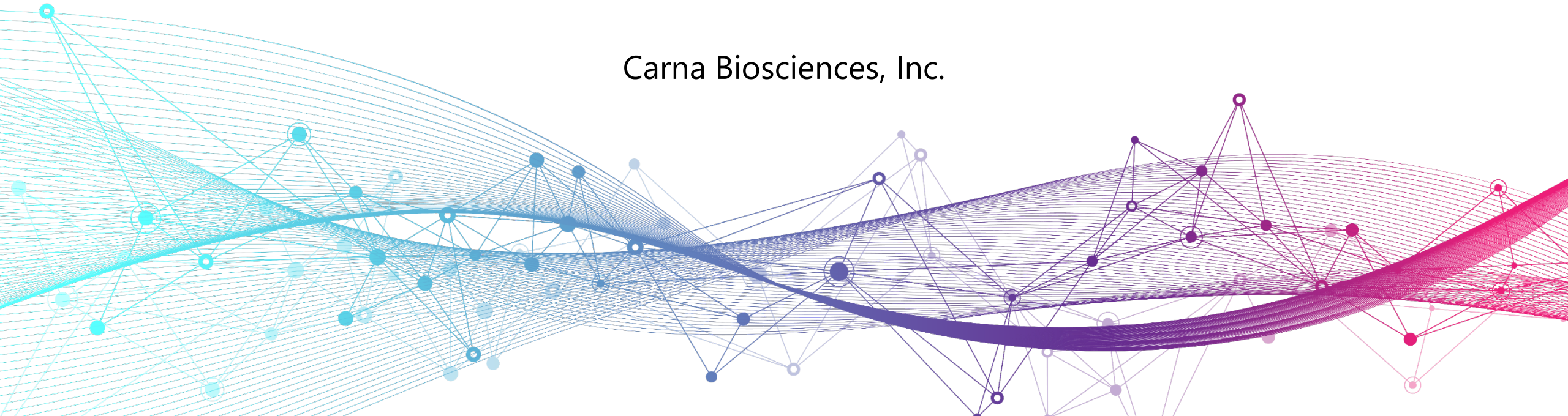
Financial Results
Q3 FY2024

（January to September 2024）

Carna Biosciences, Inc.



AGENDA

1 Updates on Pipelines in Clinical Development

2 Updates on Licensed Pipelines

3 FY2024 Q3 Results

4 Appendix

Updates on Pipelines in Clinical Development

1. **docirbrutinib (AS-1763)**
2. **sofnobrutinib (AS-0871)**
3. **monzosertib (AS-0141)**

International Nonproprietary Name (INN) : docirbrutinib, Code name : AS-1763
International Nonproprietary Name (INN) : sofnobrutinib, Code name : AS-0871
International Nonproprietary Name (INN) : monzosertib, Code name : AS-0141

Pipelines in Clinical Development

Compound	Target	Indication	Status
docirbrutinib (AS-1763)	BTK	Blood Cancer	• Phase 1b clinical trial is ongoing in the U.S. • Dose expansion part was initiated in October in parallel with the dose escalation part to accelerate the development timeline. • Encouraging preliminary data was presented at EHA 2024 in June. Multi-center clinical study Study Lead ：Prof. Nitin Jain, MD, Department of Leukemia, University of Texas MD Anderson Cancer Center.
sofnobrutinib (AS-0871)	BTK	Immune-inflammatory diseases	• Completed Phase 1 clinical trial in healthy volunteers in the Netherlands, in which a favorable safety and tolerability profile as well as a promising PK/PD profile were confirmed. • Performed a preclinical study to establish a best-in-class status; potential advantages of sofnobrutinib over other BTK inhibitors. • Seeking a strategic partner for further development.
monzosertib (AS-0141)	CDC7/ ASK	Cancer	• Dose escalation part of Phase 1 clinical trial in cancer patients is ongoing in Japan. Clinical trial site : National Cancer Center Hospital and National Cancer Center Hospital East

Docirbrutinib (AS-1763) : Highlights

Key Highlights

Orally available small molecule inhibitor of Bruton's Tyrosine Kinase (BTK) targeting B-cell malignancies

✓ Docirbrutinib has a potential to be effective for patients who have developed resistance to the existing BTK inhibitors.

CLL: Chronic lymphocytic leukemia SLL: Small lymphocytic lymphoma B-cell NHL: B-cell non-Hodgkin lymphoma

Status

Phase 1b study is ongoing in the U.S.

Multi-center clinical study
Study Lead : Prof. Nitin Jain, MD, Department of Leukemia, University of Texas MD Anderson Cancer Center

✓ Dose expansion part was initiated in October in parallel with the dose escalation part to accelerate the development timeline.

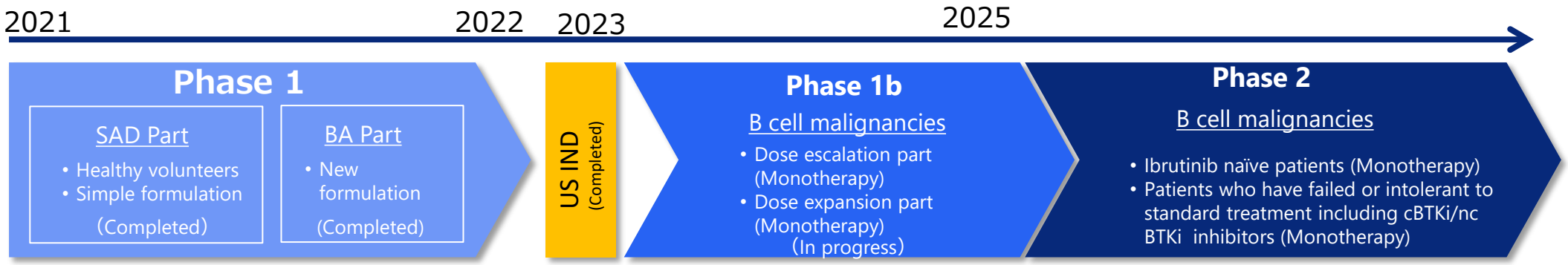
Phase 1b study is conducted at nine clinical sites. Planning to activate additional clinical sites.

- UC Irvine Health
- Mount Sinai Comprehensive Cancer Center
- Moffitt Cancer Center
- Northwestern Memorial Hospital
- University of Maryland Medical Center-Greenebaum Comprehensive Cancer Center
- University of Massachusetts Memorial Medical Center
- Clinical Research Alliance, Inc.
- University of Texas MD Anderson Cancer Center
- The Medical College of Wisconsin

Docirbrutinib (AS-1763) : Next Generation BTK Inhibitor

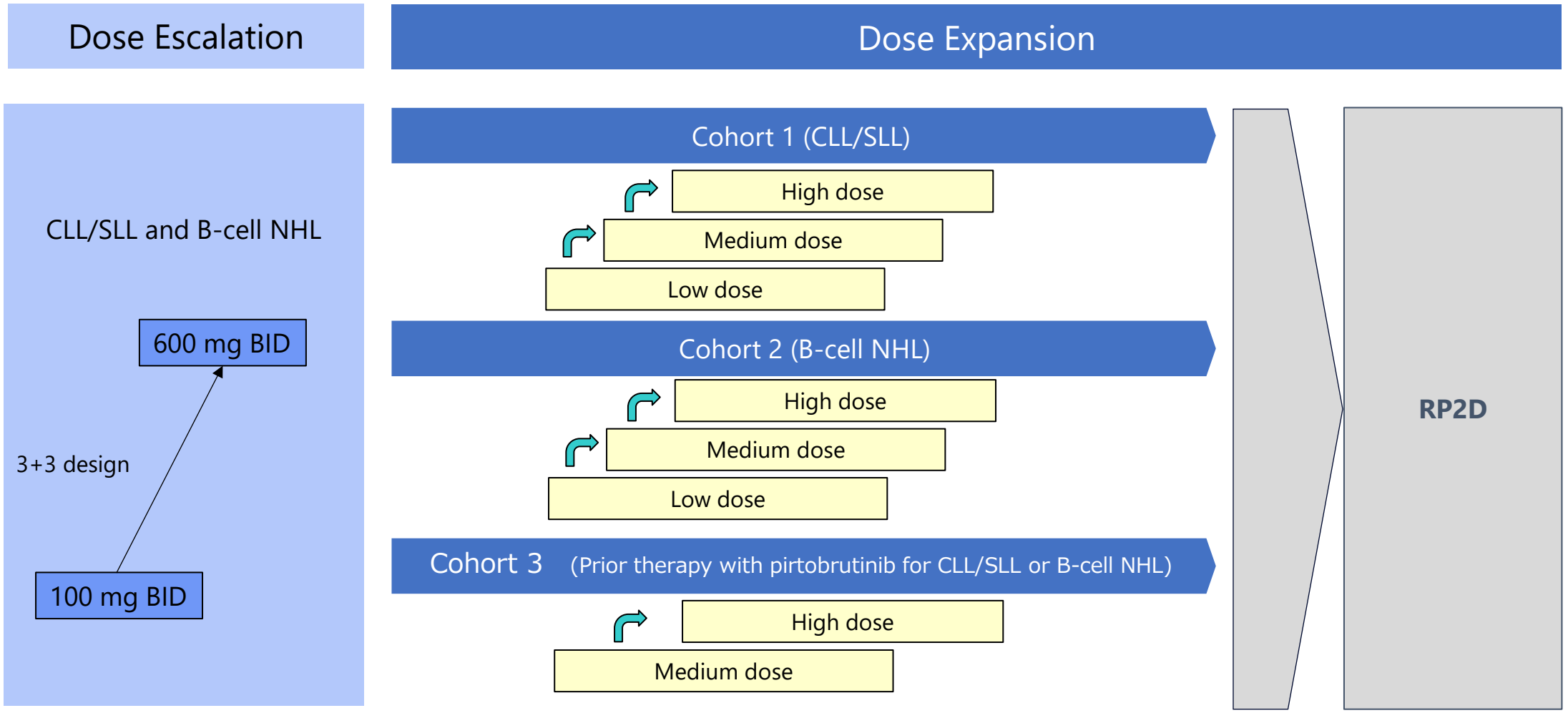
Docirbrutinib : Targeting Blood Cancer

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Wild type and pan-mutant BTK inhibitor
- Orally available
- Active against covalent/non-covalent BTK inhibitor-resistant mutations found in patients (C481x, T474x, T316A, L528x).
- The first patient was dosed in August 2023 in dose escalation part of Ph 1b study in the U.S.
- Dose expansion part was initiated in October 2024.



IND application: Investigational New Drug application
SAD: Single Ascending Dose
BA: Bioavailability
B-cell malignancies: Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), and B-cell non-Hodgkin Lymphoma (B-cell NHL), etc.
cBTKi: covalent BTK inhibitor
ncBTKi: non-covalent BTK inhibitor

Docirbrutinib (AS-1763) : Phase 1b Trial Design



RP2D: recommended phase 2
BID: Twice a day

Patients with CLL/SLL or B-cell NHL who have failed or intolerant to at least two lines of systemic therapy.

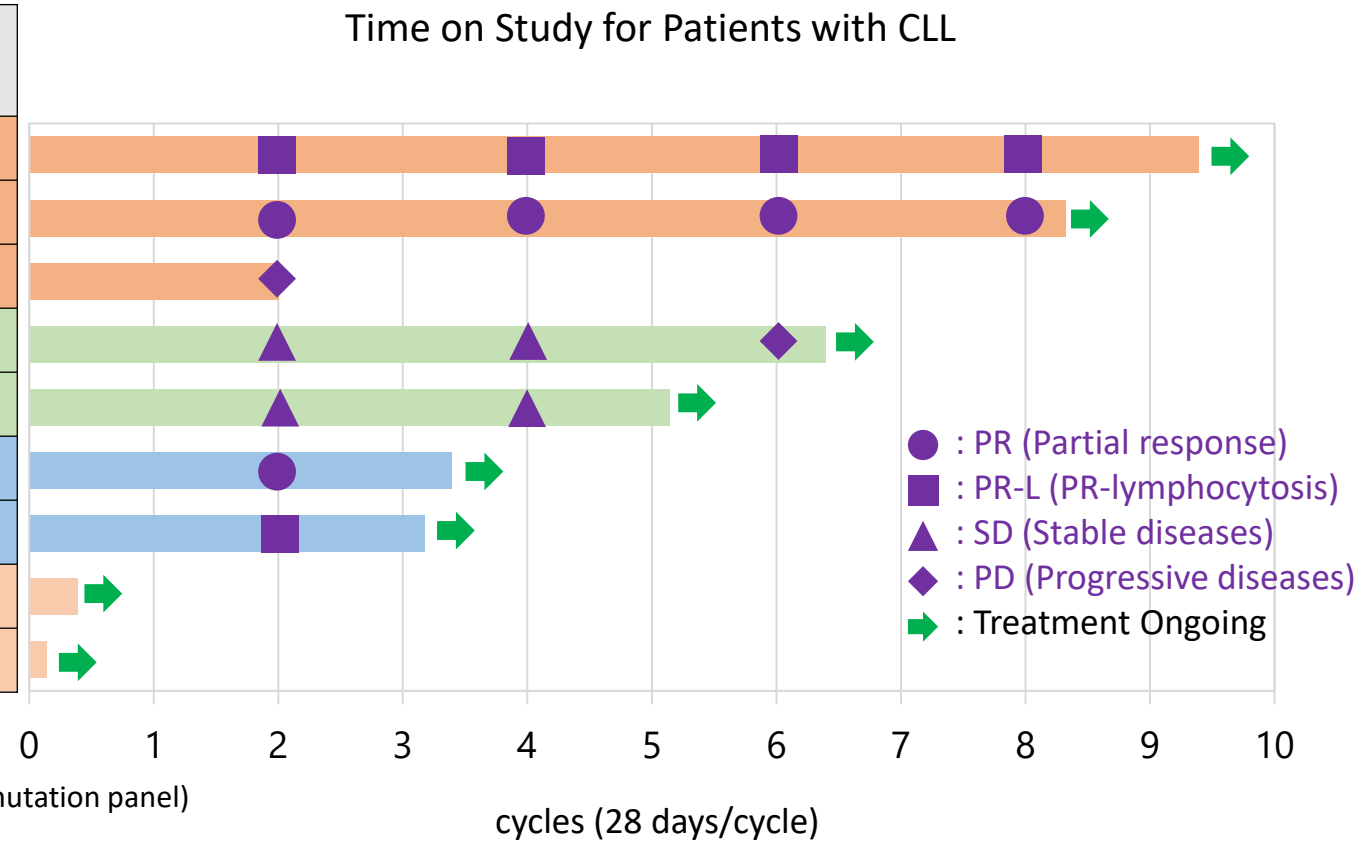
Prior therapy with a covalent BTKi is permitted.

Docirbrutinib (AS-1763) : Preliminary Phase 1b Data in Patients with CLL

Docirbrutinib demonstrates impressive clinical responses in heavily pretreated patients with CLL, including covalent BTK inhibitors and BCL2 inhibitors.

Data cutoff: 19 April 2024
Latest data will be presented at ASH in December 2024.

Prior cBTKi	Prior BCL2i	Prior lines	BTK mutation	Pts	Doses
Ib + Ven		4	WT	CLL	100 mg BID
Ib	-	2	WT	CLL	100 mg BID
Ac	Ven	5	WT	CLL	100 mg BID
Ib	Ven	5	C481S*	CLL	200 mg BID
Ib	-	3	C481S*	CLL	200 mg BID
Ib	Ven	4	C481S#	CLL	300 mg BID
Ac	-	3	WT	CLL	300 mg BID
Ib + Ven		3	WT	CLL	400 mg BID
Ib	Ven	4		CLL	400 mg BID



*BTK C481S detected centrally by next generation sequencing (CLL mutation panel)
#BTK C481S detected locally by Sanger sequencing
Ib: ibrutinib, Ac: acalabrutinib, Ven: venetoclax, Ib + Ven: combo
ASH : The 66th American Society of Hematology Annual Meeting & Exposition, December 7-10, 2024

Docirbrutinib (AS-1763) : Summary of Preliminary Phase 1b Data

Data cutoff :19 April 2024 Latest data will be presented at ASH in December 2024.

- **Docirbrutinib demonstrates encouraging preliminary results in ongoing Phase 1b trial.**
  - 8 of 9 CLL patients are still on treatment.
  - No discontinuation due to adverse events related to docirbrutinib.

    No atrial fibrillation or moderate to severe bleeding-related events, commonly observed with covalent BTK inhibitors including ibrutinib, were reported.

The dose escalation part is ongoing at 500 mg BID.
The dose expansion part was initiated in October 2024 based on the encouraging efficacy and safety data.

Poster Presentations on docirbrutinib (AS-1763) at ASH

Two posters on docirbrutinib including the latest preliminary data of Phase 1b study will be presented at ASH in December 2024.

＊ASH：The 66th American Society of Hematology Annual Meeting & Exposition, December 7-10, 2024

(1)

Preclinical data on docirbrutinib (Publication Number：1850)

Poster title: Impact of Docirbrutinib (AS-1763) Treatment in CLL: Preclinical Data and Early Clinical Biomarkers

The abstract is available at: https://ash.confex.com/ash/2024/webprogram/Paper210788.html

Summary： Preclinical findings of docirbrutinib using blood samples obtained from CLL patients treated with docirbrutinib

Presenter： Natalia Timofeeva, MD, Department of Experimental Therapeutics, University of Texas MD Anderson Cancer Center et al.

(2)

Preliminary data from ongoing Phase 1b study of docirbrutinib (Publication number：1866)

Poster title: Preliminary Results from a Phase 1b Study of Non-Covalent Pan-Mutant BTK Inhibitor Docirbrutinib (AS-1763) in Patients with Previously Treated B-Cell Malignancies

The abstract is available at: https://ash.confex.com/ash/2024/webprogram/Paper208549.html

Summary： Preliminary data from Phase 1b study of docirbrutinib

Presenter： Prof. Nitin Jain, MD, Department of Leukemia, University of Texas MD Anderson Cancer Center et al.

Docirbrutinib (AS-1763) : Sponsorship to CLL Society

CLL Society

CLL Society is the world's leading authority for chronic lymphocytic leukemia and small lymphocytic lymphoma cancer patients.

Mission

CLL Society is an inclusive, patient-centric, physician-curated nonprofit organization that addresses the unmet needs of the chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL / SLL) community through patient education, advocacy, support, and research.

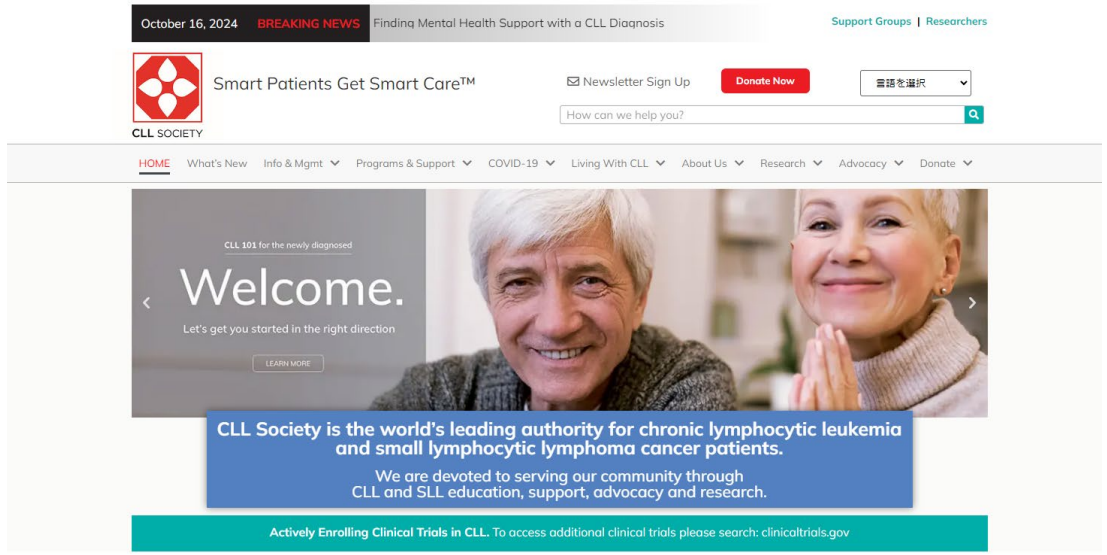
Vision

We envision a world in which the entire CLL / SLL community can equitably access quality education, support, and care, to lead healthier and richer lives.

－Cited from the website of CLL Society－

Carna offered sponsorship at the request of CLL Society.

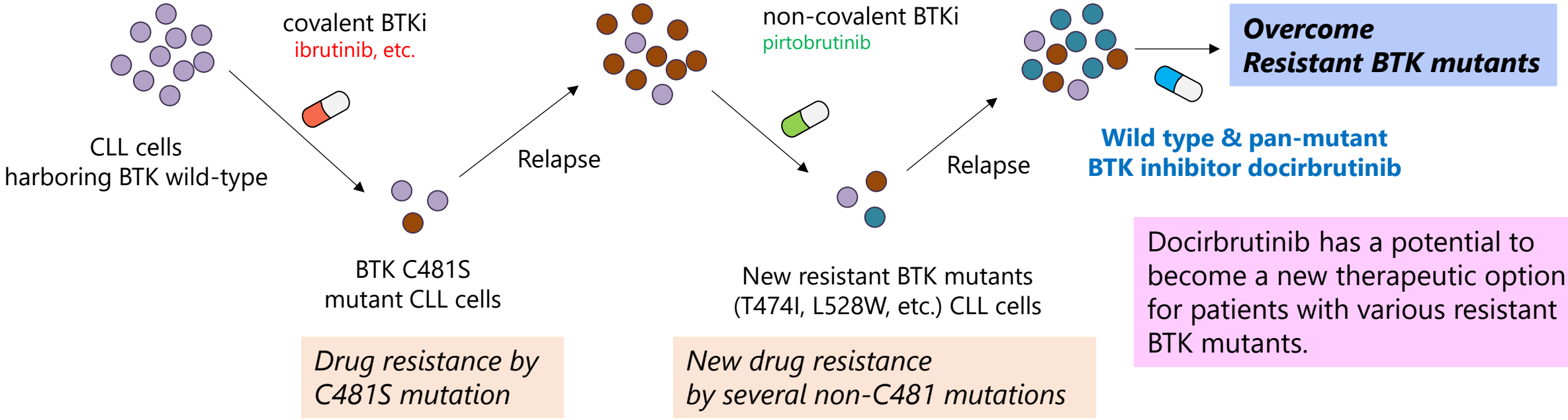
https://cllsociety.org/



A clinical trial ad for docirbrutinib is on CLL Society's website to promote patient enrollment.

Docirbrutinib (AS-1763) : Wild-type & Pan-mutant BTK Inhibitor

- Covalent BTK inhibitors have been widely appreciated as a promising targeted therapy for patients with B-cell malignancies.
- However, patients are reported to develop resistance during the treatment due to substitution of cysteine residue at 481 position with serine (C481S mutation) in BTK, which reduces the efficacy of the covalent BTK inhibitors.
- In addition, the emergence of other types of resistance mutations to non-covalent BTK inhibitor, pirtobrutinib approved in 2023, has been reported.
- Docirbrutinib potently inhibited both wild type and those mutant BTKs, strongly suggesting that docirbrutinib will be a new therapeutic option for treating patients with B-cell malignancies both having wild type and resistance mutations in BTK.



Docirbrutinib has a potential to become a new therapeutic option for patients with various resistant BTK mutants.

Discontinuation of ibrutinib treatment is commonly due to intolerance

The discontinuation rate of ibrutinib treatment was 41% in the US, and the cause of the majority of discontinuation was AEs.

Reasons for ibrutinib discontinuation	Ibrutinib in front-line	Ibrutinib in relapse
Toxicity	63.1%	50.2%
CLL Progression	15.8%	20.9%
Others	21.1%	28.9%

Data cited from Mato AR, et al., Haematologica. 2018;103(5):874-879

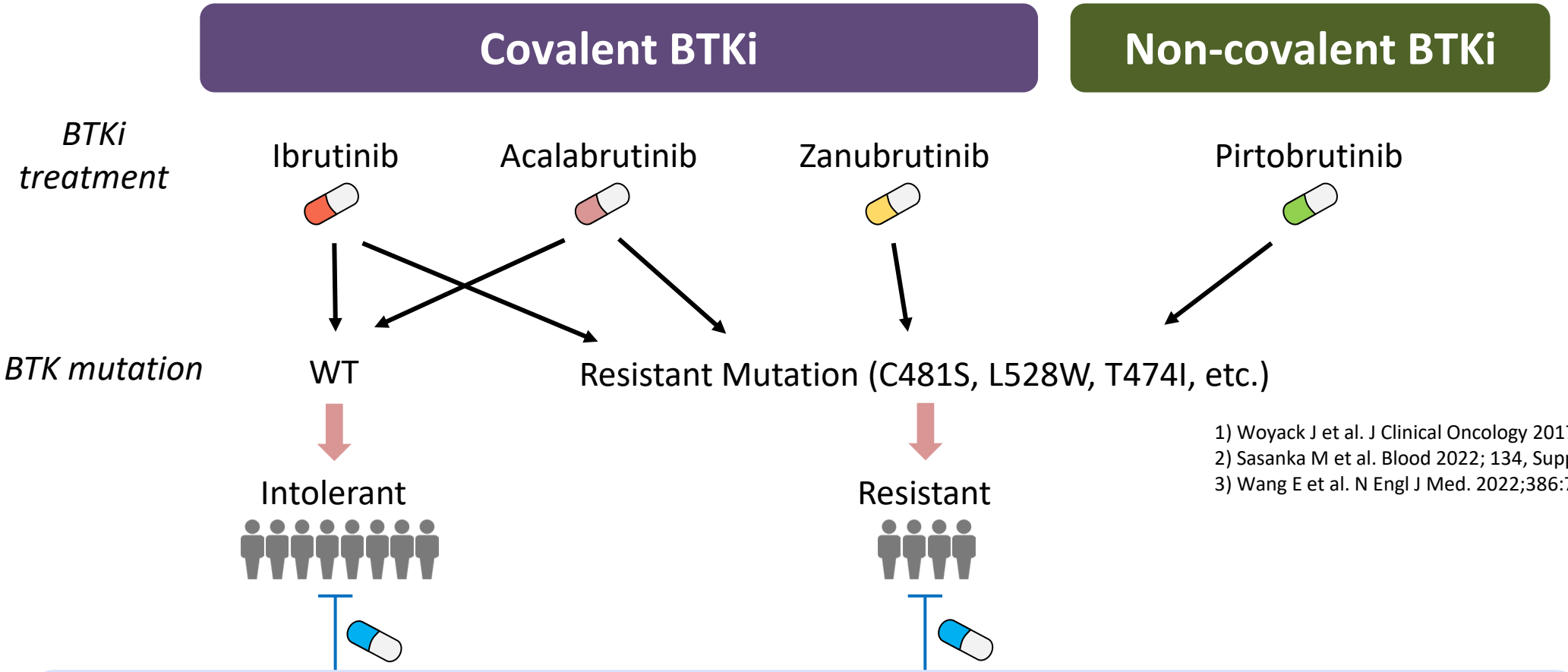
Docirbrutinib (AS-1763) in Phase 1b :

No discontinuation due to adverse events have been reported so far

Docirbrutinib demonstrates safer profiles,

suggesting better option for effective therapy

Docirbrutinib (AS-1763): Potential Target Patients



1) Woyack J et al. J Clinical Oncology 2017;35:1437–1443.
2) Sasanka M et al. Blood 2022; 134, Supplement 1, 170-174.
3) Wang E et al. N Engl J Med. 2022;386:735-743.

Safer, Pan-mutant BTK inhibitor docirbrutinib
The Best-in-Class profile of docirbrutinib will bring a benefit to wide range of patients.

BTK Inhibitors in clinical development

Competitors: other non-covalent BTK inhibitors in clinical development

Compound	Company	Development Phase
pirtobrutinib (LOXO-305)	Lilly (Loxo)	Approved/P3
nemtabrutinib (ARQ 531)	Merck (ArQule)	P3
TT-01488	TransThera	P1
HMPL-760	HutchMed	P1

- FDA granted an accelerated approval to pirtobrutinib, the most advanced competitor to docirbrutinib (AS-1763), in the U.S early 2023.
- Focused differentiation strategy from pirtobrutinib is the key to the success of docirbrutinib.
- In preclinical studies, docirbrutinib demonstrated to be effective for mutant BTKs that confer resistance to pirtobrutinib* in addition to ibrutinib**.

*N. Engl. J. Med. 2022;386(8):735–743.
**Poster presentation at ASH 2023

Docirbrutinib (AS-1763): Potential Market Size (B-cell Malignancies)

Present

Covalent BTK inhibitors including ibrutinib, acalabrutinib, and zanubrutinib are key therapeutic options.

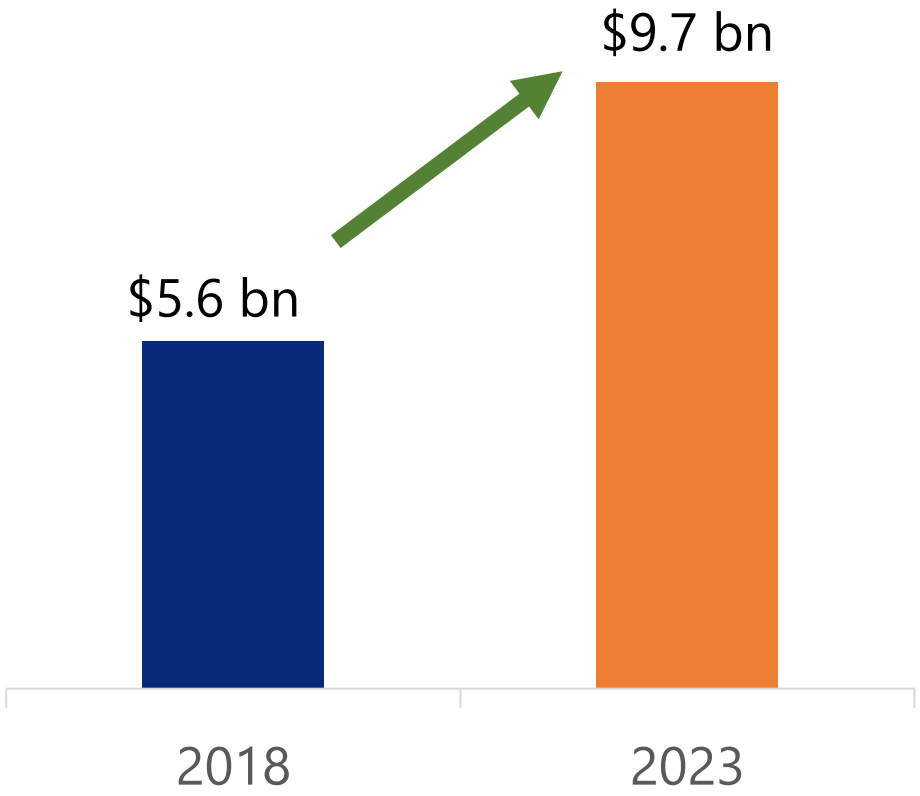
Opportunity

Patients treated with covalent BTK inhibitors are reported to develop resistance to the drugs

High unmet needs for new therapeutic options to treat patients with B-cell malignancies who have developed resistance to covalent BTK inhibitors

- Next generation **non-covalent BTK inhibitors** including docirbrutinib are expected to be promising therapeutic options for the patients who have developed resistance to covalent BTK inhibitors. Our goal is to take a certain share of this potential large market, making docirbrutinib a blockbuster drug.

BTK Inhibitors for Blood Cancer



BTK Inhibitors WW sales
(1st generation/covalent type)

The sales growth of first-generation BTK inhibitors has slowed due to potential side effects and drug-resistance by C481S mutation.

Next generation BTK inhibitors including docirbrutinib (AS-1763) are under development to overcome side effects and drug-resistance.

Global BTK inhibitors market size is still expanding significantly and expected to reach > $22Bn by 2030!

https://www.insightaceanalytic.com

Sofnobrutinib (AS-0871) ： Highlights

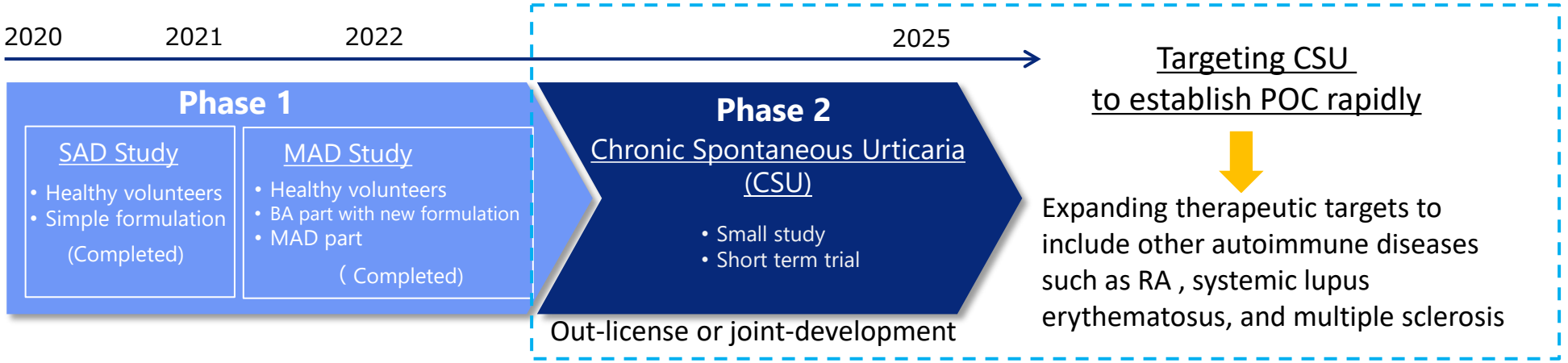
Mechanism/ Indication	Sofnobrutinib is an **orally available** Bruton's Tyrosine Kinase (BTK) inhibitor to treat autoimmune diseases by inhibiting activation of immune cells such as B cells, macrophages, and mast cells.
Clinical trials	Completed Phase 1 clinical trial in healthy volunteers in the Netherlands. A favorable safety and tolerability profile as well as a promising PK/PD profile were confirmed and these results support to advance sofnobrutinib into Phase 2 clinical development.
Status	✓ Performed a preclinical study to establish a best-in-class status; potential advantages of sofnobrutinib over other BTK inhibitors. ✓ Seeking a strategic partner for further development.

Sofnobrutinib (AS-0871) : Non-covalent BTK Inhibitor

Sofnobrutinib : Targeting Immune-inflammatory diseases

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Orally available

- Demonstrated significant efficacies in arthritis models
- Showed efficacy in systemic lupus erythematosus model
- Phase 1 Clinical Trial was completed
- Find a partner to conduct further development



SAD: Single Ascending Dose
MAD: Multiple Ascending Dose
BA: Bioavailability
POC: Proof of Concept

Sofnobrutinib (AS-0871) : Potential best-in-class

Embryo-Fetal Development (EFD) toxicity study was performed to prove potential advantages of sofnobrutinib over other BTK inhibitors.

Sofnobrutinib showed "No Teratogenic Effect“ in the EFD study, suggesting it is suitable for the treatment of dermatologic diseases including CSU.

As most BTK inhibitors approved are teratogenic, their use should be limited especially for women.
Sofnobrutinib is confirmed to be non-teratogenic in the EFD toxicity study, providing a treatment option for a wider range of patients.

Sofnobrutinib is the only BTK inhibitor having a non-covalent inhibitory mechanism of action with no teratogenic effect.

Sofnobrutinib (AS-0871) : CSU is a skin disease with unmet medical needs

Chronic Spontaneous Urticaria (CSU) is a distressing skin disorder that is characterized by itching and hives lasting for more than 4 weeks with unknown causes. The symptoms can last months or years, affecting QoL of patients.

Challenges of CSU

- A significant number of patients having uncontrolled CSU by existing drugs.
- High socio-economic costs for patients with high disease activity*
- Large number of patients; approximately 1% of the global population is affected*

High unmet medical needs with potential large market

＊Br J Dermatol 2021;184:226-36.

Competitors

Compound	Company	Development Phase
Remibrutinib (LOU064)	Novartis	P3

The Phase III trials met the primary endpoints and showed rapid symptom control in CSU, supporting the potential of BTK inhibitors as a new treatment option for those uncontrolled by first-line H1-antihistamines.*

＊https://www.novartis.com/news

Opportunity

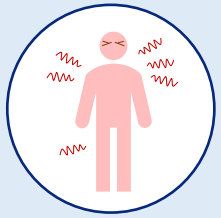
- Approval of new treatment options may trigger the expansion of CSU market.
- We plan to pursue the clinical implications of sofnobrutinib (non-covalent BTK inhibitor) to provide clinical benefits by minimizing potential adverse events associated with covalent BTK inhibitors including remibrutinib.

Chronic Spontaneous Urticaria (CSU)

CSU is a debilitating disease of chronic itch, hives and angioedema, lasting six weeks or more.

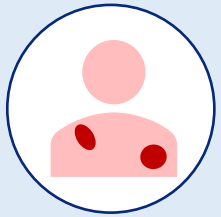
Symptoms

There is no specific external trigger for CSU, but the autoimmune system may play a role

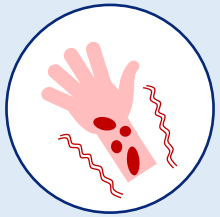


Spontaneously present & re-occur

Lack of Energy
Depression/Anxiety
Chronic (Lasting for at least six weeks)



Red swollen hives



Itch

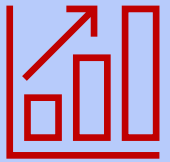
Number of Patients

2.8 million

diagnosed prevalent cases in major seven markets

- ✓ Approximately 1% of the population worldwide is affected.
- ✓ Approximately 50% of CSU patients don't respond to H1-antihistamine.
- ✓ Curative treatment is not available.
- ✓ High socio-economic costs for patients with high disease activity.

Market Size



$2,844 million

in 2020 in seven major markets

- ✓ The market size of CSU in major seven countries is expected to reach $8,043 mn by 2030

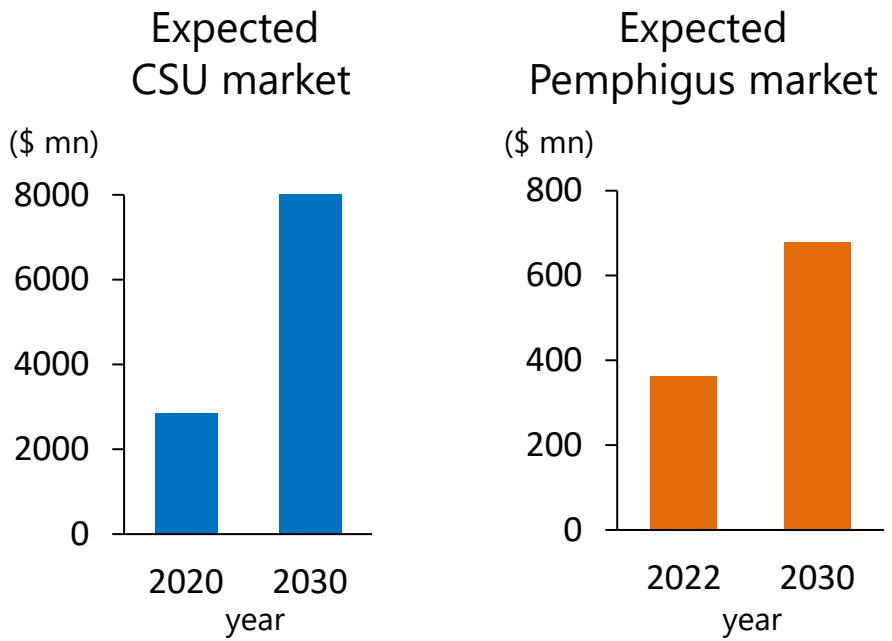
https://www.delveinsight.com/
Source : Clarivate

Potential Market Size for Sofnobrutinib (AS-0871)

Initial focus

Diseases	Number of patients
CSU	• Diagnosed prevalent cases : 2.8 mn* • WW population affected: 76 mn
Pemphigus	• Diagnosed prevalent cases : 40,000*

*in major 7 markets



Other potential therapeutic area

Diseases	Number of patients	Market size in value
Systemic lupus erythematosus (SLE)	Global SLE prevalence is estimated to be 15.87 to 108.92 per 100,000 people	expected to reach $3,517 mn by 2030
Multiple sclerosis (MS)	In 2016, an estimated 2.2 million people worldwide had MS, corresponding to a prevalence of 30.1 cases per 100,000 population	expected to reach $34 bn by 2031
Rheumatoid arthritis (RA)	18 million people worldwide were living with RA	expected to reach $70 bn by 2030

https://www.delveinsight.com/
https://www.databridgemarketresearch.com/
https://ard.bmj.com/
https://straitsresearch.com/
https://www.skyquestt.com/
https://www.who.int/
Ann Rheum Dis 2023;82:351–356
Lancet Neurol 2019 ; 18: 269–85
Source : Clarivate

Monzosertib (AS-0141) : CDC7 Inhibitor

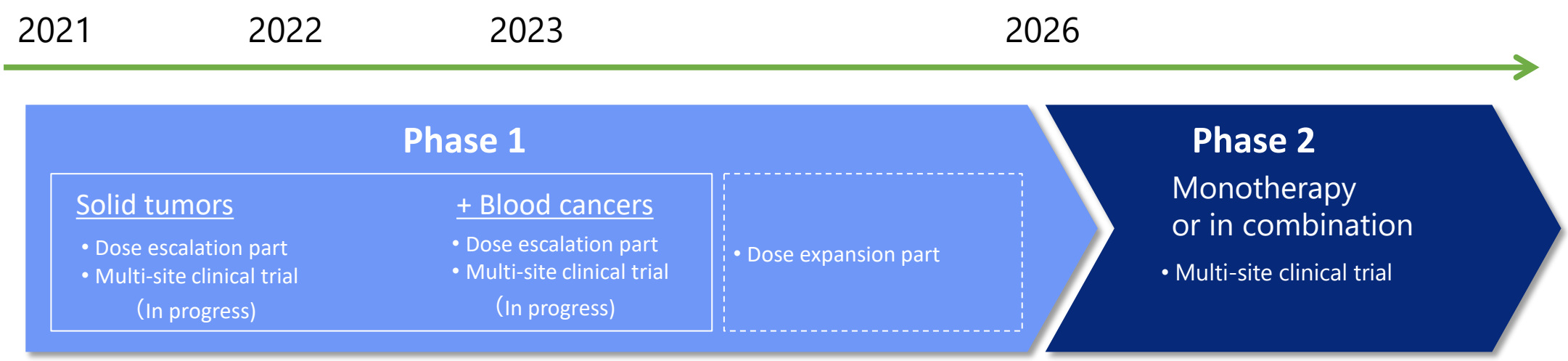
Highlights	Monzosertib is an orally available CDC7 kinase inhibitor targeting cancer
Clinical trials in progress	Conducting Phase 1 study in Japan targeting solid tumors and blood cancers ✓ Dose escalation part is ongoing. ✓ Expected to move to dose expansion part in 2024. Clinical trial sites - National Cancer Center Hospital and National Cancer Center Hospital East - The Cancer Institute Hospital of JFCR will be added as an active trial site for the dose expansion part.

Monzosertib (AS-0141) : CDC7 Inhibitor

Monzosertib：Targeting Cancer

- Small molecule CDC7 inhibitor
- High kinase selectivity
- Potential First-in-class drug
- Orally available

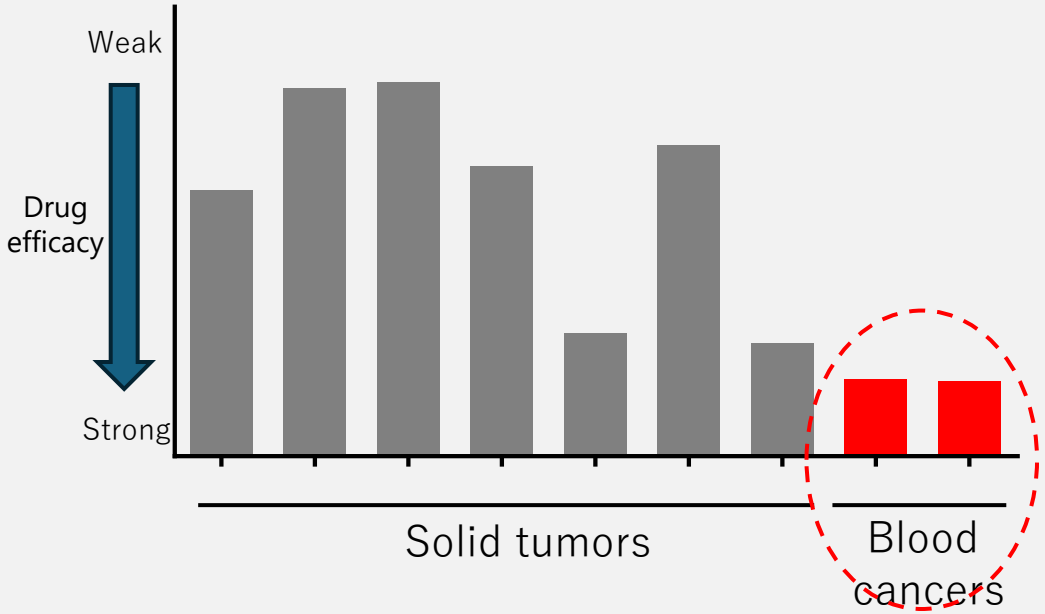
- Potent anti-proliferative activity against various cancer cell lines
- Demonstrated strong anti-tumor activity in several human tumor xenograft models
- Conducting Phase 1 study in Japan targeting solid tumors and blood cancers



Monzosertib (AS-0141) : Initiated dose escalation part targeting blood cancer

Non-clinical study

Antiproliferative effects of monzosertib on 35 human cancer cell lines
(Each bar are presented as mean of different cell lines (N = 1 – 7)



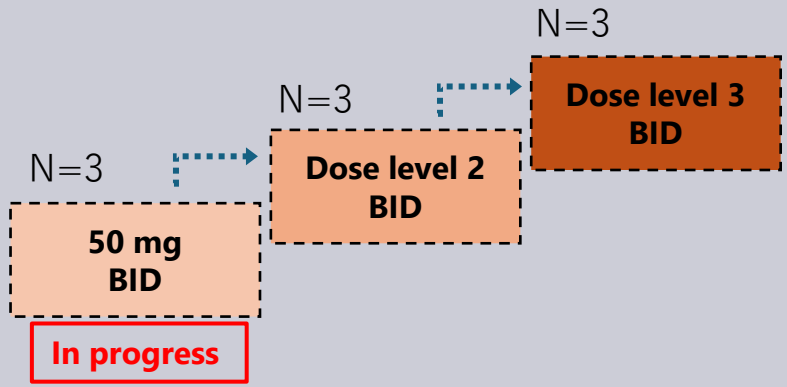
✓ Monzosertib demonstrated robust tumor growth inhibition in a human AML xenograft mouse model.

Phase 1 study

Patient Population: advanced, relapsed, refractory or distant metastasis malignant tumors

Initiated dose escalation part targeting blood cancer patients and the first patient has been dosed.

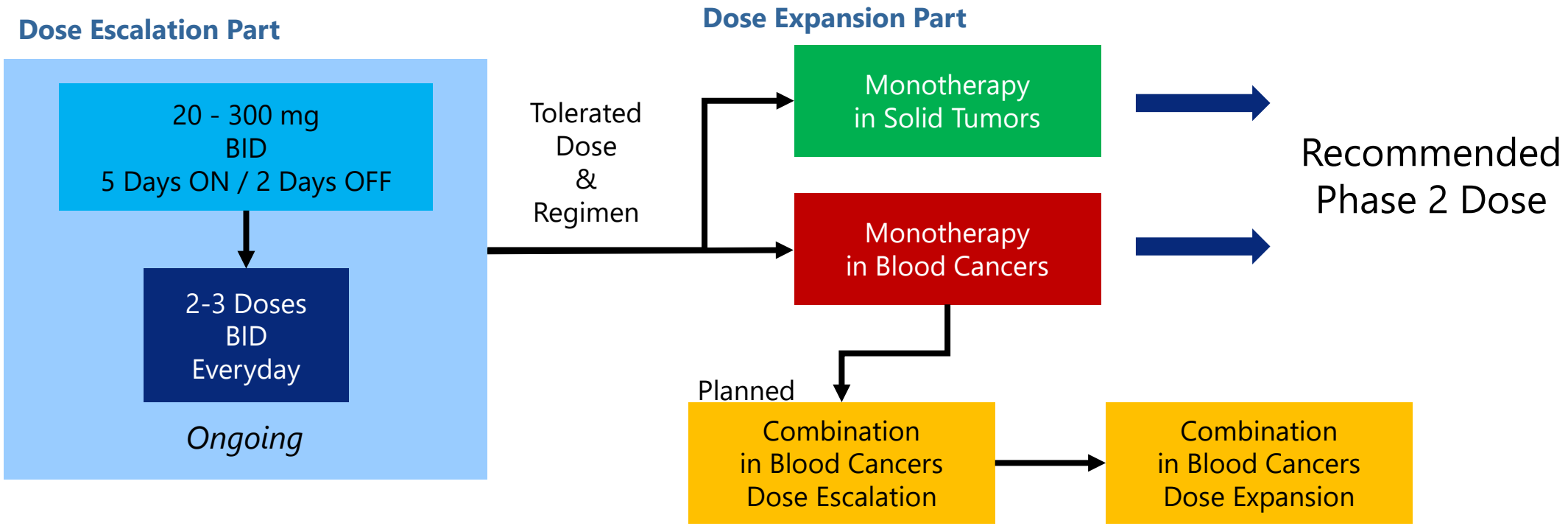
3+3 design



Monzosertib (AS-0141) : Phase 1 Clinical Trial

Phase 1 study targeting cancer patients

- The Phase 1 study in patients with advanced, metastatic, relapsed or refractory malignancies. The protocol has been changed to include patients with blood cancers.
- The study consists of two parts, a dose escalation and an expansion.
- The primary objective is to assess safety, tolerability, maximum tolerated dose (MTD), preliminary anti-tumor activity, and PK / PD as well as to determine RP2D.
- Pharmacodynamic effect of monzosertib was confirmed at 40 mg BID and above.



Monzosertib (AS-0141) : Phase 1 Dose Escalation Part : Continuous Dosing Regimen

As of Oct. 31, 2024

Switched to a continuous dosing schedule (without drug holiday) allowing persistent inhibition of CDC7 to maximize efficacy

Dose escalation part targeting solid tumor

- 80 mg BID (twice a day) was well-tolerated and safe
- 5 of 7 efficacy-evaluable patients (50 mg BID and 80 mg BID) achieved SD
- One patient receiving 50 mg BID (every day) is still on treatment (>200 days)

Doses	Regimen	n	DLT
50 mg BID	every day	3	0
80 mg BID	every day	3	0
100 mg BID	every day	1	

Dose Escalation with “every day” regimen is on-going

Updates on Licensed Pipelines

1. **DGKα Inhibitor** (Gilead Sciences, Inc.)
2. **Joint Research with Sumitomo Pharma**

Out-licensed Programs

Program/ Partner	Compound (Target)	Status	Upfront payment	Total milestone payments expected	Royalty	Region	Contract date	Milestones received
DGKα inhibitor Gilead Sciences (Out-license)	GS-9911 (Immuno-oncology)	Phase 1	$20M	$450M	Undisclosed	Worldwide	Jun. 2019	Received milestones twice, totaling $15M
Joint Research with Sumitomo Pharma	Kinase inhibitor (Psychiatric and neurological disorders)	Late discovery	JPY80M (including research milestone)	JPY10.6B	Undisclosed	Worldwide	Mar. 2018	

DGKα Inhibitor

Partner

Gilead Sciences, Inc.
Out-licensed in June 2019 (worldwide rights)

Deal size	• Upfront payment $20 million • Maximum of $450 million potential milestone payments upon achievement of certain development and commercial milestones
Royalties	• Royalties on future net sales

1. Investigational DGKα inhibitor: GS-9911

2. Indication: Cancer (immunotherapy)

- At JP Morgan Annual Healthcare Conference held in January 2024, Gilead introduced DGKα as next generation target in oncology and presented GS-9911 as the DGKα inhibitor in Phase 1 trials.

3. The Phase 1 study in patients with solid tumors is ongoing.

Refer Gilead's website for details of the study.
https://www.gileadclinicaltrials.com/study?nctid=NCT06082960

Joint Research with Sumitomo Pharma

Partner

Sumitomo Pharma

Sumitomo Pharma Co., Ltd.
Joint Research Agreement in March 2018
(worldwide rights)

Deal size	• Upfront payment + Research milestone JPY80 million • Maximum of JPY10.6 billion potential milestone payments upon achievement of certain development and commercial milestones
Royalties	• Royalties on future net sales

1. **Joint research to discover novel kinase inhibitors to treat psychiatric and neurological disorders.**
2. **The term of the joint research was extended in December 2021.**
3. **Joint research is ongoing to identify preclinical candidates.**

FY2024 Q3 Results

FY2024 Q3 Results by Business Segment

(JPY million)	Q3FY2023 Actual	**Q3FY2024 Actual**	YoY Change	FY2024 Plan	
Total Sales	711	**487**	-224 -31.5%	925	
ddSP business	711	**487**	-224 -31.5%	925	• Overall sales declined due to weaker than expected overseas sales while sales in Japan remained solid.
ddRD business	—	**—**	—	—	
Total Operating Profit/Loss	-1,201	**-1,578**	-376	-2,201	
ddSP business	218	**-13**	-232	229	
ddRD business	-1,420	**-1,564**	-144	-2,431	• Continued investment in the clinical-stage programs.
Ordinary Loss	-1,203	**-1,579**	-375	-2,208	
Net Loss	-1,230	**-1,588**	-358	-2,225	
R&D cost	1,323	**1,441**	+118	2,309	• Phase 1b study of docirbrutinib (AS-1763) is on track. • Continued investment in the clinical-stage programs including costs related to clinical studies and manufacturing of investigational new drugs for docirbrutinib and monzosertib (AS-0141).

Business plan for FY2024 dose not include potential milestone payments or upfront payments as the timing or the amounts are difficult to predict.

ddRD: Drug Discovery R&D business ddSP: Drug Discovery Support business

Note : Rounded down to the nearest million yen

Consolidated Balance Sheet

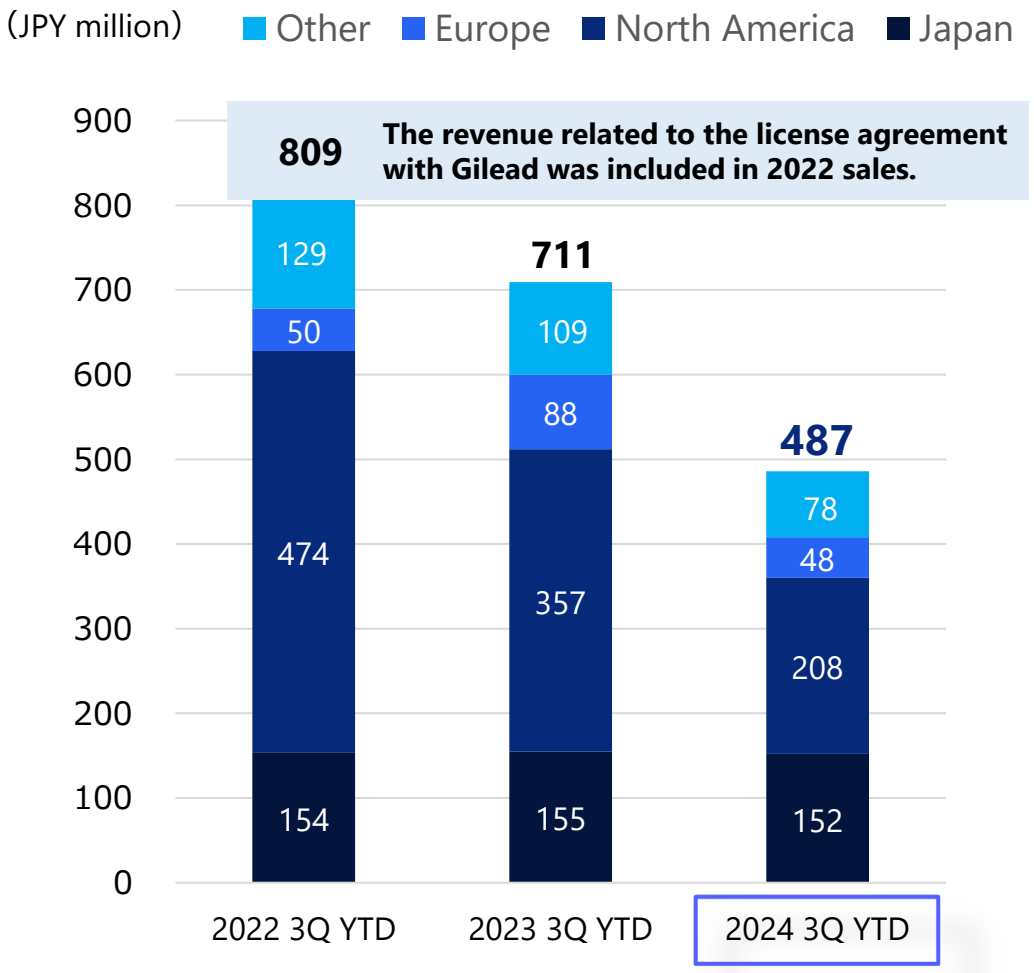
(JPN million)	As of Dec. 31,2023	As of Sep. 30,2024	Change	Reason for changes
Current assets	4,191	2,846	-1,345	• Cash and deposits -607 • Accounts receivable-trade -711
Cash and deposits	2,889	**2,281**	-607	
Non-current Assets	158	131	-27	
Total assets	4,349	2,977	-1,372	
Current liabilities	375	242	-133	• Long-term loans payable within 1 year -74 • Accounts payable -26
Non-current liabilities	96	80	-15	
Total liabilities	472	323	-149	
Total net assets	3,877	2,654	-1,223	• Capital stock and capital surplus +364 • Retained earnings -1,588
Total liabilities and net assets	4,349	2,977	-1,372	

Shareholders' equity ratio	89.1%	89.1%
BPS	226.16yen	147.09yen
PBR	2.3x	2.5x
Share price of Carna	522yen	375yen

Note: Share price is the closing price of the term end.

FY2024 Q3 YTD Drug Discovery Support Business Sales Trend

Drug Discovery Support Business Sales Trend by Region (Consolidated)



Japan

Decreased 1.8% YoY

- Sales of proteins to pharmaceutical companies and distributors were robust, overall sales remained at the same level YoY.

North America

Decreased 41.7% YoY

- Sales decreased YoY. Accompanied with our major customers' projects progress, the needs of kinase protein declined.
- Sales of profiling services to AI-driven drug discovery companies remained strong.

Europe

Decreased 45.4% YoY

- Overall sales declined YoY due to the progress of research of our major customers.

Other

Decreased 28.8% YoY

- The economic recession and the possibility of restraint of trade with Chinese biotech companies by the U.S. government had negative impacts on Chinese market and decreased demand from CROs.

Financing

Raised an additional capital through the 3rd party allotment of common shares in October.

- **Allotee　Athos Asia Event Driven Master Fund**

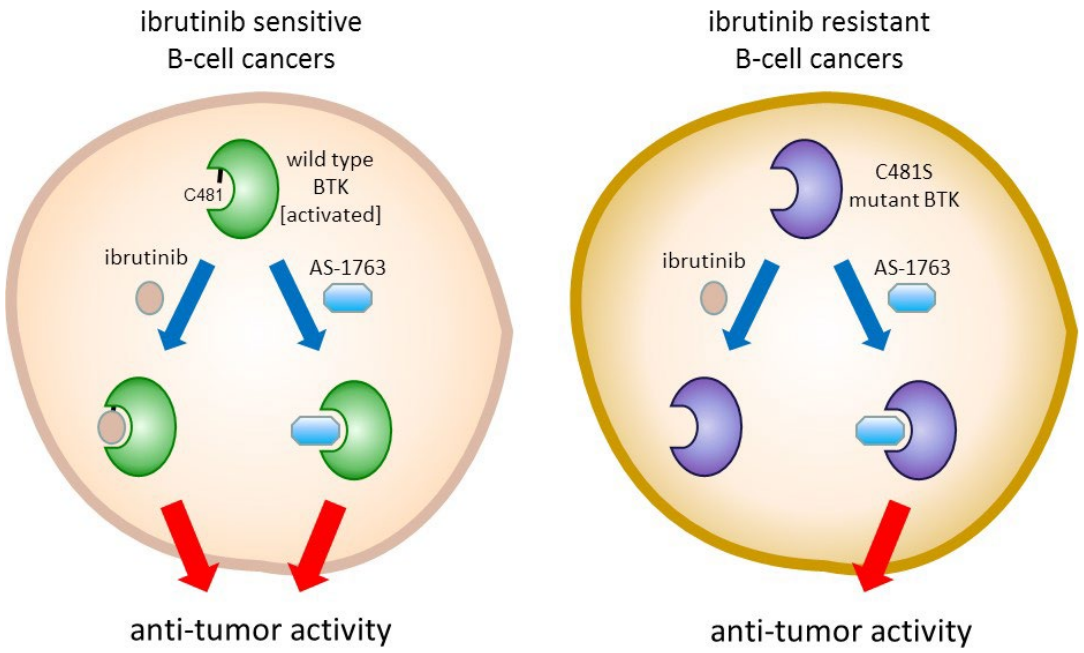
Settlement date	May 31st, 2024	October 11th, 2024
Net proceeds (JPN million)	362	378
Use of proceeds	Investment in development of docirbrutinib (AS-1763) and monzosertib (AS-0141)	

Financing

Additional financing may be considered as necessary in order to accelerate the clinical trials of docirbrutinib (AS-1763), our most important asset.

Appendix

Docirbrutinib (AS-1763): Potent Inhibitor of C481S mutant BTK



Journal of Medicinal Chemistry

pubs.acs.org/jmc Drug Annotation

Discovery of AS-1763: A Potent, Selective, Noncovalent, and Orally Available Inhibitor of Bruton's Tyrosine Kinase

Wataru Kawahata,* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Shigeki Kashimoto, Hatsuo Furuichi, and Masaaki Sawa

Cite This: *J. Med. Chem.* 2021, 64, 14129–14141 Read Online

- **IC_{50} values of docirbrutinib against wild-type and C481S-mutant BTK**

	IC_{50} (nM)	
	BTK[A]	BTK^{C481S}
docirbrutinib	0.85	0.99

J Med Chem. 2021 Oct 14;64(19):14129-14141.

Docirbrutinib (AS-1763): Strong Cellular Activity and High Kinase Selectivity

ARNA BIOSCIENCES

◆ In vitro pharmacological activities of docirbrutinib

	IC_{50} (nM)	
	docirbrutinib	Ibrutinib
Autophosphorylation BTK (Ramos)	1.4	1.1
CD69 activation (Human whole blood)	11	8.1
Cancer cell growth OCI-Ly10 cells	1.8	0.75
Cancer cell growth OCI-Ly10 [BTK C481S] cells	20	1030
Normal cell growth HEL299 cells	6370	6870

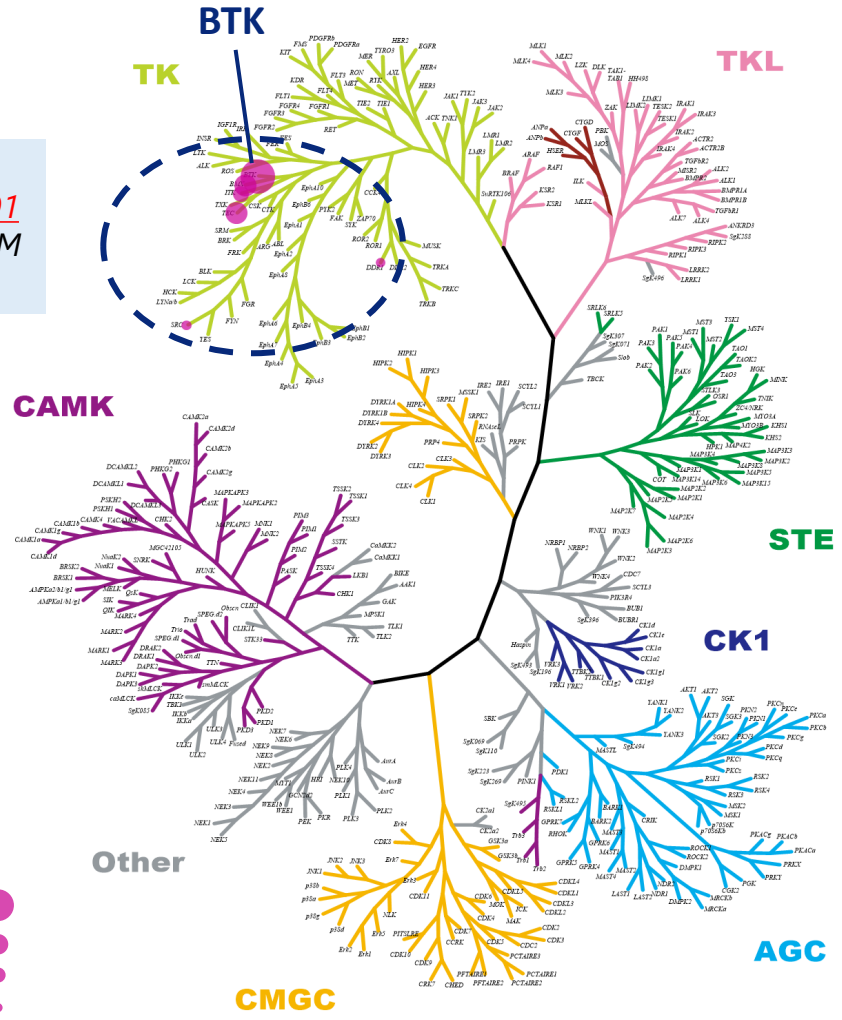
50-fold Stronger activity

Ramos: human Burkitt lymphoma cell line
OCI-Ly10: human B-cell non-Hodgkin lymphoma cell line
OCI-Ly10 [BTK C481S]: BTK[C481S] knock-in OCI-Ly10 cells
HEL299: human embryo lung cell line

J Med Chem. 2021 Oct 14;64(19):14129-14141.

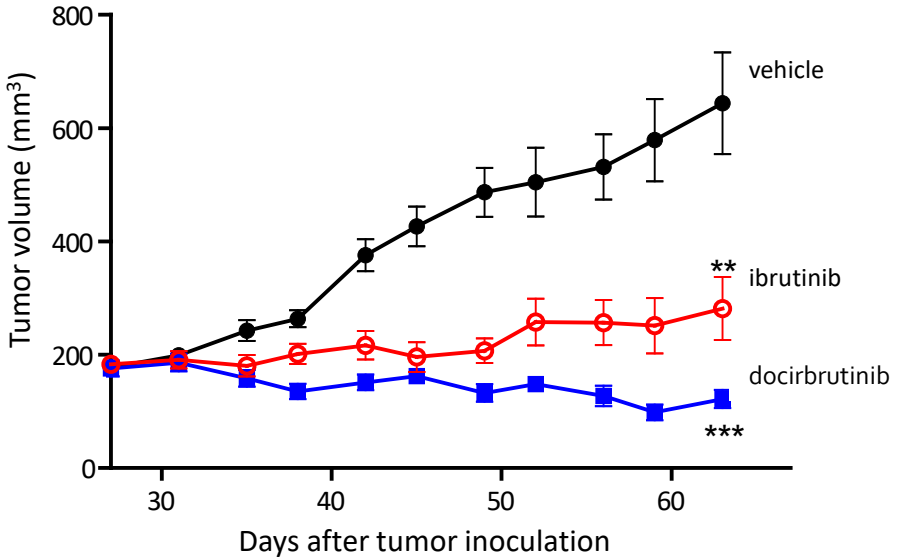
◆ Kinase selectivity profiling

Only inhibited 6 other kinases in a total of 291 kinases tested at 0.3 μM concentration.



Docirbrutinib (AS-1763) : In Vivo Antitumor Effect against BTK^{C481S} Mutant

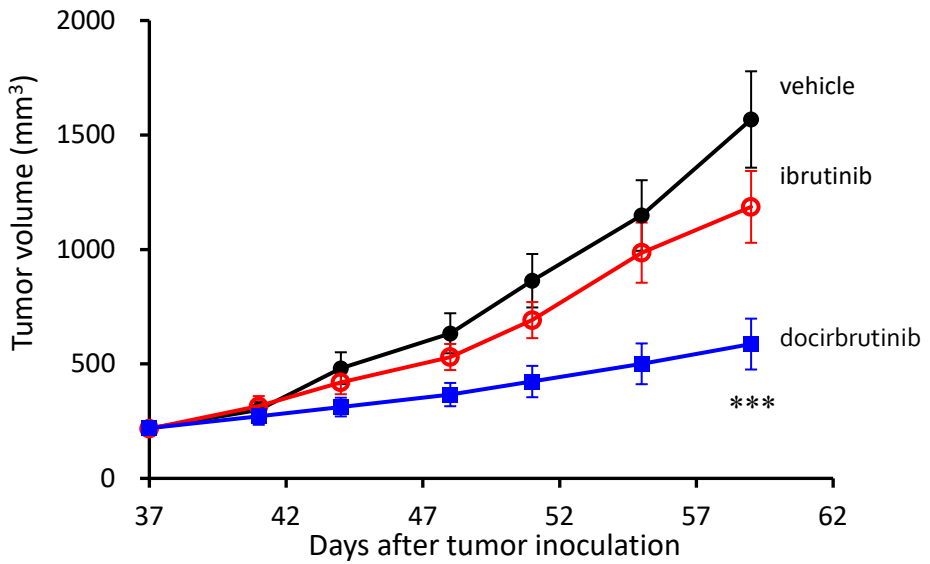
- **In vivo antitumor effects of docirbrutinib on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)**



Ibrutinib: 25 mg/kg QD
Docirbrutinib : 60 mg/kg BID

**: p<0.01
***: p<0.001

- **In vivo antitumor effects of docirbrutinib on ibrutinib-resistant BTKC481S knock-in OCI-LY10 tumor xenograft mouse model (n=11)**



Ibrutinib: 25 mg/kg QD
Docirbrutinib : 60 mg/kg BID

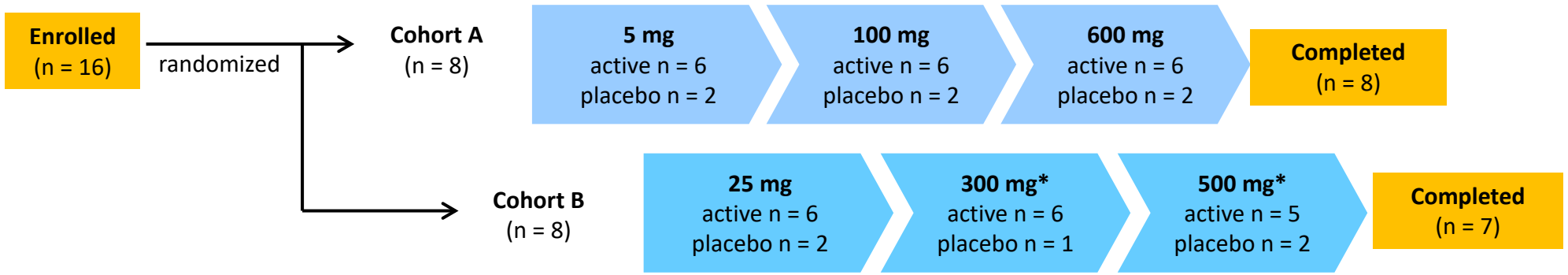
***: p<0.001

J Med Chem. 2021 Oct 14;64(19):14129-14141.

Docirbrutinib (AS-1763): FIH Phase 1 Clinical Trial in Healthy Volunteers

Study Design

Step 1 Single Ascending Dose (SAD) Part	Step 2 Relative Bioavailability (BA) Part
• Double-blind, placebo-controlled, randomized FIH study • Simple formulation (solution) • 6 dose levels (8 subjects/cohort A, 8 subjects/cohort B) • 6 active / 2 placebo for each dose level • Safety and tolerability • Pharmacokinetics and pharmacodynamics (PD; CD69 upregulation on naïve B cells)	• Open label study • Another cohort of 8 subjects • The subjects were dosed with a single dose of docirbrutinib 100-mg tablet, and relative bioavailability with simple formulation was evaluated



*One subject was withdrawn from the study on Day 1 of 300-mg period before the intake of treatment medication (placebo) by physician's decision. This subject showed AEs (Grade 2 lymphocytosis and Grade 2 neutropenia) which were considered treatment-emergent but not trial medication-related. No replacement was done at 300-mg and the following 500-mg periods.

Docirbrutinib (AS-1763): SAD Part

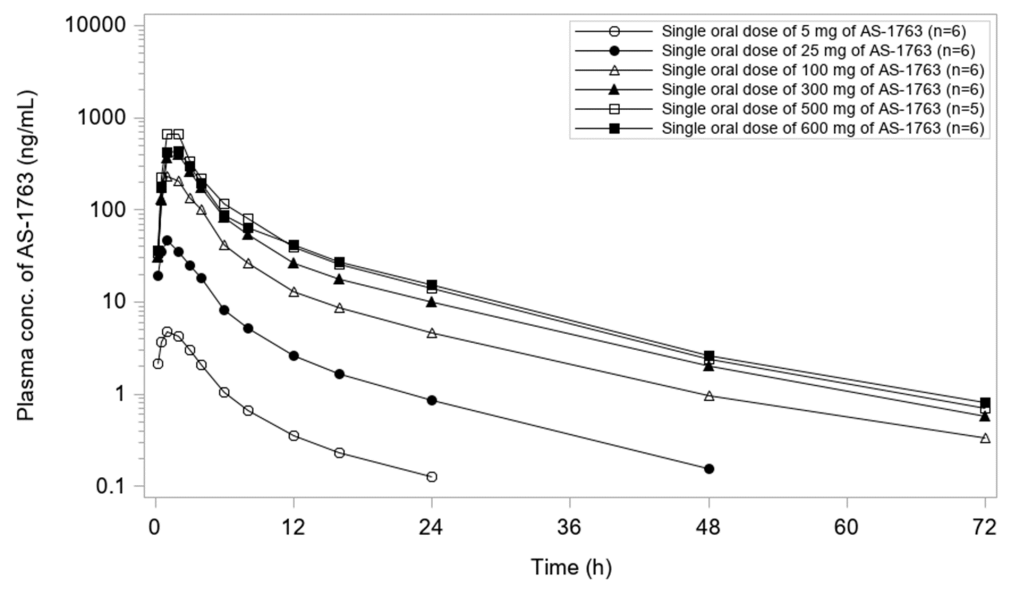
Safety and tolerability

- Docirbrutinib was well-tolerated after single dose administration up to the maximum dose level (600 mg).
- No serious adverse events (AEs) were reported during the trial.
- Two Grade 2 AEs were reported in one subject, which were considered not related to trial medication.
- Other AEs reported were of mild intensity and showed no apparent dose-relationship in frequency.
- No clinically relevant changes from baseline were observed in all other safety parameters assessed (clinical laboratory, 12-lead safety ECGs, vital signs, or physical examinations).

Pharmacokinetics

- After a single-dose oral administration, plasma concentration of docirbrutinib rapidly reached the maximum and then declined in a biphasic manner across the dose range (median tmax between 0.5 and 1.5 hours; mean t1/2 between 8.4 and 12.1 hours).
- Mean docirbrutinib exposures generally increased with dose up to 500 mg.

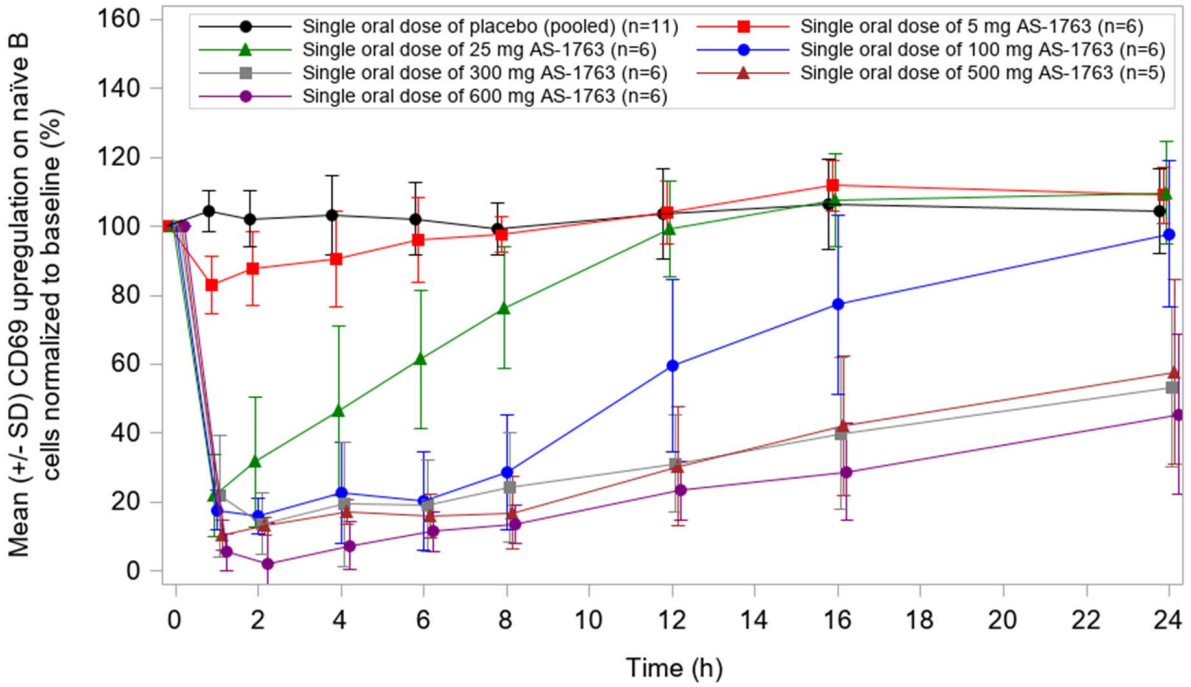
< Plasma concentration of a single oral dose of docirbrutinib >



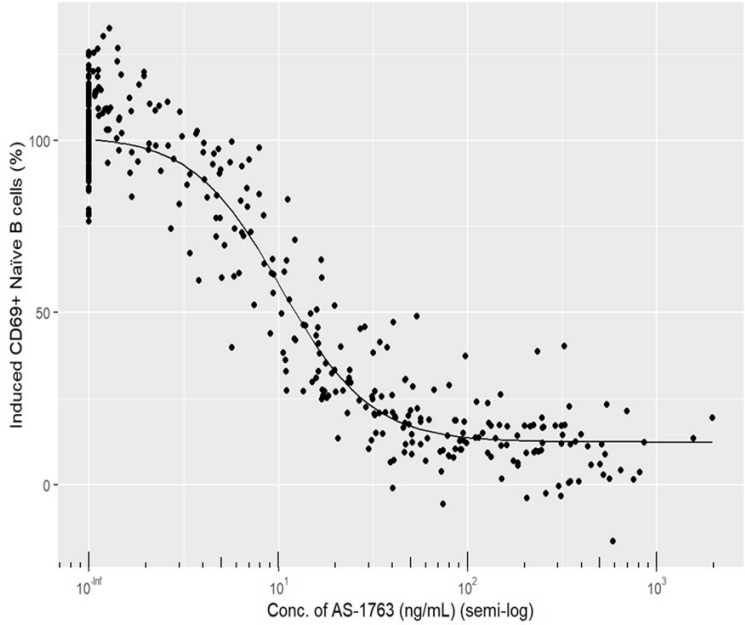
Pharmacodynamics of docirbrutinib (AS-1763)

- Inhibition of B cell CD69 upregulation was observed for 5 mg onwards.
- Maximum inhibition (arbitrarily defined as ≥80%) was observed at 1-2 hours post-dose from 100 mg to 600 mg, and the duration of inhibition was dose-dependent with values of 2, 6, 8 and 8 hours for 100, 300, 500, and 600 mg, respectively.
- Based on a PK/PD correlation analysis, the IC50 value of docirbrutinib on CD69 upregulation was calculated to be 10.5 ng/mL.

< B cell CD69 upregulation after a single oral dose of docirbrutinib >



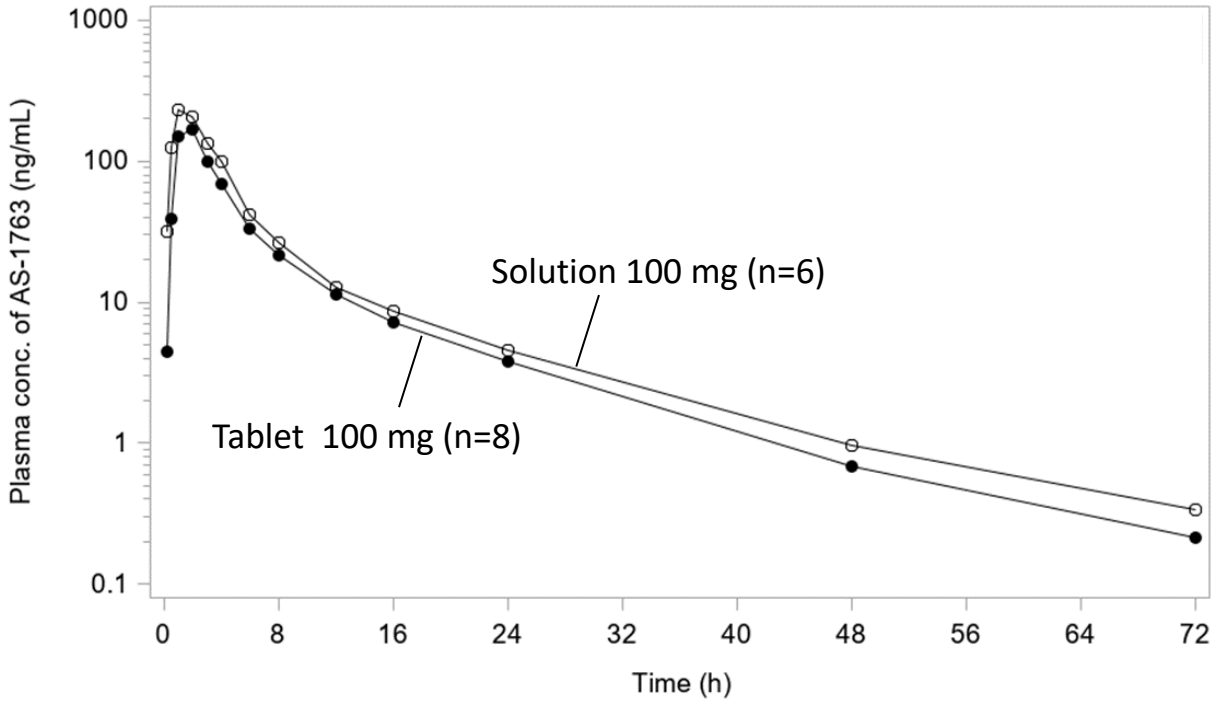
< PK/PD correlation analysis >



Docirbrutinib (AS-1763): BA Part

- In the BA part, 100 mg tablet and the solution showed almost similar PK profile while the exposure of 100 mg tablet was slightly lower than the that of the solution.
- The PK/PD data and favorable safety profile in healthy volunteers support a planned Phase 1b clinical study with docirbrutinib tablet twice daily dosing in relapsed/refractory CLL and B-cell NHL.

<PK of Tablet vs Solution after a Single oral dose docirbrutinib>



Docirbrutinib (AS-1763) : Ph I Clinical Trial in Healthy Volunteers

Objectives of the study

A single dose of docirbrutinib was administered orally to healthy volunteers to evaluate:

- plasma concentration of docirbrutinib
- safety assessments (clinical laboratory, ECGs, or vital signs, etc.)
- inhibitory potency on B cell activation

Result of the study

After a single-dose administration of 5 mg, 25 mg, 100 mg, 300 mg, 500 mg, and 600 mg of docirbrutinib :

- plasma concentrations of docirbrutinib were increased in a dose dependent manner.
- no clinically meaningful issues were reported in all safety assessments.
- dose-dependent inhibition in B-cell activation was observed.

New tablet formulation for Phase 1b study

Relative oral bioavailability was evaluated after administering newly developed tablet formulation containing 100 mg of docirbrutinib to healthy volunteers.

- the new tablet formulation demonstrated good oral bioavailability, supporting that the tablet formulation can be used for Phase 1b study.

Sofnobrutinib (AS-0871) : Excellent Kinase Selectivity

Targeting Inactive Conformation of BTK

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

TR-FRET binding assay targeting unactivated form of Bruton's tyrosine kinase

Tokiko Asami *, Wataru Kawahata, Masaaki Sawa

Carna Biosciences, Inc., BMA 3F, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

Journal of Medicinal Chemistry

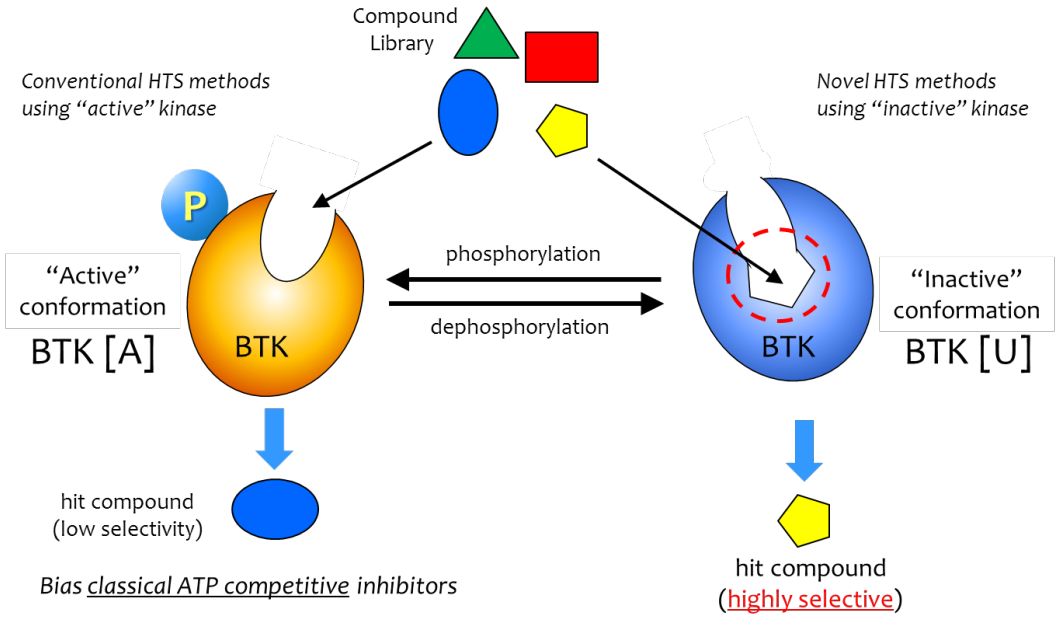
Article

pubs.acs.org/jmc

Design and Synthesis of Novel Amino-triazine Analogues as Selective Bruton's Tyrosine Kinase Inhibitors for Treatment of Rheumatoid Arthritis

Wataru Kawahata,*[] Tokiko Asami, Takao Kiyoi, Takayuki Irie, Haruka Taniguchi, Yuko Asamitsu, Tomoko Inoue, Takahiro Miyake, and Masaaki Sawa[]

Research and Development, Carna Biosciences, Inc., 3rd Floor, BMA, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

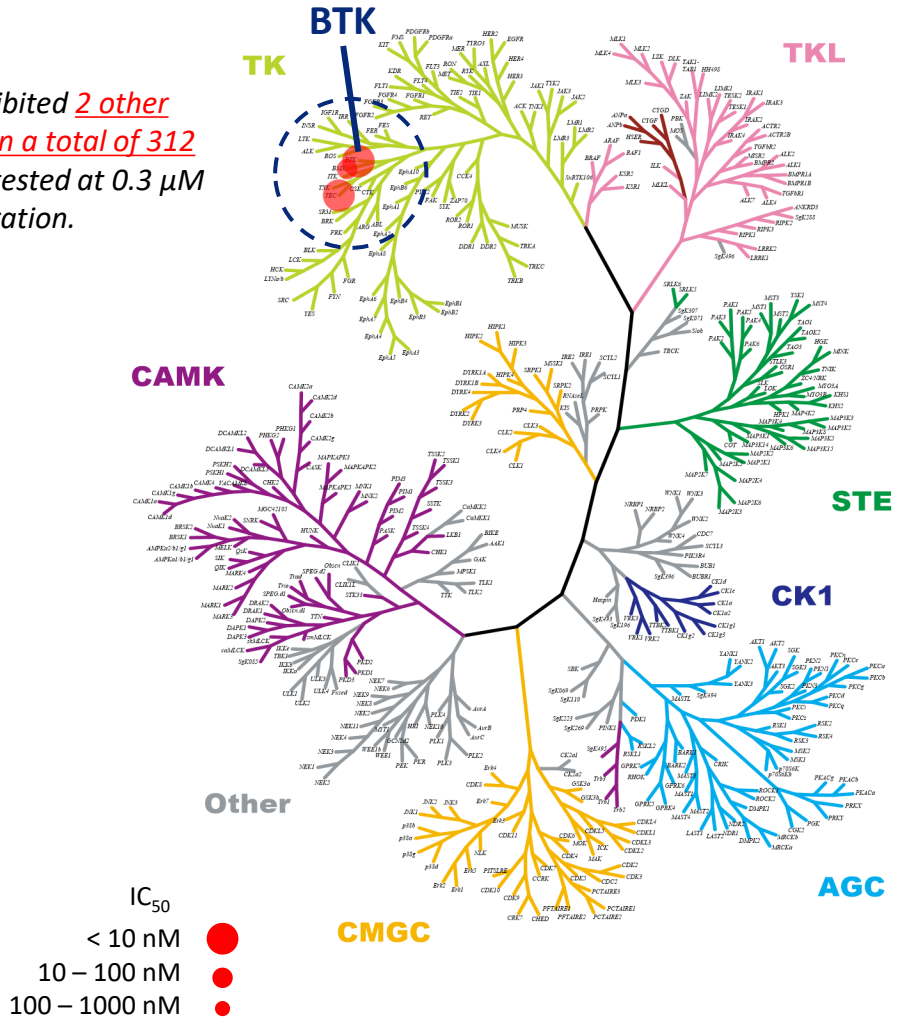


Bias classical ATP competitive inhibitors

	BTK IC_{50} (nM)	
	BTK[A]	BTK[U]
sofnobrutinib	3.4	0.3

Kinase Selectivity Profiling

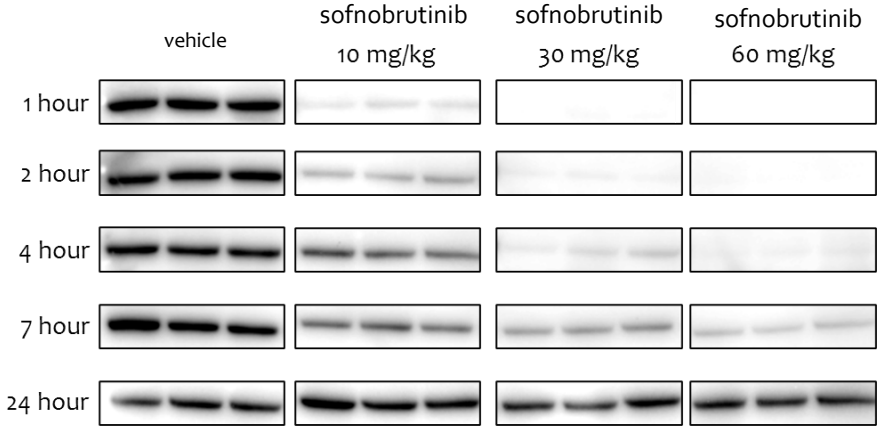
Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3 μM concentration.

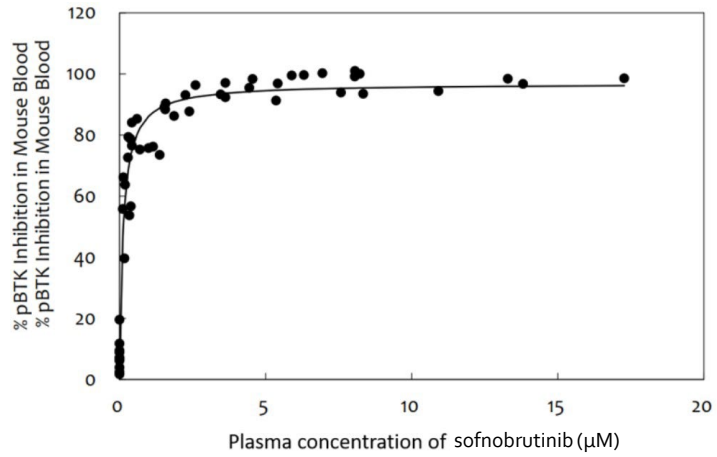


Sofnobrutinib (AS-0871) : In Vivo Therapeutic Efficacy

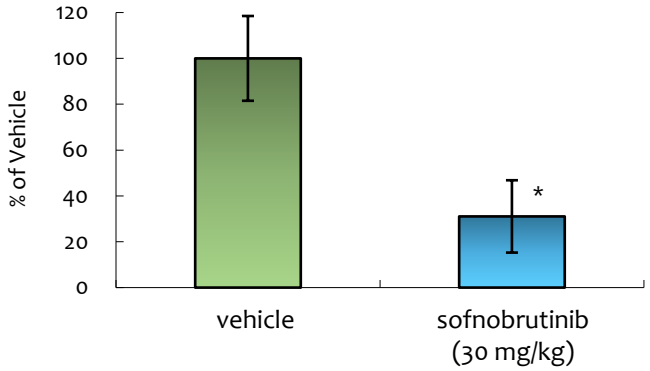
◆ PK/PD Study

Auto-phosphorylation status of BTK was measured following oral single administration of sofnobrutinib.

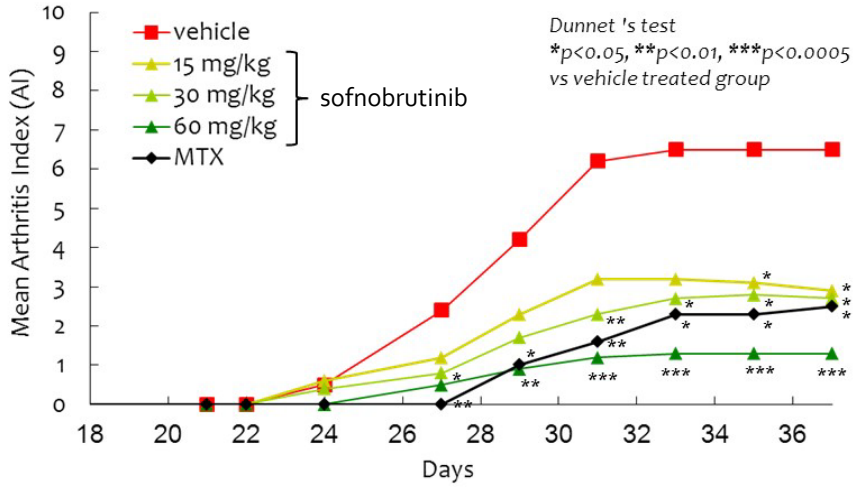




◆ Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



◆ Collagen-induced arthritis (CIA) mouse model (n=10)



Sofnobrutinib (AS-0871): Phase 1 Clinical Trial in Progress

CARNA BIOSCIENCES

Phase 1 in the Netherlands
SAD study (Healthy volunteers)

Completed

- Safe and well-tolerated at all dose levels
- Favorable Pharmacokinetic (PK) Profile
- Promising Pharmacodynamic(PD) effects
- Conducted using simple formulation

Developed multiple new formulations

Phase 1 in the Netherlands
MAD study (Healthy volunteers)

BA Part

Evaluate the relative bioavailability of multiple new formulations to select the best formulation

Completed

MAD Part

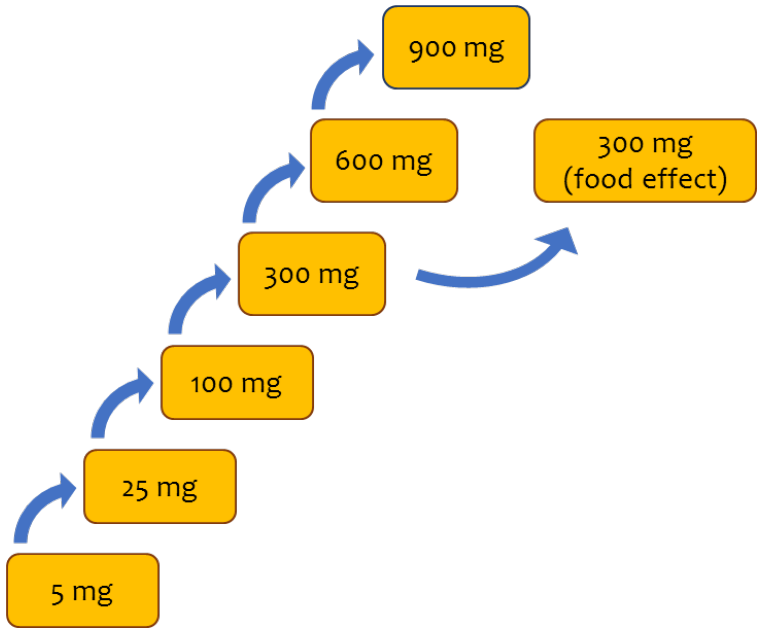
Evaluate the safety, tolerability, PK and PD in the 2-week multiple ascending dose of sofnobrutinib.

Completed

Sofnobrutinib (AS-0871) : FIH Study

SAD Part (Completed)

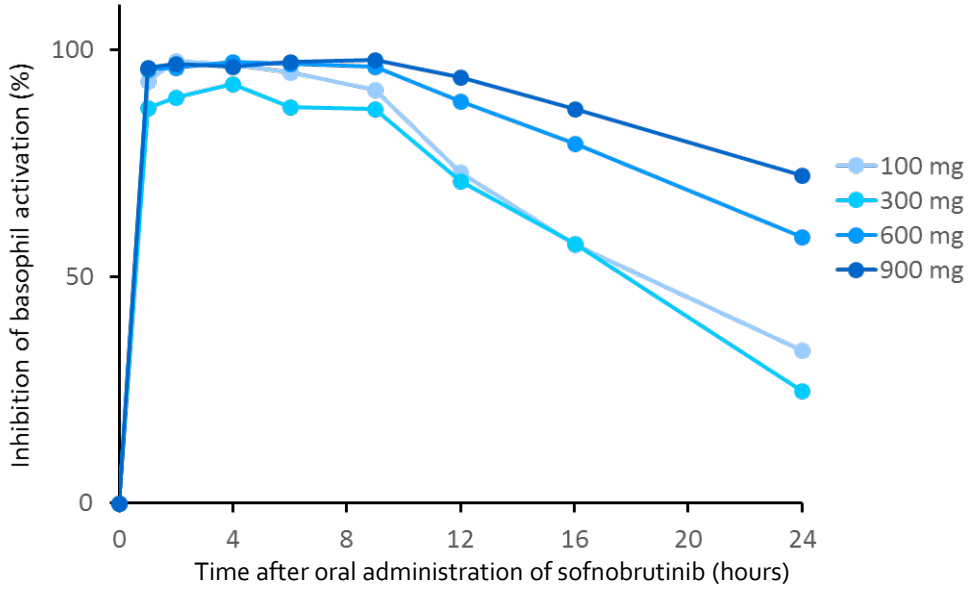
Step 1 Single Ascending Dose (SAD)	Step 2
• 6 dose levels (8 subjects/cohort) • Placebo controlled (6 active / 2 placebo) • Safety and tolerability • Pharmacokinetics and pharmacodynamics	• Food effect

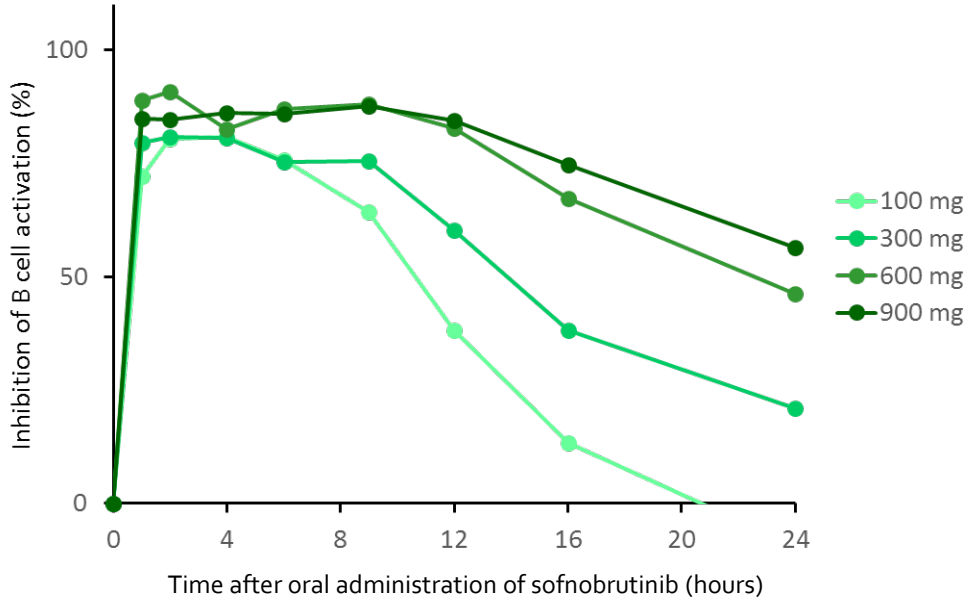


- Sofnobrutinib is well-tolerated without any safety concerns.
- Favorable pharmacokinetic profile.
- Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of sofnobrutinib at 100mg or above resulted in strong inhibition of B-cell and basophil activation.
- Switching to a new formulation in the MAD study.

Pharmacodynamics of sofnobrutinib (AS-0871)

- Pharmacodynamic study demonstrated that subjects who received sofnobrutinib showed dose proportional inhibitions in basophil and B-cell activations, and significant and sustained inhibitory effects were observed at 100 mg and above.
- Oral administration of sofnobrutinib achieved therapeutic plasma levels needed to inhibit B cells and basophils activation, suggesting that sofnobrutinib has a potential to become a new treatment option for inflammatory diseases.

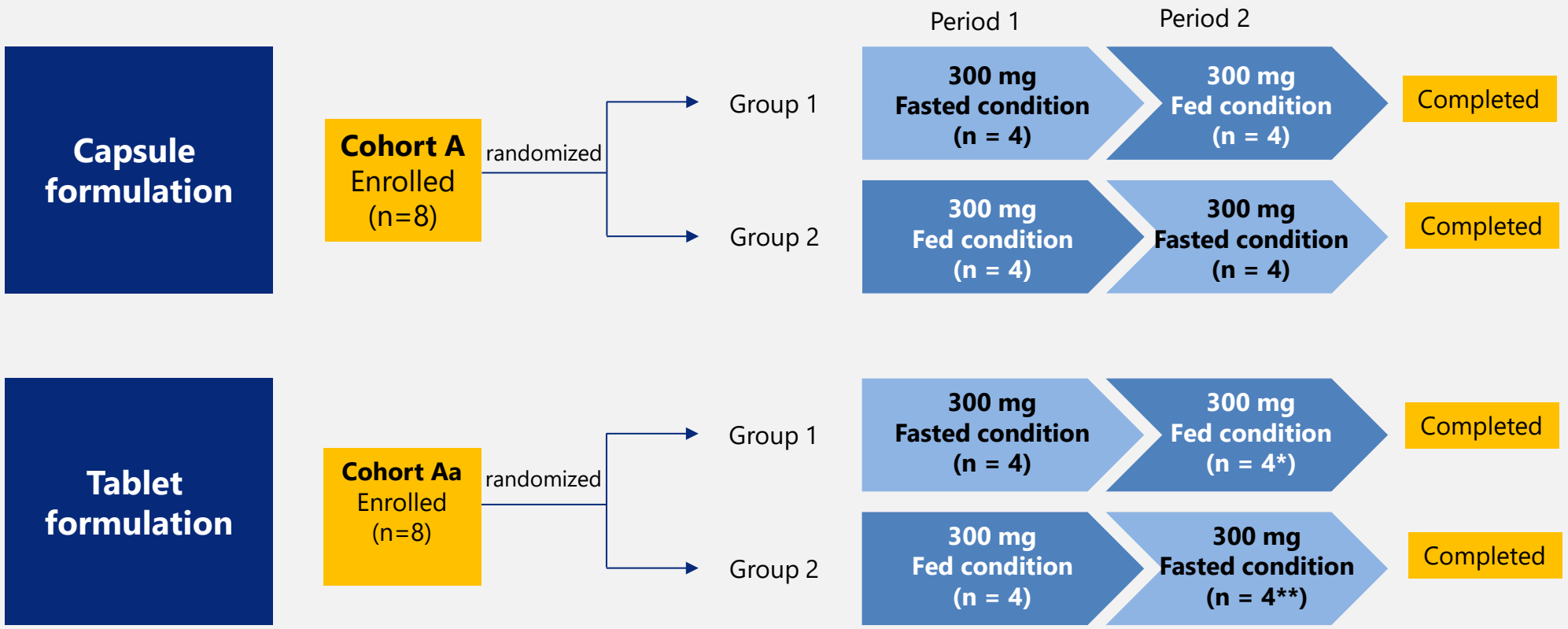




Sofnobrutinib (AS-0871) : Phase 1 MAD Study BA part

Study Design of rBA/FE part

PK, safety, and tolerability after single-dose oral administration of sofnobrutinib, formulated as capsules or tablets, were evaluated under fasted and fed conditions in an open-label, randomized, 2-period crossover design. Eight healthy subjects (Cohort A or Cohort Aa) were randomized to either Group 1 or Group 2 (4 subjects per group).

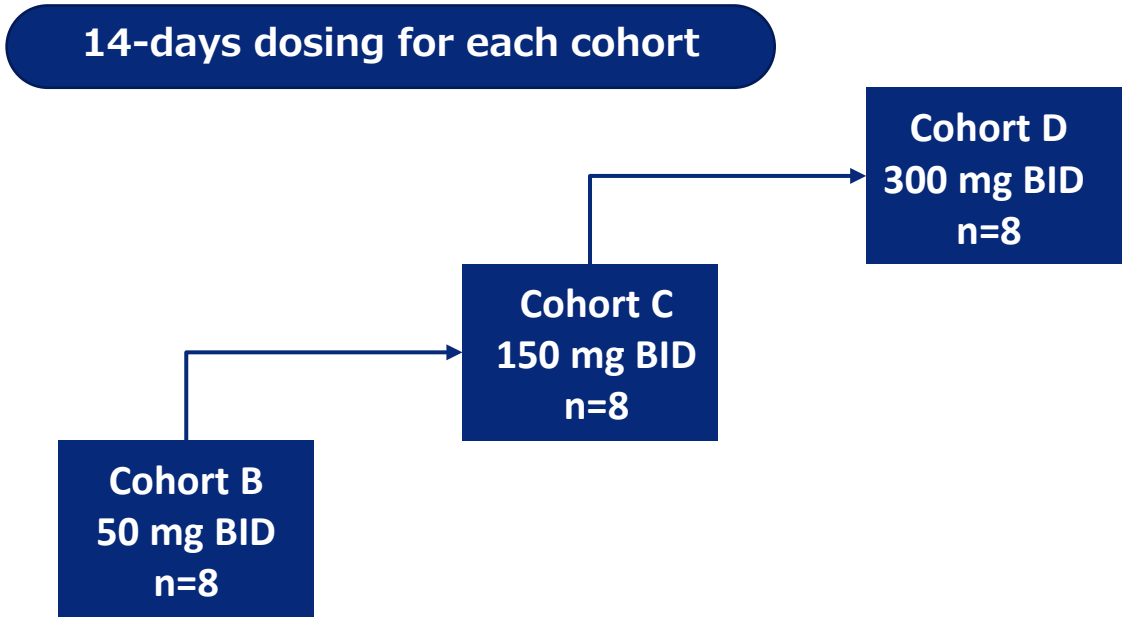


*One subject vomited after dosing (considered not related to study drug), excluded from the PK analysis.
**One subject withdrew from the study due to personal reasons before dosing.

Sofnobrutinib (AS-0871) : Phase 1 MAD Study MAD part

Study Design of MAD part

- In the MAD part, safety, tolerability, PK, and PD of 3 multiple ascending doses of sofnobrutinib, following 14-day multiple dose oral administration of sofnobrutinib, will be investigated using a double blind, placebo-controlled, randomized design in 3 cohorts of 8 healthy subjects each.
- Dosing was completed as planned.
- The final Clinical Study Report (CSR) for the Phase 1 MAD study has been finalized in November 2023.



- Well tolerated with no dose-limiting AEs.
- Favorable safety profile up to 300 mg BID.
- The exposure levels increased dose-dependently, and favorable PK profile with tablet formulation was confirmed.
- Achieved almost complete inhibition of basophil activation (PD marker) at 150 mg and 300 mg BID at a steady state

Sofnobrutinib (AS-0871) : Results from the Phase I Clinical Trial (1)

Objectives of Single Ascending Dose (SAD) study

A single dose of Sofnobrutinib was administered orally to healthy volunteers to evaluate:

- plasma concentration of sofnobrutinib
- safety assessments (clinical laboratory, ECGs, or vital signs, etc.)
- inhibitory potency on B cell and basophil activation

Result of SAD study

After a single-dose administration of 5 mg, 25 mg, 100 mg, 300 mg, 600 mg, and 900 mg of sofnobrutinib:

- plasma concentration of sofnobrutinib were increased in a dose dependent manner.
- no clinically meaningful issues were reported in all safety assessments.
- sufficient inhibition of B cell and basophil activations was observed at 100 mg or above.

New formulations for Multiple Ascending Dose (MAD) study

Plasma concentration was evaluated after administering newly developed capsule formulation and tablet formulation containing 50 mg of sofnobrutinib to healthy volunteers:

- the new tablet formulation was shown to be safe and demonstrated good oral bioavailability, and the tablet formulation was selected for the MAD part.

Sofnobrutinib (AS-0871): Results from the Phase I Clinical Trial (2)

Multiple Ascending Dose (MAD) study MAD part design

- Double blinded, placebo-controlled, randomized multiple ascending dose study in healthy volunteers
- 14-day multiple oral doses of sofnobrutinib tablets in 3 cohorts (50, 150 or 300 mg twice daily)
- The safety, tolerability, PK and PD were evaluated.

Result of MAD study MAD part

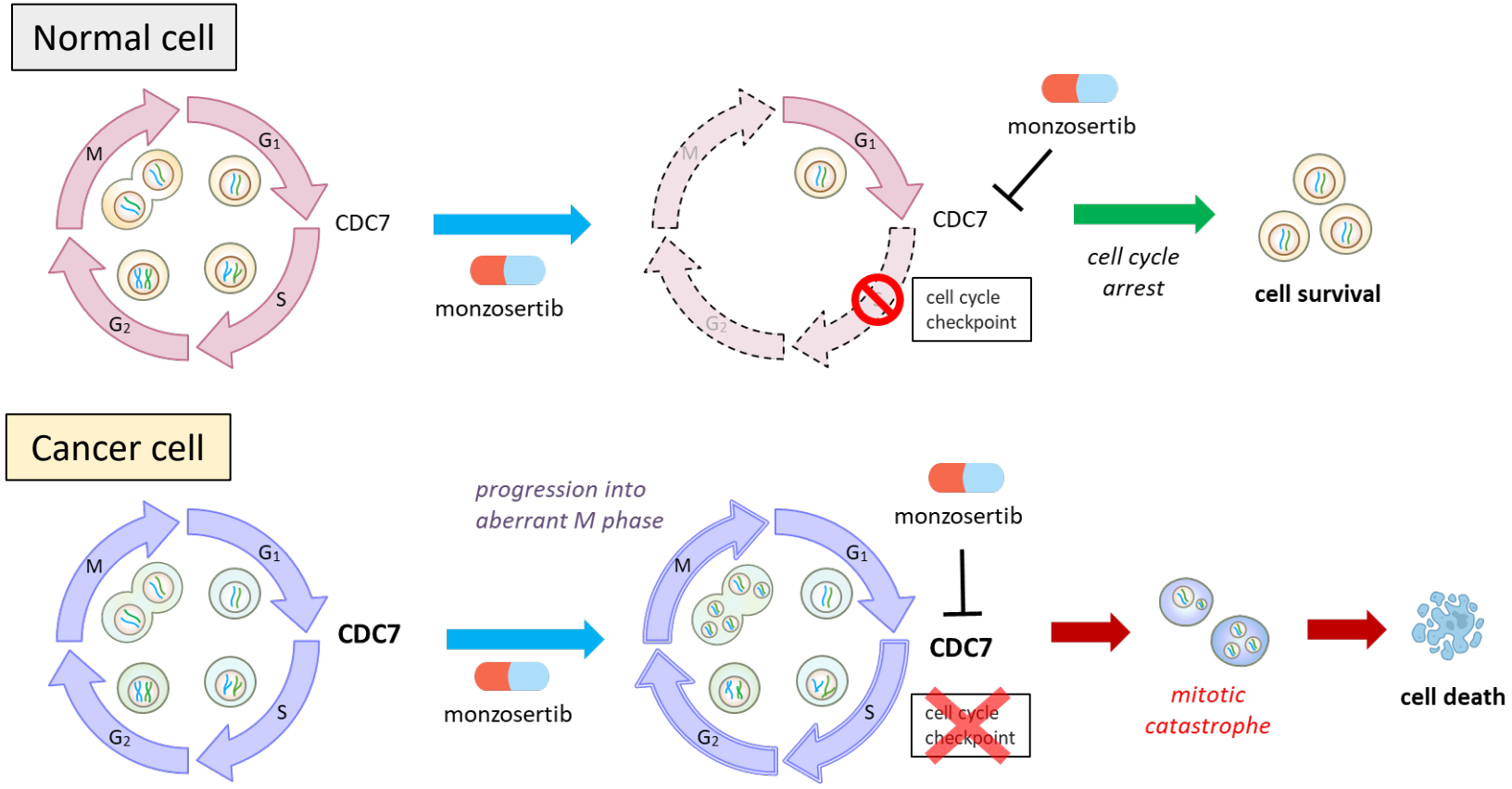
- Well tolerated with no dose-limiting adverse events (AEs): AEs were mostly mild.
- Favorable safety profile up to 300 mg twice daily
- Favorable PK profile: approximately dose proportional with increasing doses
- Robust PD effect was observed: over 90% inhibition for basophils activation on Day 14 at 150 and 300 mg BID doses.

These results from the Phase 1 studies of sofnobrutinib support to advance sofnobrutinib into Phase 2 clinical development for further investigations.

monzosertib (AS-0141)

CDC7 Kinase Inhibitor: MoA of monzosertib

- CDC7 (cell division cycle 7) is a serine/threonine kinase that facilitates DNA replication during DNA synthesis
- Over expression of CDC7 has been reported to cause uncontrolled proliferation of many cancer types

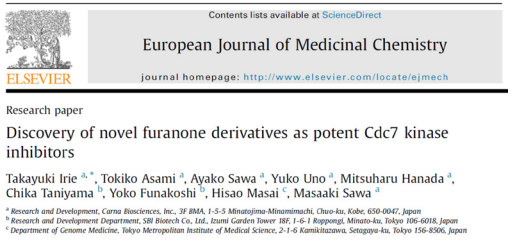


Inhibition of CDC7 in normal cells does not cause cell death, only leads to cell cycle arrest at the DNA replication checkpoint

Inhibition of CDC7 in cancer cells causes lethal S phase or M phase progression when the cancer cells have a defective cell cycle checkpoint

Monzosertib (AS-0141) : Time-Dependent Inhibitor of CDC7

◆ Monzosertib has a unique inhibitory mechanism for CDC7 kinase (time-dependent inhibition)


Contents lists available at ScienceDirect
European Journal of Medicinal Chemistry
journal homepage: http://www.elsevier.com/locate/ejmech
Research paper
Discovery of novel furanone derivatives as potent Cdc7 kinase inhibitors

Takayuki Irie [a,*], Tokiko Asami [a], Ayako Sawa [a], Yuko Uno [a], Mitsuharu Hanada [a], Chika Taniyama [b], Yoko Funakoshi [b], Hisao Masai [c], Masaaki Sawa [a]
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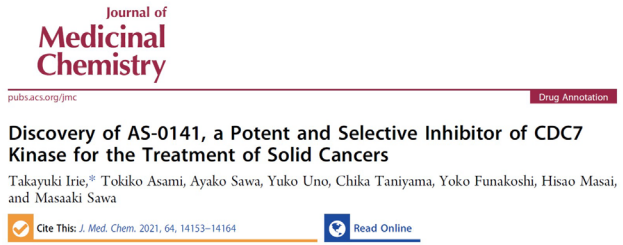
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Drug Annotation
Discovery of AS-0141, a Potent and Selective Inhibitor of CDC7 Kinase for the Treatment of Solid Cancers

Takayuki Irie,* Tokiko Asami, Ayako Sawa, Yuko Uno, Chika Taniyama, Yoko Funakoshi, Hisao Masai, and Masaaki Sawa

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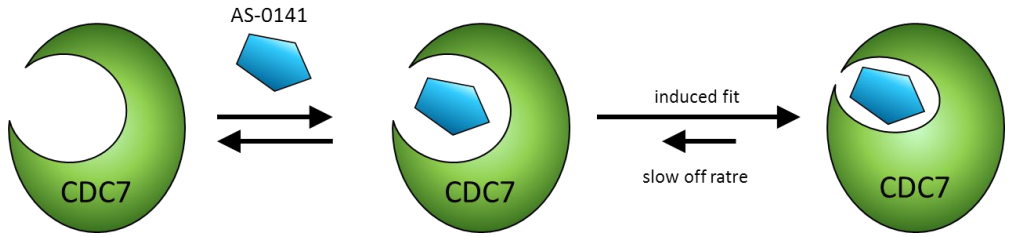

Inhibitory potency (IC50) for CDC7 in the presence of 1 mM ATP	
Without Preincubation	With Preincubation
503 nM	2.4 nM

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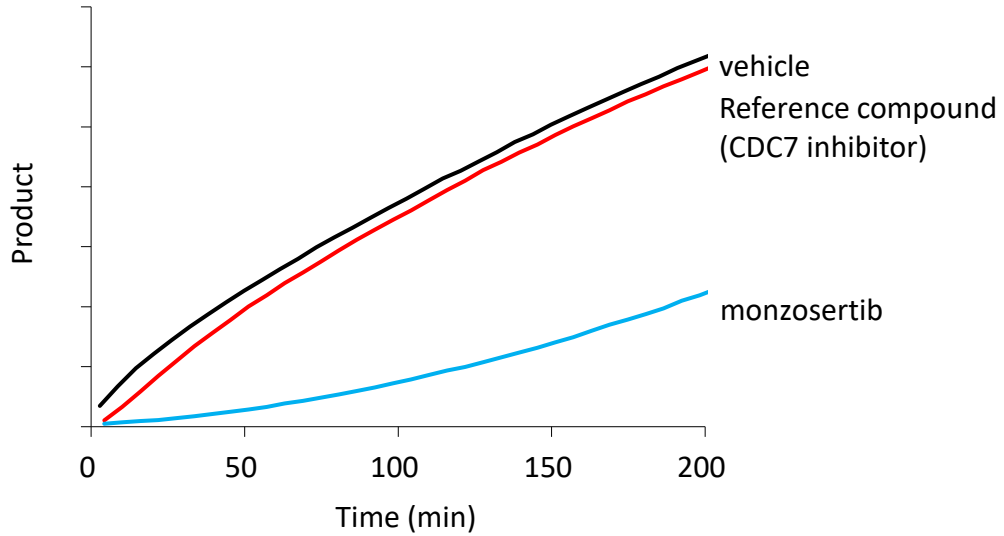
◆ Monzosertib inhibits CDC7 in a reversible fashion but has a very slow off-rate

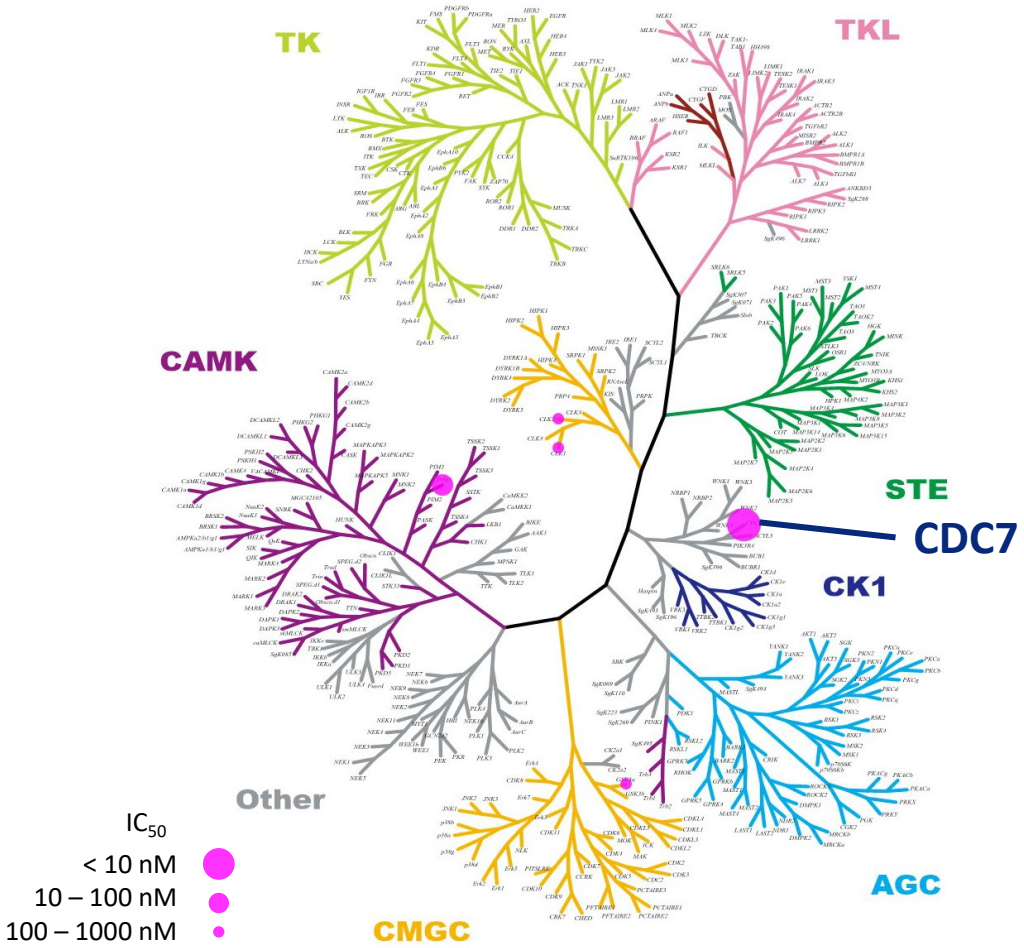
Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.



Monzosertib (AS-0141) : High Kinase Selectivity

◆ Kinase Selectivity Profiling

In the presence of 1 mM ATP with preincubation



◆ IC50 values of hit kinases（at 1 mM ATP）

	IC_{50} (nM)	
	Preincubation	
	-	+
CDC7	503	2.4
PIM1	30	34
CLK1	212	206
CLK2	270	227
GSK3α	189	251

210-fold

CDC7 is the only kinase that shows preincubation effect

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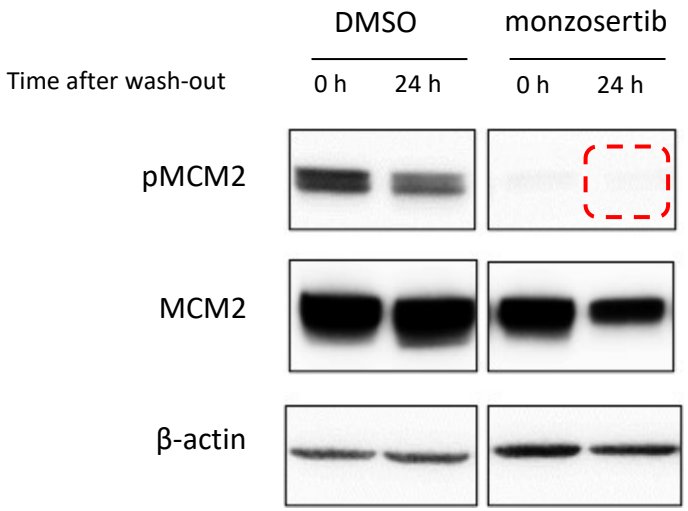
Monzosertib (AS-0141) : Strong Cellular Activity

◆ Prolonged inhibition in cells

Human colon cancer cell line, Colo-205 cells were treated with DMSO control or monzosertib. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



the inhibitory effect of monzosertib on the phosphorylation of MCM2 in cells continued up to 24 h after washing out

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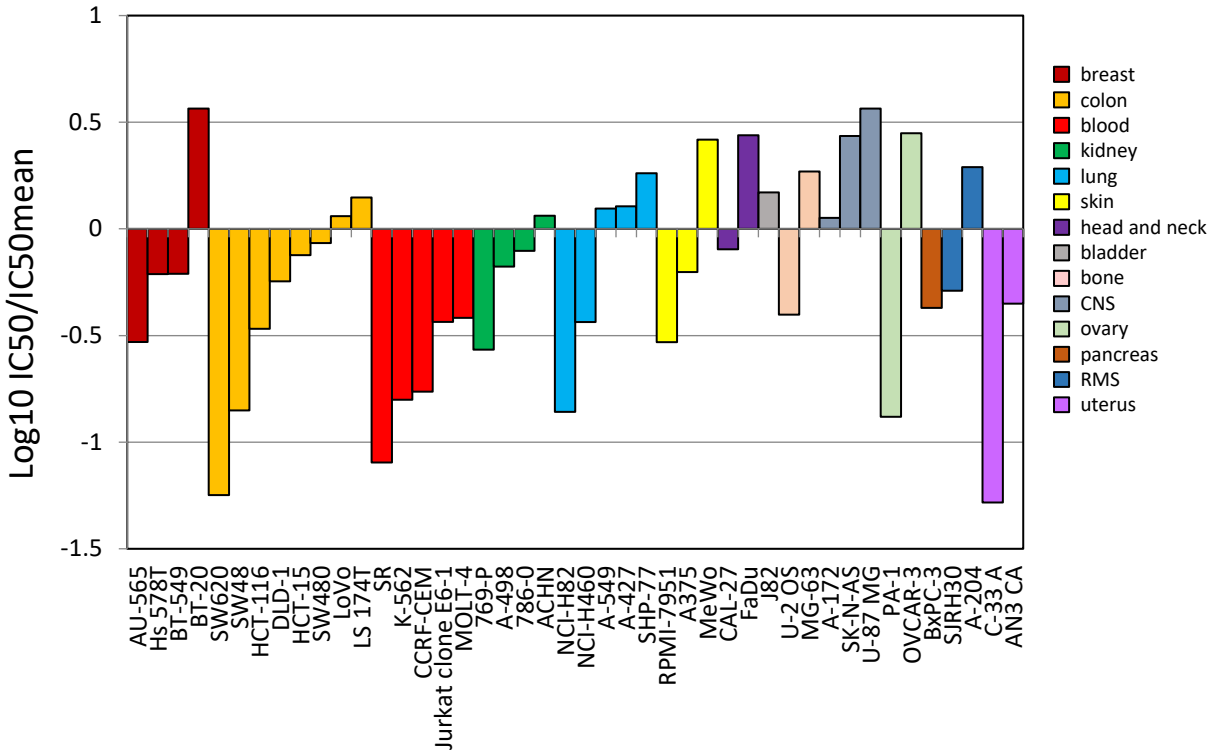
◆ Monzosertib potently inhibited growth in a wide range of tumor cell lines, including solid and hematological tumors

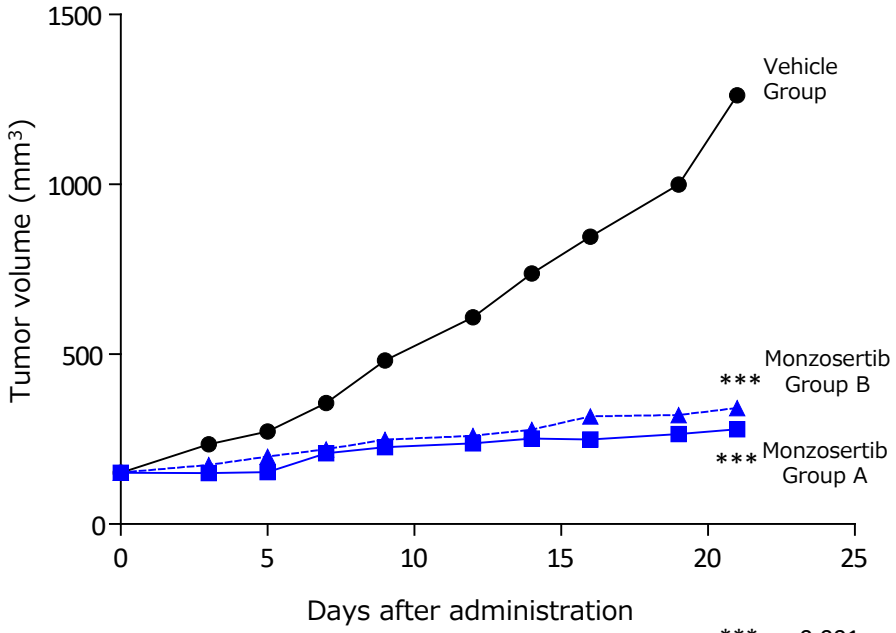


44 Cancer cell lines (Oncolines at NTRC)

Monzosertib (AS-0141): Robust In Vivo Antitumor

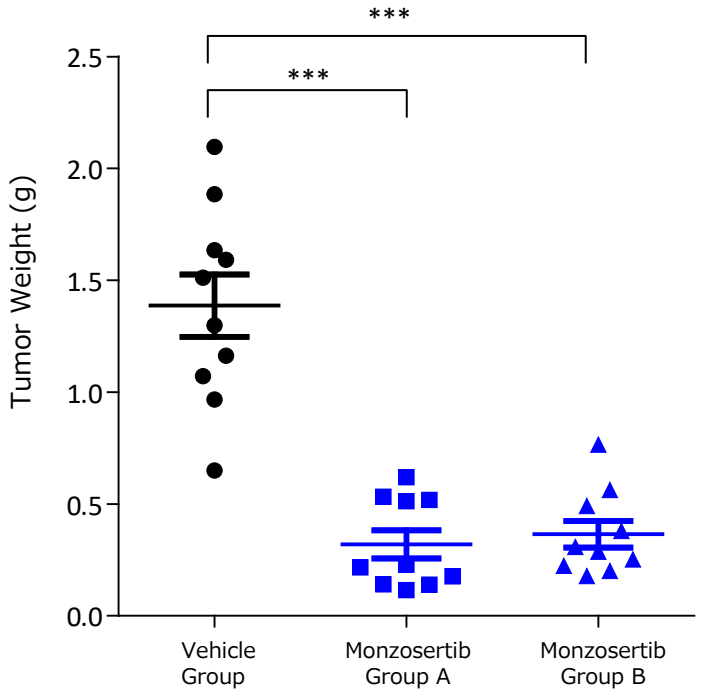
In vivo antitumor efficacy of monzosertib in a SW620 (human colon cancer) xenograft mouse model

Tumor Growth Curve (Mean, n = 10)



***: p<0.001

Final Tumor Weight of Each Mouse



***: p<0.001

Monzosertib group A: 60 mg/kg TID, 4d ON/2d OFF
Monzosertib group B: 120 mg/kg QD

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"Carna" is a goddess of Roman mythology who takes care of human health, protecting the human heart and other organs as well as everyday life, and is said to be the root for the word "cardiac."

The word "biosciences" is derived from the words 'biology' and 'life sciences.'

Carna Biosciences has created contemporary Carna goddess with protein kinase.

Carna Biosciences, Inc.

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