Total	IDH1-R132	IDH2-R140	IDH2-R172
Brain tumor	Grade 2 and 3 glioma	60-80%	60-80%	0%	1%
	Secondary glioblastoma	70%	70%	0%	1%
Hematopoietic tumor	Acute myeloid leukemia (AML)	15-25%	5-10%	5-15%	0-5%
	Myelodysplastic syndrome (MDS)	10%	5%	5%	0%
Angioimmunoblastic T-cell lymphoma		26%	0%	1%	25%
Solid tumor	Chondrosarcoma	55%	40%	0%	15%
	Osteosarcoma	25%	0%	0%	25%
	Cholangiocarcinoma	22%	20%	0%	2%
	Giant cell tumors of bone	80%	0%	0%	80%

Source:
Amary et al., 2011; Paschka et al., 2010; Yan et al., 2009; Fujii T et al., 2016, Abstract 3101, AACR 2016.

HMPL-306 is a dual inhibitor of IDH1 mutant and IDH2 mutant

HUTCHMED

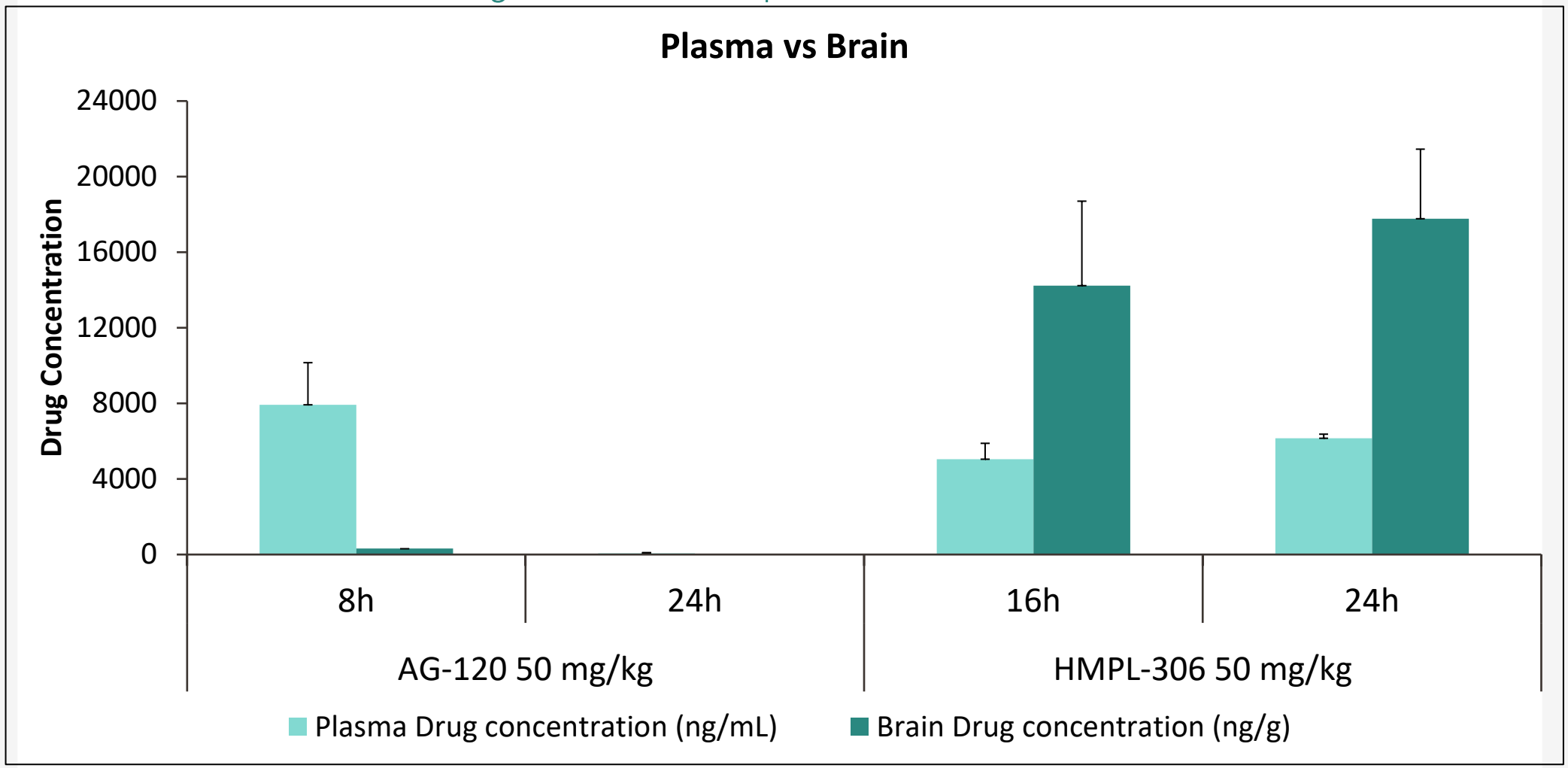
HMPL-306 provided strong and sustainable 2-HG inhibition in both IDH1-mutant and IDH2-mutant tumor cell lines

		HMPL-306	Ivosidenib (AG-120)	Enasidenib (AG-221)
IDH1-mutant cells IC_{50} (uM)	$U87MG^{IDH1\text{-}R132H}$	0.050±0.012	0.032±0.006	
	$TF1^{IDH1\text{-}R132H}$	0.031±0.006	0.068±0.025	
	HT1080 (IDH1-R132C)	0.026±0.004	0.009±0.002	
	RBE (IDH1-R132S)	0.094±0.019	0.058±0.019	
IDH2-mutant cells IC_{50} (uM)	$U87MG^{IDH2\text{-}R140Q}$	0.031±0.0005		0.043±0.007
	$TF\text{-}1^{IDH2\text{-}R140Q}$	0.021±0.010		0.055±0.013
	$HEK293^{IDH2\text{-}R172K}$	0.425 (n=2)		5.162 (n=2)
	SW1353 (IDH2-R172S)	0.458±0.077		1.458±0.368

HMPL-306 is highly brain-penetrable in preclinical model

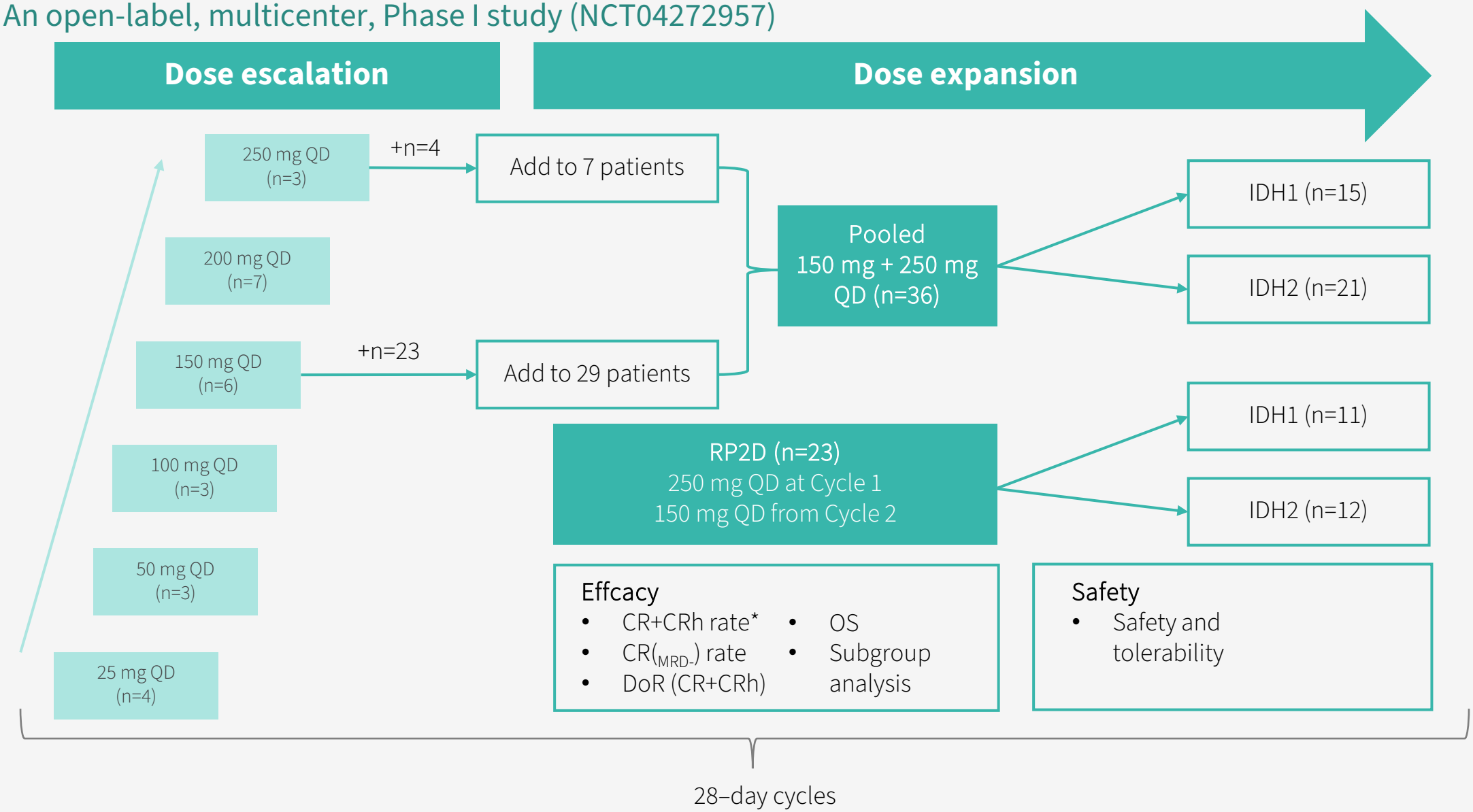
HMPL-306 showed significant drug concentration in brain, which is a desirable feature for treating glioma

Drug concentrations in plasma and brain of mice



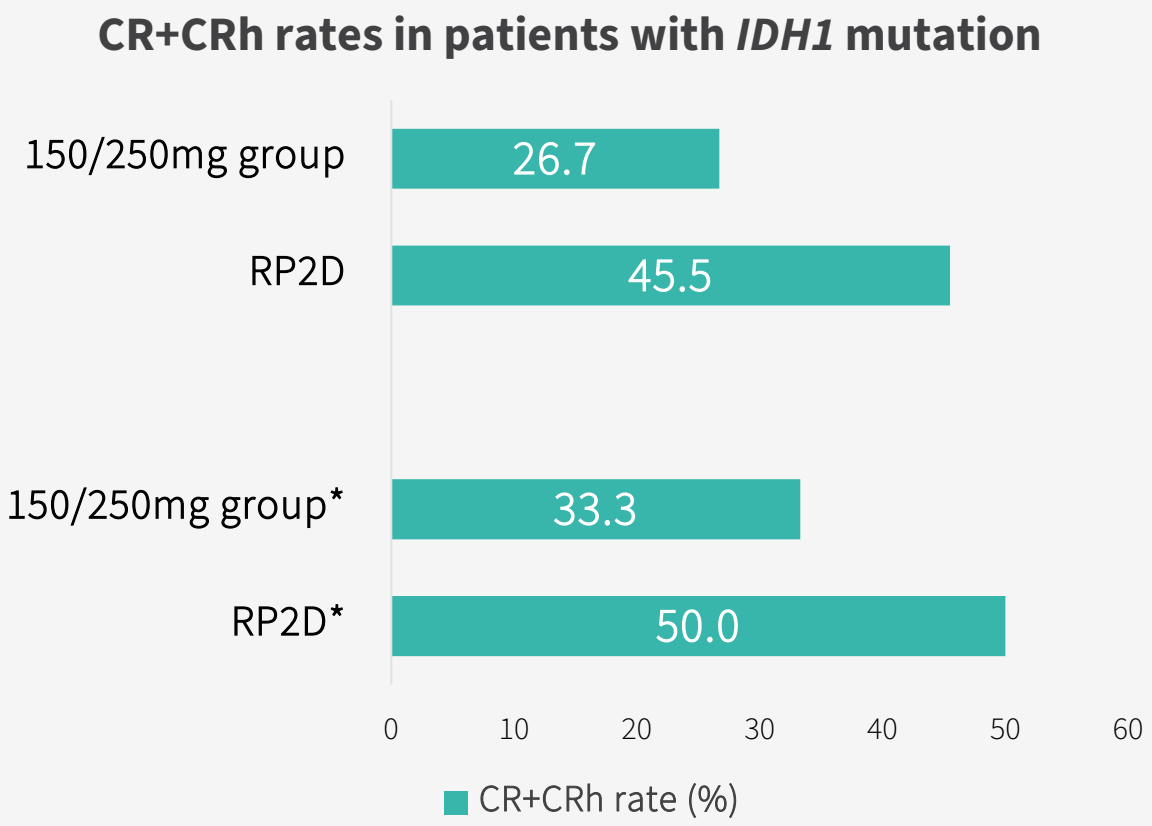
Study design

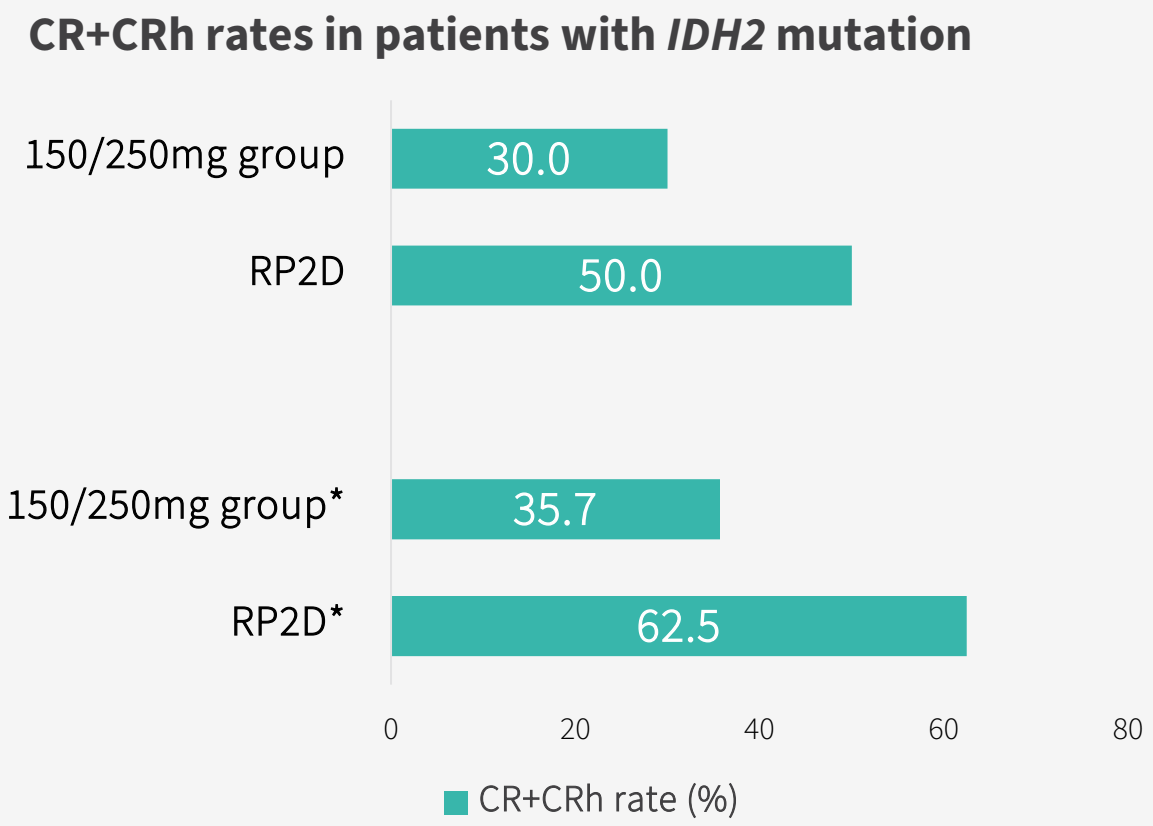
An open-label, multicenter, Phase I study (NCT04272957)



CR+CRh rates in patients with IDH1 mutation and IDH2 mutation

RP2D as 250 mg QD for Cycle 1 and 150 mg QD from Cycle 2





*Patients with *FLT3/RAS* mutation were excluded
CR: complete remission; CRh: CR with partial hematologic recovery; RP2D: recommended phase 2 dose.

OS for patients with IDH1 mutation and IDH2 mutation

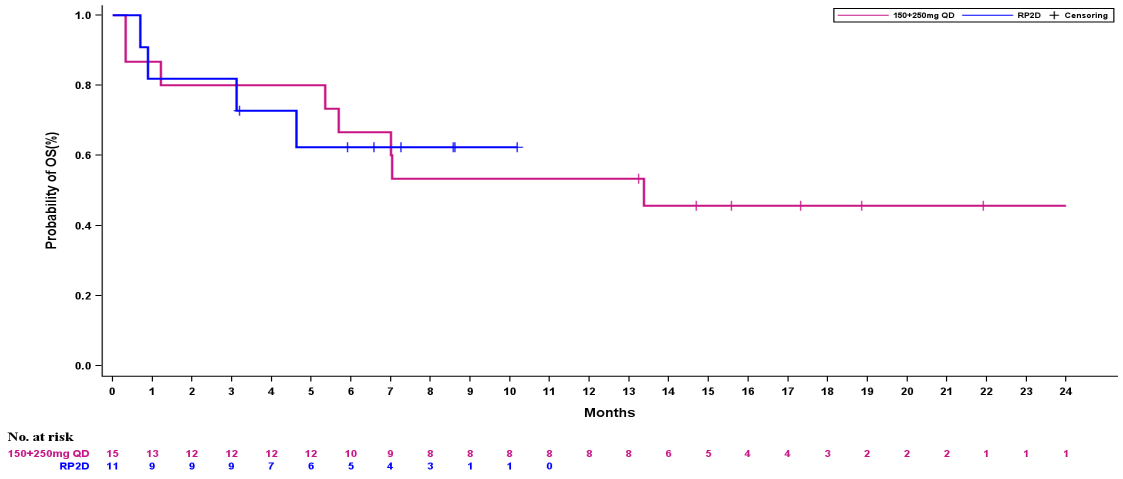
HUTCHMED

RP2D as 250 mg QD for Cycle 1 and 150 mg QD from Cycle 2

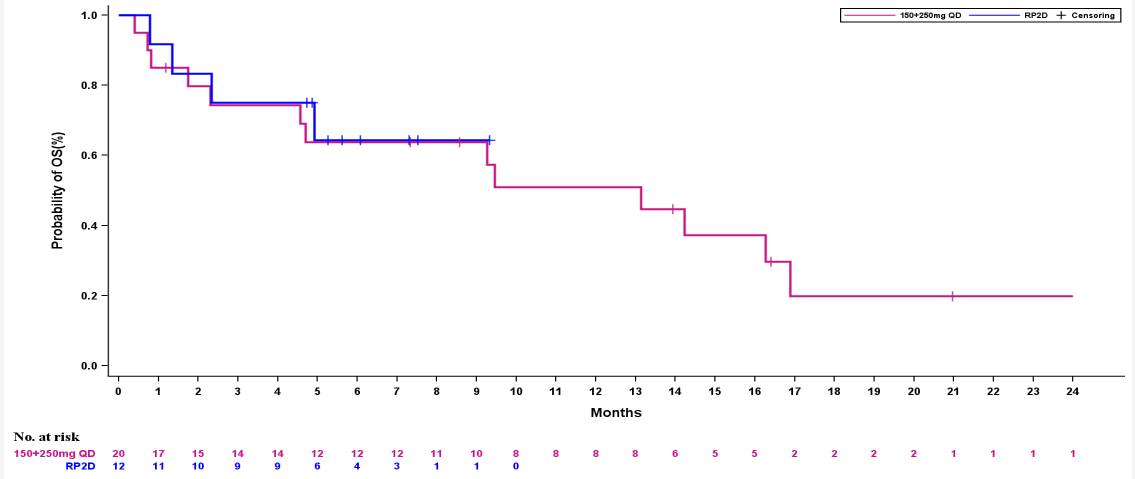
	OS event, n (%)	Median OS (95% CI), month
150/250 mg group	8 (53.3)	13.4 (1.2-NR)
RP2D group	4 (36.4)	NR (0.9-NR)

	OS event, n (%)	Median OS (95% CI), month
150/250 mg group	13 (65.0)	13.1 (2.3-16.9)
RP2D group	4 (33.3)	NR (1.3-NR)

Kaplan–Meier plots of OS for patients with IDH1 mutation



Kaplan–Meier plots of OS for patients with IDH2 mutation



HMPL-306 summary of adverse events

Adverse Events	Total (n=59)	Adverse Events	Total (n=59)
Any TEAEs	58 (98.3)	Any TRAEs	49 (83.1)
Grade ≥3 TEAEs	48 (81.4)	Grade ≥3 TRAEs	34 (57.6)
SAEs	28 (47.5)	TRSAEs	13 (22.0)
TEAEs leading to death	14 (23.7)	TRAEs leading to death	3 (5.1)
		TRAEs in ≥10% of patients	
		Platelet count decreased	32 (54.2)
		Anaemia	23 (39.0)
		Neutrophil count decreased	21 (35.6)
		White blood cell count decreased	19 (32.2)
		White blood cell count increased	10 (16.9)
		Nausea	7 (11.9)
		Pyrexia	7 (11.9)
		Peripheral edema	7 (11.9)
		Pneumonia	6 (10.2)

TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event; TRSAE: treatment-related serious adverse event; SAE: serious adverse event.

Overview of HMPL-306 with approved and ongoing IDH inhibitors - efficacy

HUTCHMED

HMPL-306 showed deeper remission, well-tolerable safety profile with mild liver TOX and low grade of DS

		HMPL-306	Idhifa® (Enasidenib, AG-221, CC-90007)	Tibsovo® (Ivosidenib, AG-120)	Rezlidhia® (Olutasidenib, FT-2102)	LY3410738
Status		Ph3 ongoing	Launched	Launched	Launched	Ph1 ongoing
Target		IDH1/2	IDH2	IDH1	IDH1	IDH1/2
Company		HUTCHMED	BMS / Celgene / Servier	Servier / CStone	FORMA (Now Novo Nordisk) / Rigel	Eli Lilly
Indication		r/r IDH1 or IDH2-mut AML	≥2L IDH2-mut AML	≥2L IDH1-mut AML	r/r IDH1-mut AML	r/r IDH1 or IDH2-mut AML
Efficacy (@ RP2D dose)	IDH1m	CR+CRh: 50.0%*		CR: 22%; CRh: 8% CRi or CRp: 12% mOS: 8.8 mos	CR: 32%; CRh: 3% CRi: 10% mOS: 11.6 mos (in 153 pts)	CR+CRh: 21% CRi/CRp: 15%
	IDH2m	CR+CRh: 62.5%*	CR: 19%; CRh: 4% mOS: 9.3 mos mFollow-up: 6.6mos			CR+CRh: 17% CRi/CRp: 6%

CRi, complete remission with absolute neutrophil count < 1,000/μL; CRp, complete remission with platelet < 100,000/μL; CR_{MRD-}: CR with minimal residual disease negative;
*Patients with *FLT3/RAS* mutation were excluded

Overview of HMPL-306 with approved and ongoing IDH inhibitors - safety

HMPL-306 showed deeper remission, well-tolerable safety profile with mild liver TOX and low grade of DS

		HMPL-306	Idhifa® (Enasidenib, AG-221, CC-90007)	Tibsovo® (Ivosidenib, AG-120)	Rezlidhia® (Olutasidenib, FT-2102)	LY3410738
Company		HUTCHMED	BMS / Celgene / Servier	Servier / CStone	FORMA (Now Novo Nordisk) / Rigel	Eli Lilly
Safety %TRAE	N (safety dataset)	59	214	179	153	130
	QTc prolongation, any grade (≥grade3), %	-	-	25% (8%)	8% (1%)	2% (<1%)
	Differentiation syndrome, any grade (≥grade3), %	8.5% (6.8%) No grade ≥4 occurred	10% (6%)	11% (5%)	14% (8%) 1 fatal	9% (5%)
	Bilirubin increased, any grade (≥grade3), %	5.1% (1.7%)	81% (15%) UGT1A1 inhibition	16% (1%)	4% (-)	-
	AST increased, any grade (≥grade3), %	8.5% (0)	5% (1%)	27% (1%)	6% (2%) 1 fatal DILI*	-
	ALT increased, any grade (≥grade3), %	8.5% (0)	9% (2%)	15% (1%)	8% (3%)	-
Source		EHA 2024 #P532	Blood 2017 130(6) 722-31;FDA review files and label, NDA209606	N Engl J Med 2018 378(25) 2386-98; FDA review files, NDA211192	ASH 2022 #2757; FDA review files, NDA215814	AACR 2023 CT026

*DILI, drug-induced liver injury, death not in pivotal cohort

HMPL-306 phase I data summary

HUTCHMED

1.

PK/PD

Long half-life

>90% 2-HG inhibition achieved at both 150 and 250 mg QD

2.

RP2D

Full target inhibition reached much earlier at 250 mg QD than at 150 mg QD

RP2D (250 mg QD for Cycle 1 and 150 mg QD from Cycle 2) selected to reach the steady state faster and allow patients exposed to a lower but equally efficacious dose after the steady state

3.

EFFICACY

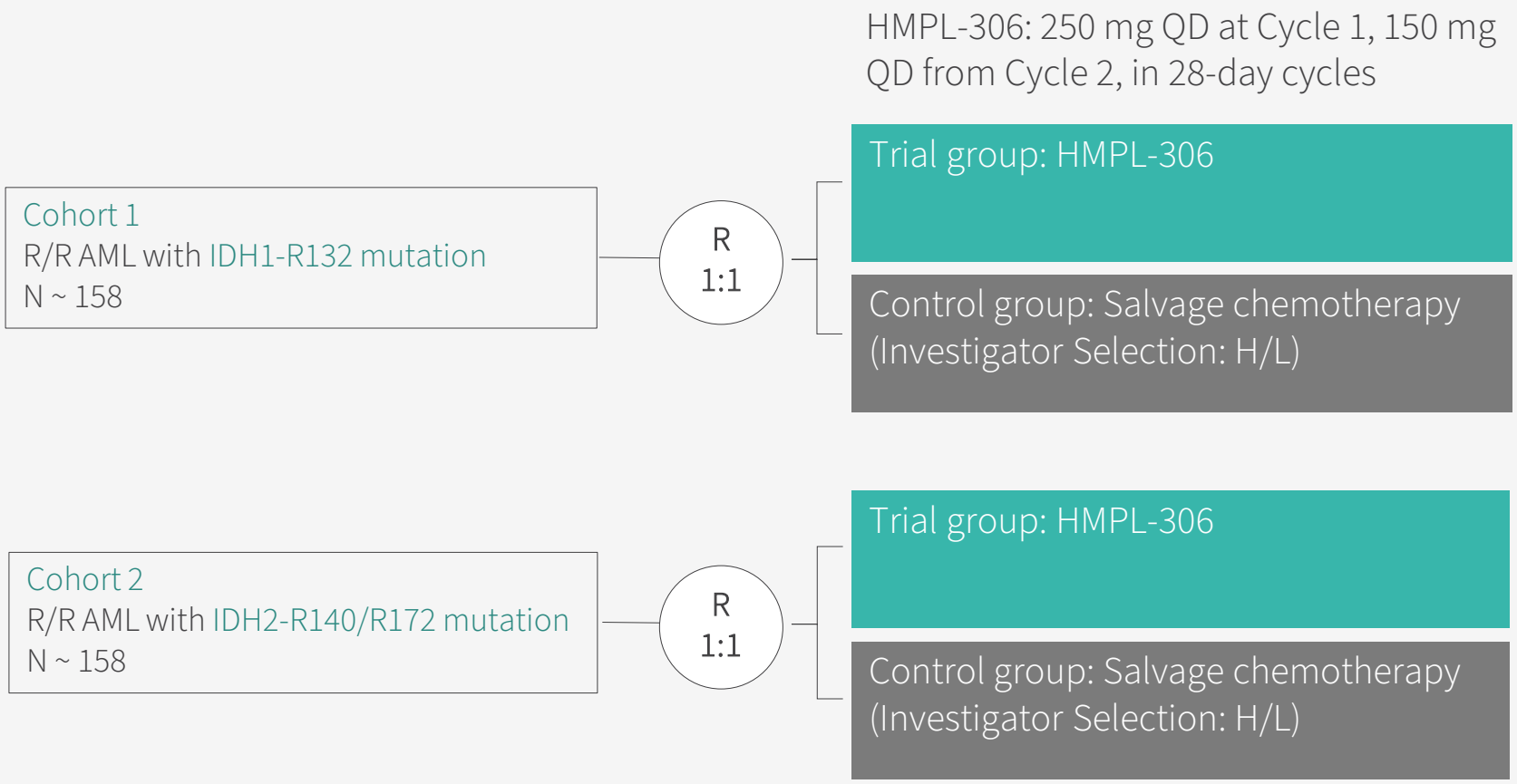
HMPL-306 targets both IDH1 and IDH2 mutation to overcome the resistance from isoform switch

High CR+CRh rate observed in R/R AML patients harbouring IDH1 or IDH2 mutation

OS benefits seen at RP2D

RAPHAEL pivotal registration phase III study initiated

This study includes cohort 1 for R/R AML patients with **IDH1m** and cohort 2 for R/R AML patients with **IDH2m**



Primary Endpoint: OS

Intensive chemo regimen (H)

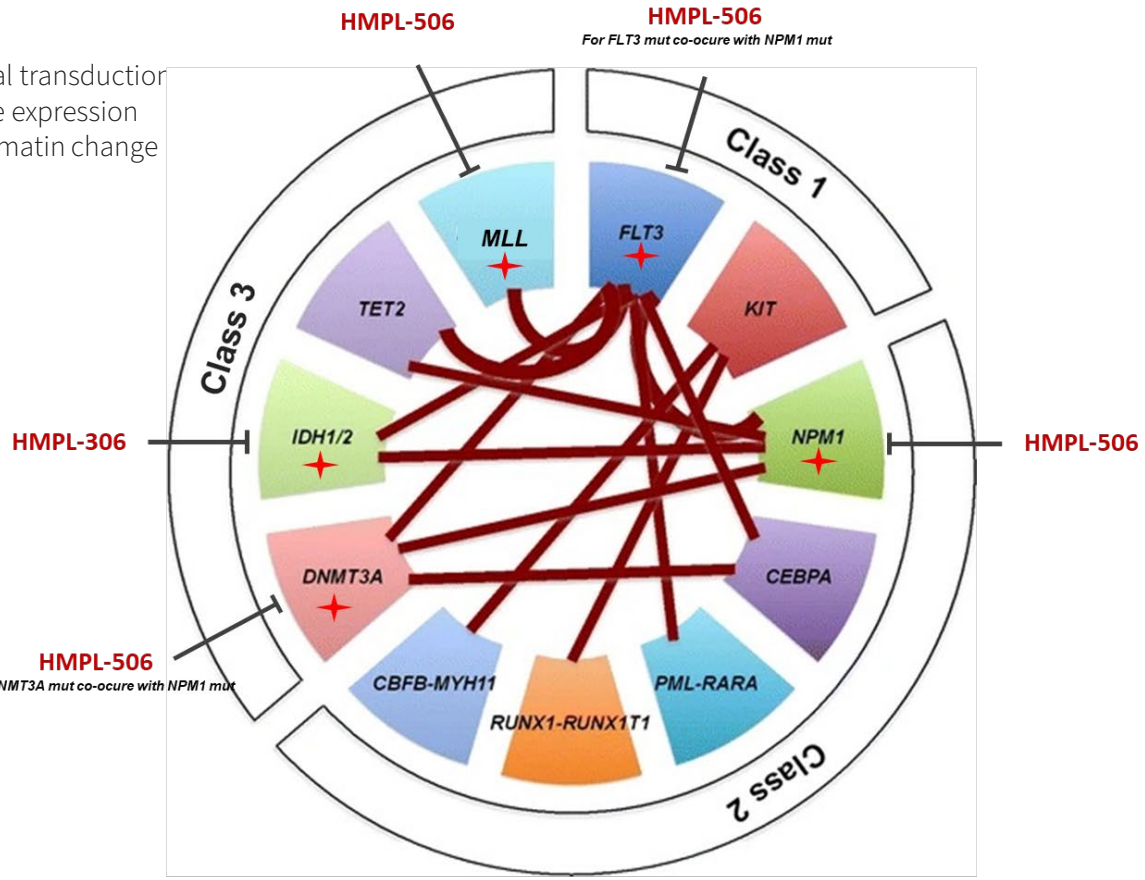
- MEC regimen (IV.)
- FLAG-Ida regimen (IV. SC.)

Non-intensive chemo regimen (L)

- Low dose Ara-c (IV. or SC.)
- AZA (IV. or SC.)

Opportunities of targeted therapies in AML and other indications

Class 1: Constitutive signal transduction
Class 2: Deregulated gene expression
Class 3: Epigenetics/chromatin change



Modified from Int J Hematol 97, 165–174 (2013)

Note:
~60% of FLT3 mut co-occurs with NPM1 mut
~50% of DNMT3A mut co-occurs with NPM1 mut

- HUTCHMED pipeline covers major mutations in leukaemia
- HMPL-306 in earlier line IDH1/2+ AML
- MENIN inhibitor (HMPL-506) in NPM1m and KMT2Ar AML
- Other IDH1/2+ indications such as glioma, cholangiocarcinoma, etc

Unlocking potential of our 1st, 2nd and 3rd innovative wave

(US$)	1st Wave Surufatinib	2nd Wave Sovleplenib	3rd Wave HMPL-306 IDH1/2 dual-inhibitor
China Market	PDAC Incidence 100k[1] $800m-$1bn Chemo as SOC	ITP Actively treated 250k[2] $500m-$700m Potential #1 Syk inhibitor in China	AML Incidence 20K[5] $100m-$200m No IDH1/2 dual-inhibitor approved globally
Global Market	Incidence 510k[1]	Incidence 57k[3] Prevalence 520k[4]	Incidence 190k[6]

[1] International Agency for Research on Cancer. World Health Organization. Accessed June 28, 2024; [2 IQVIA analysis; [3]] Clarivate,; Immune Thrombocytopenic Purpura Niche & Rare Disease Landscape & Forecast. 2018 Apr
[4] Prevalence estimated based on Rigel presentation and DelveInsight, only considering China and 7MM markets
[5] Lin J et al. IDH1 and IDH2 mutation analysis in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. Ann Hematol. 2012;91(4):519-525. doi:10.1007/s00277-011-1352-7
[6] AbbVie. (2024). Acute myeloid leukemia (AML). AbbVie Science. Retrieved July 1, 2024, from https://www.abbviescience.com/cancer-types/acute-myeloid-leukemia.html

Today's key insights

Sovleplenib

Our first potential novel medicine in autoimmune diseases

An efficacious and tolerable treatment option for ITP patients, even in heavily treated primary ITP patients

- Durable response: 48%
- Significant improvement of QoL

Encouraging results for wAIHA patients

- Overall response: 66.7%; durable response: 47.6%

Surufatinib

Expending to a new indication with sizeable market potential

Chemo as PDAC SOC

Encouraging IIT results

- mPFS: 9.0mo
- mOS: 13.3mo

HMPL-306 IDH1/2 dual inhibitor

Our third-wave portfolio entering Phase III registration trial

Encouraging Phase I data

No IDH1/2 dual inhibitor for AML approved globally

Highly brain-penetrable in preclinical model

Q&A

HUTCHMED

www.hutch-med.com