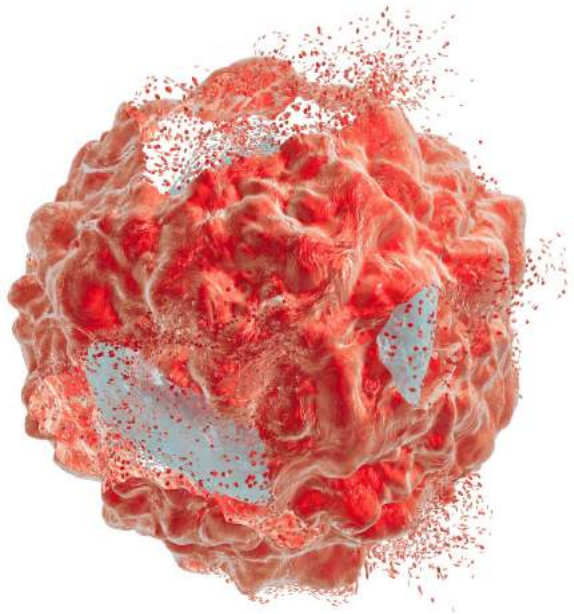

Patient-Centric Innovation

Global Cutting-Edge Therapies

Ascentage Pharma Group

April, 2023

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Innovative and Proprietary Platform Delivering Potentially First and/or Best-in-Class Drugs

Breakthrough Science

- **235** issued patents
- **600+** pending applications

Strong Pipeline

- **1** NDA Approval
- **20+** indications
- **12** novel compounds
- **40+** Clinical trials
- **30+** INDs

Dedicated team

- **1** vision: building a global biopharmaceutical company
- **20+** years commitment of executive team
- **~600** employees

Global development

China, United States, Europe and Australia

Integrated global organization

2022 Annual Review: Significant progress in commercialization and comprehensive advancement of pipelines

Significant progress in commercialization，from biotech to biopharma

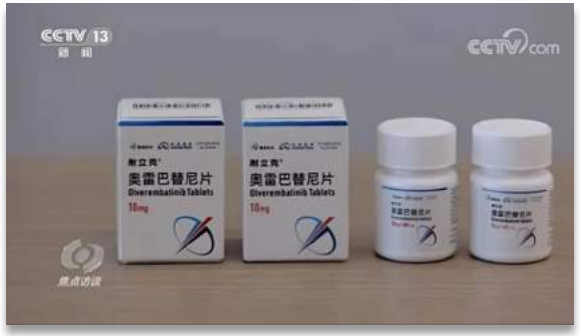
Olverembatinib is included **2022 NRDL** successfully

Accumulated Sales (Tax included) 182million, indicating commercial ability and market potential

Ascentage established **commercialized core team and core competencies**, which were fully reflected in various performance indicators in the first year of Olverembatinib launch

MAH type A certificate was issued and the **global headquarter** was in use

Validate global first-in-class/best-in-class potential



For the fifth consecutive year, the clinical data of olverembatinib were selected for Oral Presentations at the ASH Annual Meeting (taking 3 out of the 6 Oral Presentations at the special session on CML this year). These results showed the drug’ s potential for changing the treatment paradigm in CML globally.

An NDA for the **full approval** of olverembatinib was accepted and granted **Priority Review** by the CDE in China

The latest Ib/II clinical data of olverembatinib in patients with succinate dehydrogenase- (SDH-) deficient GIST was presented at the 2022 ASCO annual meeting

The first dataset of lisaftoclax plus a BTK inhibitor was announced in an Oral Presentation at the ASH Annual Meeting. With an **ORR of 98%,** these data showed impressive clinical utility in R/R CLL/SLL.

APG-2575 has become the second Bcl-2 inhibitor to enter the **registration study** in the world, and registration phase II clinical trial for the treatment of r/r CLL/SLL is ongoing

APG-5918 was cleared to enter a clinical study in advanced solid tumors and hematologic malignancies in both China and the US. Meanwhile, the clinical trial of APG-5918 in anemia diseases was also approved in China, potentially **opening a new therapeutic area for the drug**.

Expectation for 2023: Pipeline achievement and further build a Biopharm with commercialization capabilities

Olverembatinib

Being included in NRDL will boost the sales

We are expected to receive the approval by CDE of an NDA for olverembatinib **for the treatment of patients with CMP-CP who are resistant/intolerant to 1st and 2nd generation TKIs**

We will continue to **explore a wider range of new indications in addition to the approved indications,** including Ph+ ALL, GIST.

APG-2575

We expect to complete the enrollment for the pivotal Phase II study and **submit the NDA in the first half of 2024**.

We will consult with FDA/CDE on the **proposed global pivotal registration Phase II study** and initiate more **pivotal registration studies** in China and the United States

APG-2449

We will consult with CDE on the **proposed global pivotal registration Phase II study**

Year 2022 : Accelerating Commercialization of Olverembatinib

Revenue

RMB 210 MILLION

change as of same period last year

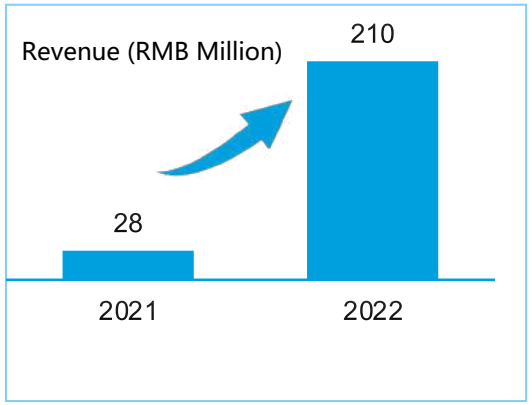
652%

Cash Amount

RMB 1.5 billion

As of reporting day

RMB 1.8 billion



Year 2022

Olverembatinib invoiced sales 182M

Commercialization license fees from Innovent 24.35M

Service income 3.17M

Cash Flow from Operating Activity

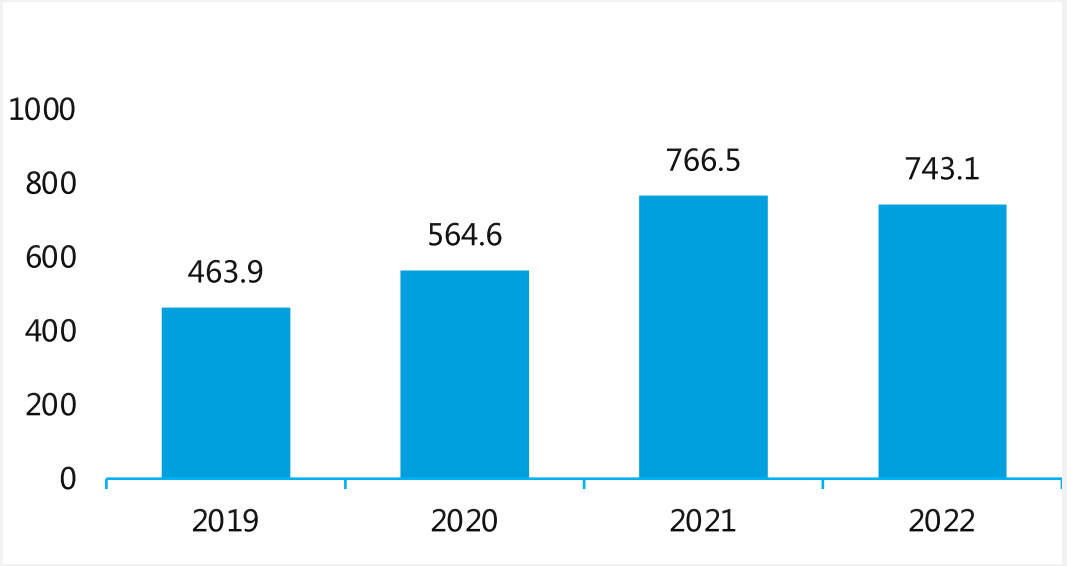
RMB 2.5 billion

change as of same period last year

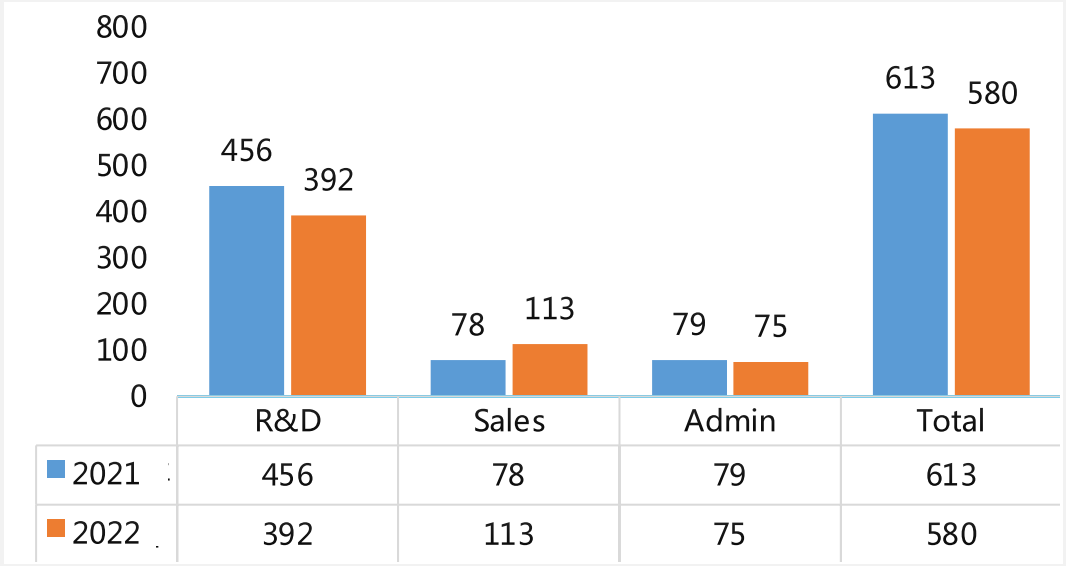
Almost similar

Sustainable Investments in Research & Development

Sustainable Investments in R&D
(RMB mm)



Increasing number of R&D Staff



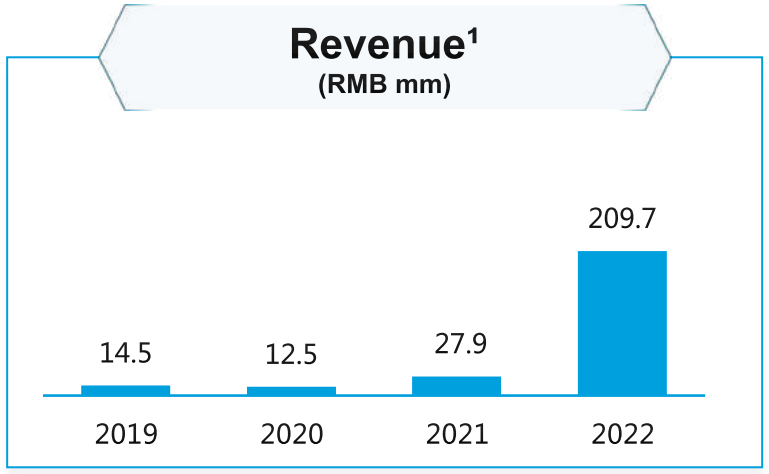
	R&D	Sales	Admin	Total
2021	456	78	79	613
2022	392	113	75	580

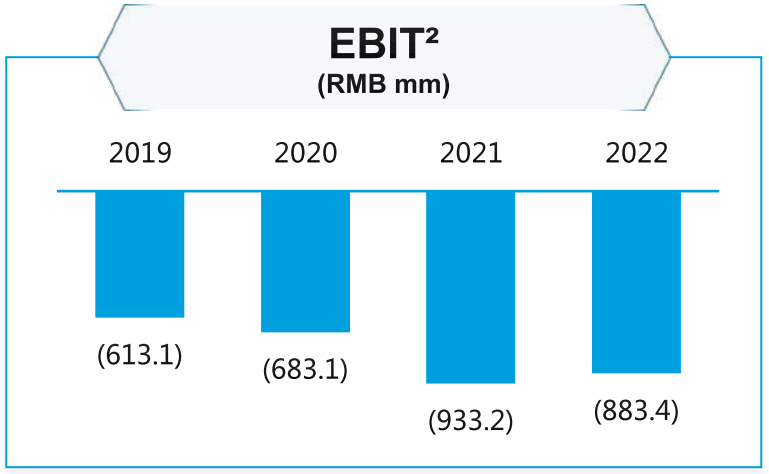
Reduce the R&D personnel, ensure the pipeline development and promote the progress of key clinical trials

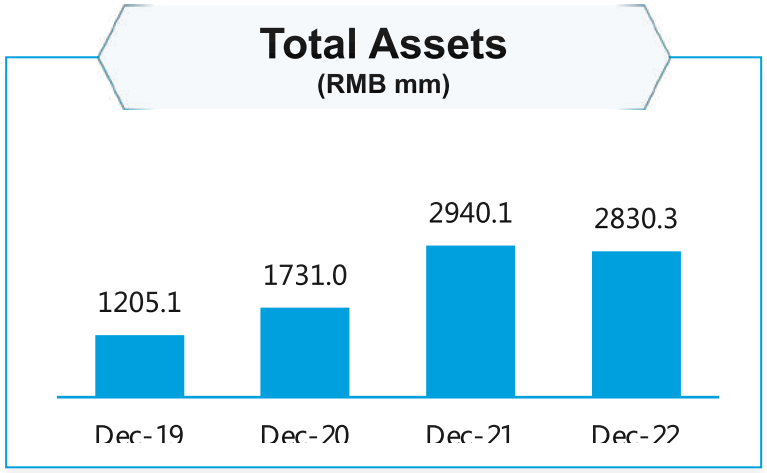
Clinical studies with APG-2575 prioritized with accelerating patient enrollment

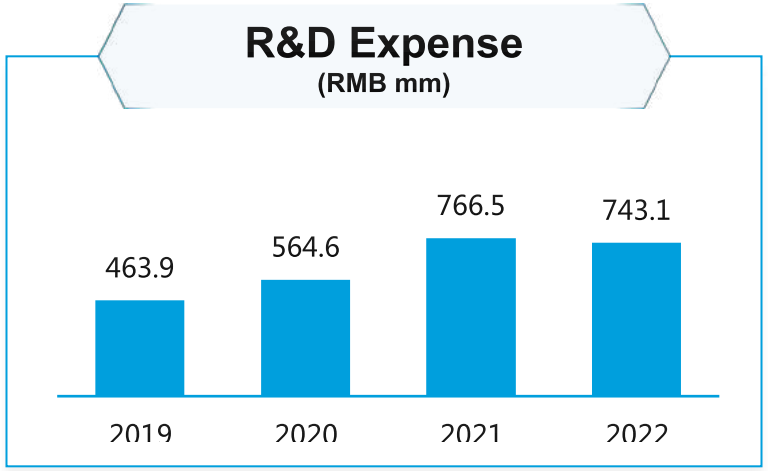
Further build the commercial team to cover the lower-tier cities and hospitals.

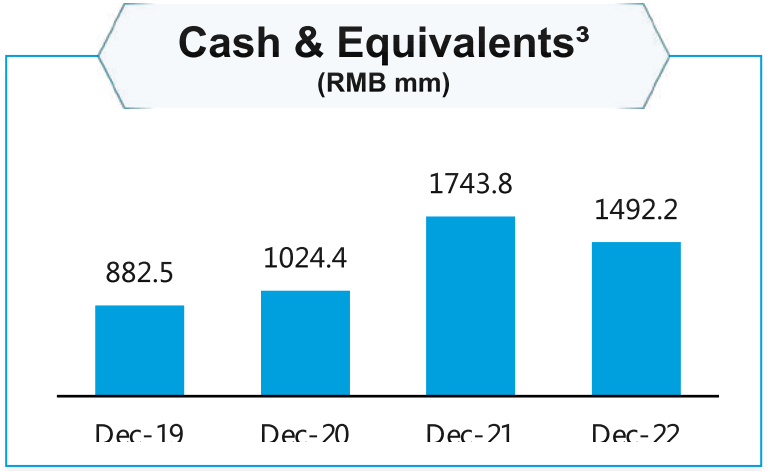
Year 2022 : Increasing revenue while keeping a stable cash reserve











1) Revenue from provision of research and development services, and compounds library and intellectual property license fee income; 2) EBIT = Gross Profit – R&D Expense – Other OPEX 3) Cash & Equivalents include cash and bank balances, and other financial assets, which represent mainly investment in short-term financial products

Accelerating commercialization of Olverembatinib - Accumulated revenue RMB 182 mn

olverembatinib

The first and only third-generation BCR-ABL inhibitor approved in China

Received support from the National New Drug Development and Manufacturing program

Joint commercialization with Innovent Biologics in China

Realized an accumulated invoice sales of RMB 182million (since approval till Dec 31, 2022, audited, tax included)

2021.11	Gained Conditional Approval
2021.12	Frist batch of prescriptions
2021.12	First commercial insurance
2022.04	Included in 2022 edition of CSCO and CACA Guidelines
2022.06	Listed in 34 cities and 10 provinces' Huimin Medical Insurance
2022.07	Launched NPP with Tanner Pharma. Plans to cover over 130 countries and regions globally
2022.12	Accumulated invoiced sales RMB 182 million (tax included)

In November 2021, Olverembatinib was approved in China, fulfilling a major unmet medical gap in patients with CML harboring T315I mutation

November 2021
Gained NDA Approval

End of 2021
Sales (Tax included)
6.147 million

Accumulated
Sales (Tax included)
182million

Expanding market coverage

Product distributors collaboration

Commercial team of +100 staff. Fully on-board in 20221H

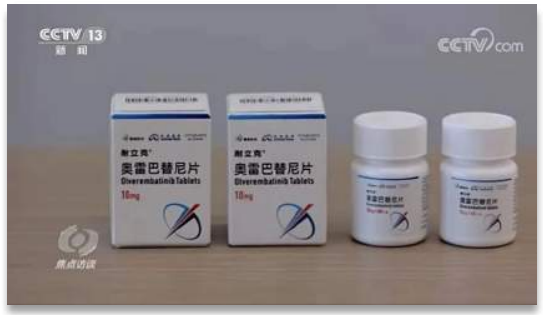
34 cities and 10 provinces' Huimin Commercial Insurance

80% of the total CML market in China

Around 800 hospitals

Olverembatinib was included in 2022 NRDL; Mainstream media coverage drives patient prescriptions

- As a key product to be included in the NRDL in 2022, Olverembatinib was featured on CCTV-1 comprehensive channel and CCTV-13 news channel "Focus Interview". The efficacy of Olverembatinib has been recognized by physicians and patients effectively
- The mainstream media coverage improves the brand image of Olverembatinib nationwide



人民日报 新华社 XINHUA NEWS 健康报 HEALTH NEWS
中国新闻网 WWW.CHINANEWS.COM 经济日报

Increased media press frequency for both HCPs & patients after NRDL

Two weeks after NRDL is effective since March 1st . The number of box sales has tied the highest sales volume in a single month in 2022

Year 2023: Olverembatinib Market Outlook

2023

T315I mutation patient numbers

↗ 3 times

T315I mutation market share

66.7%

Average DOT

↗ 2 times

Drug resistance market share

20%

Dual Channel

100%

Medical insurance pharmacy access

2023

Target hospital listings

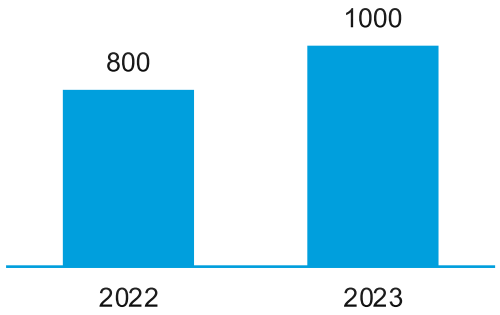
300 hospitals

70% market potential

Year 2023

Make full use of Olverembatinib's first medical insurance period to increase hospital coverage.

Collaborate with Innovent to increase the coverage of hospitals to 1,000.



Drug-resistant indications approved

- ✓ Further expand the user population of Olverembatinib
- ✓ Accelerate the updates of Huimin Insurance nationwide
- ✓ Prepare for the 2023 NRDL negotiation

Rapid Progress with Global Clinical Development Programs

Compounds	Target	Indications	Preclinical	Phase I	Phase II	Registration Trial	NDA Approval	Trial Region	Rights Region
Olverembatinib	BCR-ABL/KIT	Resistant CML					耐立克 奧雷巴替尼 olverembatinib		
		Resistant CML , Ph+ ALL							
		GIST							
		Ph+ ALL							
APG-2575	Bcl-2 Selective	r/r CLL/SLL (China)							
		r/r CLL/SLL (Global)							
		WM							
		AML							
		MDS							
		MM							
		T-PLL							
		MCL							
		ER+/HER2-BC and Solid Tumors							
APG-115	MDM2-p53	Melanoma and Solid Tumors(IO Combo)							
		ACC							
		AML,MDS							
APG-1387	IAP/XIAP	Solid tumors(IO Combo)							
		PDAC+ Chemo							
		CHB							
APG-1252	Bcl-2/Bcl-xL	NSCLC+ TKI							
		SCLC+ Chemo							
		NET							
		NHL							
APG-2449	FAK/ALK/ROS1	NSCLC/ Solid tumors							
APG-5918	EED Selective	Tumors/Hemoglobinopathy							
APG-265	PROTACs MDM2	Tumors							
UBX1967/1325	Bcl Family	DME							

● POC ● POC in progress

Global Clinical Footprint: 40+ Clinical Trials Worldwide

APG-2575	CLL, MM, WM, AML MDS, T-PLL & other Hematologic malignancies; ER+ breast Ca and solid tumors
APG-115	AML, MDS,T-PLL Melanoma, MPNST, ACC and other solid tumors
APG-1387	Solid tumors
HQP1351	TKI resistant CML and Ph+ ALL
APG-5918	solid tumors or hematologic malignancies

APG-2575	CLL/SLL
HQP1351	TKI resistant CML, Ph+ALL

HQP1351	TKI resistant CML, Ph+ALL, GIST
APG-2575	CLL, AML, WM ， MM, T-PLL, MCL
APG-115	AML, MDS, T-PLL, Sarcoma and solid tumors
APG-1387	Pancreatic cancer, solid tumors, CHB
APG-1252	NSCLC, NET,NHL
APG-2449	NSCLC, OC
APG-5918	Advanced solid tumors or hematologic malignancies, anemia

HQP1351	TKI resistant CML, Ph+ ALL

APG-2575	CLL, WM, AML
APG-115	Advanced solid tumors
APG-1387	Advanced solid tumors
APG-1252	SCLC
HQP1351	TKI resistant CML and Ph+ALL

Recognitions by the Global Research Community

ASCO 2022

7 **abstracts selected for presentations**

Drug candidate： Olverembatinib ， Lisaftoclax ， Alrizomadlin ， APG-2449 ， APG-1252

AACR 2022

6 **abstracts selected for presentations**

Drug candidate ： Lisaftoclax ， Alrizomadlin ， APG-2449 ， APG-5918 etc.

EHA 2022

1 **abstract selected for presentation**

Drug candidate: Lisaftoclax

ASH 2022

4 **abstracts selected for oral presentation**

Drug candidate: ： Olverembatinib, Lisaftoclax

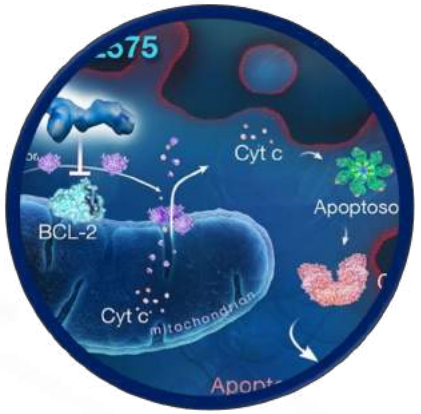
Transition Towards a Fully-Integrated Global Biopharma Company

Ascentage Pharma

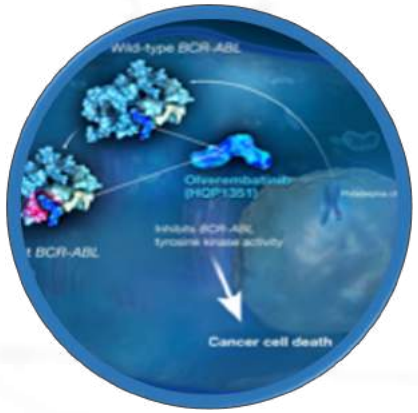
Global Headquarter/R&D Center and Manufacturing Facility in Suzhou, China

- MAH type A certificate was issued in Nov 2022
- Capabilities for incubator and accelerator with angel innovation funding support

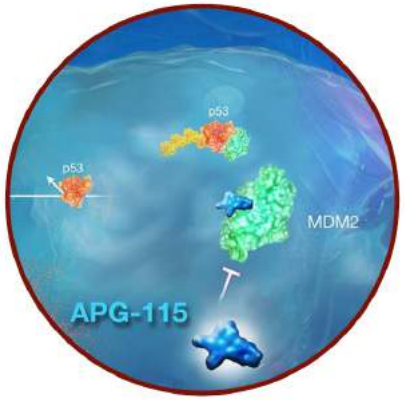
Ascentage Pharma Hematology Portfolio



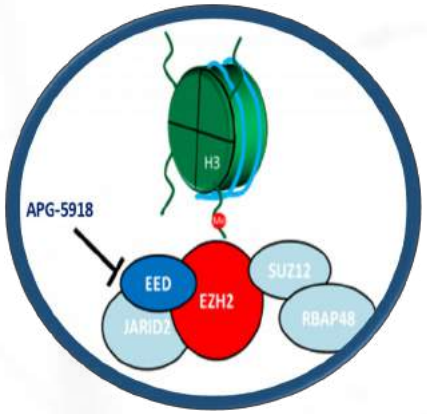
Lisaftoclax a Bcl-2 Selective Inhibitor



Olverembatinib Multi-Kinase BCR-ABL TKI



Alrizomadlin an MDM2-p53 inhibitor



APG-5918 a potent EED inhibitor

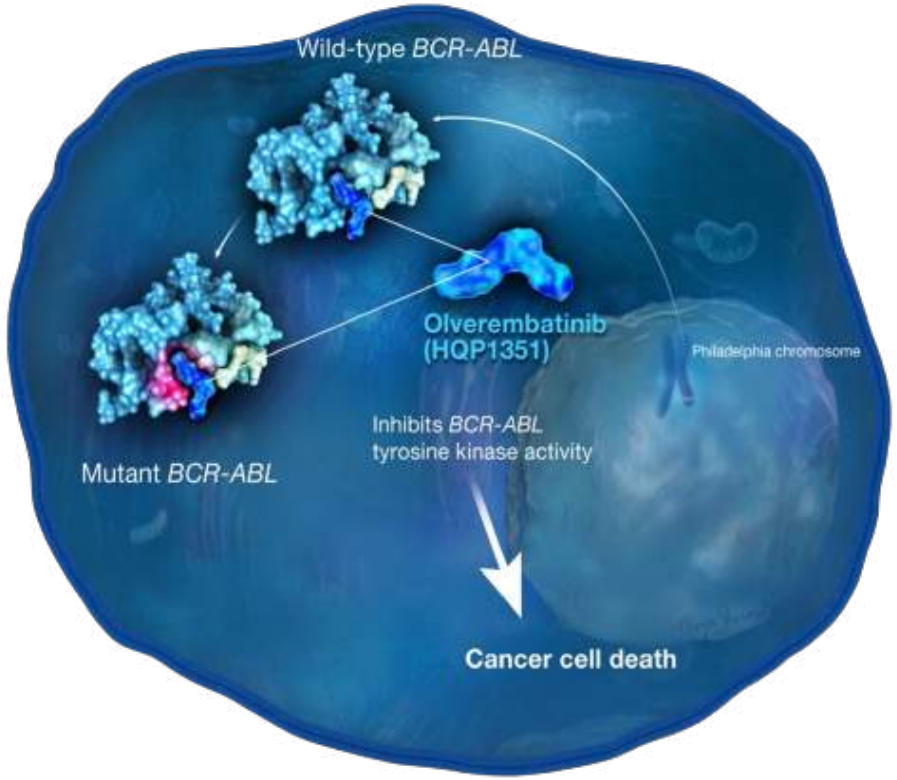
HQP1351
Olverembatinib
Overview

The first and the only commercialized third generation BCR-ABL inhibitor in China

Targeting BCR-ABL mutants, including the T315I mutation

Best-in-class drug potential globally

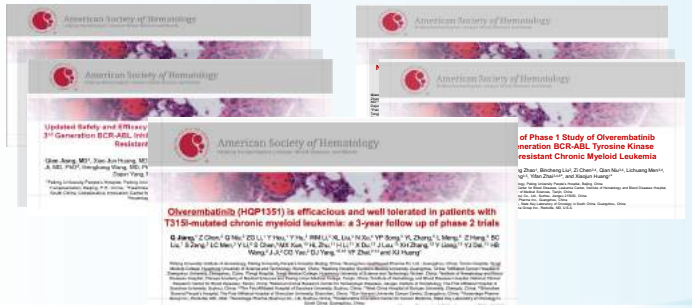
olverembatinib



5 years roadmap: From IND to NDA Approval

- 2020.04: granted **Orphan Drug Designation(CML) and Fast Track Designation** by FDA
- 2020.06: submitted **NDA to the CDE** for T315I-mutant CP-CML and AP-CML in China
- 2020.10 Olverembatinib has granted **Priority Review**

- 2019.01: awarded National Major Innovative Drug Project
- 2019.07: entered Phase Ib clinical study for TKI rCML in US
- 2019.09: finished enrollment of 2 pivotal Phase II trials in China
- Clinical results of olverembatinib in CP|AP TKI resistant / intolerant CML were orally presented at ASH for 5 years from 2018 to 2022 , nominated as "**Best of ASH" in 2019**



2015

- 2015.04: submitted an IND TKI resistant CML in China

2016

- 2016.02: NMPA issued a "one-time umbrella approval" for r/r CML

2018

- 2018.07: held a pivotal Phase II clinical trial kick-off meeting with PI

2019

2020

2021

- 2021.03: received **Breakthrough Therapy Designation**
- 2021.11: received **NDA Approval**
- 2021.11: granted **Orphan Drug Designation (CML)** by European Commission
- 2021.12 granted **Orphan Drug Designation (AML)**

2022

- 2022.03: granted **Orphan Drug Designation (ALL)**
- 2022.04: Included in 2022 CSCO and CACA guidelines for CML and Ph+ ALL
- 2022.07: Received NDA acceptance for full approval and priority review by CDE
- 2022.07 : Gained Canada CTA clearance in Canada
- 2022.09: granted **Orphan Drug Designation (GIST)**

2023

- 2023.01: Has been successfully included in the 2022 NRDL

Basic Information of Olverembatinib Tablets

China Developed, New Chemical Structure, Class 1 Innovative Drugs with Global IP

Generic Name	(Olverembatinib Tablet)
Former Name	HQP1351、耐克替尼
Product Name	Nailike (耐立克®)
NDA Approval Time in China	2021.11.24
Registered Specifications	10mg/tablet

The targeted medicines for CML continue to emerge, and **the five-year survival rate of CML has increased from less than 50% to 90%.** Most patients can achieve long-term survival.

After the currently marketed CML-targeted drugs are widely used, drug resistance is still a difficult clinical problem. More than 50% of drug resistance are t BCR-ABL mutation. T315I mutation is the most common mutation type, accounting for about **10%-30%** of all mutation types.

Currently, all the CML drugs listed in China are ineffective for the treatment of T315I mutation. Before Olverembatinib was launched, **there was no effective treatment for Chinese patients with T315I mutation**, and the survival prognosis was significantly worse than that of other CML patients, which had a huge unmet clinical need.

Medicare reimbursement of Imatinib is the first step for CML patients

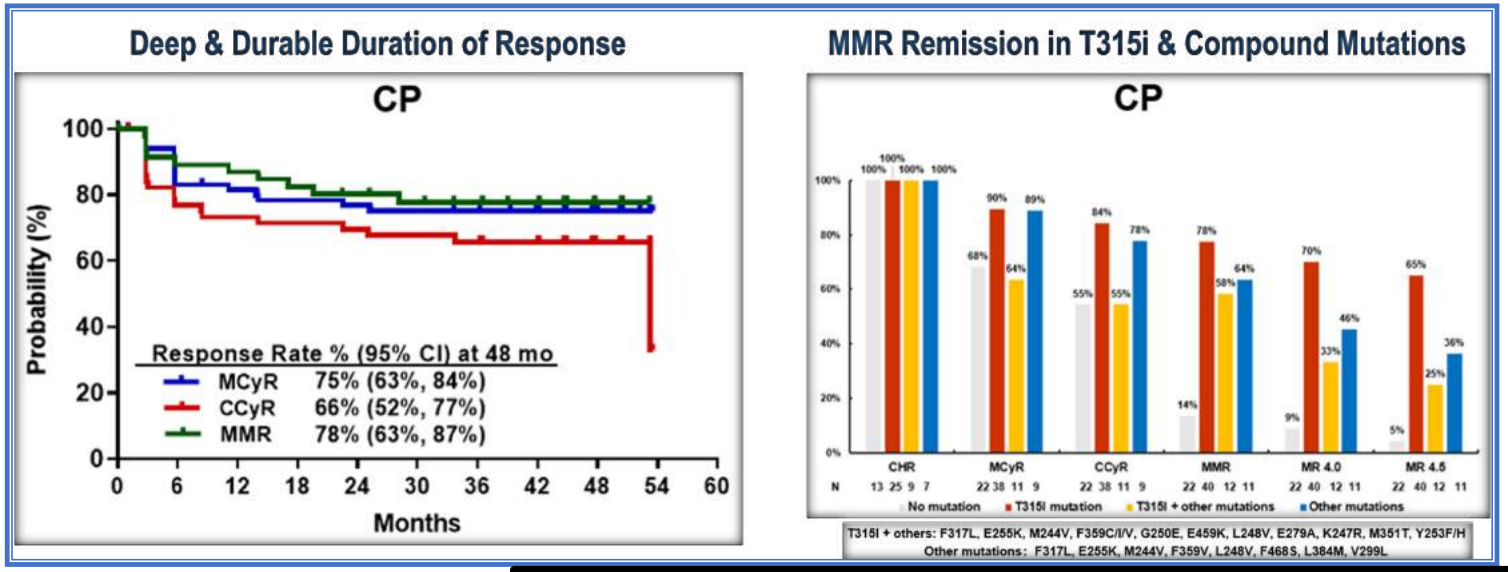
However, Chinese CML patients with T315I mutation have no effective treatments

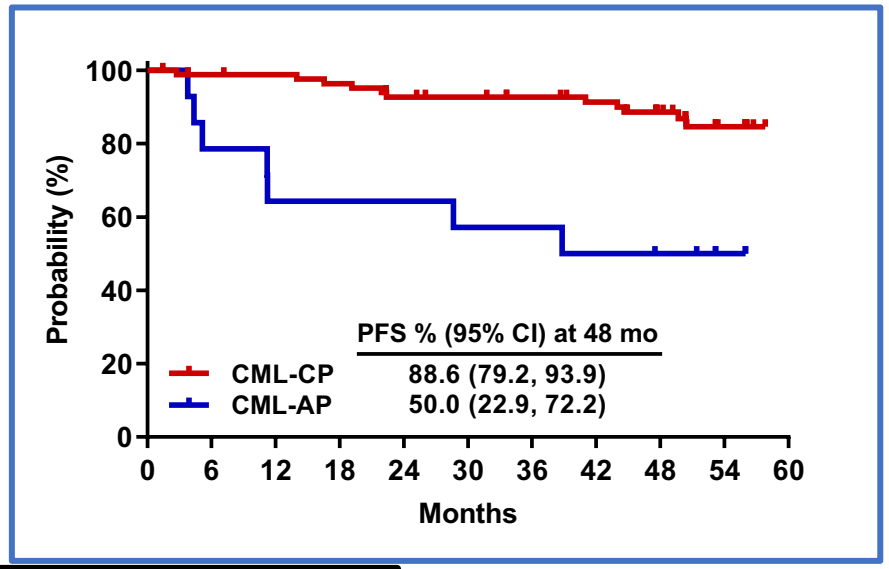
Other drug recommendation

- No domestic comparable drugs

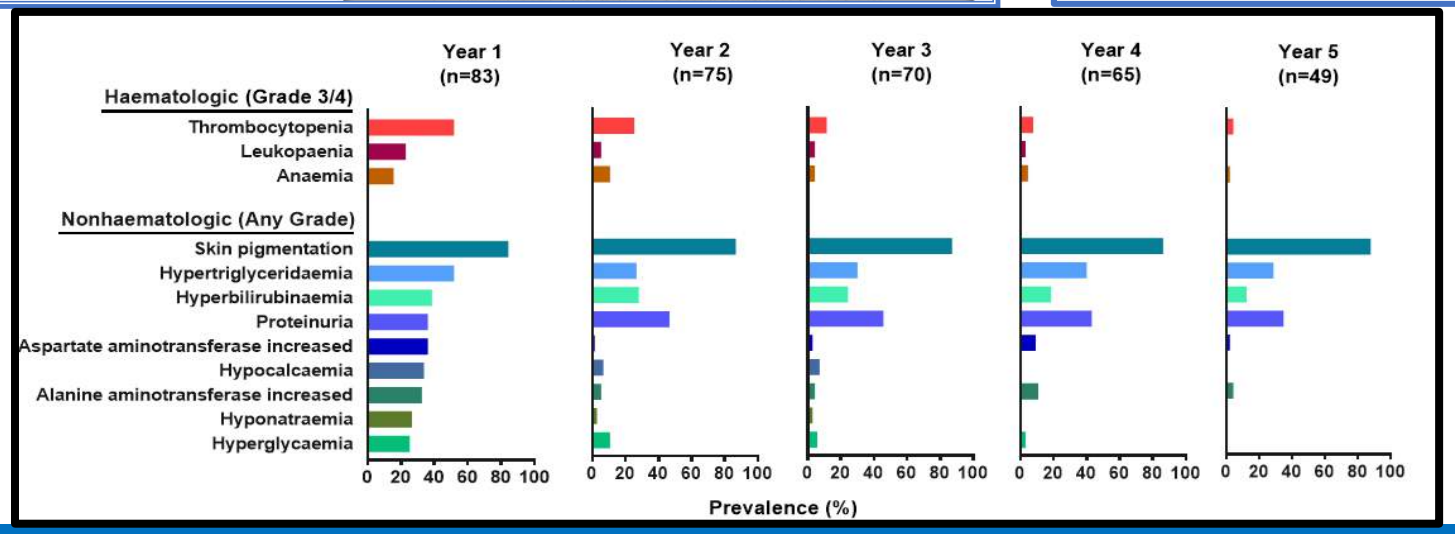
Ph I: Demonstrated Durable Efficacy and Differentiated Safety Profile

Ph I: 5-year data for Olverembatinib





80% of patients remain on therapy for more than 5 years

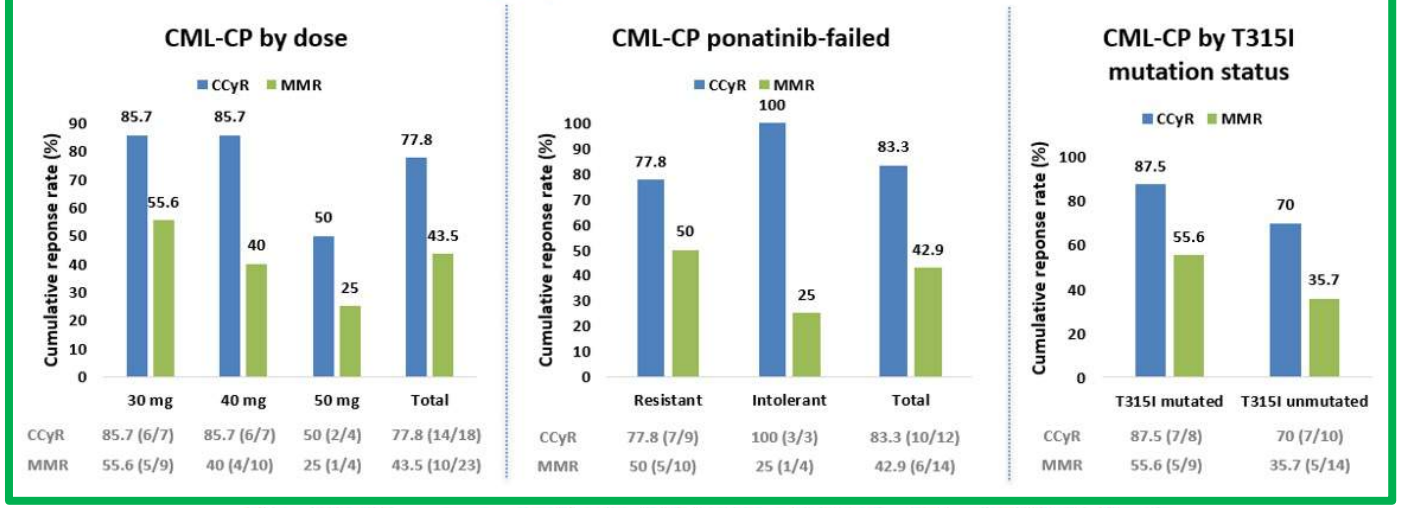


Jiang Q et al. (2022) A Five-Year Follow-up on Safety and Efficacy of Olverembatinib (HQP1351), a Novel Third-Generation BCR-ABL Tyrosine Kinase Inhibitor (TKI), in Patients with TKI-Resistant Chronic Myeloid Leukemia (CML) in China,

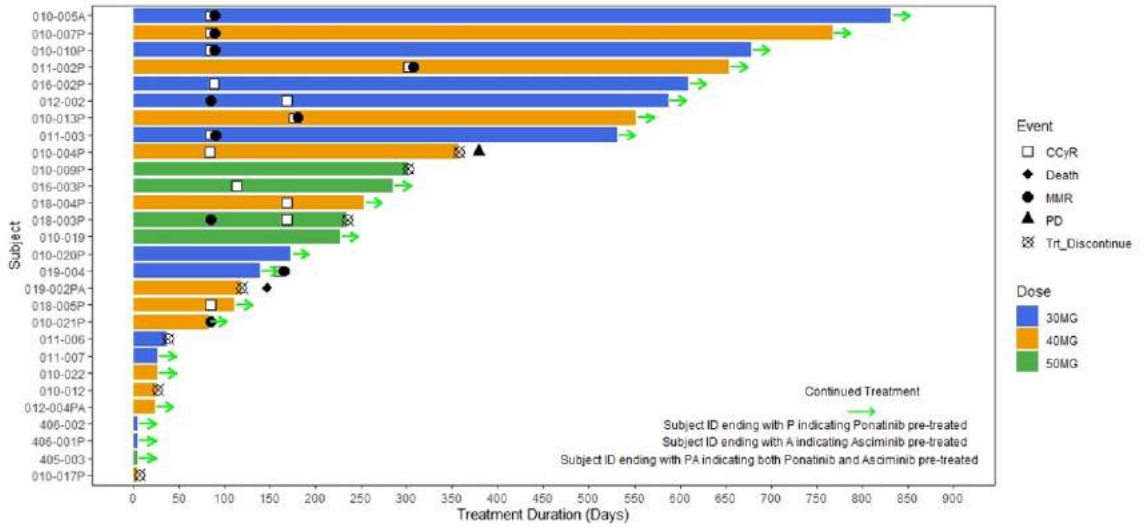
US Ph Ib/II: Olverembatinib is Potentially Effective in Ponatinib Resistant CML

Characteristic	CML-CP	Advanced Ph+ leukemia	Total
N	38	13	51
Line of therapy, n. (%)			
Primary refractory	0	0	0
Salvage 1	6 (15.8)	1 (7.7)	7 (13.7)
Salvage 2	11 (28.9)	3 (23.1)	14 (27.5)
Salvage 3+	18 (47.4)	7 (53.8)	25 (49.0)
Missing	3 (7.9)	2 (15.4)	5 (9.8)
Prior ponatinib use, n (%)	20 (52.6)	8 (80.0)	28 (54.9)
Resistant	14 (70.0)	7 (87.5)	21 (75.0)
Intolerant	6 (30.0)	1 (12.5)	7 (25.0)
T315I mutation	14 (36.8)	5 (38.5)	19 (37.3)

Olverembatinib is Highly effective in Ponatinib Resistant CP-CML



Durable Responses In Asciminib & Ponatinib Resistant CML Patients



Jabbour E et al. ASH (2022) Olverembatinib (HQP1351) Overcomes Ponatinib Resistance in Patients with Heavily Pretreated/Refractory Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) 64th ASH annual meeting

Olverembatinib in patients with TKI-resistant SDH deficient gastrointestinal stromal tumor (GIST)

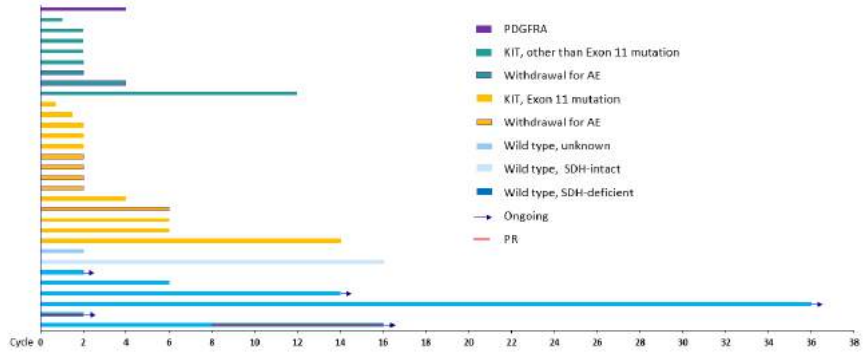
Clinical Result

- Total 39 patients (median age, 52 [19-72] years) received at least 1 dose of olverembatinib.
- Among 31 patients enrolled with KIT/PDGFRA mutations, 13 had stable disease (SD) for at least 2 cycles as the best response, 8 withdrew early, and 10 had progressive disease before Cycle 3.
- Total 6 out of 8 patients with KIT wild-type GIST were confirmed as SDH deficient; of these patients, there were:
- 2 partial responses (PRs); one patient's tumor shrunk by 35.9% and the effect lasted for 16 cycles; another patient's tumor shrunk by 54.2% during the first evaluation.
- 4 SDs for 2, 6, 14, and 36 cycles.
- Clinical benefit rate (CBR) (CR + PR + SD > 4 cycles) of the pts with SDH deficient was 83.3%.
- Treatment-related adverse events (TRAEs; ≥ 20%) included increased leukocytes (59.0%) and neutrophils (46.2%), anemia (20.5%), constipation or asthenia (35.9% each), hyperuricemia (25.6%), hypoalbuminemia (23.1%), and elevated AST or ALT (20.5% each)

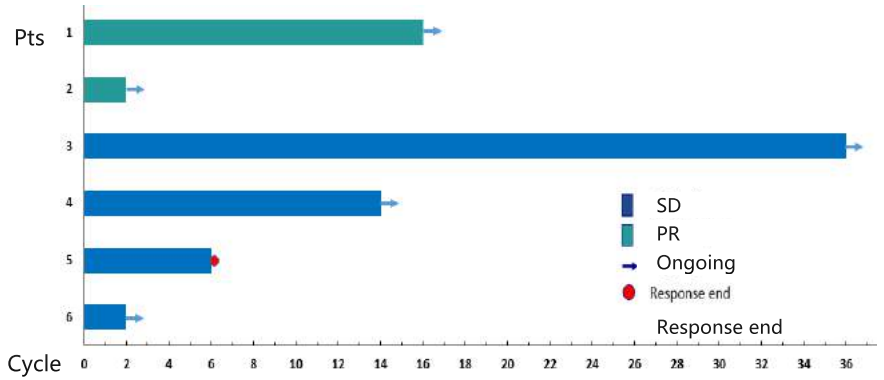
Conclusion

- Olverembatinib was well tolerated at doses up to 50 mg QOD in the patients with TKI resistant GIST.
- Olverembatinib showed antitumor activity in patients with TKI-resistant SDH-deficient GIST, with 2 PRs, 83% clinical benefit rate of 6 evaluable patients and 1 with SD for 36 cycles.
- These promising findings warrant further investigation.

31 Swimmer Plot of 31 Evaluable Pts with TKI Resistant GIST



6 Swimmer Plot of 6 Evaluable TKI Resistant Pts with SDH Deficient GIST



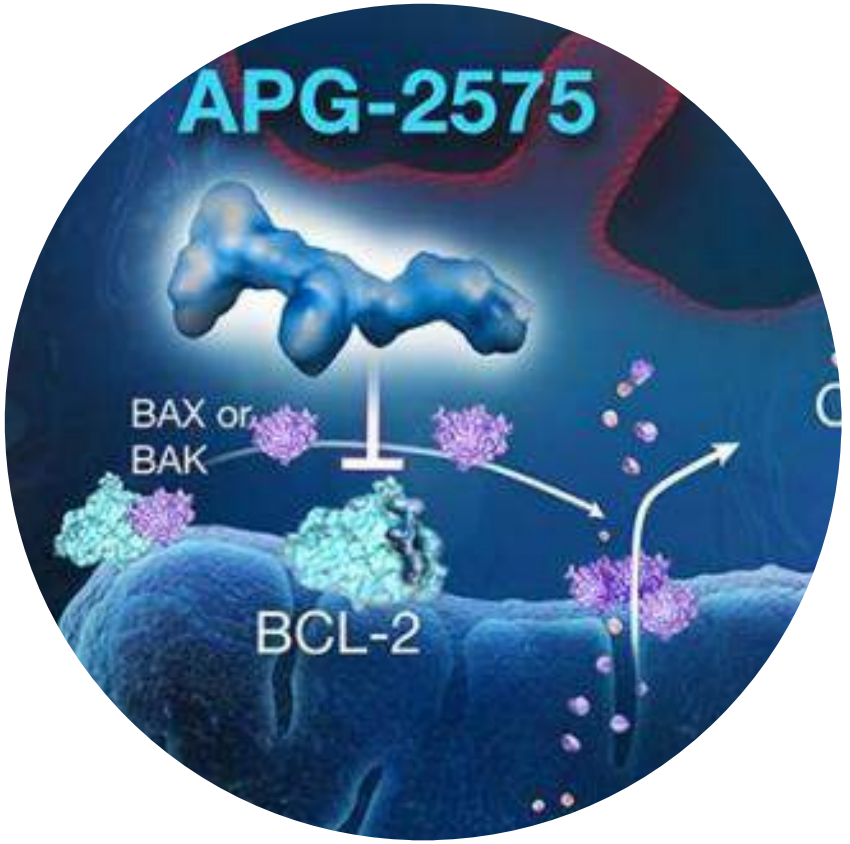
Source: Qian Jiang et al.(2021), Updated results of pivotal phase 2 trials of olverembatinib (HQP1351) in patients (pts) with tyrosine kinase inhibitor (TKI)-resistant BCR-ABL1 T315I-mutated chronic- and accelerated-phase chronic myeloid leukemia (CML-CP and CML-AP) , 2021 ASH Annual Meeting and Exposition

APG-2575 Overview

Novel, orally administered Bcl-2 selective inhibitor, follow to Venclexta®

The second drug entered into pivotal phase II study globally

Best in class potential

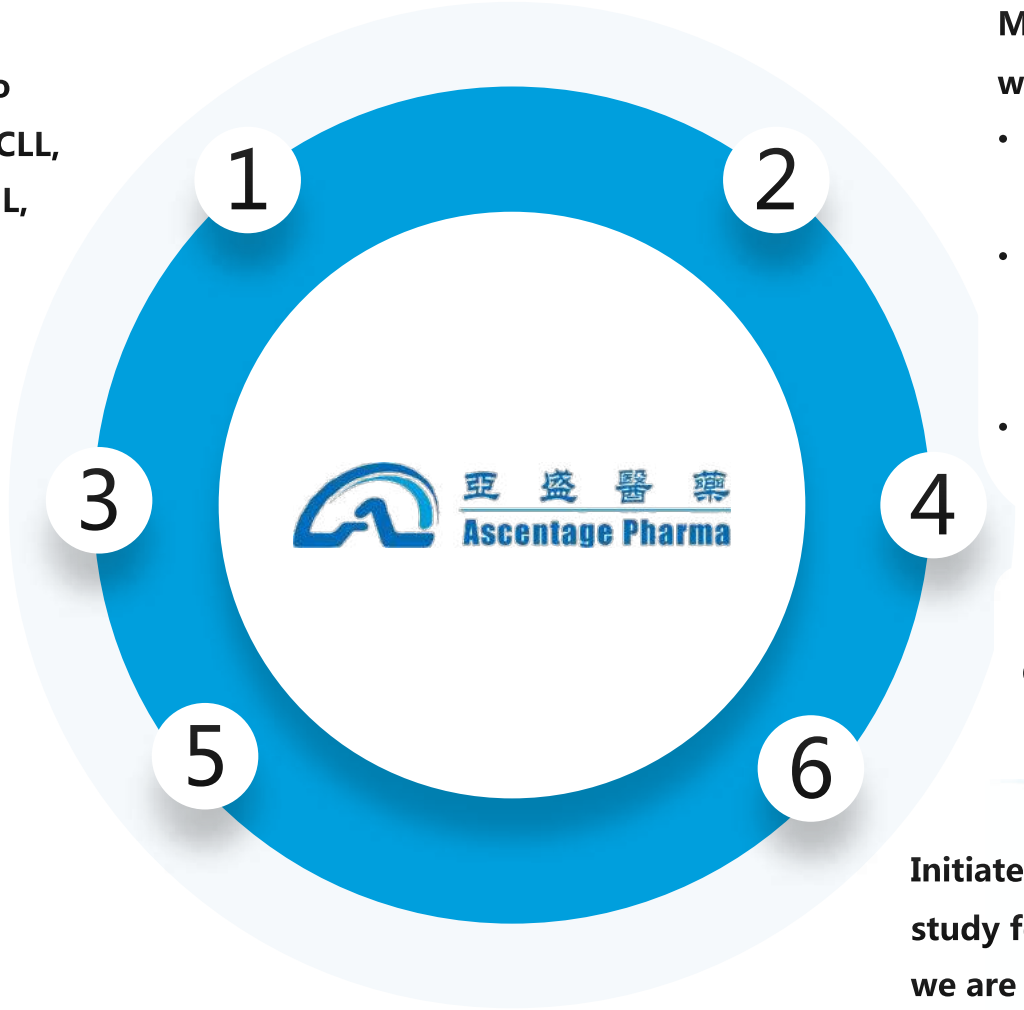


Lisaftoclax：Potential best-in class Bcl-2 inhibitor

More than 500 subjects enrolled into the APG-2575 studies, including r/r CLL, FL, MCL, MZL, DLBCL, WM, MM, AML, MDS and HCL patients

Potential Best-in-Class with well tolerated safety profile, no DLT, no MTD reported

IND clearance for ER+ breast cancer and other solid tumors by FDA



More than 250 CLL patients have been treated with APG-2575 with POC achieved

- 80% PR in Evaluable rrCLL/SLL Patients in US Phase I Study
- Demonstrated 67% ORR in Evaluable rrCLL/SLL Patients in doses ≥ 400 mg, China Phase I Study
- With an ORR of 98%, these data showed impressive clinical utility in R/R CLL/SLL.

5 Orphan Drug Designations (ODD): CLL, WM, MM, AML, FL

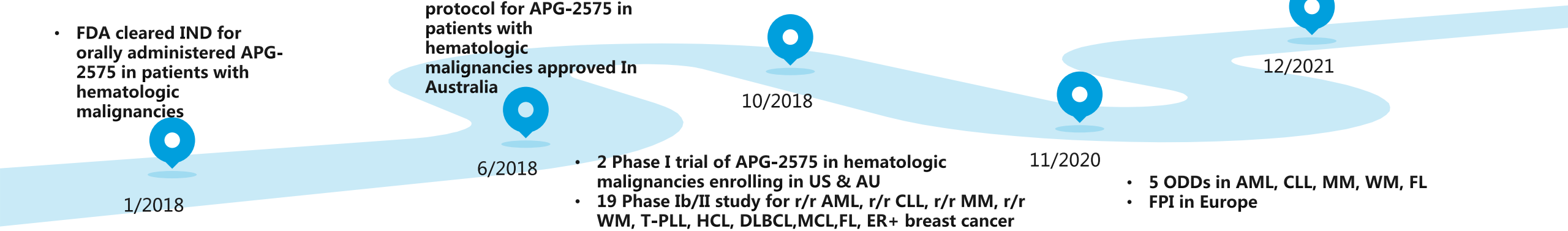
Initiated registrational pivotal Phase II study for treatment of r/r CLL/SLL and we are actively recruiting patients

Lisaftoclax: IND Clearance to Pivotal Study Initiated in 3 Years

- 1 Phase 1 in US/AU
- 6 Phase Ib/II studies in r/r CLL/SLL, MM, WM, AML, MDS, T-PLL, ER+ breast cancer and other solid tumors in US/AU

- 1 Phase 1 in China
- 9 Phase Ib/II studies in r/r AML, r/r CLL/SLL, WM ,MM, T-PLL,MCL, ER+ breast Cancer and solid tumors in China

- 3 Phase Ib/II studies in r/r CLL/SLL in Europe



- FDA cleared IND for orally administered APG-2575 in patients with hematologic malignancies

1/2018

- Phase I clinical trial protocol for APG-2575 in patients with hematologic malignancies approved In Australia

6/2018

- NMPA cleared: An IND for APG-2575 for treatment of patients with hematologic malignancies

10/2018

- 2 Phase I trial of APG-2575 in hematologic malignancies enrolling in US & AU
- 19 Phase Ib/II study for r/r AML, r/r CLL, r/r MM, r/r WM, T-PLL, HCL, DLBCL,MCL,FL, ER+ breast cancer

11/2020

- CDE cleared: Pivotal study in China of APG-2575 for treatment of patients with r/r CLL/SLL

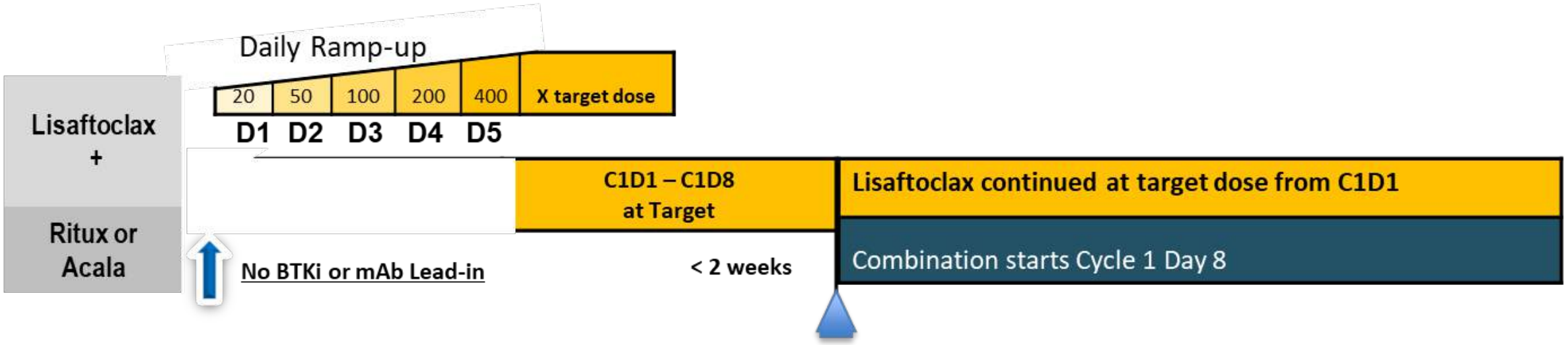
12/2021

- 5 ODDs in AML, CLL, MM, WM, FL
- FPI in Europe

Global Phase II Study in the US: Safety+ Efficacy

Daily Dose Ramp-up: More HCP & Patient Friendly & Eliminated TLS Risk

Lisaftoclax + combination: lisaftoclax daily ramp-up, combination treatment starts < 2 weeks

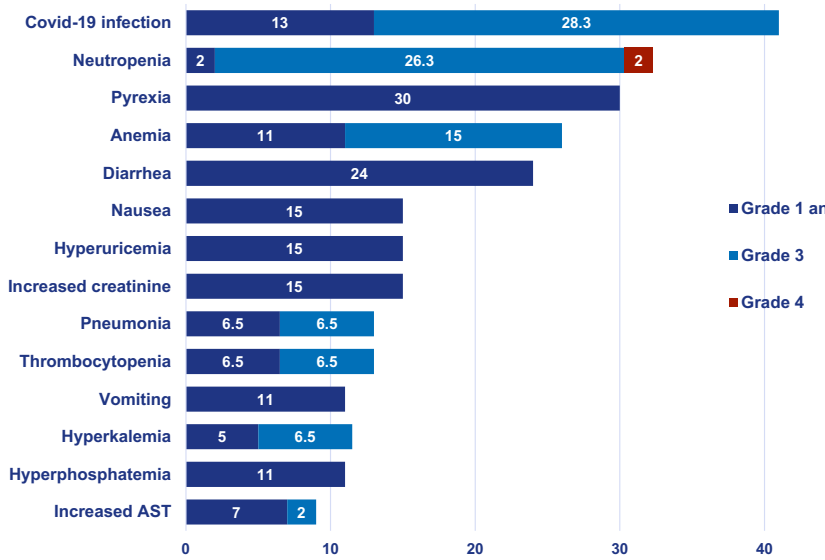


Source: Davids M et al. ASH abstract #964, 2022

Global Phase II Study: Lisaftoclax shows Best-In-Class Safety Profile

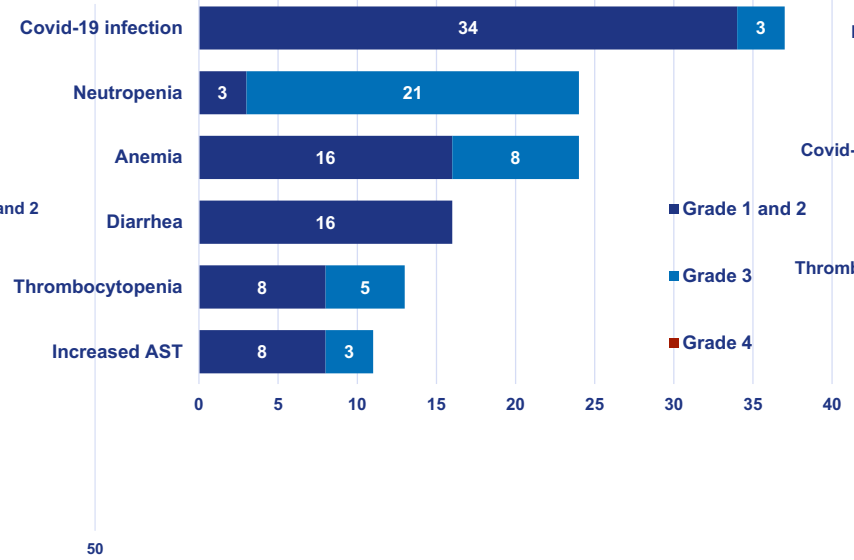
Lisaftoclax monotherapy

Reported Treatment Emergent AEs in ≥ 10% of pts (n = 46)



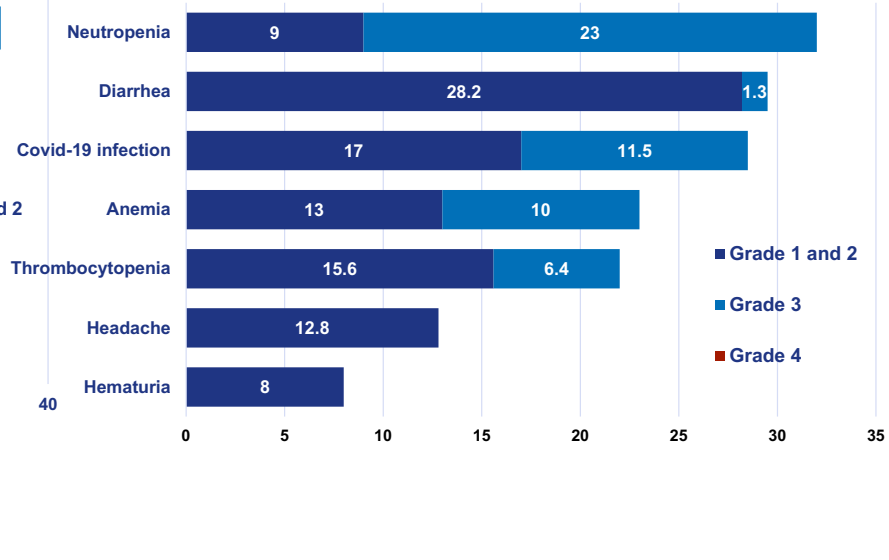
Lisaftoclax + Rituximab

Reported Treatment Emergent AEs in ≥ 10% of pts (n = 39)



Lisaftoclax + Acalabrutinib

Reported Treatment Emergent AEs in ≥ 10% of pts (n = 79)



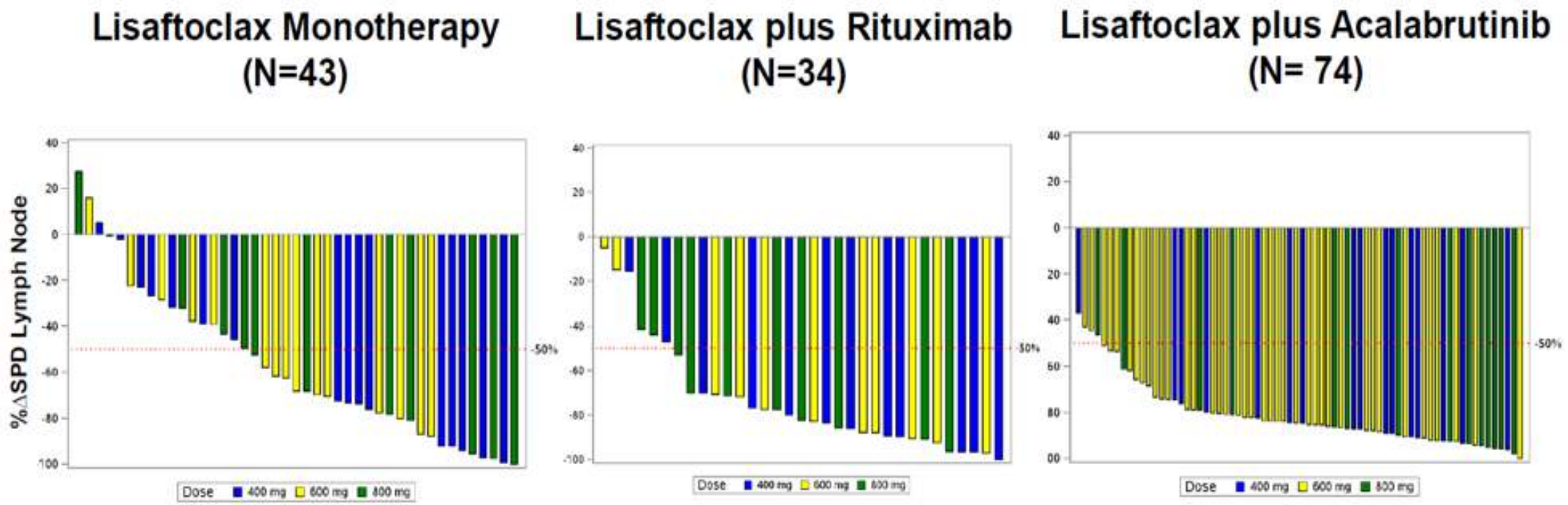
Lisaftoclax: differentiated safety as a single agent or in combination with rituximab or with acalabrutinib

- No DLTs observed, the MTD has not been reached.
- TLS (n = 4; 2 clinical/2 laboratory), Dose reductions due neutropenia (n = 2, 1 in CD20)
- No treatment-related discontinuation or deaths

Source: Davids M et al. ASH abstract #964, 2022

Global Phase II Study: APG-2575 Efficacy Summary

APG-2575 Demonstrated Efficacy is on par with Venetoclax



In r/rCLL, with ORR of:

- Monotherapy(n=43): **67.4%**
- APG-2575 + Rituximab (n=34): **79.4%**
- APG-2575 + Acalabrutinib: TN(n=16):**100%**
- APG-2575 + Acalabrutinib R/R (n=57): **98%**
  - APG-2575 + Acalabrutinib：**R/R BTKi** naïve (n=46): **100%**
    APG-2575 + Acalabrutinib：R/R **Venetoclax** refractory (n=4): **75%**

Source: Davids M et al.(2022) Lisaftoclax (APG-2575) Safely and Activity As Monotherapy or Combined with Acalabrutinib or Rituximab in Patients (pts) with Treatment-Naïve, Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (R/R CLL/SLL): Initial Data from a Phase 2 Global Study, 64th ASH annual meeting

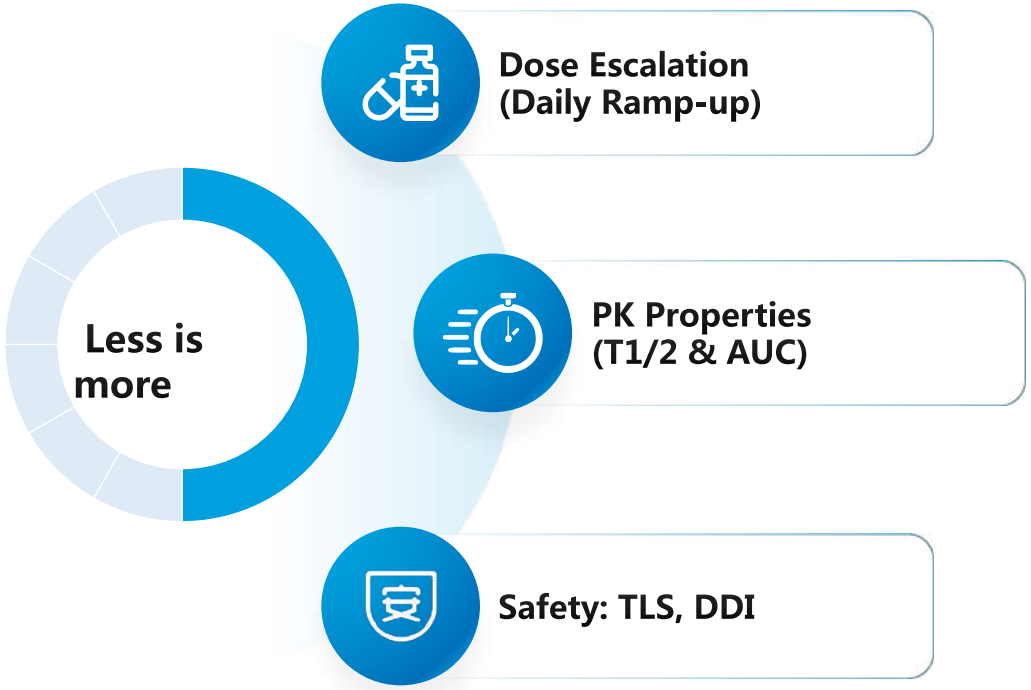
Strong Differentiation From Venetoclax

APG-2575 Compared to Venetoclax

- Efficacious in BTK resistant WM PDX model in which Venetoclax shows no effect
- Daily ramp-up verse weekly ramp up
- Extremely low lab and clinical TLS
- Less neutropenia and thrombocytopenia
- Short T1/2 & exposure--potentially lower risk with better safety profile
- Second BCL-2 registration clinical trial globally
  First BCL-2 registration clinical trial for CLL in China

Conclusion

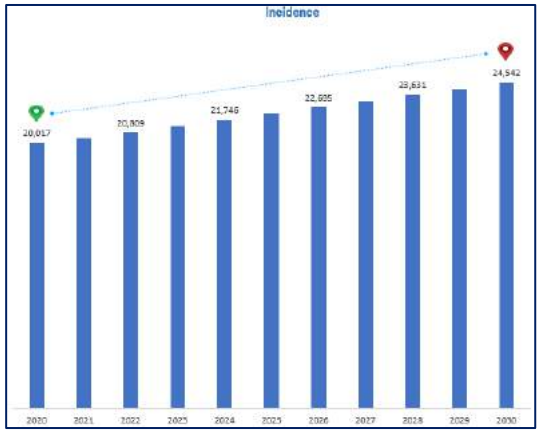
When Selectively Targeting BCL-2



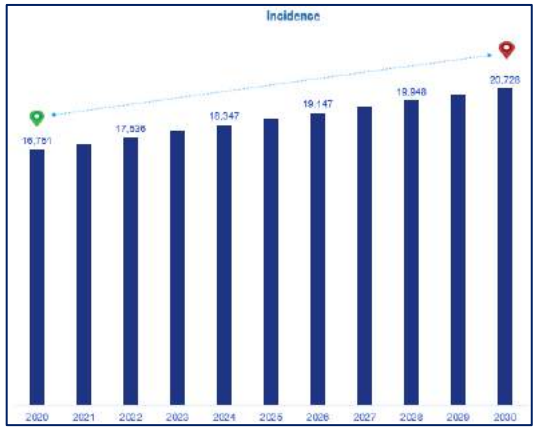
Lisaftoclax Potential

Significant Opportunity for 2nd Gen, Better Safety Profile, More Patient & HCP Friendly BCL-2 Inhibitor

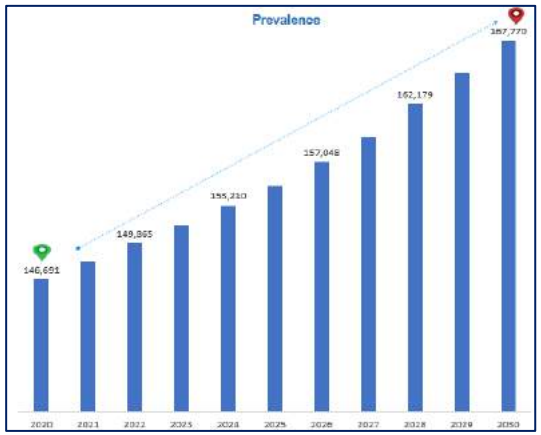
US CLL Patient Forecast

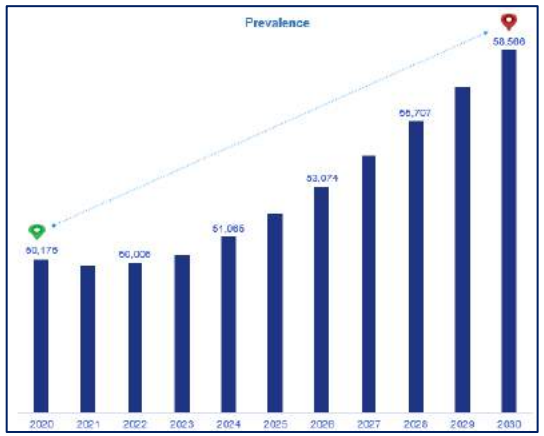


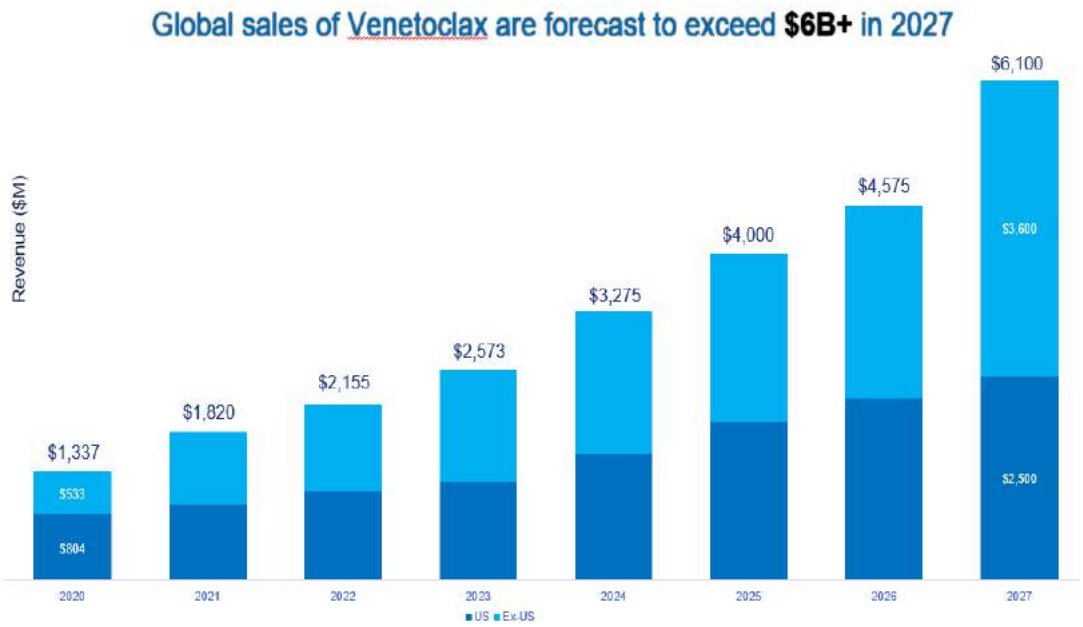
US AML Patient Forecast



Significant Patient Growth in each Disease







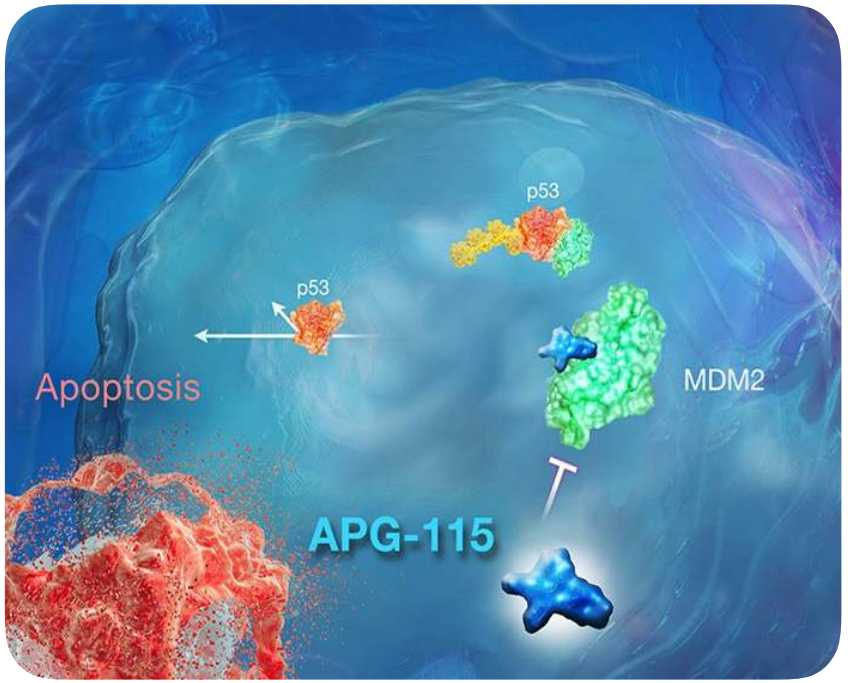
Source: Cerner Enviza CancerMPact 2022, Clarivate; Reported Sales and Consensus Forecasts

APG-115

MDM2-p53 Inhibitor

Activates p53 tumor suppression via MDM2-p53 PPI

Potential First-in-Class Drug



Alrizomadlin : Mechanism

APG-115 Delivers Anti-tumor Activity by Multiple MOAs

Tumor Cells Apoptosis

Activates WT p53-dependent intrinsic apoptosis.

T-Cell Mediated Anti-tumor Immunity

MDM2 protein expression is upregulated in T-cell and is essential in enhancing T-cell function via stabilization of STAT5 protein (Zhou et al. Nature 2021)

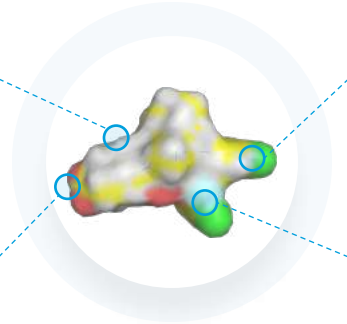
nature immunology ARTICLES

The ubiquitin ligase MDM2 sustains STAT5 stability to control T cell-mediated antitumor immunity

Jiajia Zhou[1,2], Ilona Kryczek[1,2], Shasha Li[1,2], Xiong Li[1,2], Angelo Aguilar[3,4,5], Shuang Wei[1,2], Sara Grove[1,2], Linda Vatan[1,2], Jiali Yu[1,2], Yijian Yan[1,2], Peng Liao[1,2], Heng Lin[1,2], Jing Li[1,2], Gaopeng Li[1,2], Wan Du[1,2], Weichao Wang[1,2], Xueting Lang[1,2], Weimin Wang[1,2], Shaomeng Wang[3,4,5] and Weiping Zou[1,2,4,5,6]

Targeting the p53–MDM2 pathway to reactivate tumor p53 is a chemotherapeutic approach. However, the involvement of this pathway in CD8+ T cell-mediated antitumor immunity is unknown. Here, we report that mice with MDM2 deficiency in T cells exhibit accelerated tumor progression and a decrease in tumor-infiltrating CD8+ T cell survival and function. Mechanistically, MDM2 competes with c-Cbl for STAT5 binding, reduces c-Cbl-mediated STAT5 degradation and enhances STAT5 stability in tumor-infiltrating CD8+ T cells. Targeting the p53–MDM2 interaction with a pharmacological agent, APG-115, augmented MDM2 in T cells, thereby stabilizing STAT5, boosting T cell immunity and synergizing with cancer immunotherapy. Unexpectedly, these effects of APG-115 were dependent on p53 and MDM2 in T cells. Clinically, MDM2 abundance correlated with T cell function and interferon-γ signature in patients with cancer. Thus, the p53–MDM2 pathway controls T cell immunity, and targeting this pathway may treat patients with cancer regardless of tumor p53 status.

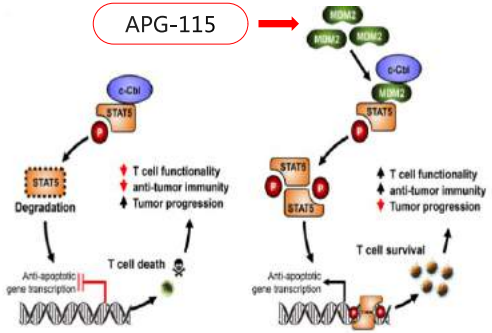
- APG-115 synergizes with IO and enhances T-cell mediated antitumor immunity



APG-115

Inhibition of MDM2-p53 interaction

Host immunomodulat



Zhou J et al. Nat Immunol 2021;22:460-470.

STAT5, signal transducer and activator of transcription 5.

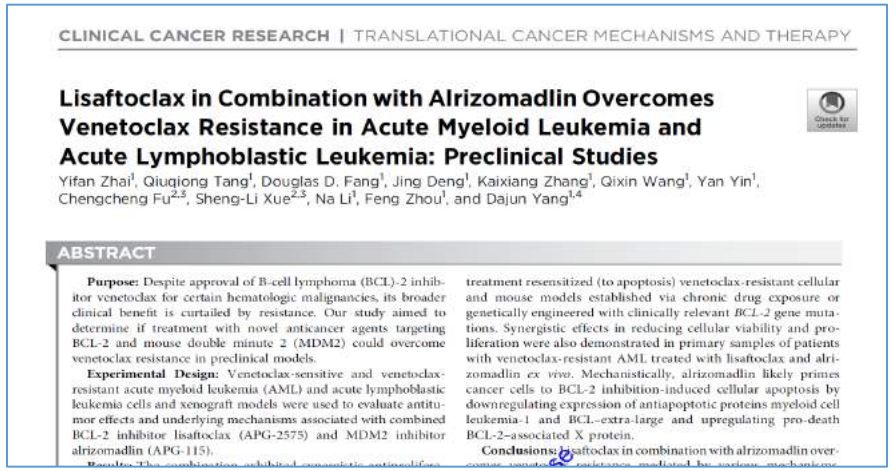
5. Tolcher AW et al. Molec Cancer Ther 2019;18:A086.

Tumor microenvironment

Activates innate immunity by reprograming macrophages M2 to M1 to suppress tumorigenesis (Fang et al. 2019).

Synthetic Lethality

Alrizomadlin in combination with Lisaftoclax overcomes Venetoclax resistance in AML (Zhai et al. Clinical Cancer Research 2023)



CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Lisaftoclax in Combination with Alrizomadlin Overcomes Venetoclax Resistance in Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia: Preclinical Studies

Yifan Zhai[1], Qiuqiong Tang[1], Douglas D. Fang[1], Jing Deng[1], Kaixiang Zhang[1], Qixin Wang[1], Yan Yin[1], Chengcheng Fu[2,5], Sheng-Li Xue[2,5], Na Li[3], Feng Zhou[1], and Dajun Yang[1,4]

ABSTRACT

Purpose: Despite approval of B-cell lymphoma (BCL)-2 inhibitor venetoclax for certain hematologic malignancies, its broader clinical benefit is curtailed by resistance. Our study aimed to determine if treatment with novel anticancer agents targeting BCL-2 and mouse double minute 2 (MDM2) could overcome venetoclax resistance in preclinical models.

Experimental Design: Venetoclax-sensitive and venetoclax-resistant acute myeloid leukemia (AML) and acute lymphoblastic leukemia cells and xenograft models were used to evaluate antitumor effects and underlying mechanisms associated with combined BCL-2 inhibitor lisaftoclax (APG-2575) and MDM2 inhibitor alrizomadlin (APG-115).

treatment resensitized (to apoptosis) venetoclax-resistant cellular and mouse models established via chronic drug exposure or genetically engineered with clinically relevant *BCL-2* gene mutations. Synergistic effects in reducing cellular viability and proliferation were also demonstrated in primary samples of patients with venetoclax-resistant AML treated with lisaftoclax and alrizomadlin *ex vivo*. Mechanistically, alrizomadlin likely primes cancer cells to BCL-2 inhibition-induced cellular apoptosis by downregulating expression of antiapoptotic proteins myeloid cell leukemia-1 and BCL-extra-large and upregulating pro-death BCL-2–associated X protein.

Conclusions: Lisaftoclax in combination with alrizomadlin over-

- APG-115 synergized with APG-2575 in inhibition of proliferation of the primary AML cells derived from venetoclax resistant patients ex vivo

Source: Jiajia Z, et al.(2021)The ubiquitin ligase MDM2 sustains STAT5 stability to control T cell-mediated antitumor immunity
Y. Zhai, et al.(2023) Lisaftoclax in Combination with Alrizomadlin Overcomes Venetoclax Resistance in Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia: Preclinical Studies.

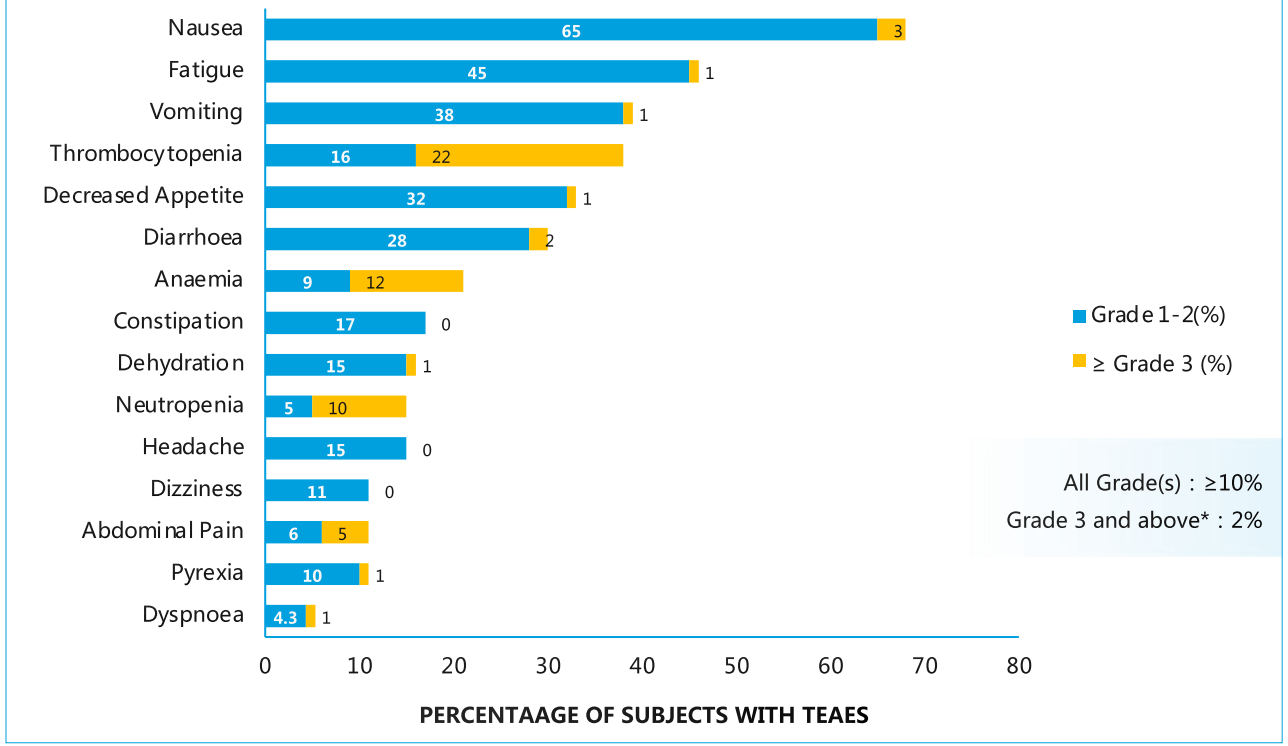
Alrizomadlin plus pembrolizumab: phase 2 study in adults and children with various solid tumors

Safety

	Any TEAE(s)		
Safety Population	Any Grade	Grade 3+	Serious
N (%)	n (%)	n (%)	n (%)
150 (100%)	145 (96.7)	86 (57.3)	52 (34.7)

	Related TEAE(s)		
Safety Population	Any Grade	Grade 3+	Serious
N (%)	n (%)	n (%)	n (%)
150 (100%)	130 (86.7)	51 (34.0)	10 (6.7)

There have been no significant new safety alerts observed to date for this study that are either unanticipated and/or unmanageable.
*Corresponding events selected.
Data cutoff date: March 1, 2022.



- This phase 2 study continues to demonstrate that alrizomadlin in combination with pembrolizumab is well tolerated in 150 subjects.
- These preliminary and interim results demonstrate clinical benefit of alrizomadlin combined with pembrolizumab in patients with melanoma with relapse/refractory disease, with a 55% and 73% DCR in cutaneous and uveal melanoma, respectively.
- Alrizomadlin combined with pembrolizumab demonstrates clinical benefit in patients with MPNST, with a 50% DCR, an orphan pediatric indication with no effective standard of care.

Source: Mckean M, et al.(2022) Newly updated activity results of alrizomadlin (APG-115), a novel MDM2/p53 inhibitor, plus pembrolizumab: phase 2 study in adults and children with various solid tumors ,2022 ASCO Annual Meeting

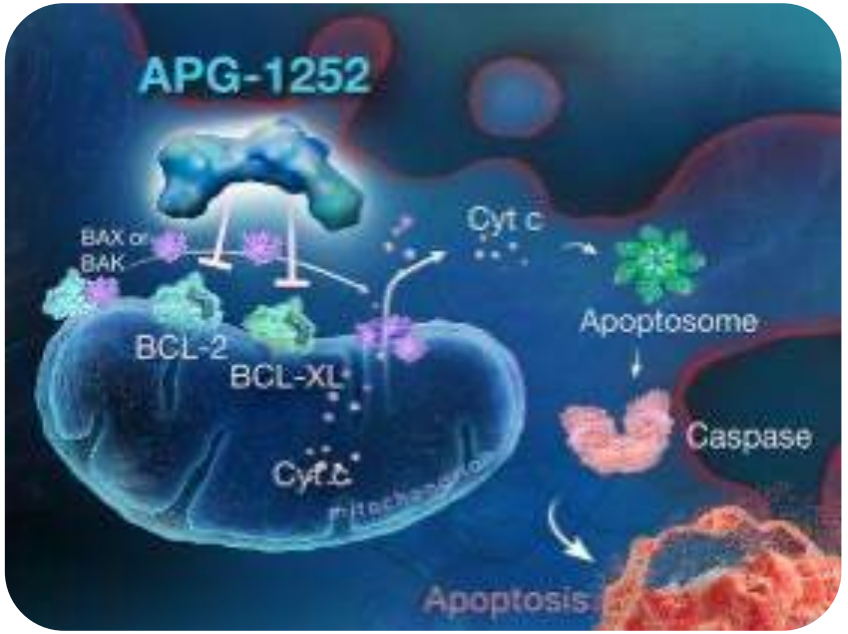
APG-1252

Bcl-2/Bcl-xL inhibitor

Combination use for the treatment of solid tumors and hematologic malignancies

Granted an ODD
for the treatment of SCLC

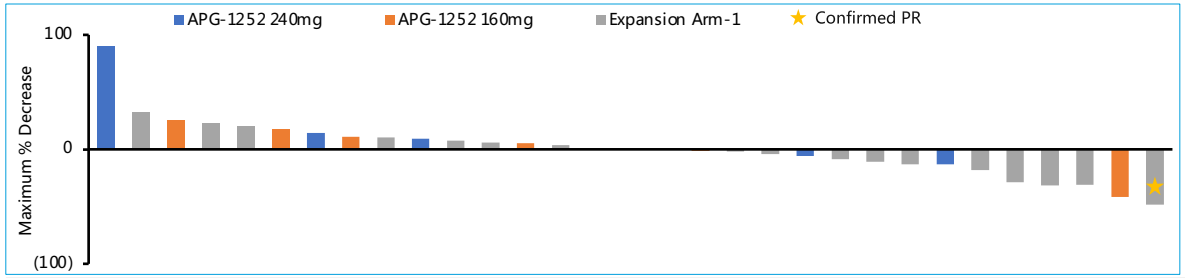
Potential Best-in-Class Drug



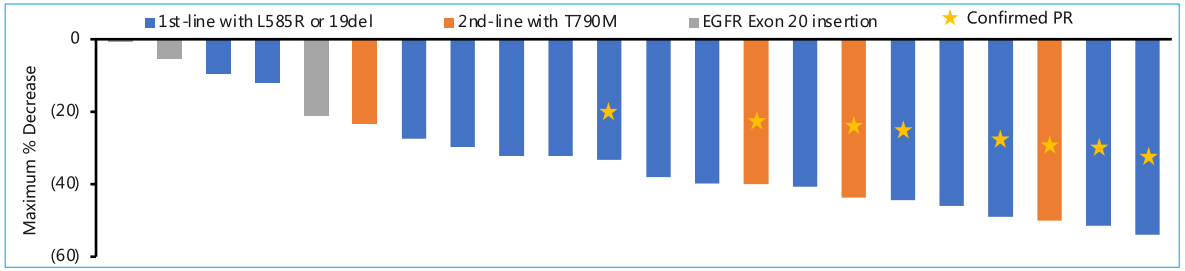
APG-1252 plus Osimertinib：Efficacy

Best response, n (%)	Dose determination 240mg (n=6)	Dose determination 160mg (n=5)	Expansion Arm-1 (n=20)	Expansion Arm-2 (n=22)
Partial response (unconfirmed)	0 (0.0)	1 (20.0)	3 (15.0)	13 (59.1)
Partial response (confirmed)	0 (0.0)	0 (0.0)	1 (5.0)	8 (36.4)
Stable disease	5 (83.3)	2 (40.0)	13 (65.0)	8 (36.4)
Progressive disease	1 (16.7)	2 (40.0)	4 (20.0)	1 (6.3)
DCR	5 (83.3)	3 (60.0)	16 (80.0)	21 (95.5)

Dose determination and expansion Arm-1 N=31



Expansion Arm-2 N=22



- In arm 1 of dose-expansion phase: 3 PRs and 13 SDs in 20 evaluable patients with ORR of 15% and DCR of 80%
- In arm 2 of dose-expansion phase, 13 PRs and 8 SDs in 22 evaluable patients, including 3 patients harboring EGFR Exon 20 insertion with ORR of 59.1% and DCR of 95.5%.

Combination treatment with APG-1252 and osimertinib at RP2D was safe and feasible.

Preliminary synergy and efficacy of both APG-1252 and osimertinib were also observed in some patients with EGFR TKI osimertinib-resistant and naïve NSCLC.

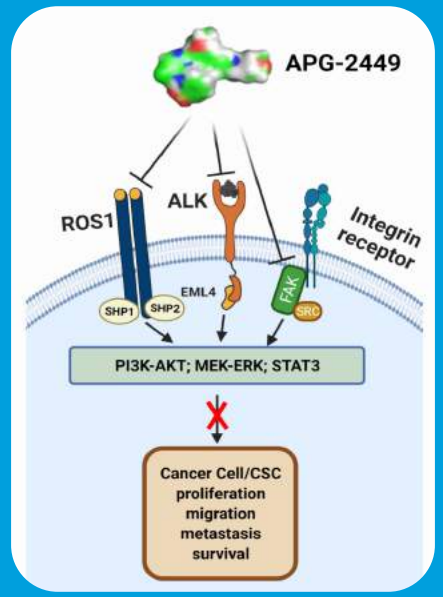
In treatment-naive and second-line patients with the EGFR T790M mutation or Exon 20 insertion, APG-1252 showed similar efficacy compared with navitoclax when combined with osimertinib

No significant difference in PK profiles of APG-1252 and osimertinib observed in combination treatment when compared to monotherapy.

Source: Li Zhang et al.(2021), Phase Ib Study of Pelcitoclax (APG-1252) in Combination With Osimertinib in Patients With EGFR TKI-Resistant NSCLC , 2021 World Conference on Lung Cancer (WCLC)

APG-2449

ALK/FAK/ROS1



Milestones & Clinical Developments

APG-2449

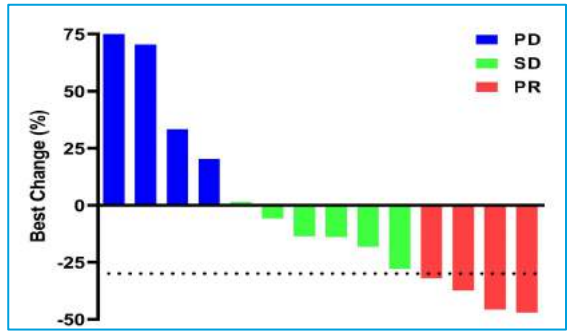
- APG-2449 is a novel, orally active, small molecule FAK/ALK/ROS1 triple ligase kinase inhibitor designed and developed by Ascentage. It is the first third-generation ALK inhibitor being developed in China.
- Pre-clinical data indicated that It is a very potential novel anticancer drug targeting FAK-expressing tumors and/or ALK/ROS1 fusion gene-positive non-small cell lung cancer.
- APG-2449 dose-dependently inhibited the expression of phosphorylated ALK protein (P-ALK) and its downstream proteins in Ba/F3 cells harboring ALK WT or EML4-ALK L1196M mutation.

Clinical development of APG-2449

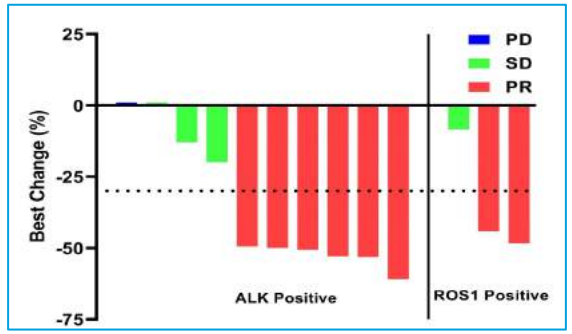
- Dose Escalation study was completed for phase I study in which patients with ALK+ NSCLC or other solid tumors were enrolled. Enrollment is ongoing for Dose Expansion Cohorts for efficacy assessment in different patient population
- In April 2022, the preclinical study presented at AACR 2022 demonstrated that FAK inhibitor APG-2449 and CDK4/6 inhibitor palbociclib synergistically suppress mesothelioma tumor growth via autophagy induction.
- In June 2022, the Phase I study results were published as a poster presentation at ASCO 2022. The preliminary result showed that APG-2449 has a favorable safety profile and anti-cancer activity was observed in patients who failed second-generation TKIs treatment and in TKI-naïve patients.
- Based on the preliminary efficacy result of phase I study, the engagement with CDE for pivotal phase II registration study design is to be initiated.

First-in-human phase 1 results of APG-2449 with second-generation TKI-resistant ALK/ROS1+ NSCLC or mesothelioma

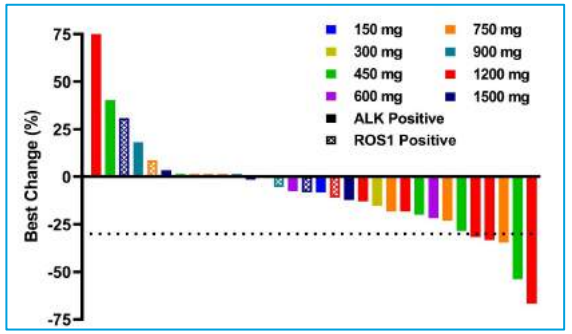
Efficacy



Best tumor change (%) in pts with second-generation TKI resistant ALK+ NSCLC treated with RP2D of APG-2449



Best tumor change (%) in pts with TKI-naïve ALK/ROS1+ NSCLC treated with RP2D of APG-2449



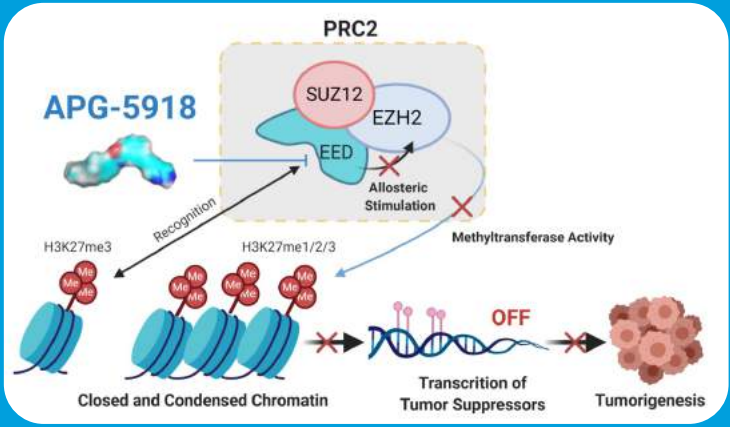
Best tumor change (%) of brain metastases observed in pts with second-generation TKI resistant ALK+ NSCLC treated with APG-2449 at different assigned doses

- APG-2449 has demonstrated a favorable safety and PK profile and was well tolerated in 84 patients with NSCLC or mesothelioma.
- Preliminary efficacy was observed in patients who were resistant to second-generation TKIs, especially among those with brain metastases, and in TKI-naïve patients.
- Biomarker data suggests potential target engagement on FAK and immunomodulatory effects of APG-2449.
- RP2D was determined to be APG-2449 1,200 mg once daily.

Source: Zhao H, et al.(2022) First-in-human phase 1 results of APG-2449, a novel FAK and third-generation of ALK/ ROS1 tyrosine kinase inhibitor (TKI), in patients (pts) with second-generation TKI-resistant ALK/ROS1+ NSCLC or mesothelioma, 2022 ASCO Annual Meeting

APG-5918

EED inhibitor



Target background and therapeutic rationale

PRC2- an epigenetic regulator mainly consists of EZH1/2, EED, and SUZ12.

EZH2 and EED – catalytic subunit of PRC2, function as histone methyltransferase leading to gene silencing and dysregulation in many cancers. APG-5918 is efficacious on inhibition of H3K27me3

APG-5918 show similar activities to EZH2 inhibitors in vitro and in vivo.

EED inhibitors also effectively inhibit PRC2 containing a mutant EZH2 protein resistant to EZH2 inhibitors. EED inhibitor may inhibit the methyltransferase activities of both PRC2–EZH2 and PRC2–EZH1 and therefore may provide therapeutic(s) similar or complementary to the EZH2 inhibitors.

EZH2 inhibitor tazemetostat has shown promising efficacy and tolerable safety in epithelioid sarcoma (tazemetostat approved) and FL (tazemetostat approved)

China's first EED inhibitor to enter clinical trials

Mechanism

- APG-5918 binds to the H3K27me3-interacting EED domain, resulting in a conformational change in the EED H3K27me3 binding pocket, and prevents EED from interacting with histone EZH2, affecting the expression of its downstream target genes, thereby playing a role in carcinogenesis

Preclinical

- APG-5918 has high binding affinity (IC50 = 1.3 nM)。
- APG-5918 is potent in vitro and in vivo targeted pharmacological activity in cancer cell lines and xenograft models of NHL and solid tumors as a single agent or in combination with other therapeutic agents.
- Priority is given to those patients with EZH2 mutations, BAP1 mutations, or SMARCB1 deficiency
- The results of preclinical study were released in 2022 AACR meeting

Received IND approval

- APG-5918 obtained IND clearance by the FDA and we launched first-in-human study that will assess the safety, pharmacokinetics, and preliminary efficacy of APG-5918 in patients with advanced solid tumors or hematologic malignancies. We completed the first patient enrollment.
- APG-5918 obtained approval from CDE to enter a Phase I study in patients with advanced solid tumors or hematologic malignancies.
- APG-5918 obtained approval from CDE to enter the clinical study in patients with anemia related indications

Overview of the application of EED selective inhibitor APG-5918 in sickle cell anemia (SCD)

Fetal Hemoglobin
HbF

$\alpha_2\gamma_2$

Hemoglobin Conversion

Adult Hemoglobin
HbA

$\alpha_2\beta_2$

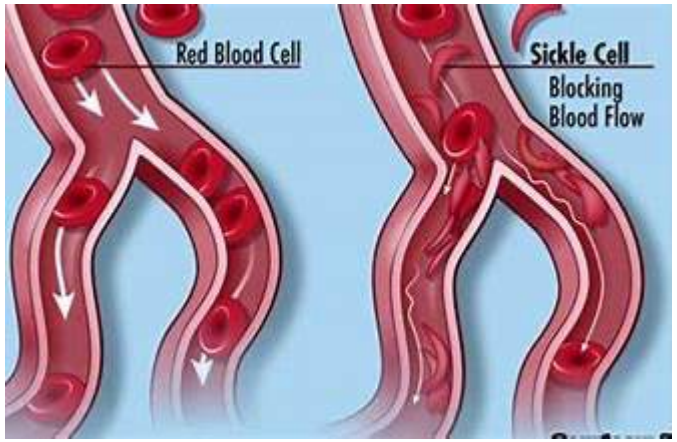
β6Glu → Val

Hemoglobin
HbS

$\alpha_2\beta^S_2$

Polymerization

Sickle Cells



SCD

APG-5918

Current Treatment

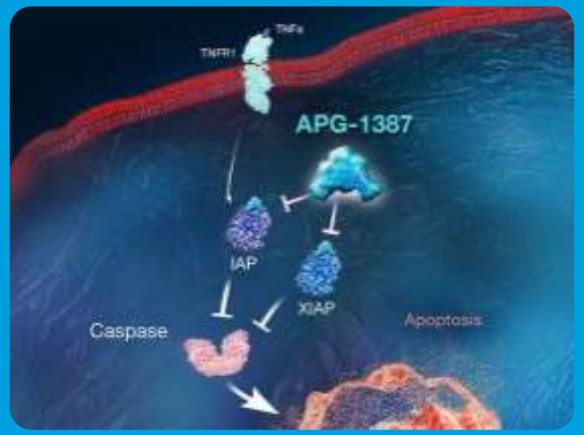
- Blood Transfusion, Bone Marrow Transplant, and Drug Therapy
- Hydroxyurea (HbF↑/chemotherapy/Inconsistent efficacy)
- L-Glutamine (Oxidative stress↓/ BID-TID/Expensive)
- Voxelotor (Oxygen Affinity↑ , Polymerization↓)
- Crizanlizumab (Vascular adhesion↓/IV Medication inconvenience /Expensive)
- Stem Cell Transplant (Phase III, Expensive)

Efficacy and prospect of EED inhibitors in SCD

- FTX-6058 (Fulcrum Therapeutics)
  - Preclinical data, whole blood HbF levels increased in SCD model mice
  - The interim results of the clinical phase I trial are positive, and dose-dependent changes in pharmacokinetic indicators are observed
- APG-5918 (Ascentage)
  - Confirmation of changes in pharmacokinetic indicators in normal mice
  - In vivo and in vitro pharmacodynamic studies are in progress

APG-1387

An Antagonist of
IAP/XIAP
(SMAC Mimetic) Dimmer



Milestones & Clinical Developments

CHB Development

- We have released results from a Phase I study of APG-1387 in Chinese patients with CHB, in an oral presentation at the 73rd AASLD in November 2022. This study reported favorable safety and preliminary efficacy of an IAP antagonist for the treatment of patients with CHB.
- We have already completed a phase I study for the treatment of patients with CHB.
- The stage 1 safety evaluation of APG-1387 in combination with Entecavir (ETV) for a phase II study has completed. With well-tolerated safety data, the study moved forward to stage 2, efficacy evaluation of APG-1387 in combination with ETV compared to ETV monotherapy.

Immuno-Oncology Development

- A phase I clinical trial in the United States, testing combination of APG-1387 with pembrolizumab, an anti-PD-1 mAb in solid tumors is ongoing.
- In China, a phase Ib/II clinical trial of APG-1387 in combination with toripalimab in solid tumors are currently being conducted. The phase Ib patient enrollment has been completed and the trial has entered into phase II phase. Among 4 efficacy-evaluable patients in PD-1 naïve NPC, three achieved objective response, including 1 CR and 2 PRs, per Ricist 1.1.
- A Phase I/II study to investigate the combination of APG-1387 with chemotherapy, nab-paclitaxel and gemcitabine for the treatment of advanced pancreatic cancer is ongoing. Among 3 AG-naïve patients, 2 achieved confirmed partial response.

Our Experienced Executives Team

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Chairman & CEO

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Yifan Zhai, M.D., Ph.D.
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University of Michigan · Journal of Medicinal Chemistry · Ascenta

Yifei Zhu
Chief Commercial Officer

西安杨森 xian janssen · BeiGene · 齐鲁制药 · 天境生物

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Jeff Kmetz
Chief Business Officer

pharmacyclics · Pulse Biosciences · Alexion · Bayer

Chongdong Fu, Ph.D.
CMC head

复旦大学 · 和黄医药 HUTCHMED

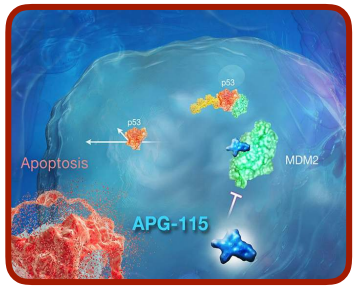
IP Portfolio for Key Clinical Assets

Key Clinical Assets	Estimated Patent Expired Year
HQP1351	2035-2041*
APG-2575	2037-2042*
APG-115	2035-2042*
APG-1387	2033-2042*
APG-1252	2034-2041*
APG-5918	2040-2042*

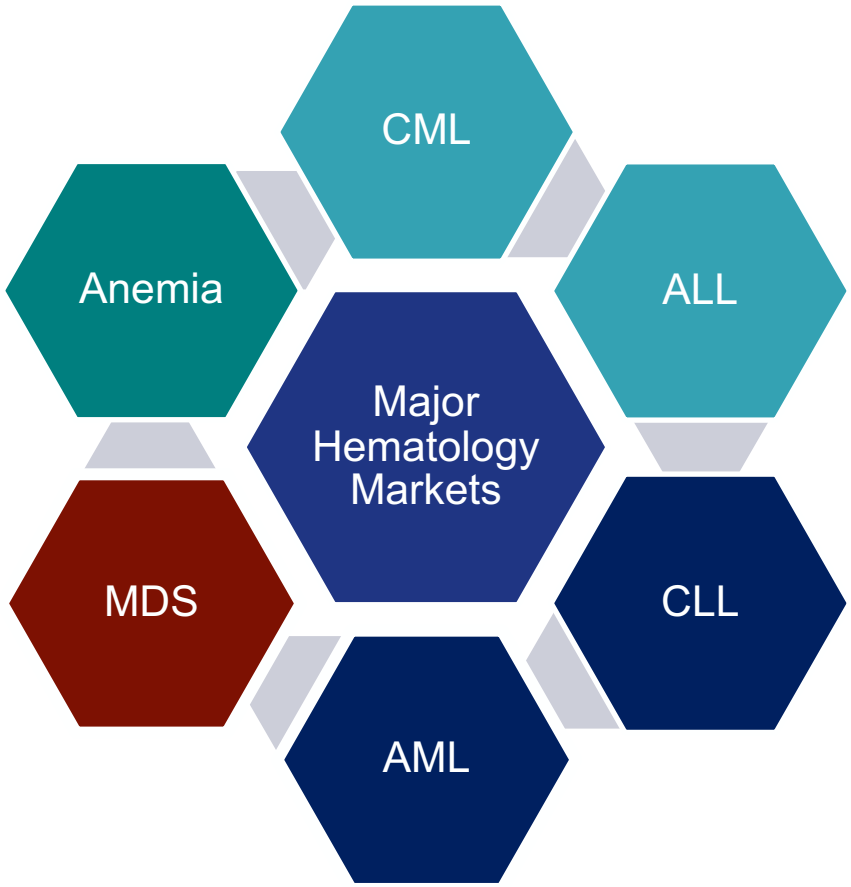
*including composition, process, formulation, combination, use, new indication etc；(issued or pending)
Source: Company data Note: All data as of June 30, 2022

Patient-Centric Innovation；Global Cutting-Edge Therapies

Lisaftoclax
Bcl-2 Selective Inhibitor



Alrizomadlin
MDM2-p53 Inhibitor



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