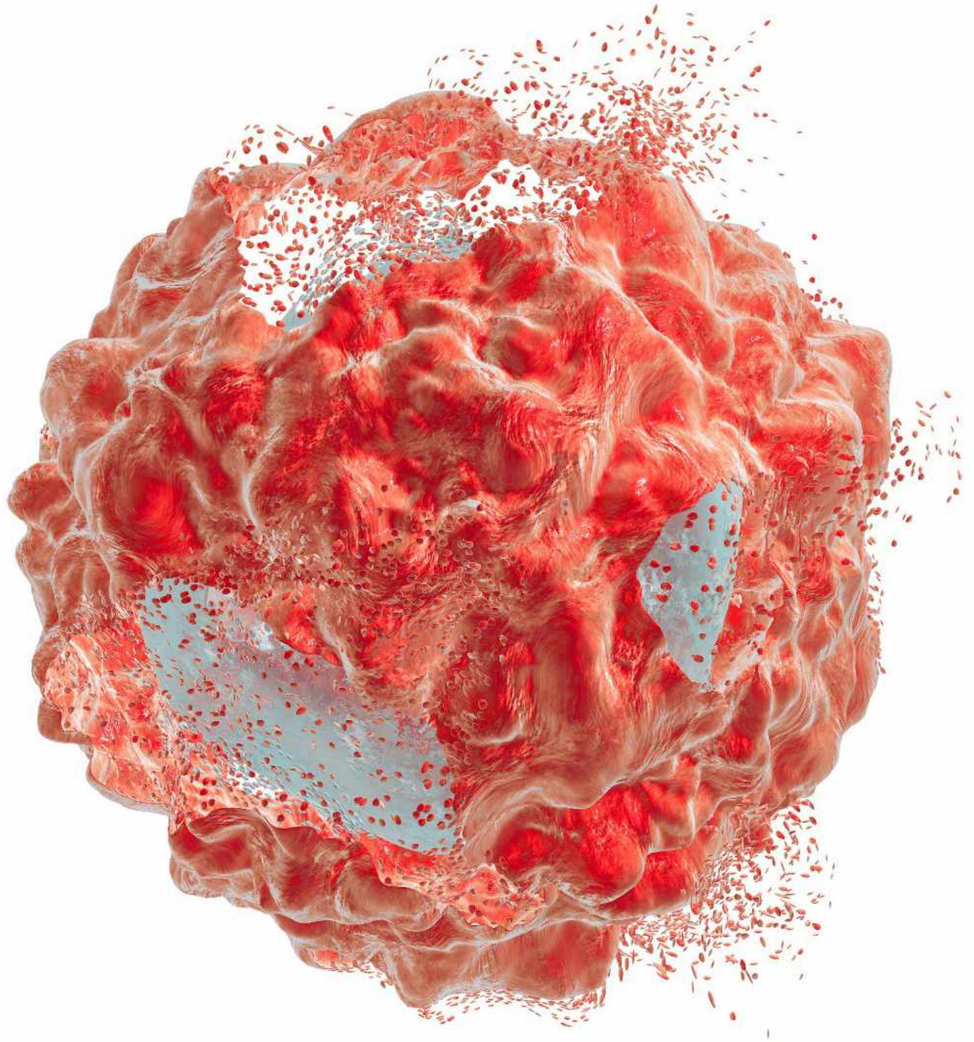

Ascentage Pharma Group

Patient-Centric Innovation

Cutting-Edge Therapies

Dr. Dajun Yang

January 11, 2023

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Year 2022：Accelerating Commercialization of Olverembatinib

Revenue

RMB 95.76 million

change as of same period last year

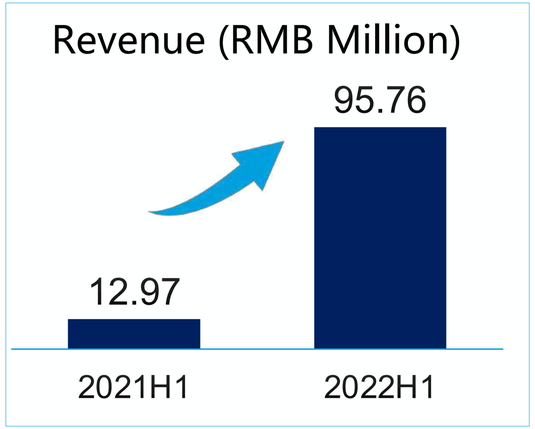
636.9%

Cash Amount

RMB1.7 billion

change as of same period last year

Almost similar



2022 1H

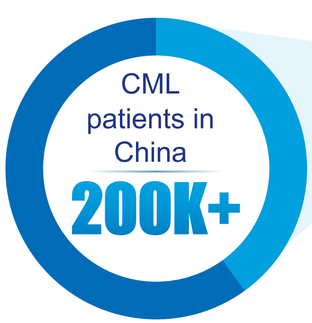
Commercial team of 100+ staff to cover 800+ hospitals, with Innovent

Covering >80% of the total CML market in China

- Included in 2022 edition of **CSCO** and **CACA** Guidelines for CML and Ph+ ALL
- Listed in 29 provinces and 230 cities **Huimin Medical Insurance**
- **NPP** (Named Patient Program) with Tanner Pharma, plans to cover over 130 countries and regions globally

Global Commercialization Potential of Olverembatinib

Market potential - Maximizing market value

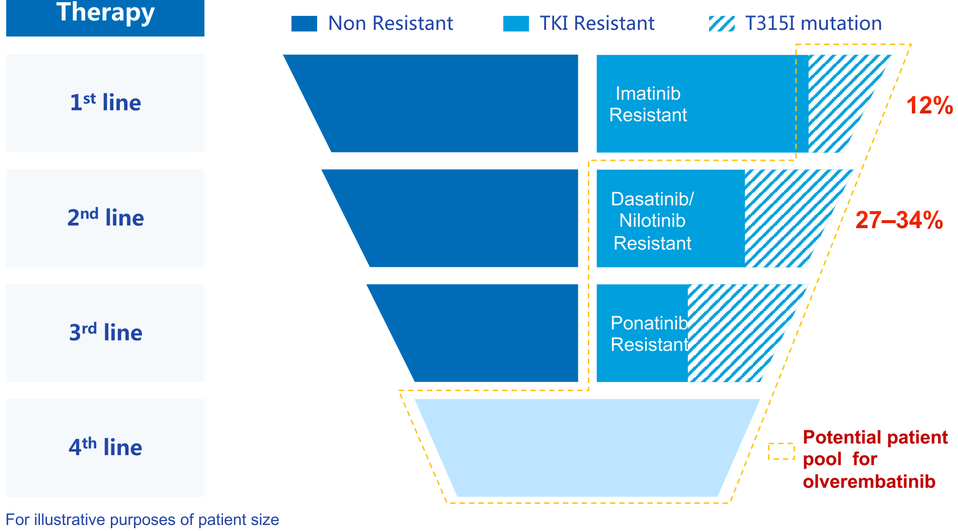


40%

~ 40% received 2nd+ line therapy

Along with the increase usage of 2nd generation TKIs, the number of patients withT315I will increase

CML patients treated with TKI may have resistance



For illustrative purposes of patient size

T315I mutation was the most frequent mutation detected in imatinib-, nilotinib-, and dasatinib resistant cases, accounting for 12.3%, 27.3%, and 34.1%[1]

CML Full Approval NDA accepted by CDE

- Olverembatinib was granted **Priority Review Designation** and acceptance of **NDA for Full Approval**

Global Commercialization

- Launched NPP with **Tanner Pharma**. Plans to cover **+130 countries and regions globally**
- Annual sales of Global CML Market is roughly **USD 6 bn**
- Annual sales of 2nd generation TKI (dasatinib, nilotinib) in 2020 and 2021 **> USD 4 bn**

Drugs	Global Launch	WW sales (USD)	Indications
Ponatinib	2013.01	469M (2021 whole year)	CML · ALL
Asciminib	2021.10	56M (2022 first half-year)	CML

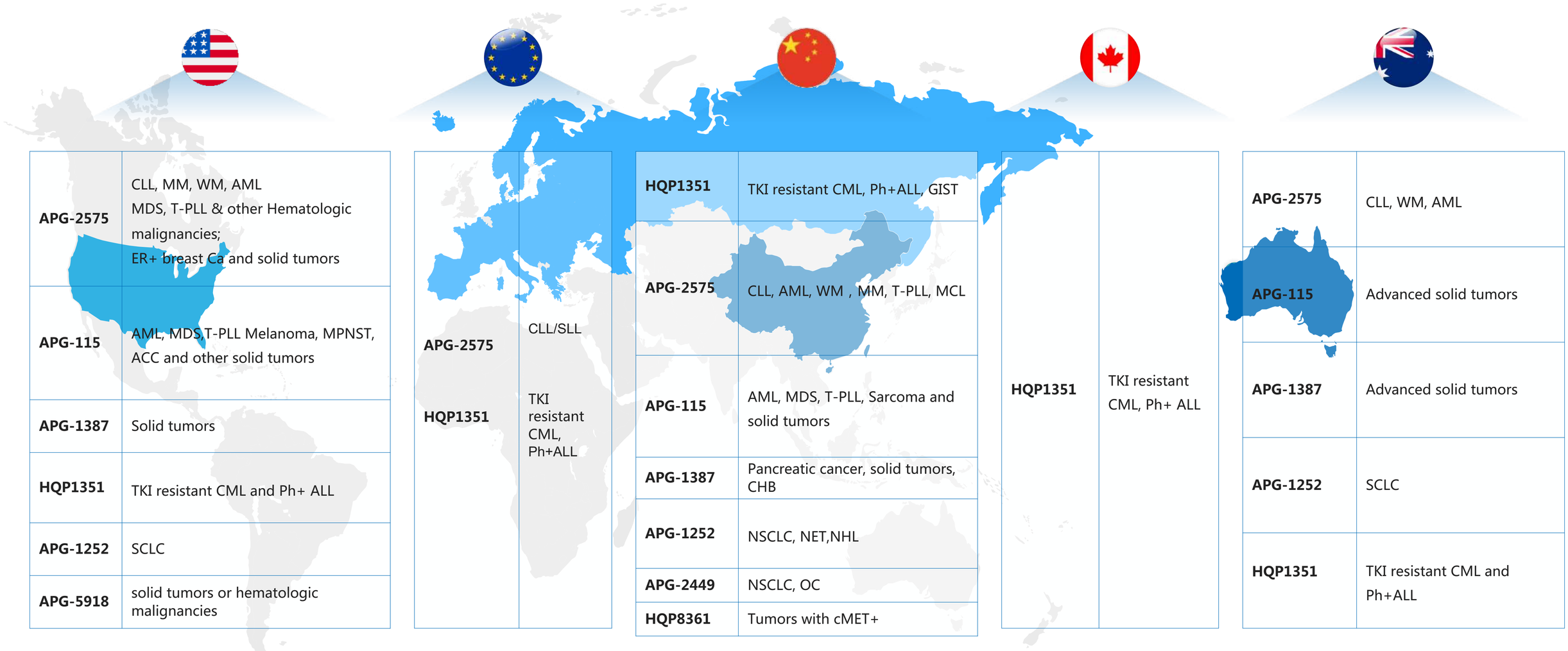
Source:1. Chin J Hematol, 2020,41(06): 469-476

Rapid Progress with Global Clinical Development Programs

Compounds	Target	Indications	Preclinical	Ph-I	Ph-II	Registration Trial	NDA Approval	Trial Region	Rights Region
HQP1351	BCR-ABL/KIT	Resistant CML							
		Resistant CML，Ph+ ALL					耐立克 奧雷巴替尼 olverembatinib		
		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: 50+ 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-1252	SCLC
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
HQP8361	Tumors with cMET+

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

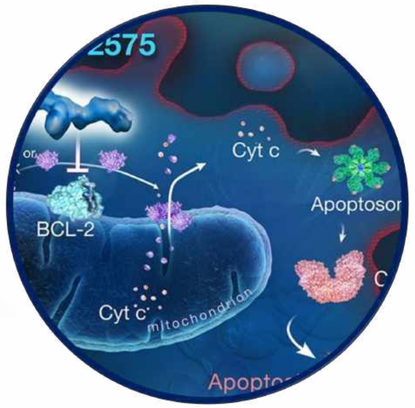
Transition Towards a Fully-Integrated Global Biopharma Company

Ascentage Pharma

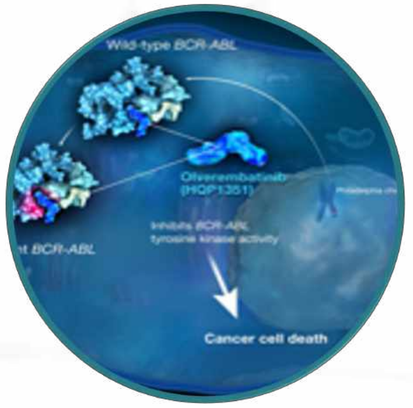
Global Headquarter/R&D Center and Manufacturing Facility in Suzhou, China

- GMP manufacturing equipment installation and qualification has been completed
- MAH type A certificate was issued in Nov 2022
- Capabilities for incubator and accelerator with angel innovation funding support

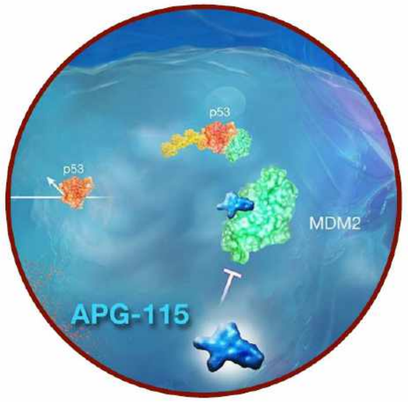
Ascentage Pharma Hematology Portfolio



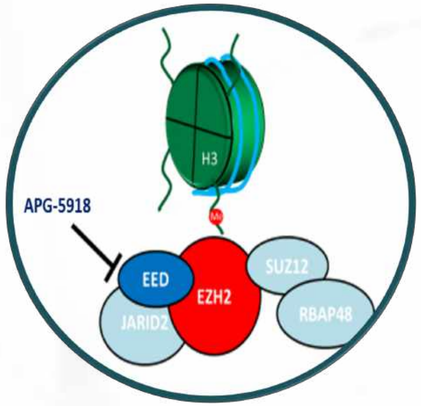
Lisaftoclax a Bcl-2 Selective Inhibitor



Olverembatinib Multi-Kinase BCR-ABL TKI



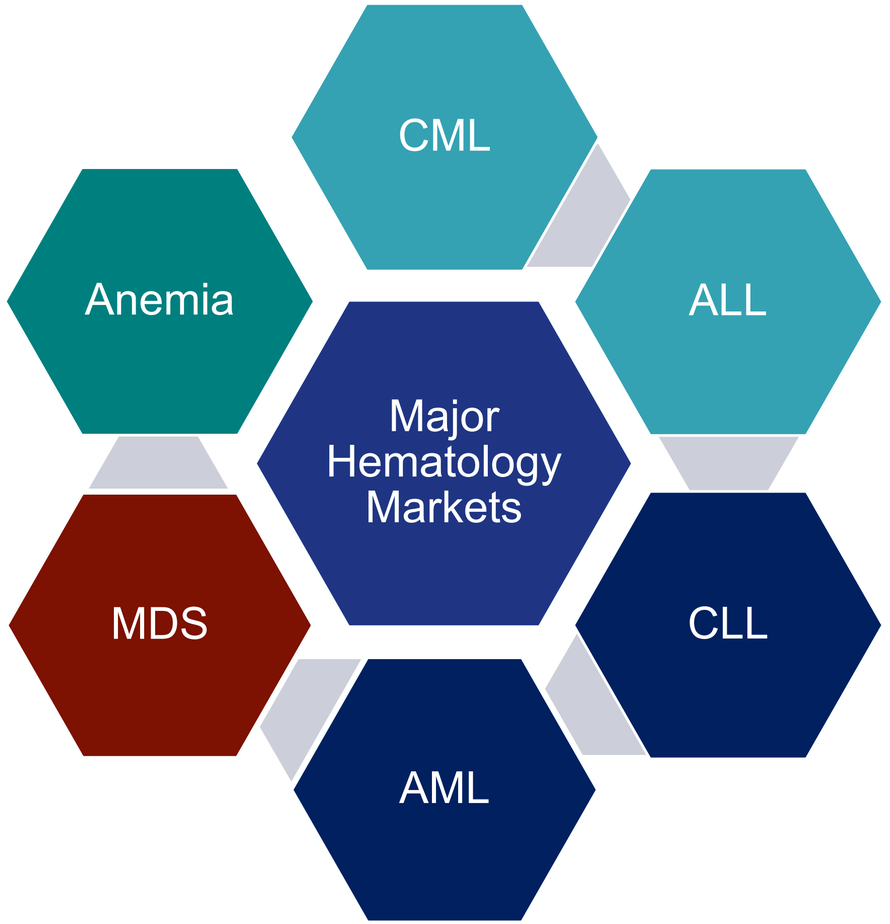
Alrizomadlin an MDM2-p53 inhibitor



APG-5918 a potent EED inhibitor

Hematology Markets

Our Portfolio aligns with
Significant Growth Opportunities



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

HQP1351

Olverembatinib

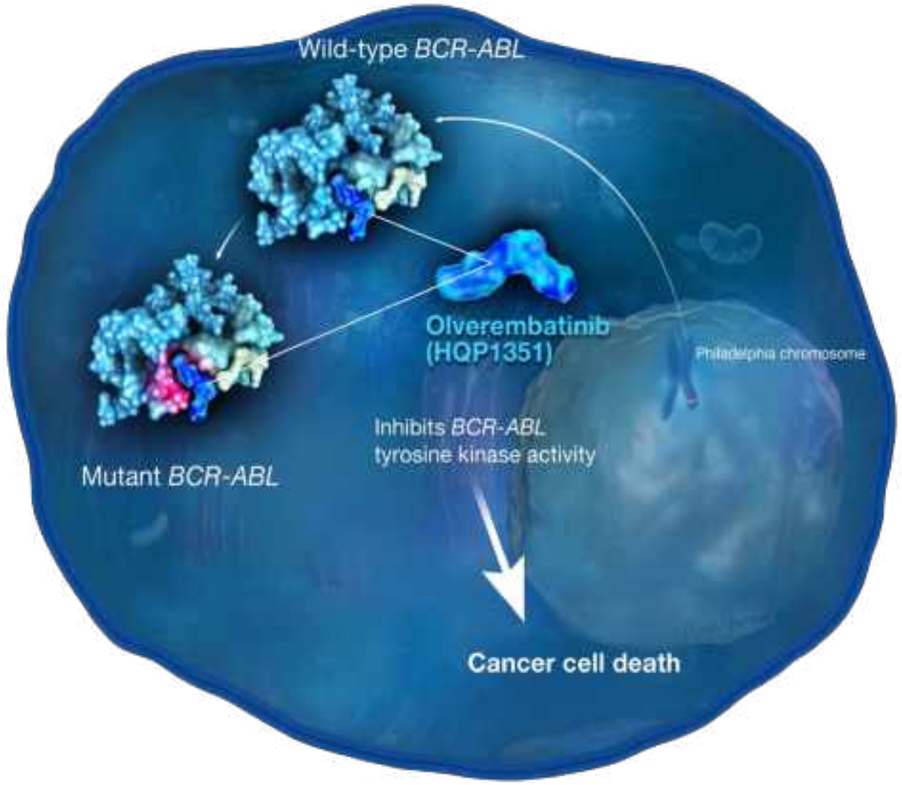
Overview

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

- Clinical results of olverembatinib in CML were selected for oral presentation at ASH 2018-2022 and 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

- 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)**

2020

2021

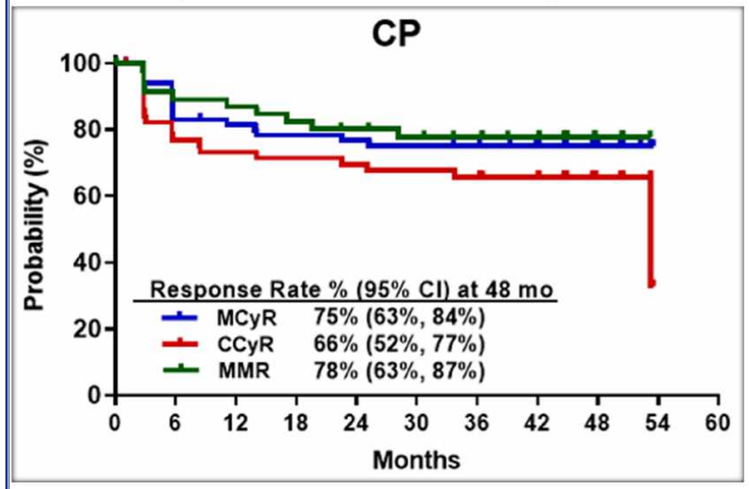
2022

- 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

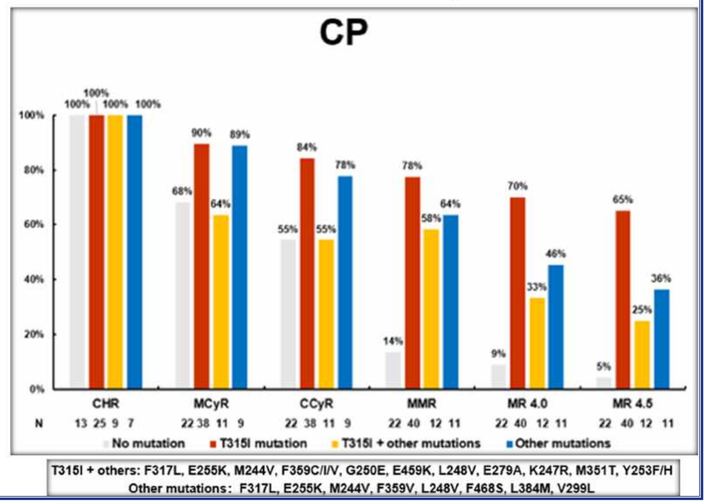
Ph I: Demonstrated Durable Efficacy and Differentiated Safety Profile

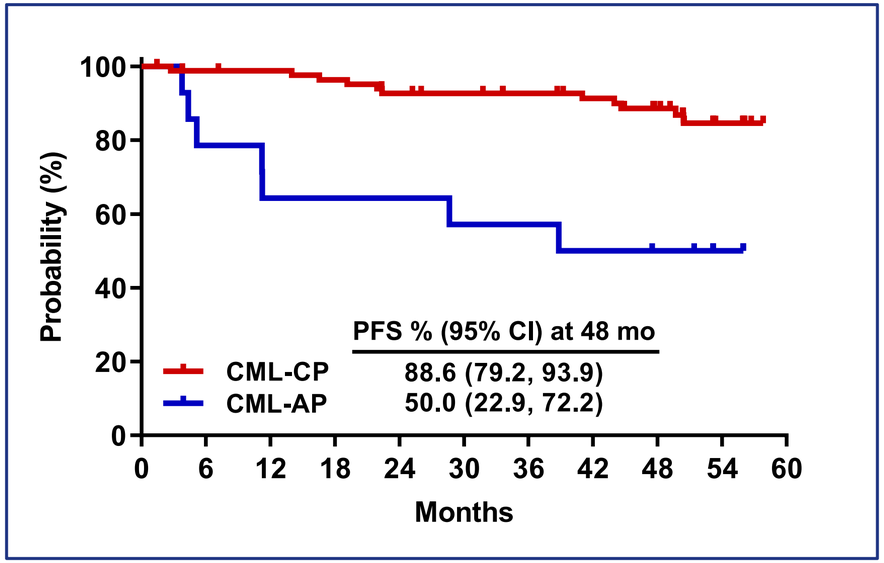
Ph I: 5-year data for Olverembatinib

Deep & Durable Duration of Response

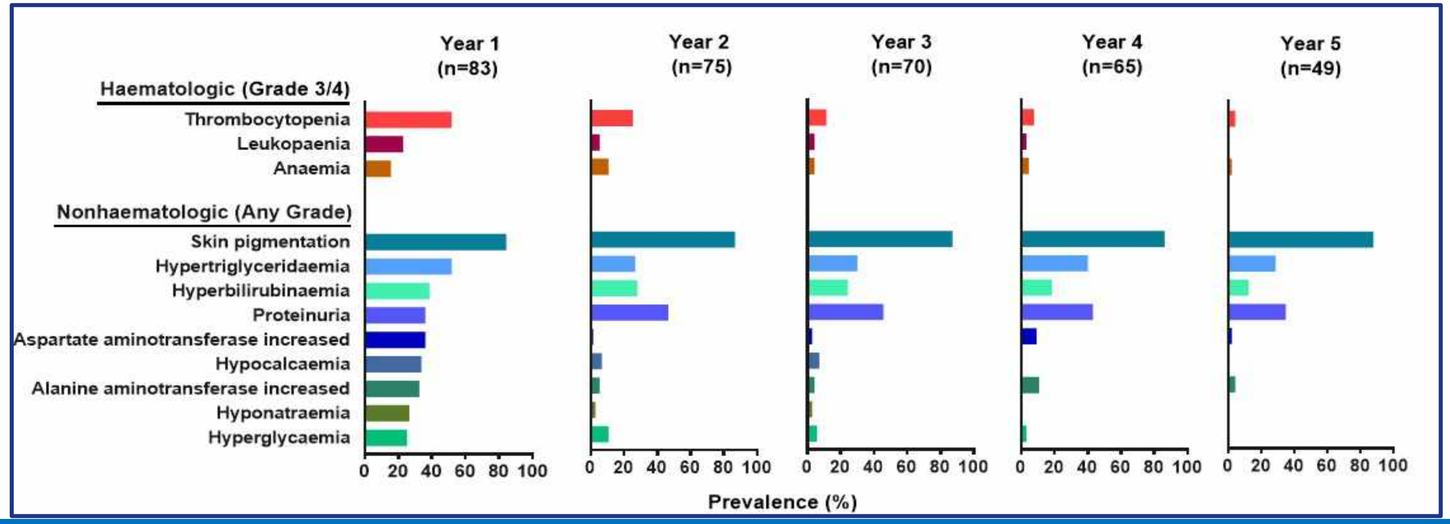


MMR Remission in T315i & Compound Mutations





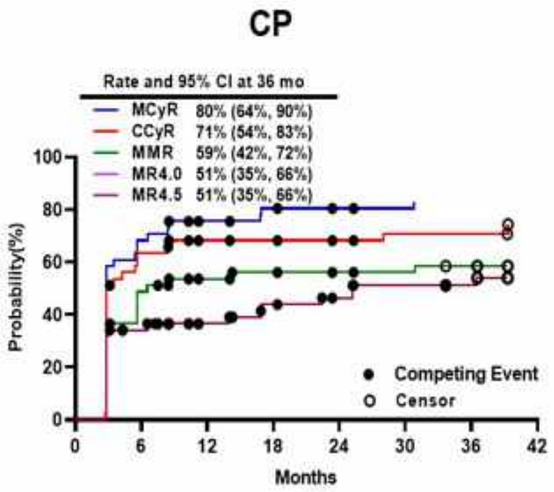
80% of patients remain on therapy for more than 5 years

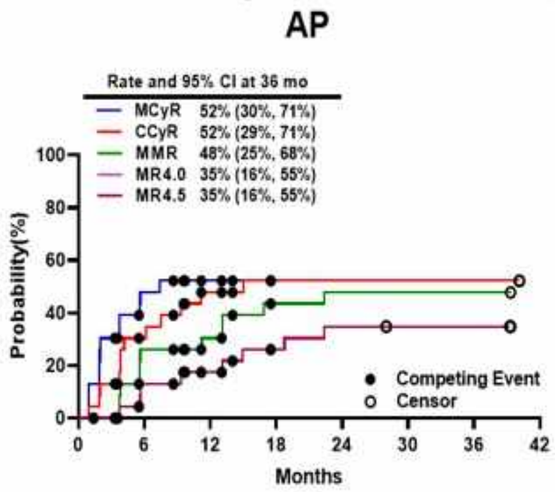


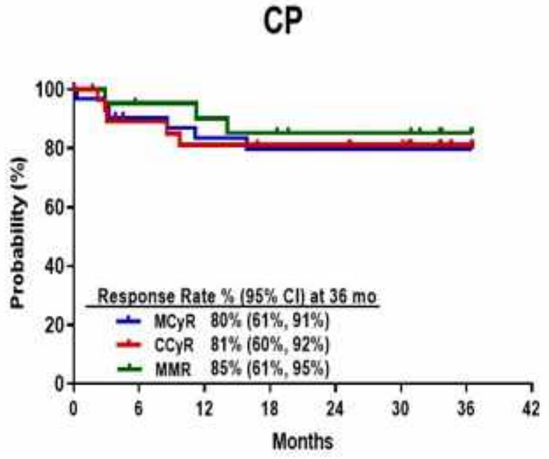
Jiang Q et al. ASH abstract #81, 2022

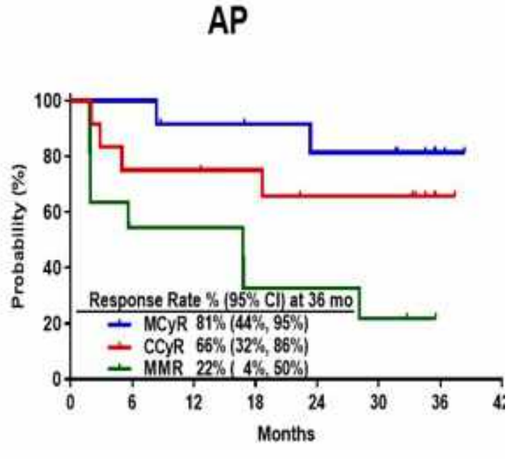
Pivotal Trial: Deep & Durable Efficacy in T315i CML

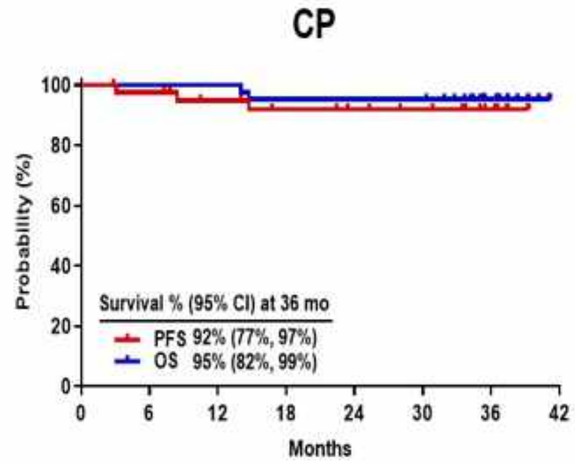
Cumulative Incidence of Responses, DOT, PFS & Response by Mutational Status

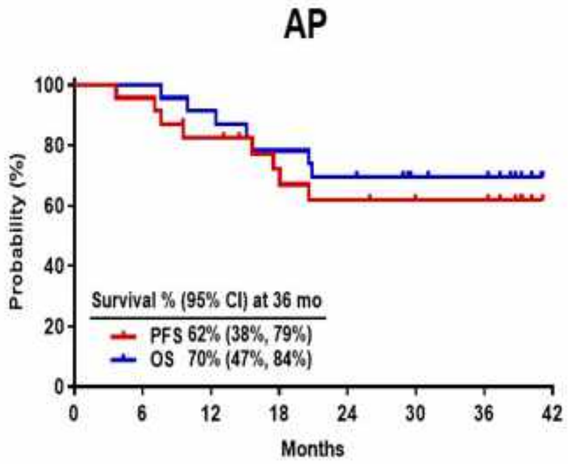


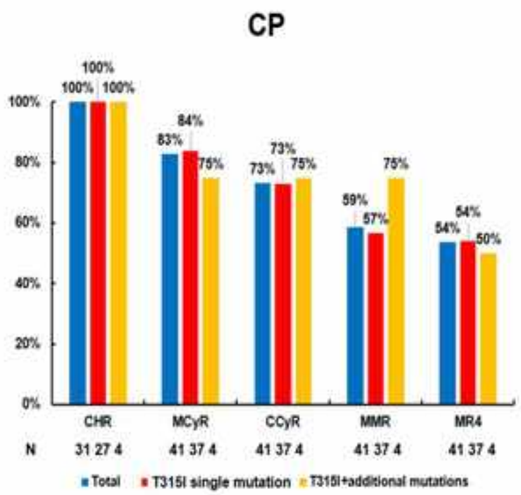


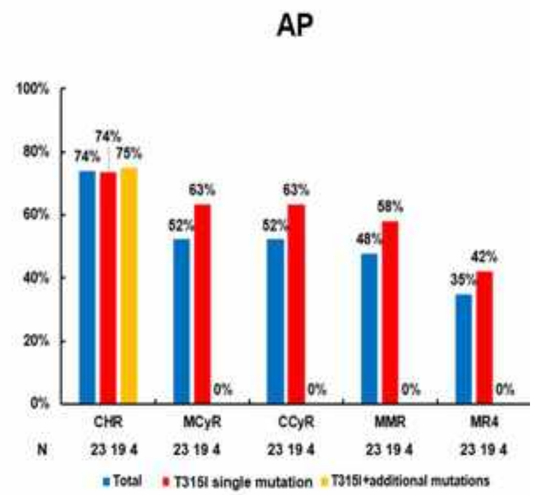










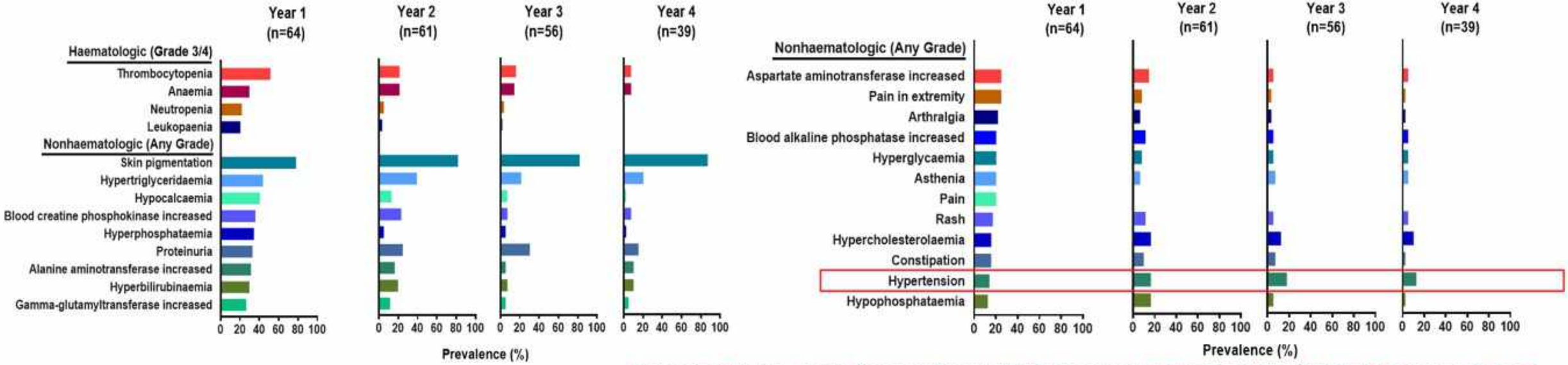


T315I + additional mutations: F317L, M244V, E459K, F359V, Y253H, E255V, E450A, E459Q

Jiang Q et al. ASH abstract #81, 2022

Pivotal Trial: Differentiated Safety Profile, enables long remissions

A Proven Safety Profile in TKI resistant CML enables Long-term Remissions



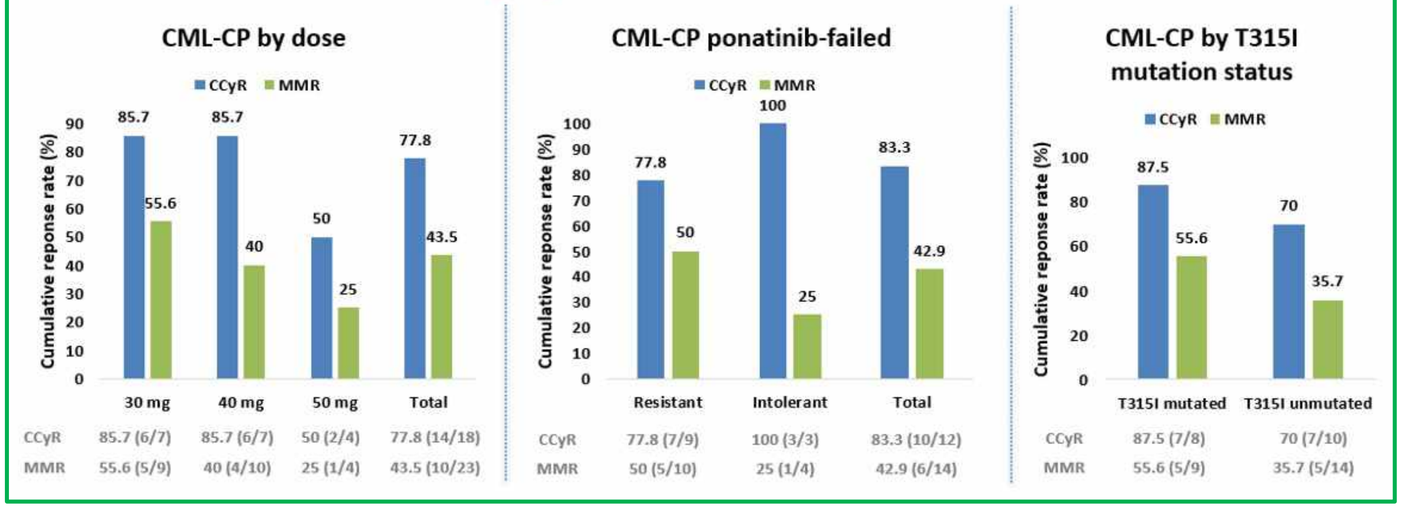
Any grade arterial occlusive & venous thrombotic AEs occurred in 3.1% of patients, of which 1.6% were grade 3 or 4.

Jiang Q et al. ASH abstract #81, 2022

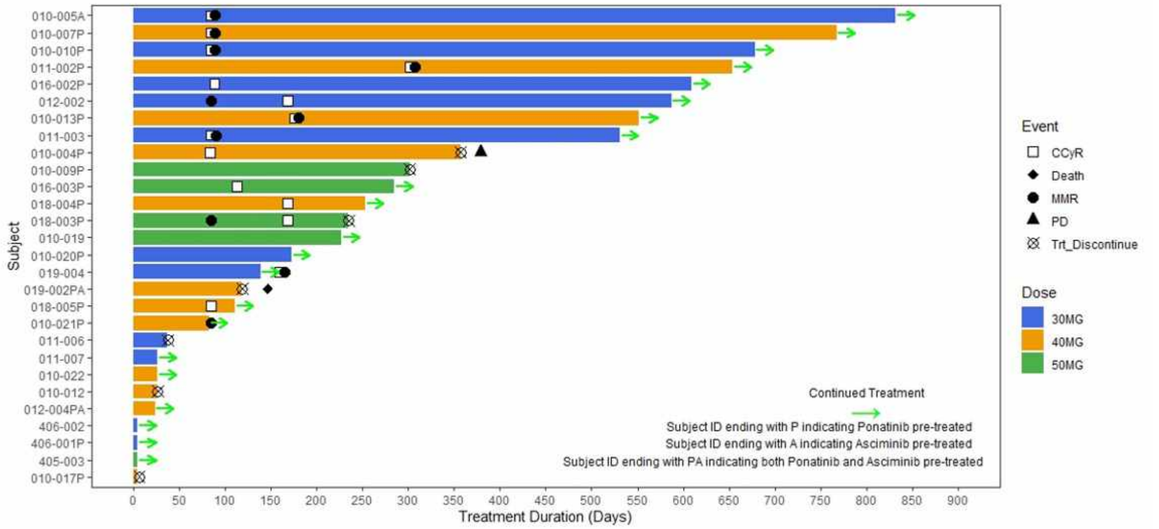
US Ph Ib/II: Olverembatinib is Potentially Effective in Ponatinib Resistant CML

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

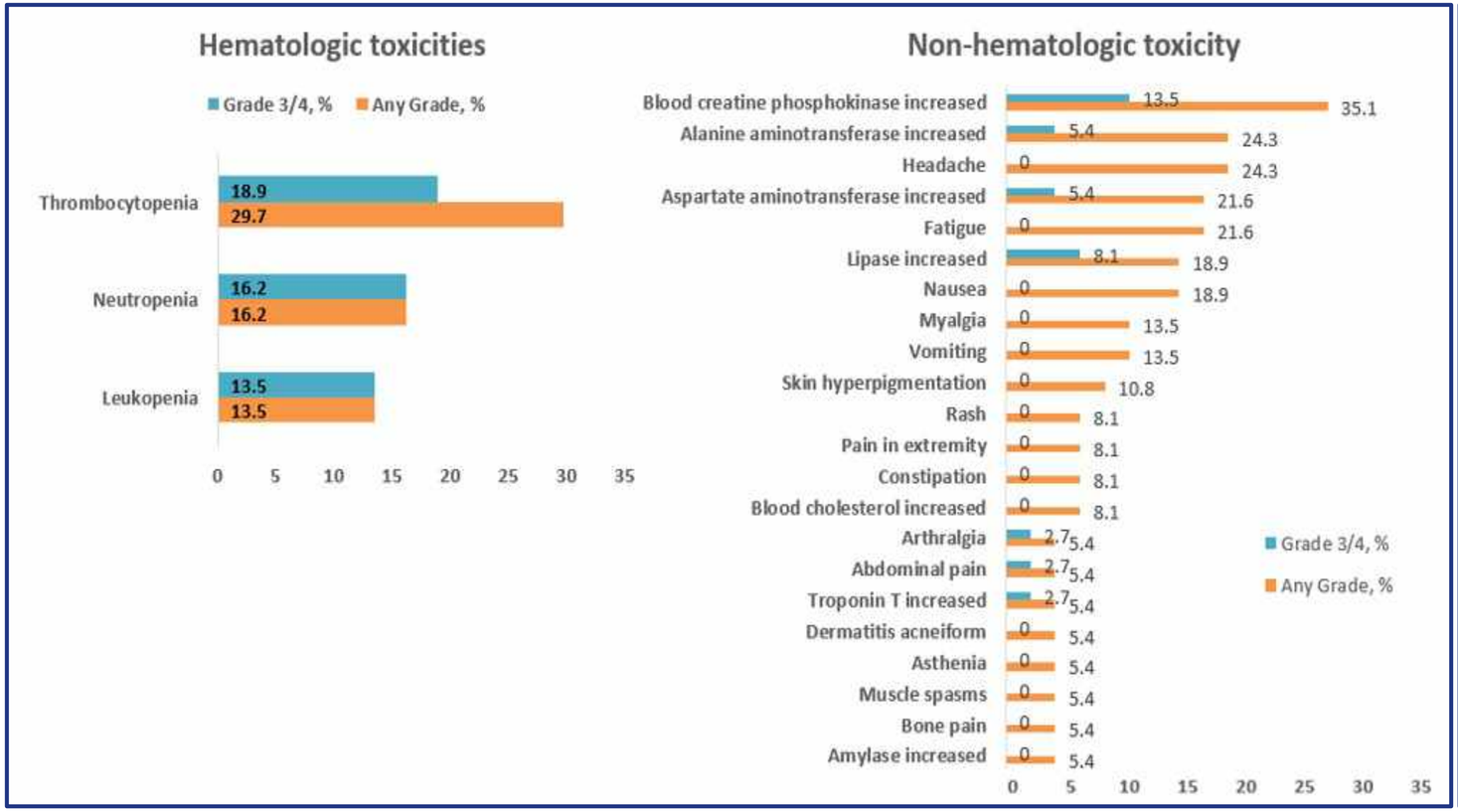


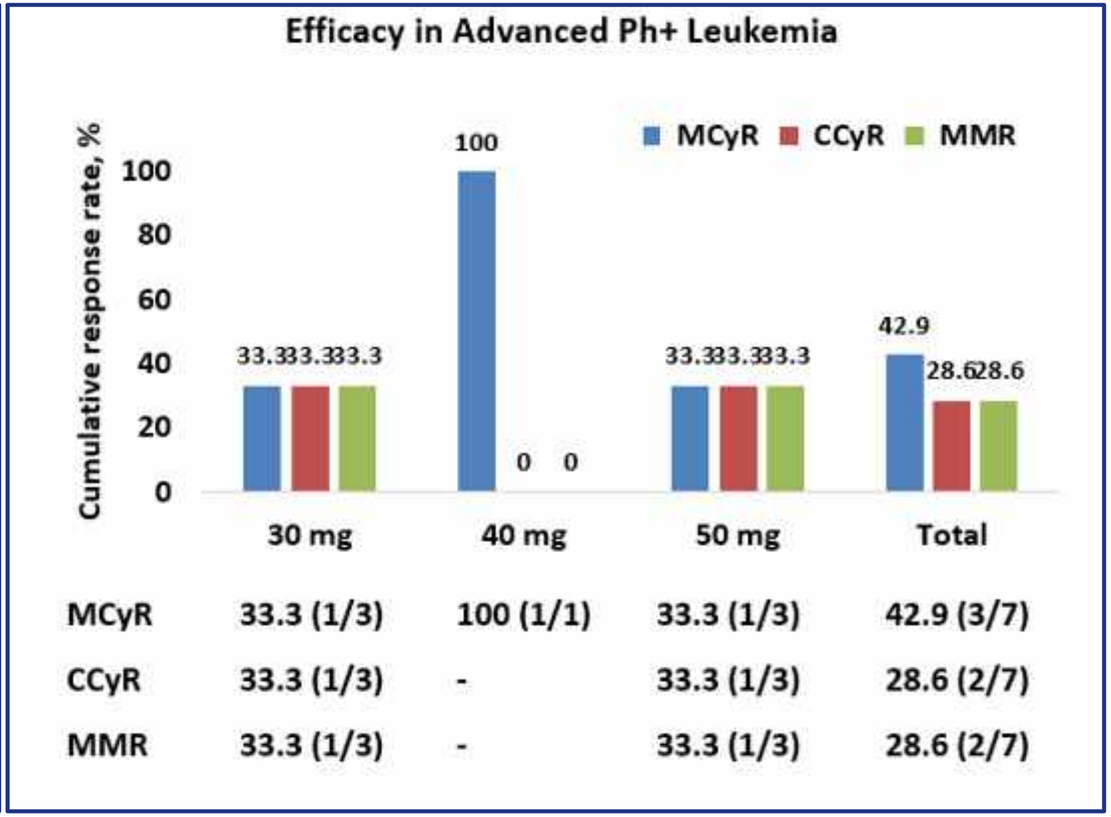
Durable Responses In Asciminib & Ponatinib Resistant CML Patients



Jabbour E et al. ASH abstract #82, 2022

US Ph Ib/II: Safety & Activity in Ponatinib Resistant PH+ALL



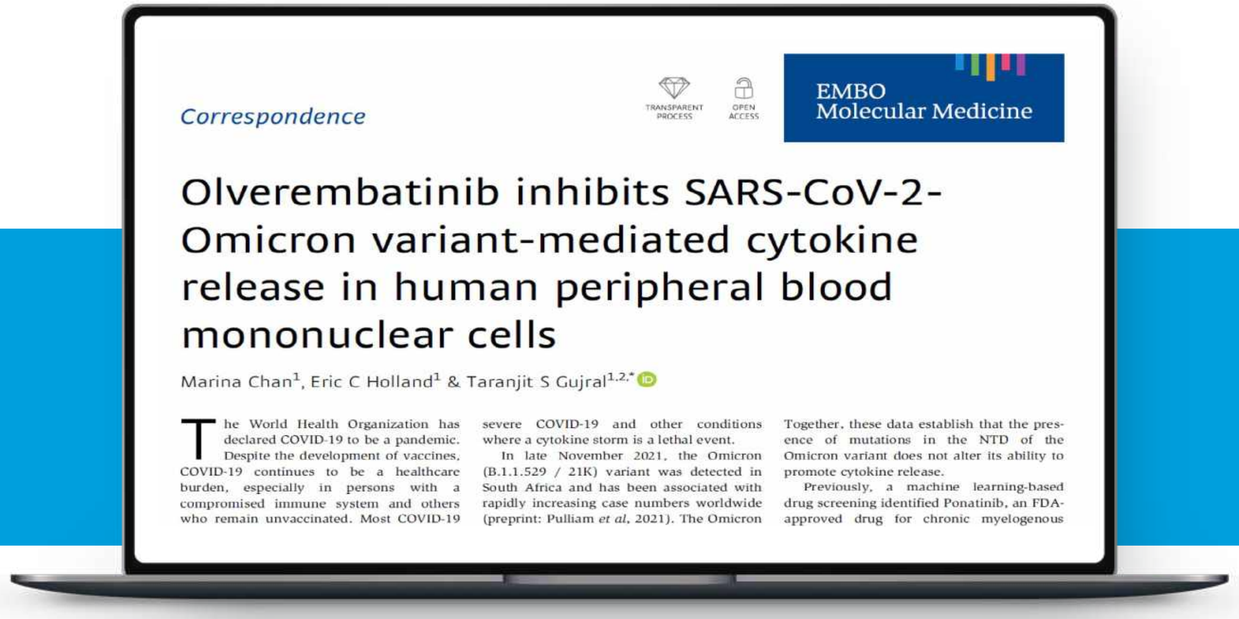


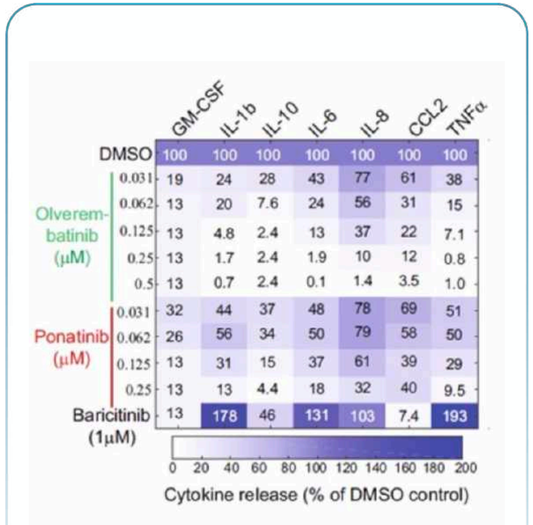
	30 mg	40 mg	50 mg	Total
MCyR	33.3 (1/3)	100 (1/1)	33.3 (1/3)	42.9 (3/7)
CCyR	33.3 (1/3)	-	33.3 (1/3)	28.6 (2/7)
MMR	33.3 (1/3)	-	33.3 (1/3)	28.6 (2/7)

Jabbour E et al. ASH abstract #82, 2022

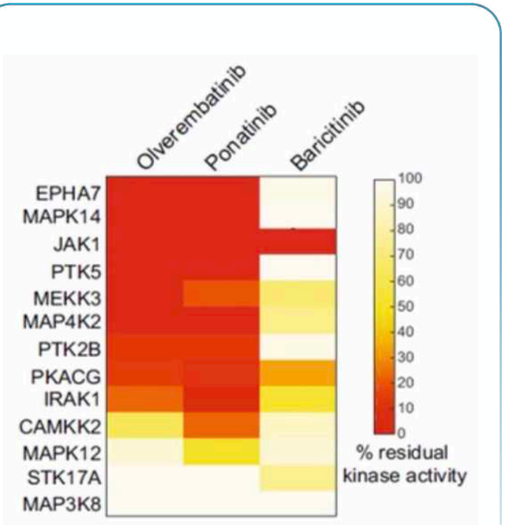
Preclinical Data Demonstrating Olverembatinib's Therapeutic Potential in Treating COVID-19

- Olverembatinib blocks the activity of several kinases essential for cytokine signalling, thereby dampening the Omicron-NTD-mediated cytokine release and reducing inflammations.
- Targeting multiple essential kinases that mediated cytokine release for SARS-CoV-2 and variants, may represent an attractive therapeutic option for treating moderate to severe COVID-19.





Effect of Olverembatinib, Ponatinib, and Baricitinib on Omicron NTD-mediated cytokine release



Comparison of kinase inhibition profiles of Olverembatinib, Ponatinib, and Baricitinib

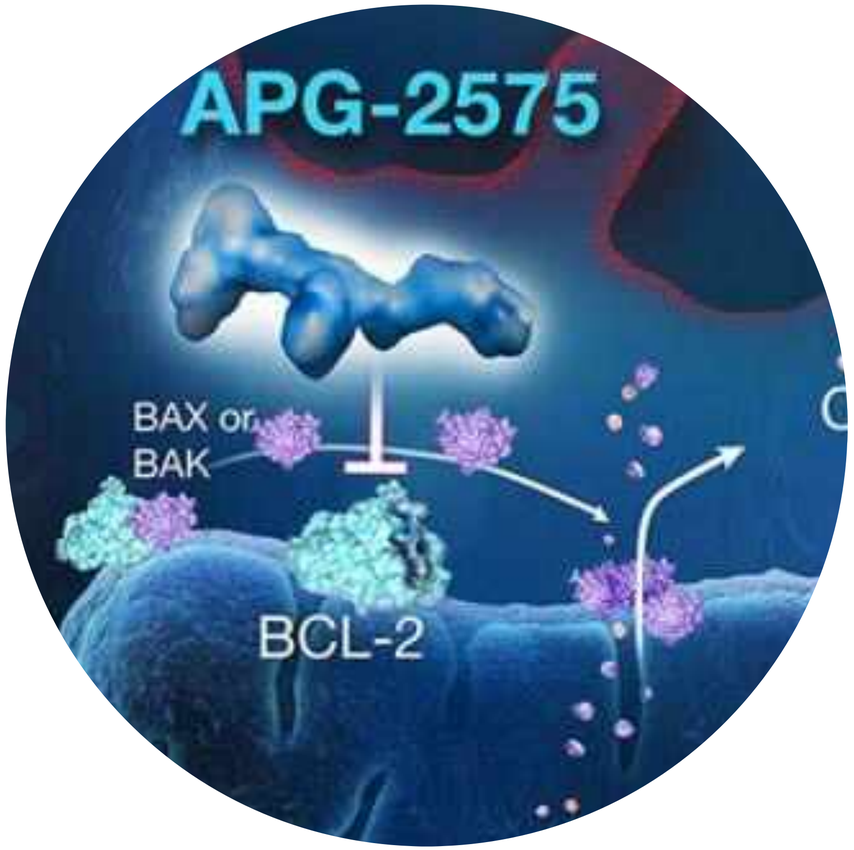
Source: Gujral T et.al. EMBO Molecular Medicine, https://doi.org/10.1101/2022.02.07.479443

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

1. More than 400 subjects enrolled into the APG-2575 studies, including r/r CLL, FL, MCL, MZL, DLBCL, WM, MM, AML, MDS and HCL patients

2. More than190 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

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

4. 5 Orphan Drug Designations (ODD): CLL, WM, MM, AML, FL

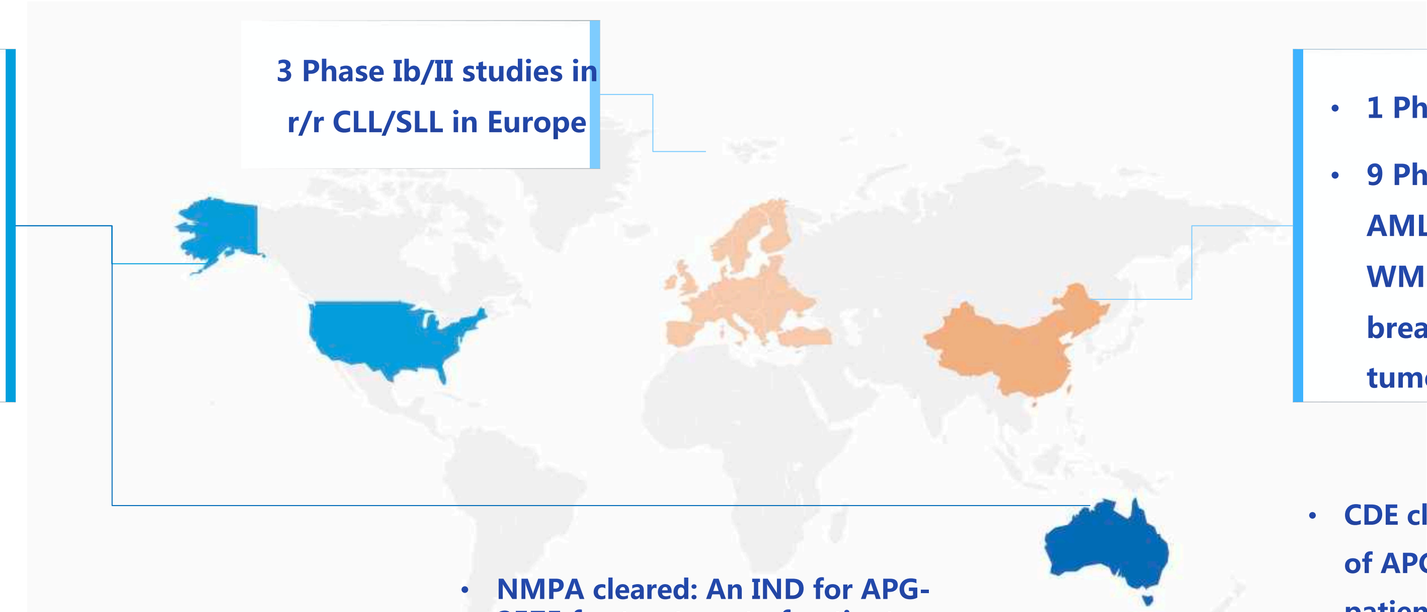
5. IND clearance for ER+ breast cancer and other solid tumors by FDA

6. Initiated registrational pivotal Phase II study for treatment of r/r CLL/SLL and the first patient has been dosed

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

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



- 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

1/2018

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

6/2018

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

10/2018

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

11/2020

- 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

12/2021

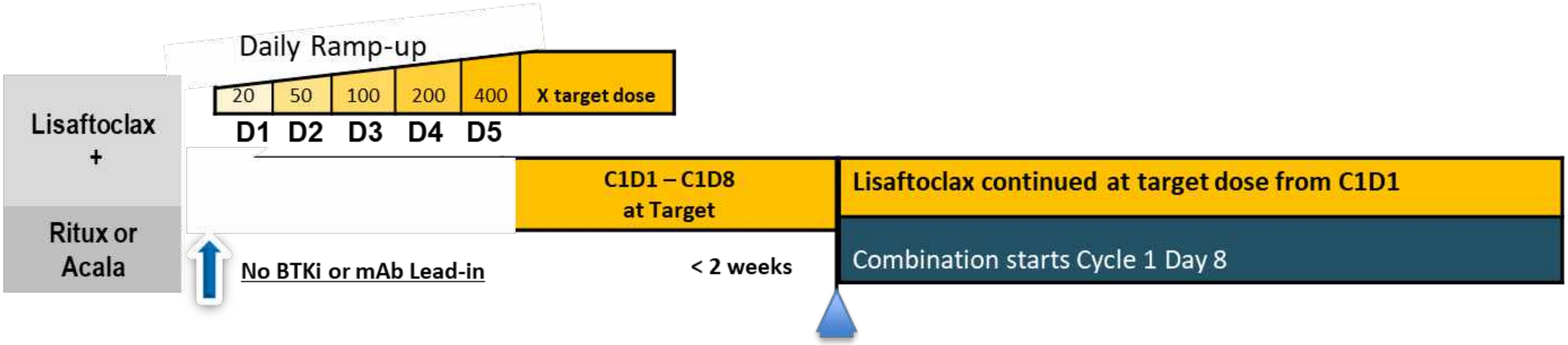
- CDE cleared: Pivotal study in China of APG-2575 for treatment of patients with r/r CLL/SLL
- 5 ODDs in AML, CLL, MM, WM, FL
- FPI in Europe

Source: Company data Note: All data as of June 30, 2022

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

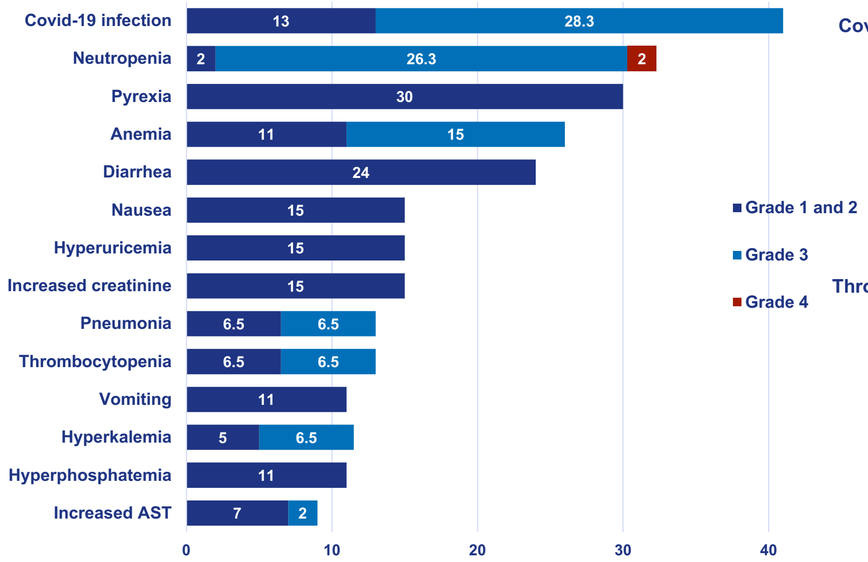


Source: Davids M et al. ASH abstract #964, 2022

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

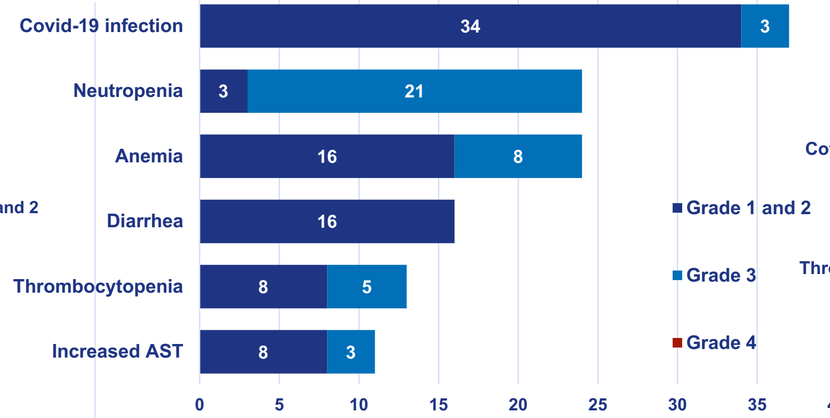
Lisaftoclax monotherapy

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



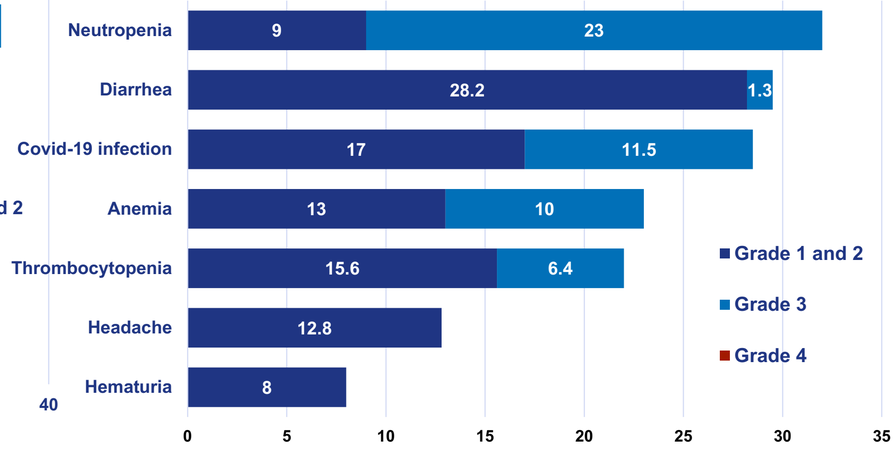
Lisaftoclax + Rituximab

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

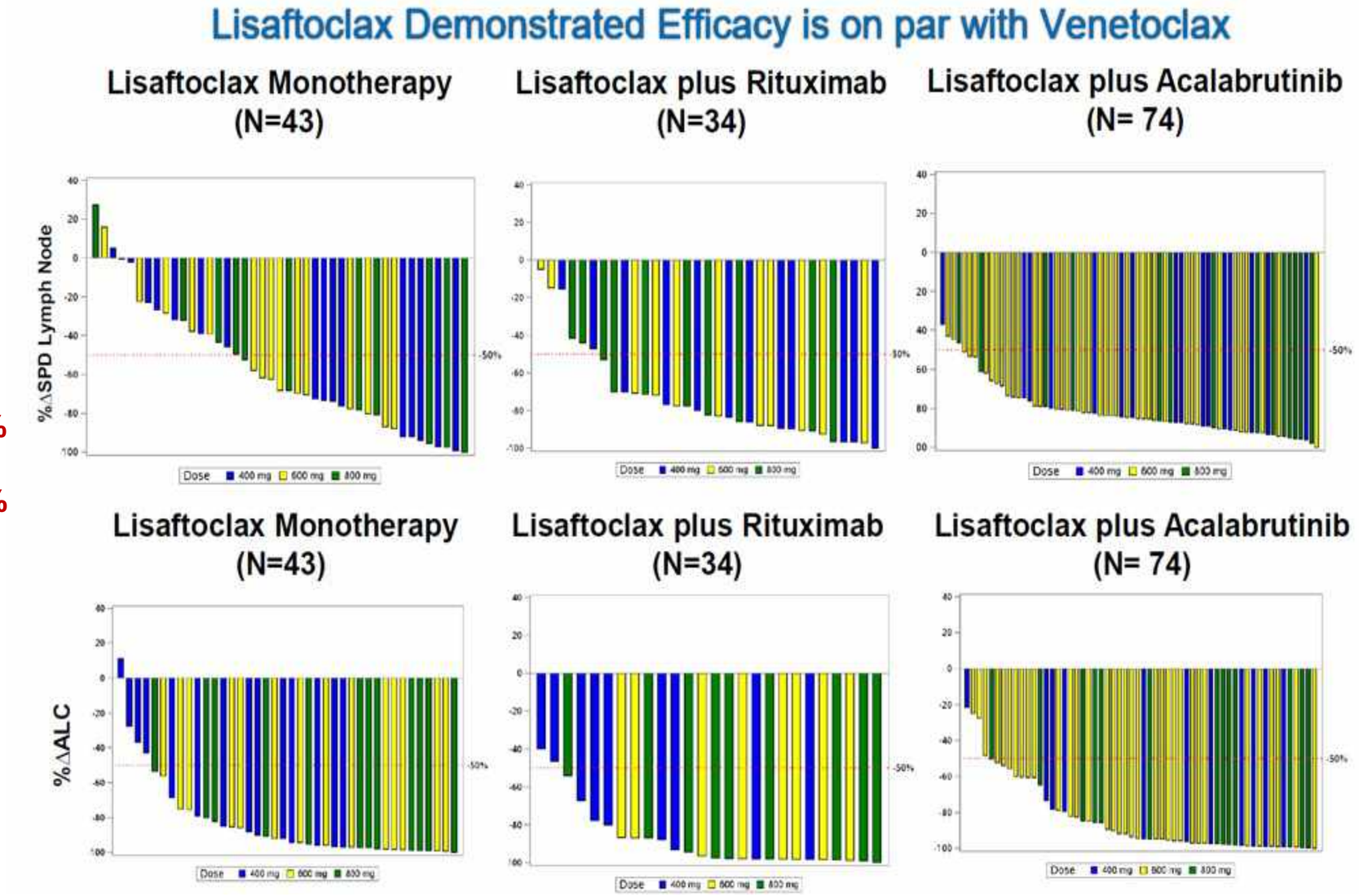
- No DLTs observed, the MTD has not been reached.
- TLS (n = 4; 2 clinical/2 laboratory), Dose reductions due neutropenia (n = 2, 1 in CD20)
- No treatment-related discontinuation or deaths

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

Global Phase II Study: Lisaftoclax Efficacy Summary

In r/rCLL, with ORR of:

- Monotherapy (n=43): **67.4%**
- Lisaftoclax + Rituximab (n=34): **79.4%**
- Lisaftoclax + Acalabrutinib: TN(n=16):**100%**
- Lisaftoclax + Acalabrutinib R/R (n=57): **98%**
  - Lisaftoclax + Acalabrutinib R/R **BTKi** naïve (n=46): **100%**
  - Lisaftoclax + Acalabrutinib R/R **BTKi** refractory (n=8): **87.5%**
  - Lisaftoclax + Acalabrutinib R/R **Venetoclax** refractory (n=4): **75%**



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

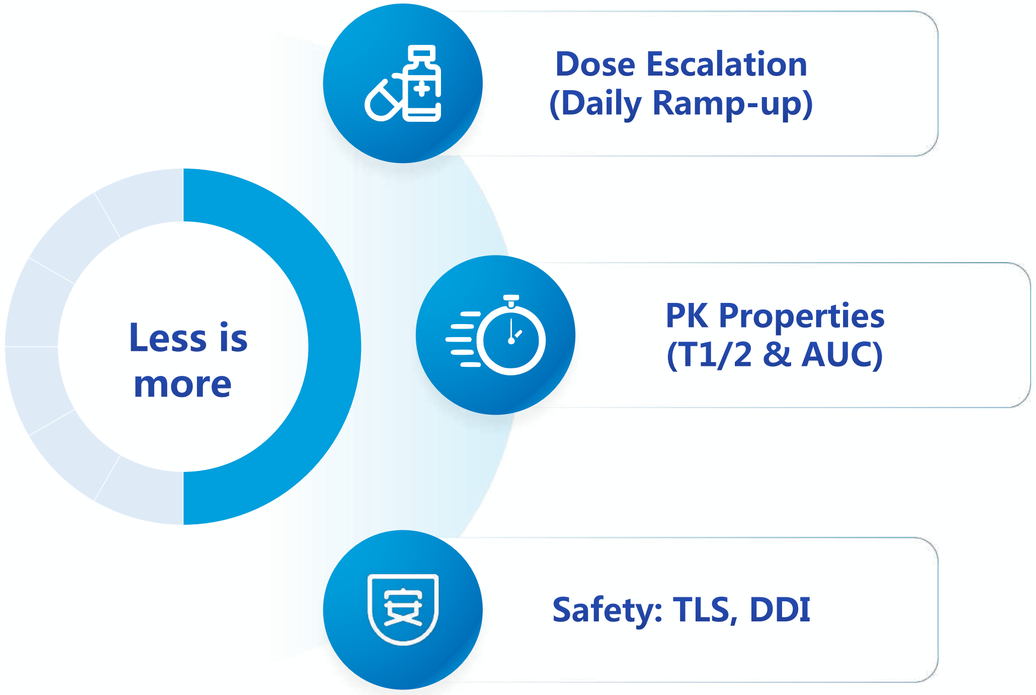
Strong Differentiation From Venetoclax

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

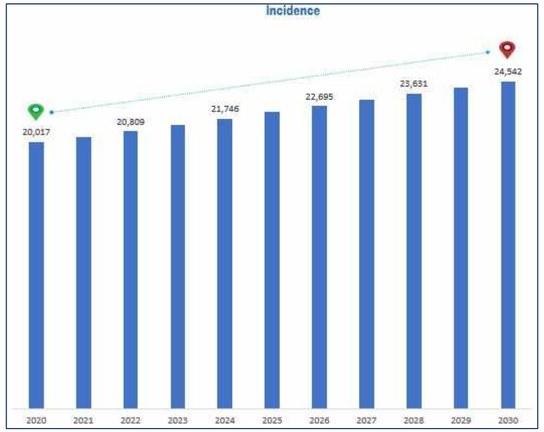
When Selectively Targeting BCL-2



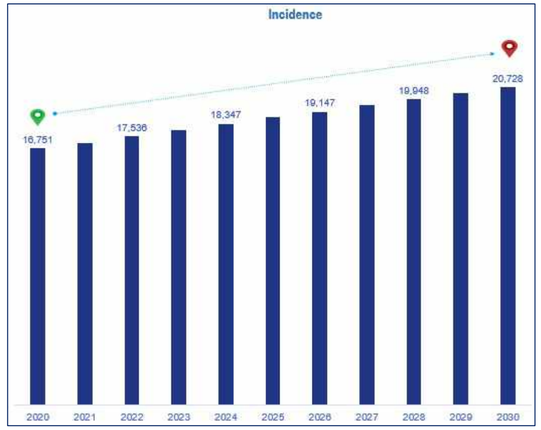
Lisaftoclax Potential

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

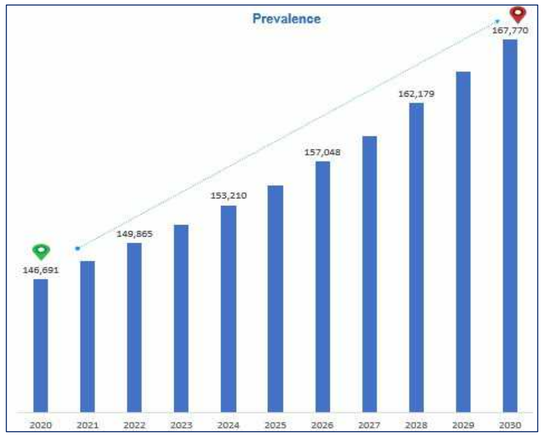
US CLL Patient Forecast

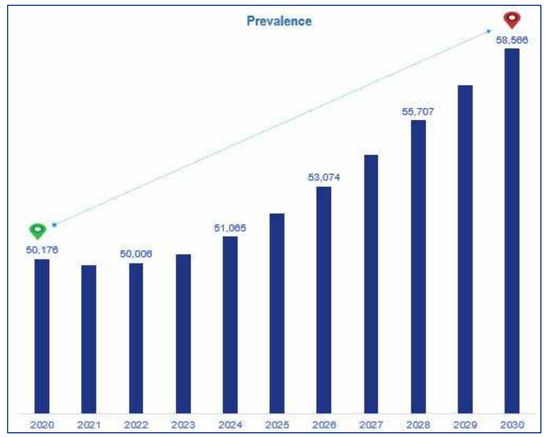


US AML Patient Forecast



Significant Patient Growth in each Disease





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

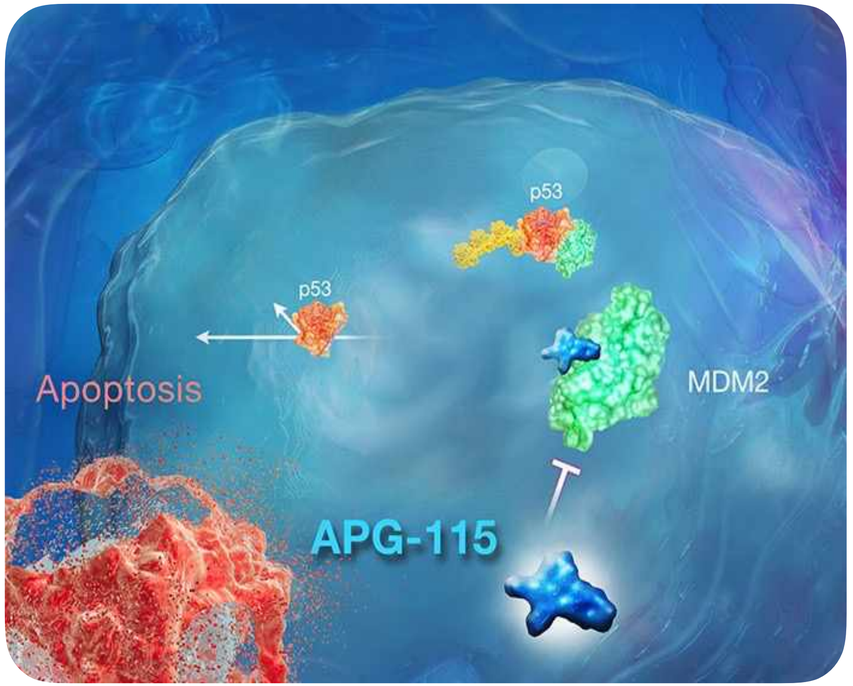
亞盛醫藥 Ascentage Pharma

Alrizomadlin (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

https://doi.org/10.1038/s41590-021-00888-3

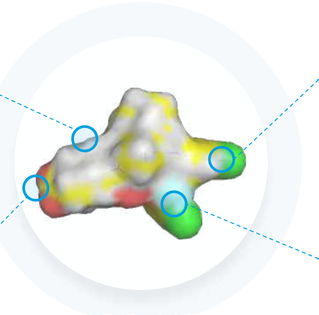
Check for updates

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[1,2,6,7,8,9]

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.

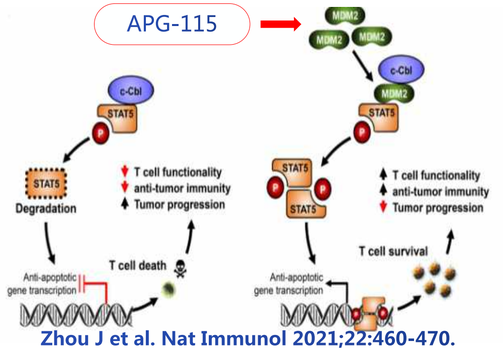
- APG-115 synergizes with IO and enhances T-cell mediated antitumor immunity



APG-115

Inhibition of MDM2-p53 interaction

Host immunomodulator



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

STAT5, signal transducer and activator of transcription 5.

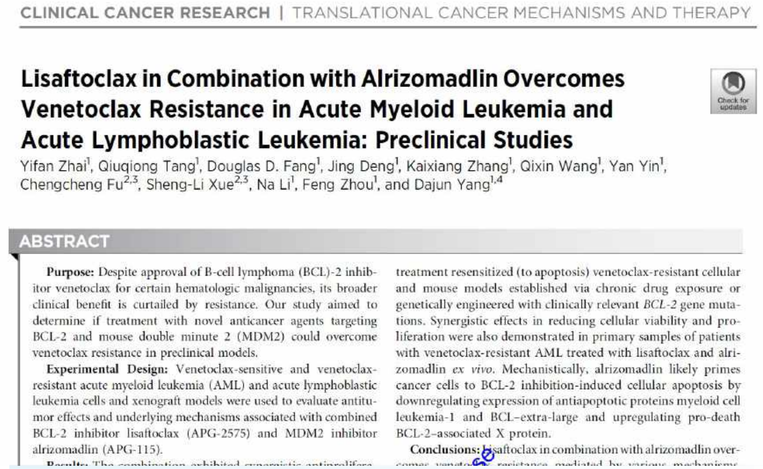
5. Tolcher AW et al. Molec Cancer Ther 2019;18:A086.

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[2,3], Sheng-Li Xue[2,3], Na Li[1], 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*

Alrizomadlin ：Clinical Development and Progress

First-in-class potential

- FDA has granted six ODDs to APG-115 for the treatment of soft tissue sarcoma, gastric cancer (GC),
- AML, Retinoblastoma, stage IIB-IV melanoma as well Neuroblastoma and 2 RPDs for neuroblastoma and Retinoblastoma

Granted a Fast Track Designation (FTD) by the FDA for the treatment of patients with unresectable or metastatic melanoma,

Obtain clinical proof of concept

Clinical Development in the US

- Combination with KEYTRUDA® in collaboration with Merck US
- The results of a phase II clinical study of APG-115 in combination with pembrolizumab demonstrated promising antitumor activity and good tolerability, and specifically in the PD-1/PD-L1 inhibitor-resistant melanoma cohort reported 1 patient with CR, ORR of 24.1%, and DCR of 55.2%.
- A phase Ib/II study of APG-115 alone or in combination with azacytidine in AML/MDS/CMML (chronic myelomonocytic leukemia).
- An investigator-initiated monotherapy phase I/II study for treatment of salivary gland cancer.

Clinical Development in China

- In May 2021, we initiated a trial of APG-115 in combination with PD-1 Inhibitor in patients with advanced liposarcoma or advanced solid tumors. First patient has been dosed for this trial.
- A phase Ib monotherapy study followed by a combination study with azacytidine or cytarabine in R/R MDS or AML.

Alrizomadlin Plus Pembrolizumab: Efficacy

Efficacy in all Cohorts

Response	Melanoma (n = 32)	NSCLC (n = 19)	STK-11 (n = 5)	ATM (n = 11)	Liposarcoma (n = 17)	UC (n = 12)	MPNST (n = 6)
ORR (CR + PR)	24.1% (7/29)	6.7% (1/15)	0	0	6.2% (1/16)	12.5% (1/8)	16.7% (1/6)
DCR (CR + PR + SD)	55.2% (16/29)	46.7% (7/15)	25% (1/4)	44.4% (4/9)	81.2% (13/16)	12.5% (1/8)	66.7% (4/6)
Best overall RECIST or iRECIST response							
CR	1	0	0	0	0	0	0
PR	6 (2 unconfirmed)	1	0	0	1(unconfirmed)	1	1(unconfirmed)
SD	9	6	1	4	12	0	3

ORR and **DCR** are based on efficacy evaluable population; stable disease (**SD**) requires a minimum duration of 2 cycles. **CR**, complete response; **DCR** disease control rate; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **UC**, urothelial carcinoma.

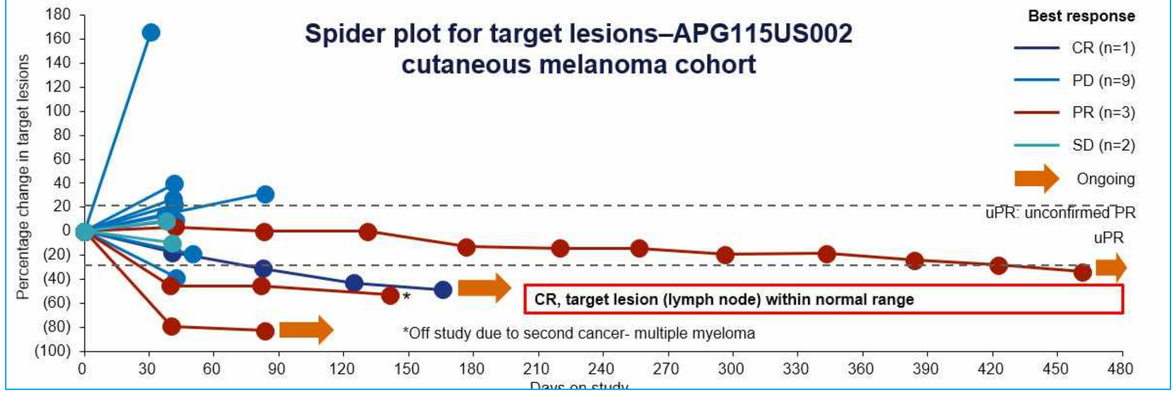
Efficacy in Patients with IO Resistant Melanoma

Response	Uveal (n = 8)	Mucosal (n = 5)	Cutaneous (n = 16)	Unknown primary (n = 3)	Total (N = 32)
ORR (CR + PR)	14.3% (1/7)	40% (2/5)	26.7% (4/15)	0	**24.1%** (7/29*)
DCR (CR + PR + SD)	71.4% (5/7)	40% (2/5)	46.7% (7/15)	100% (2/2)	**55.2%** (16/29)
Best overall RECIST or iRECIST response					
CR	0	0	1	0	**1**
PR	1	2 (1 unconfirmed)	3 (1 unconfirmed)	0	**6**
SD	4	0	3	2	**9**

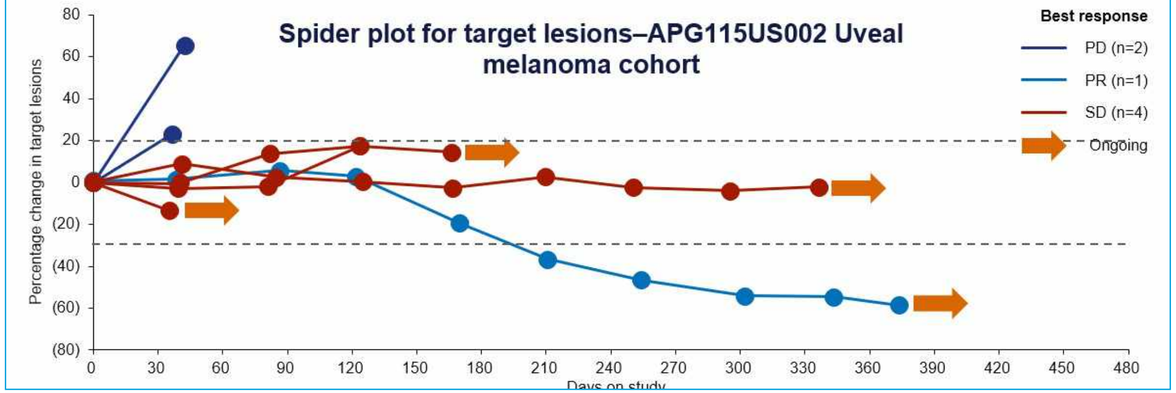
Data cutoff: April 15, 2021.

* Total evaluable patient N: 29

Efficacy in Patients with IO Resistant Cutaneous Melanoma Treated with APG-115 Plus Pembrolizumab



Efficacy in Patients with IO Resistant Uveal Melanoma Treated with APG-115 Plus Pembrolizumab



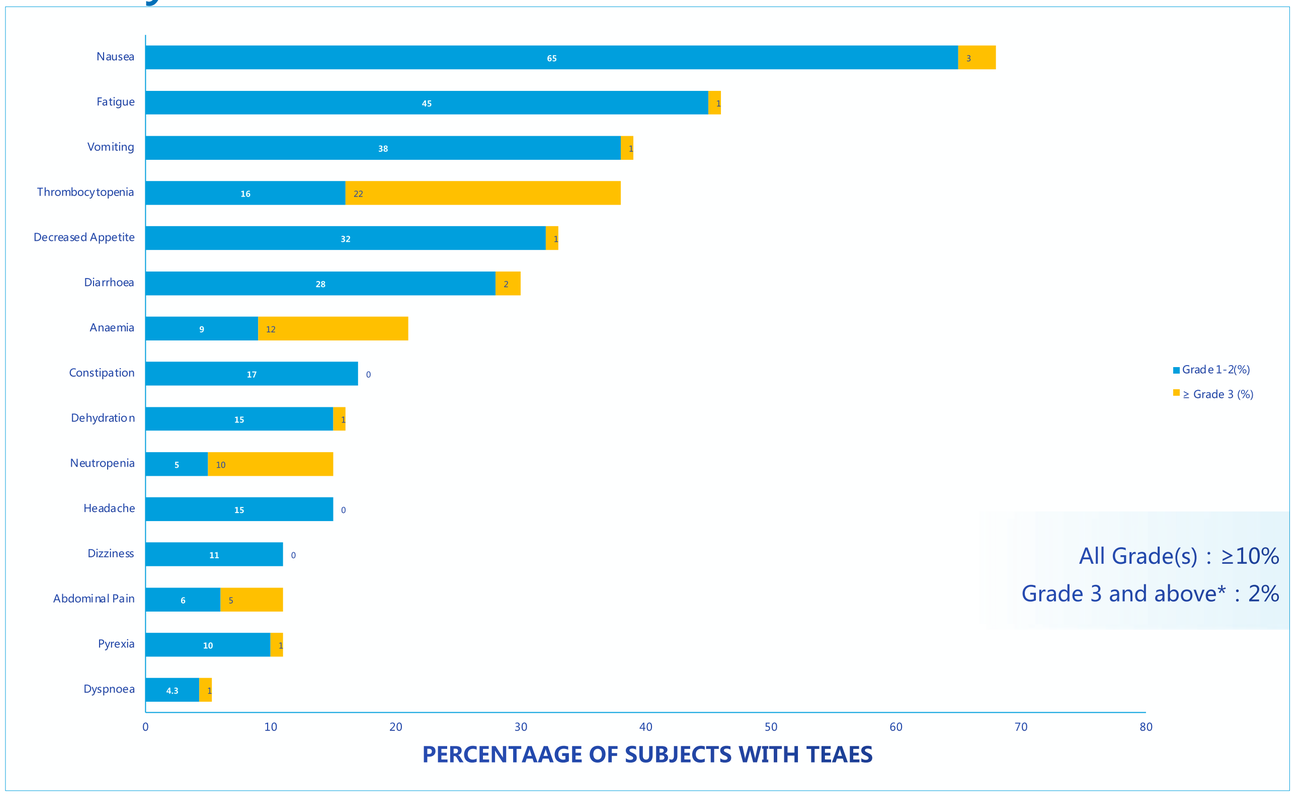
Alrizomadlin plus pembrolizumab: phase 2 study in adults and children with various solid tumors

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.**

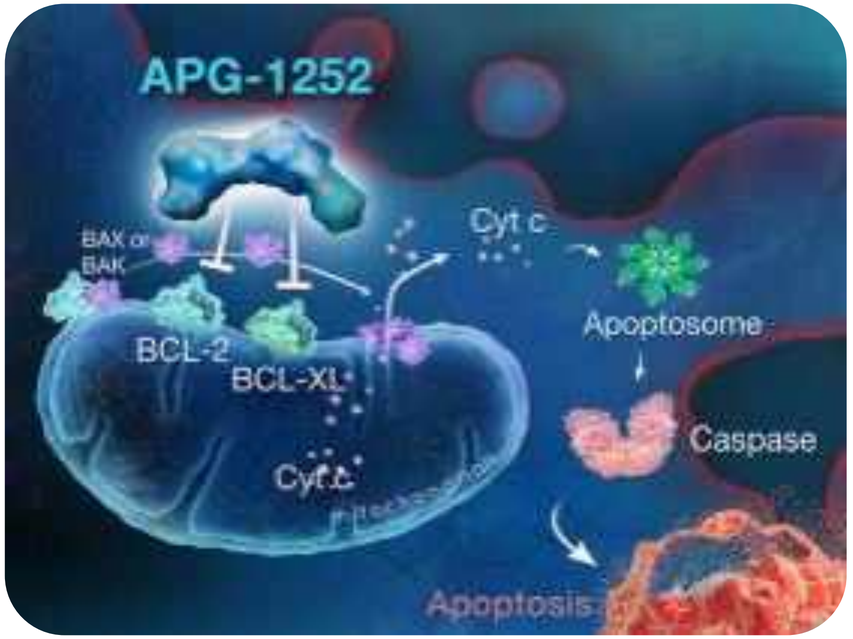
APG-1252

Bcl-2/Bcl-xL inhibitor

Combination use for the treatment of solid tumors and hematologic malignancies

Granted an ODD
for the treatment of SCLC

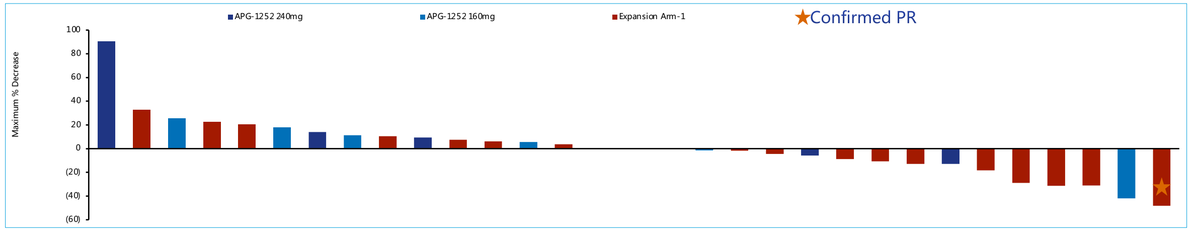
Potential Best-in-Class Drug



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 dose-escalation: 1 PR in 11 evaluable TKI resistant patients
- 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.

IASLC 2021 World Conference on Lung Cancer
SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT

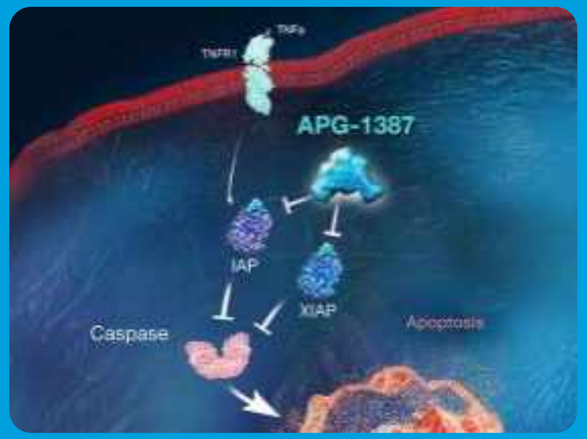
Source: Li Zhang et al.(2021), Phase Ib Study of Pelcitoclax (APG-1252) in Combination With Osimertinib in Patients With EGFR TKI-Resistant NSCLC , 2021 World Conference on Lung Cancer (WCLC)

APG-1387

An Antagonist of

IAP/XIAP

(SMAC Mimetic) Dimmer



Milestones & Clinical Developments

CHB Development

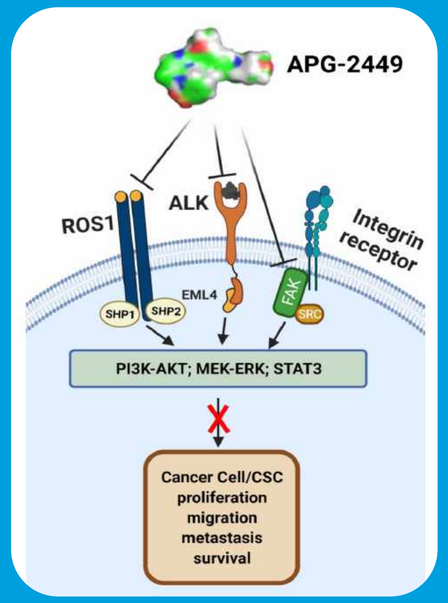
- We have already completed a phase I study for the treatment of patients with CHB.
- The stage 1 safety evaluation of APG-1387 in combination with Entecavir (ETV) for a phase II study has completed. With well-tolerated safety data, the study moved forward to stage 2, efficacy evaluation of APG-1387 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 testing the combination of APG-1387 with toripalimab (拓益), another anti-PD-1 mAb, in solid tumors, is ongoing as well. The phase Ib patient enrollment has been completed and the trial has entered into phase II
- A phase I/II study that aims to investigate the combination of APG-1387 with chemotherapy, Nab-paclitaxel and Gemcitabine for treating advanced pancreatic cancer. First patient has been dosed in March 2021.

APG-2449

ALK/FAK/ROS1



Milestones & Clinical Developments

APG-2449

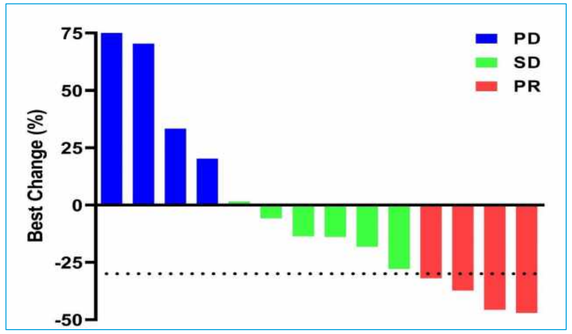
- APG-2449 is a novel, orally active, small molecule FAK/ALK/ROS1 triple ligase kinase inhibitor designed and developed by Ascentage. It is the first third-generation ALK inhibitor being developed in China.
- Pre-clinical data indicated that It is a very potential novel anticancer drug targeting FAK-expressing 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

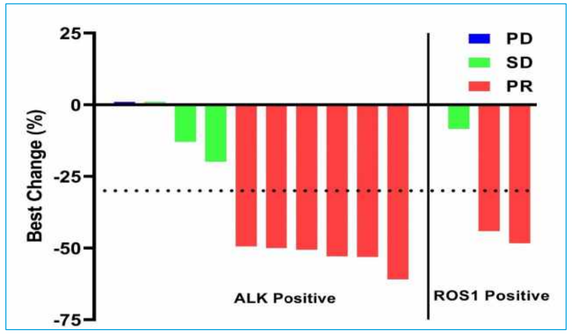
- Dose Escalation study was completed for phase I study in which patients with ALK+ NSCLC or other solid tumors were enrolled. Enrollment is ongoing for Dose Expansion Cohorts for efficacy assessment in different patient population
- Based on the preliminary efficacy result of phase I study, the engagement 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

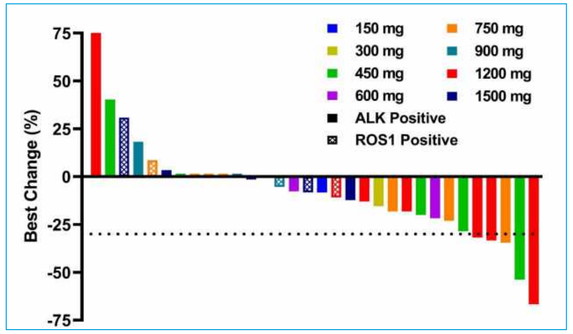
Efficacy Summaries for APG-2449 in Patient with ALK+NSCLC



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

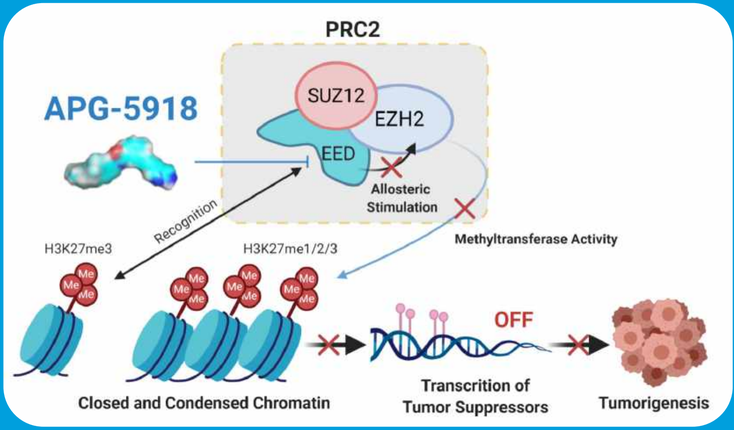


Best tumor change (%) of brain metastases observed in pts with second-generation TKI resistant ALK+ NSCLC treated with APG-2449 at different assigned doses

- 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.

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)

Study Rationale – Advanced Solid tumor & NHL

Mechanisms

- APG-5918 binds to the domain of EED that interacts with H3K27me3, which leads to a conformational change in the EED H3K27me3-binding pocket and prevents the interaction of EED with the histone EZH2, affecting the expression of its downstream target genes which play a role in carcinogenesis.

Preclinical

- APG-5918 has shown potent in vitro and in vivo on-target pharmacological activity as a single agent or combine with other therapeutic agents in CDX and PDX models of NHL and solid tumors
- Preferentially, those with EZH mutations, BAP1 mutations, or are SMARCB1 deficiency

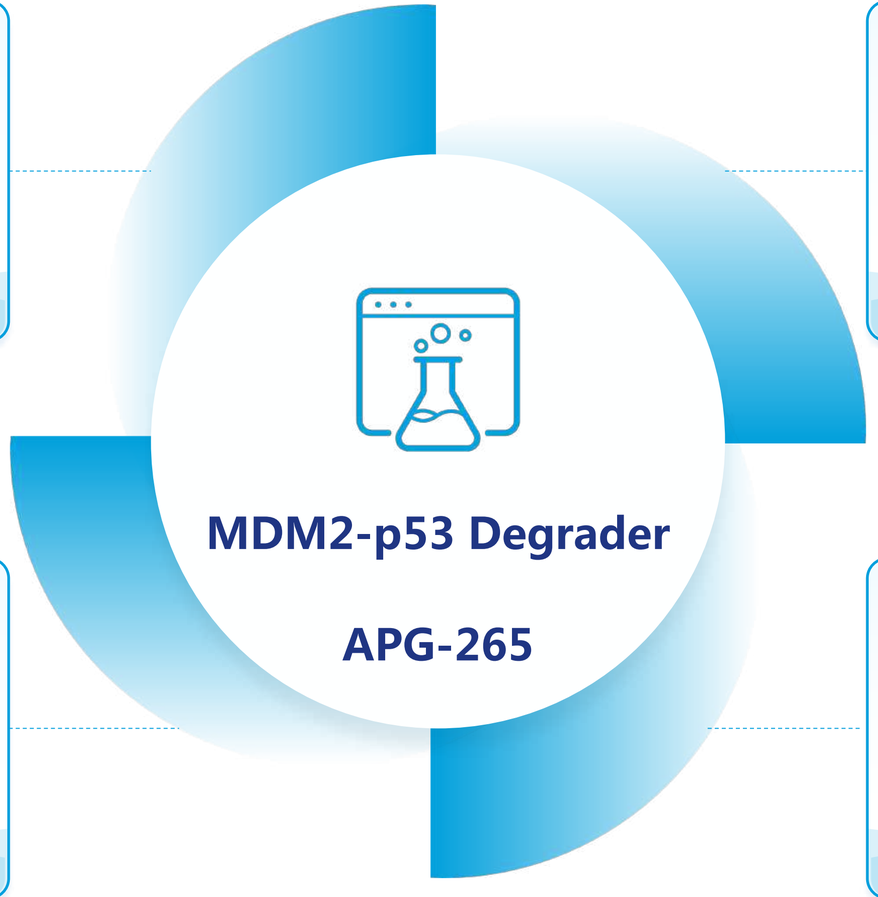
IND clearance

- Gained IND approval for first-in-human study in patients with late-stage solid tumors or hematologic malignancies
- IND application to late-stage solid tumors or hematologic malignancies accepted by CDE
- Expect to file an IND to NMPA for the treatment of anemia diseases

Pre-Clinical Assets

Focused on validated targets with clear biomarker, clinical indications and fast regulatory approval

High unmet medical needs



Transformative new technology

First-in-class or best-in-class potential

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

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Chongdong Fu, Ph.D.
CMC head

復旦大學 FUDAN UNIVERSITY · 和黃医药 HUTCHMED

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

Breakthrough Science

205 issued patents

600 pending applications

Strong pipeline

1 NDA Approval

10+ indications

12 novel compounds

50+ clinical trials

30+ INDs

Dedicated team

1 vision: building a global biopharmaceutical company

20+ years commitment of executive team

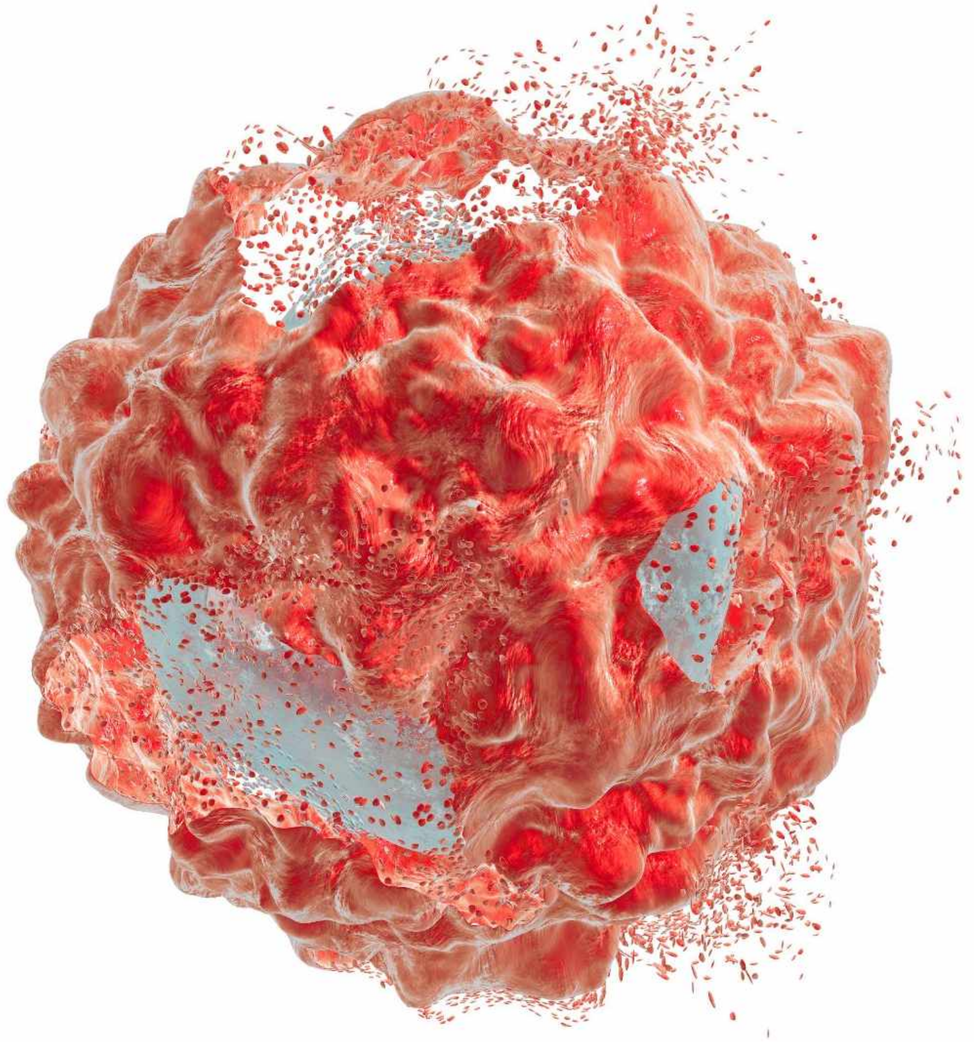
600+ employees

Global development

China, United States, Europe and Australia

Integrated global organization

Source：Company database，as of June 30, 2022



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