INNOCARE
诺诚健华

科学驱动创新

诺诚健华2022研发日

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科学驱动创新

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INNOCARE
诺诚健华

Opening Remarks and Overview

Co-Founder, Chairwoman and CEO

- *30+ years of experience in research, development and company management in the pharmaceutical industry*
- *Former CEO and CSO of BioDuro, a PPD Company*
- *Former Chair of Early Development Team, Cardiovascular Diseases at Merck US*
- *Post-doc Fellow at the Howard Hughes Medical Institute*
- *Ph.D. in Molecular Biology from Purdue University*
- *The 17th President of the Sino-American Pharmaceutical Professional Association (SAPA)*

Dr. Jasmine Cui

Today's Agenda

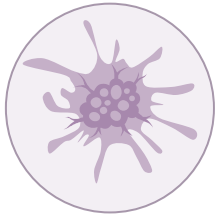
Opening Remarks and Overview
Dr. Jasmine Cui

- **Global Clinical Strategy**
  Dr. Sean Zhang
- **Biologics Strategy**
  Dr. Davy Ouyang
- **Liquid Cancer Progress**
  Dr. Renbin Zhao
- **Autoimmune Diseases Portfolio**
  Dr. Carrie Zhou
- **Solid Tumor Strategy**
  Dr. Carrie Zhou
- **Research Capability**
  Dr. Xiangyang Chen
- **Translational Medicine**
  Dr. Jason Zhang
- **DLBCL MCD Research**
  Prof. Weili Zhao
- **SLE Research**
  Prof. Zhanguo Li
- **Solid Tumor Research**
  Prof. Ye Guo

Questions & Answers

Science Drives Innovation for the Benefit of Patients

To Become
a **Global Biopharmaceutical Leader**
that Develops and Delivers
Innovative Therapies for Patients **Worldwide**

Cancer   **Autoimmune Diseases**

Our Therapeutic Focus

A Fully-integrated Biopharmaceutical Platform

宣诺凯

2 commercial product
9 clinical stage assets
4 biological molecules
Multiple at IND enabling stage

Drug Discovery

All Products Developed In-house

- **120+** research scientists
- Beijing R&D center – **8,300 m²**
  - –Chemistry, biology and CMC labs
  - –**800 m²** AAALAC-like animal facility
- Nanjing R&D center – **3,350 m²**
  - –A state-of-the-art solid-state research lab
  - –Diagnostic and biology platform

Clinical Development

Unparalleled Clinical Execution

- Expanding internal clinical development team
- **All China trials** managed in-house
- **300+** Clinical sites initiated
- **30+** trials ongoing
- New offices in Beijing Kerry Center & Shanghai Qiantan

Target Identification

Protein Structure Aided Drug Design

Prof. Yigong Shi

- Expertise in structure biology
- Deep understanding of cancer biology

Structure aided design

Novel Target Identification

Prof. Zemin Zhang

- Single cell sequencing platform
- Big Data analysis

Gene + Data → Novel I-O Target

Commercialization

- ~250 member team actively promoting Orelabrutinib
- Highly experienced and efficient sales team in hematology

Marketing | Medical | Sales Strategy | Government Relations

Manufacturing

Guangzhou

Beijing

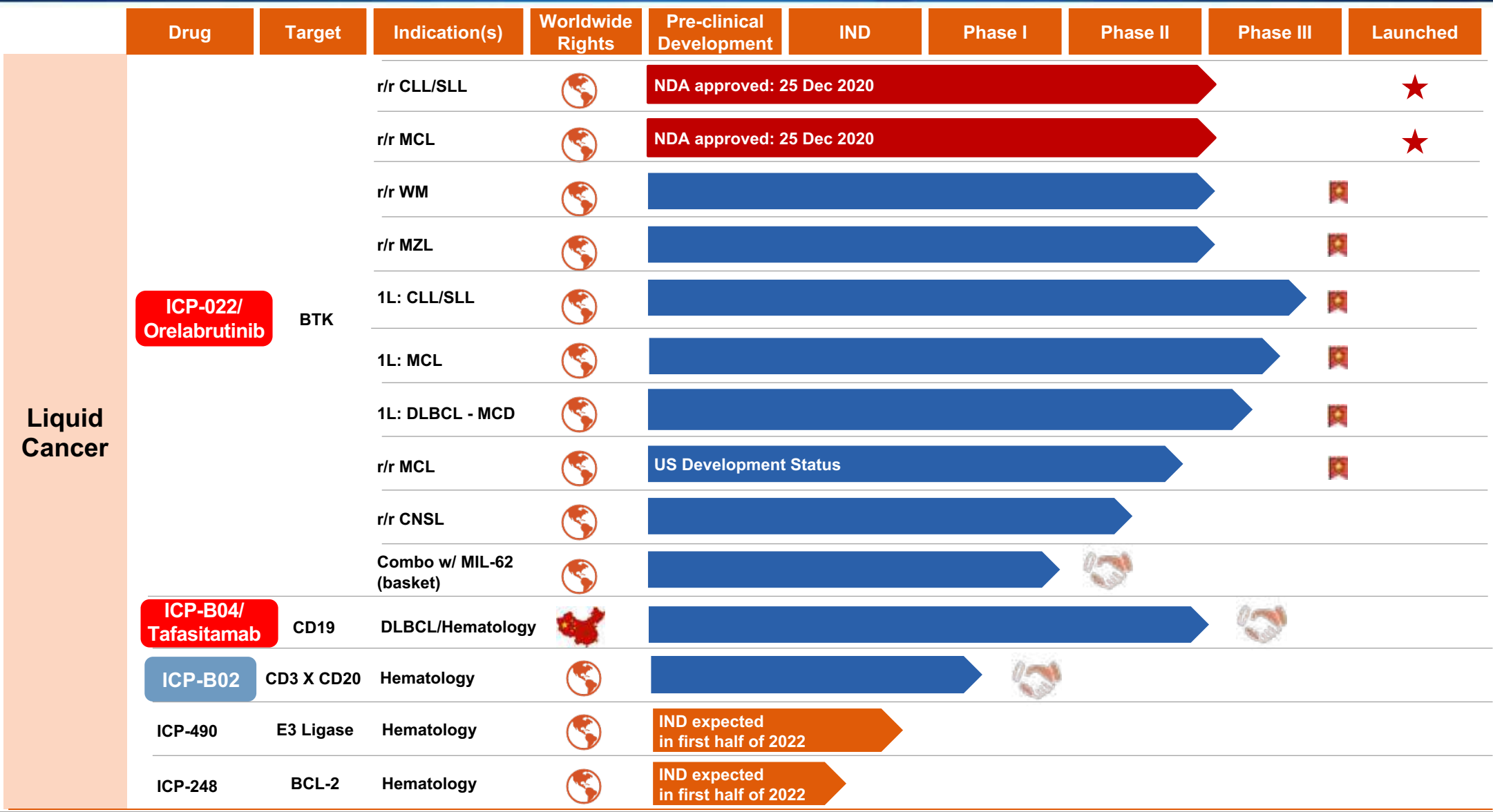
~50,000 m² Small Molecule Facility in Guangzhou

- Completed technology transfer of Orelabrutinib production and GMP verification in April 2022
- Comply with both Chinese and international GMP standards
- ~150 employees

~70,000 m² R&D Center & Large Molecule Facility in Beijing

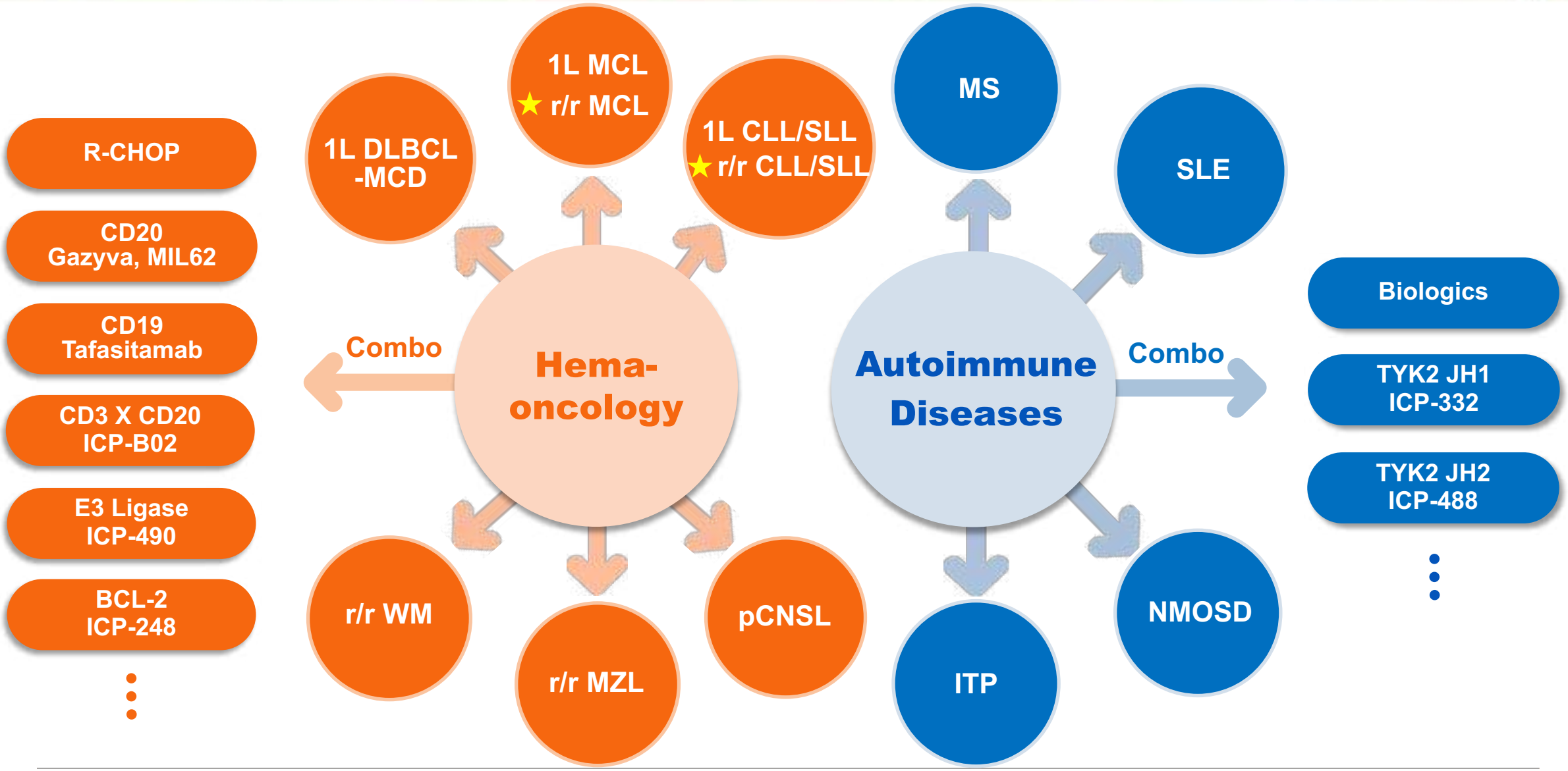
- Has completed conceptional design
- The construction is expected to be completed in 2025

Product Pipeline — Liquid Cancer



Product Pipeline — Solid Tumors and Autoimmune Diseases

Indications Covered by Orelabrutinib



Comprehensive Coverage of DLBCL

1L DLBCL -MCD

Orelabrutinib + R-CHOP

2L DLBCL + 2L+ DLBCL

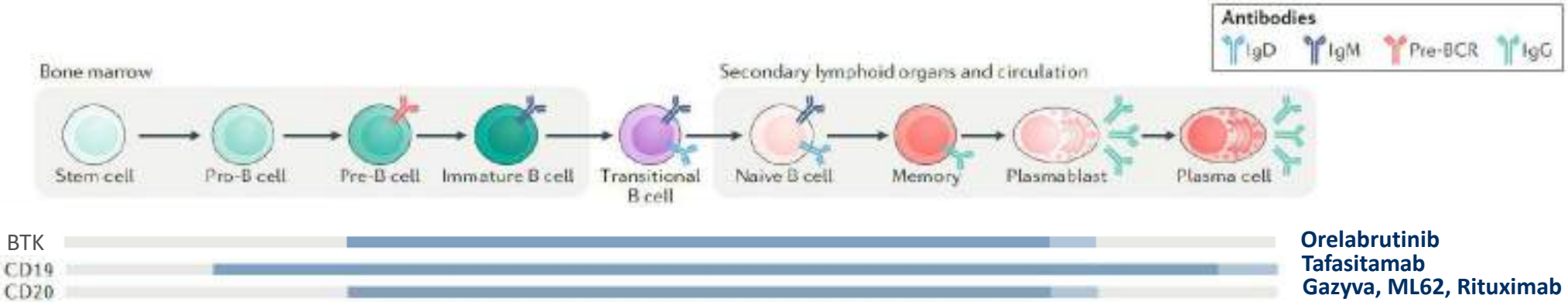
Tafasitamab + Lenalidomide

Orela + Tafa

Orela + CD20 Abs

ICP-B02 (CD3 x CD20)

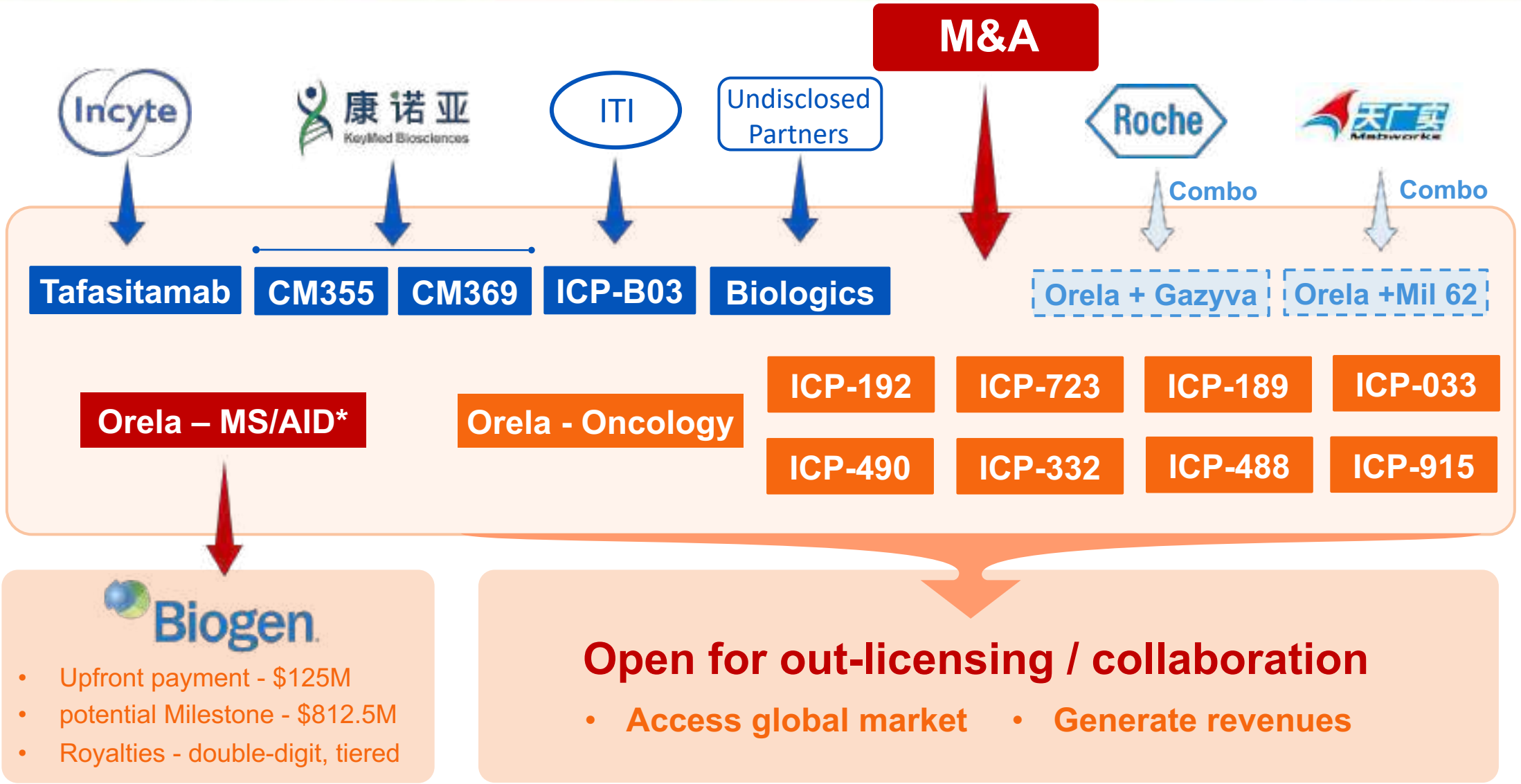
ICP-490 (E3 Ligase)



Note: Sabatino, J.J. Nat Rev Neurosci 20, 728-745 (2019).

Burger JA. Nat Rev Cancer. 2018 Mar;18(3):148-167.

Partnership Strategy



InnoCare Highlights

1 Top-tier Founder & Management Team

- ✓ Experienced founders and strong management team with an excellent track record in drug discovery, clinical development, business development and commercialization

2 Fully-integrated Drug Innovation Platform

- ✓ In-house drug discovery technology platform and effective clinical development capability
- ✓ Well established commercial capability and manufacturing facilities

3 A Leading Hema-oncology Franchise

- ✓ Orelabrutinib launched in 2021, NRDL inclusion to drive accelerated penetration in 2022 and beyond
- ✓ Differentiated approach to hard-to-treat B-cell lymphomas with Tafasitamab, E-3 Ligase, CD20xCD3, BCL-2, etc.
- ✓ Focused and effective commercial team

4 Competitive Solid Tumor Portfolio

- ✓ Highly selective FGFR, TRK and SHP2 inhibitors in Phase I or II clinical studies in both China and U.S.
- ✓ Advanced solid tumor pipeline covering multiple promising targets i.e. potential first-in-class CCR8, bispecific antibodies, etc

5 Autoimmune Diseases Drugs Covering Both B cell and T cell Pathogenic Pathways

- ✓ Orelabrutinib - Partnered with Biogen in MS; finished Phase II in SLE with promising results
- ✓ ICP-332 – Potential best-in-class selective TYK-2 inhibitor, entering Phase II in multiple indications
- ✓ Several compounds targeting different pathways offering a comprehensive coverage of autoimmune disease

6 Strong Cash Position Providing Safety and Flexibility

- ✓ Continue expansion of portfolio through internal and external opportunities
- ✓ M&A opportunities for assets and platforms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谷雨
Grain Rain
雨生百谷
万物生长

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Innovative Global Development Strategy

Chief Medical Officer

- *Over 30 years of experience in clinical practice, and global clinical development of new drugs*
- *Former CEO and Board Member of Hengrui Therapeutics Inc*
- *Former Senior Director of Clinical Development at GSK*
- *Fellow of American College of Clinical Pharmacology (FCP)*

Dr. Sean Zhang

Overall Clinical Development Strategy

❑ Our Therapeutic Area Focus

- **Liquid Tumors: with Orelabrutinib and Tafasitamab as backbone therapies**
- **Autoimmune Diseases**
- **Solid Tumors**

❑ Our Approaches

- **To develop best-in-class or first-in-class drugs with differentiation points**
- **Global clinical development team building with seamless study execution**
- **Expand pipeline through internal R&D and external collaborations (out-licensing, in-licensing, M&A)**
- **Leverage the data generated from China to expedite global clinical development process**

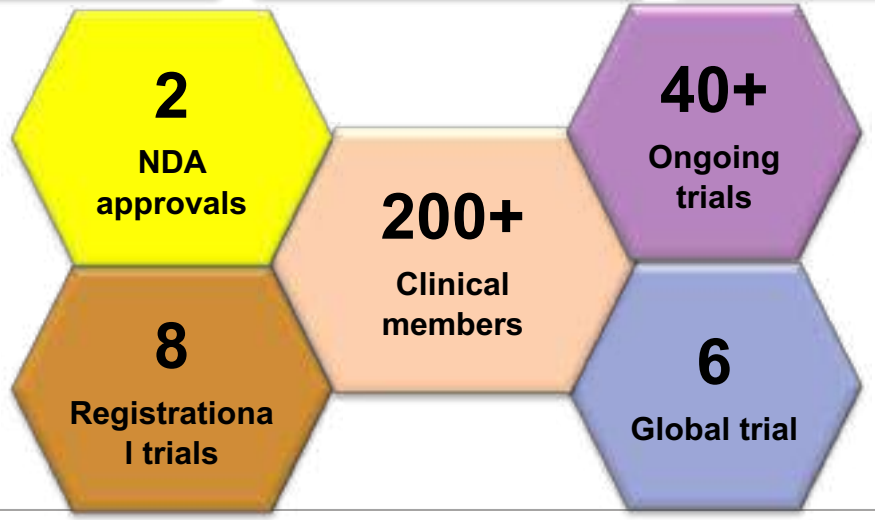
❑ Strong Commitment to Global Innovative Drug Development

- **Six clinical trials in US, EU and AU**
  - Orelabrutinib: MCL registration study, MS Phase 2, cocktail DDI
  - ICP-192 FGFRi for CCA and HNC
  - ICP-723 TRKi for NTRK-fusion solid tumors
  - ICP-189 SHP2 inhibitor for solid tumors

Integrated Clinical Team with Seamless Study Execution

Global Clinical Development Team (200+ ppl)

Translational Science	Clinical Operations	Regulatory Affairs	Medical CN	US Team
Pharmacology	*Data management*	*Clinical*	*Liquid Tumors*	*Medical*
Clinical Pharmacology/ Biomarker	*Biostatistics*	*CMC*	*Solid Tumors*	*Operation*
Early clinical development	*Pharmacovigilance*	*Medical writing*	*Autoimmune*	*Regulatory*
	Clinical Site Operations.			*Pharmacovigilance*



Orelabrutinib Global Development Plan

ICP-CL-107 Study And US Registration Strategy for r/r MCL

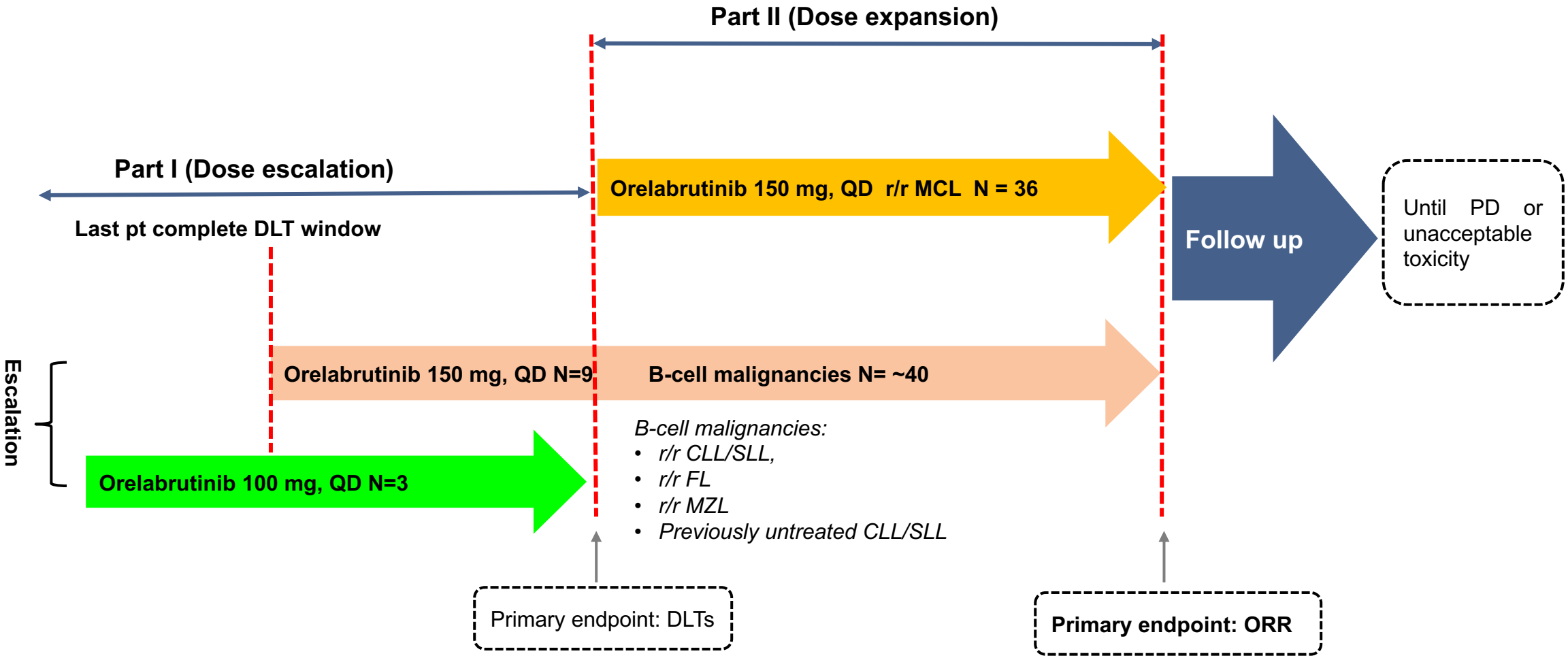
ICP-CL-107 Study is a Global Phase I/II Study to Evaluate Safety, PK and Efficacy of Orelabrutinib in r/r MCL and Other B-Cell Malignancies

- **Using the dose of RP2D-1 as starting dose to save time and budget**
  - Only 2 doses (100mg and 150mg QD) were tested in phase I since Orelabrutinib has been extensively evaluated with the dose range up to 200mg QD in Chinese B-cell malignancies

FDA Endorsed Registration Strategy for r/r MCL Indication

- **Based on two key studies for accelerated approval**
  - Study ICP-CL-00107 in US and EU (N=88 B-cell malignancies including 40 r/r MCL in Caucasian patients)
  - Study ICP-CL-00102 conducted in China (N=106 r/r MCL Chinese patients)
  - Additional safety support from multiple studies in China with different B-cell malignancy indications

ICP-CL-00107 Study Design



Orelabrutinib Demonstrated Similar Efficacy and Safety Profile in Chinese and US Patients

❑ Comparison of Orelabrutinib Efficacy in Chinese and US Patients

	ICP-CL-102 in China	ICP-CL-107 in US
Efficacy	r/r MCL (N=99)	r/r MCL (N=12 Evaluable Patients)
Best Overall Response (%)		
Complete Response (CR)	37.4%	33.3% (4/12)
Partial Response (PR)	50.5%	66.7% (8/12)
Stable Disease (SD)		
Objective Response Rate (ORR%)	88%	100%

❑ Orelabrutinib Has Been Granted Breakthrough Therapy Designation for r/r MCL Indication by the FDA

- Data cut-off date: 15Mar2022: ICP-CL107: P1 Median follow-up of 18.3 months; P1 Median duration of treatment 18.28 months; P2 median follow-up 3.7 months; Median duration of treatment 2.9 Months
- ICP-CL-102: data cutoff date 31 Dec,2020. Median follow-up 23.8 months, mDoR not reached. mPFS was 25.7m. The result was based on investigator assessment.

ICP-192 (FGFRi) Global Development Strategy

❑ Leverage China Clinical Data to Expedite Global Development

- **China Studies have extensively evaluated the safety, PK, PD and efficacy in advanced solid tumors with promising efficacy**
  - ➢ HNC: 33.3% ORR and 66.7% DCR
  - ➢ CCA: 62.5% ORR and 100% DCR with RP2D of 20mg QD
- **Based on China data, ICP-192 global (US and Australia) study started with higher dose and aggressive dose-escalation regimen (8, 12, 16 and 20mg QD)**

❑ Emerging data Support Continuous Investigation in HNC and CCA

- **China Strategy**
  - ➢ Initiate CCA registrational trial in China in FGFRi treatment naïve patients
  - ➢ Conduct PoC study in HNC with FGFRi treatment naïve patients
- **Ex-China Strategy**
  - ➢ Conduct POC Study in HNC with FGFRi treatment naïve patients: potential first-in-class for HNC
  - ➢ Conduct POC Study in CCA with 1st generation FGFRi treatment acquired resistant patients

Global Development Strategy Summary

- **Integrated Clinical Development Team Building with Seamless Study Execution**
- **Expend Pipelines through internal R&D and External Collaborations (Out-licensing, In-licensing, M&A)**
  - Experienced US clinical team to collaborate with BD team for the evaluations of potential out-licensing and in-licensing deals
- **Data-Driven Decision Making Process and Cost-Effective Mindset**
  - Leverage the clinical data generated from China to expedite global clinical development process and market application to save time and cost

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Molecule Discovery

Chief Technology Officer

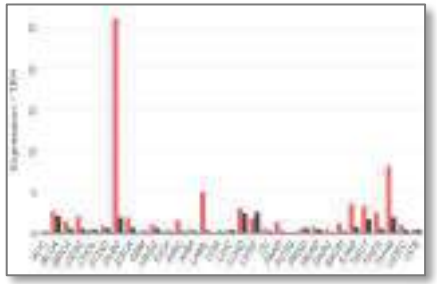
- *More than 20 years of drug discovery experience*
- *Former Executive Director of Medicinal Chemistry at BioDuro, a PPD company*
- *Former Principal Scientist at Pfizer*
- *Ph.D. in Organic Chemistry at Emory University*

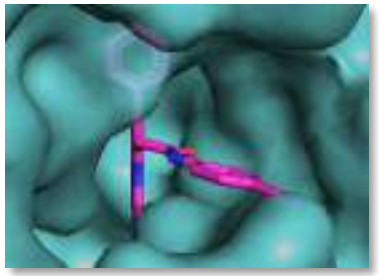
Dr. Xiangyang Chen

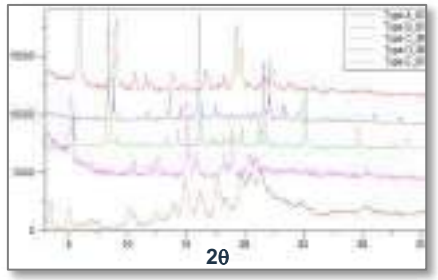
Research Capabilities

Fully integrated drug R&D platform

- Target selection
- Lead optimization
- Polymorph screening
- Poorly soluble drug formulation
- Translational research

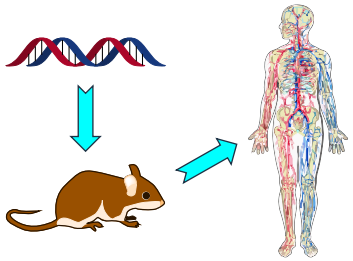







Spray Dyer

Hot-melt extruder



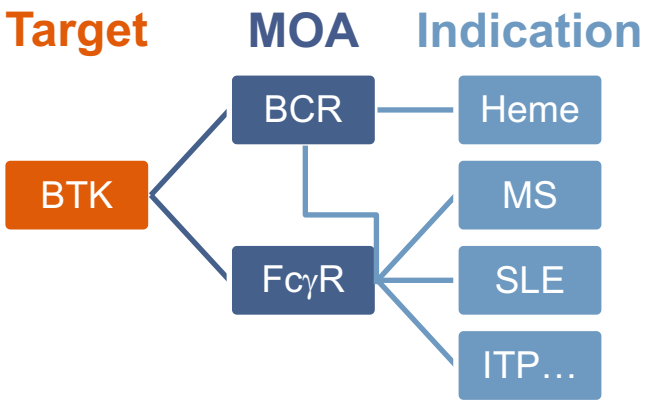
Right target → Right molecule → Right solid form → Right formulation → Right dose & patients

Discovery Programs

- **Focus on unmet medical needs in two therapeutic areas**

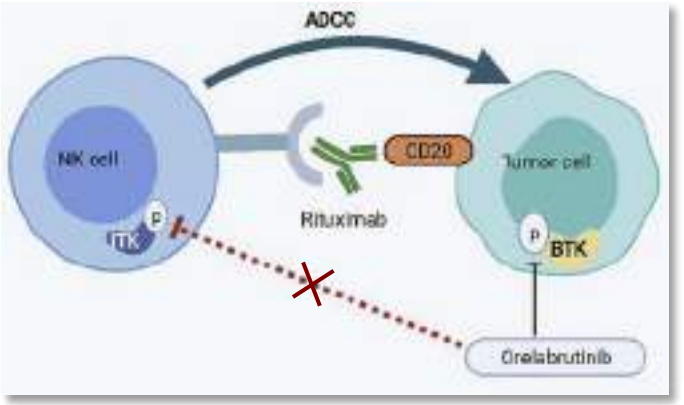
Oncology

Autoimmune Diseases



- **Leverage drug targets' crossover biological functions**
  - BTK involvement in both BCR and FcγR signalings
  - SHP2 involvement in both MAPK and PD-1 immune checkpoint pathways

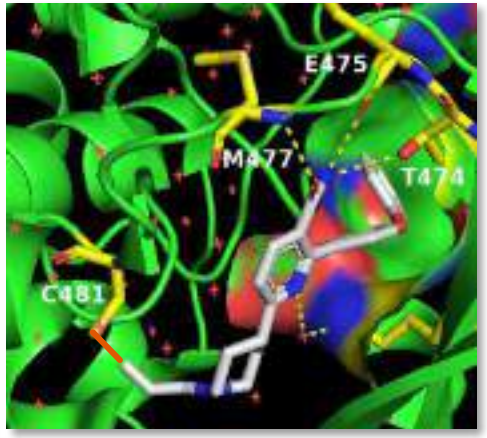
- **Build molecules with differentiated properties and potential anti-disease synergies with each other**
  - Orelabrutinib's high kinase specificity leads to the preservation of rituximab-induced ADCC effect
  - Multiple targets in the KRAS pathway



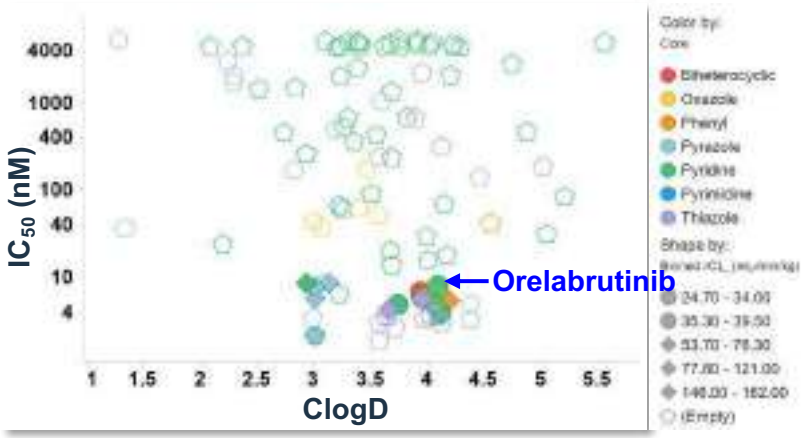
Note: picture adapted from Mol. Ther. Oncolytics 2021, 21, 158-170.

Molecular Optimization

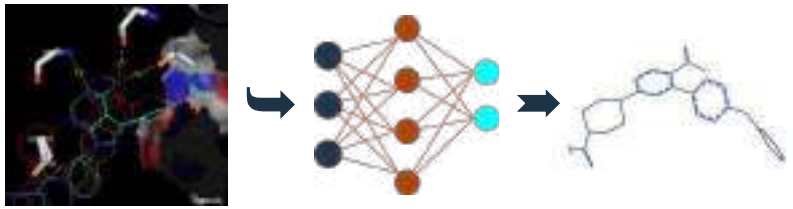
- **Integration of traditional medicinal chemistry and structure-based drug design**
  - Template selection based on scaffold physicochemical properties
  - Multi-parameter lead optimization to fine-tune compound's druggability via ligand- and structure-based designs
  - Key biological, DMPK and safety evaluations built in the testing funnel at the early stage
  - Different modalities when appropriate



Design



Data analysis

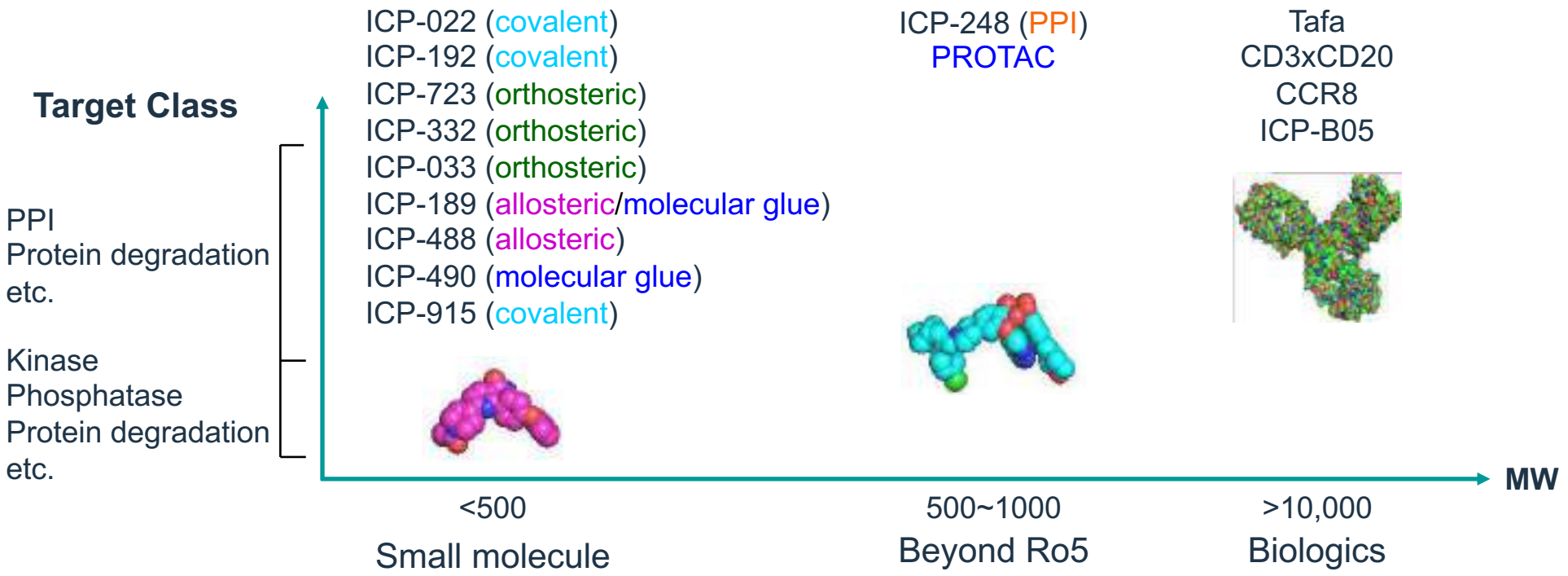


➡ Virtual screening & design

Note: structure modeled from 5P9J.

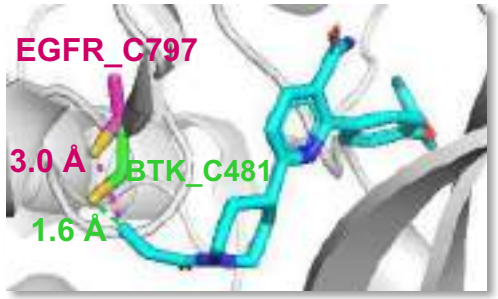
PCC Chemical Snapshot

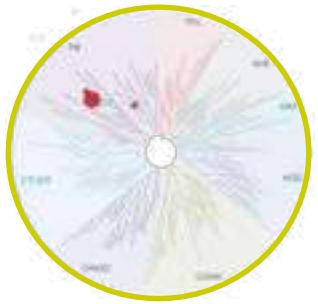
- **Modulating target biological functions with a suitable chemical modality and mode of action**



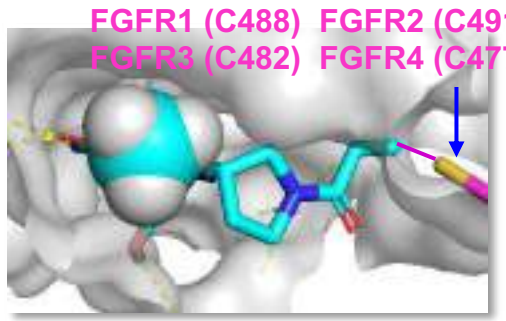
Clinical Compounds with Unique Properties

Orelabrutinib
BTK inhibitor
Covalent & selective
Market approval

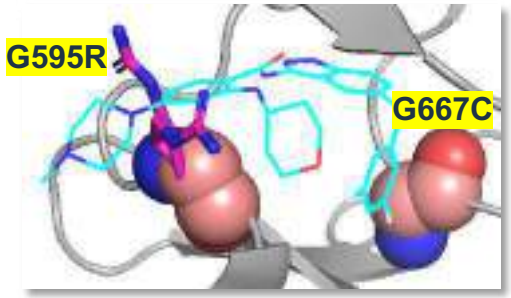




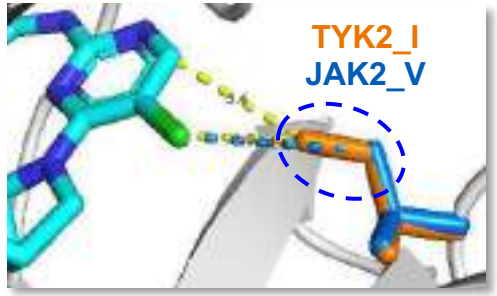
ICP-192 (gunagratinib)
pan-FGFR inhibitor
Covalent & selective
Potent against wt & mutations



ICP-723
pan-TRK inhibitor
Reversible & selective
Potent against wt & mutations



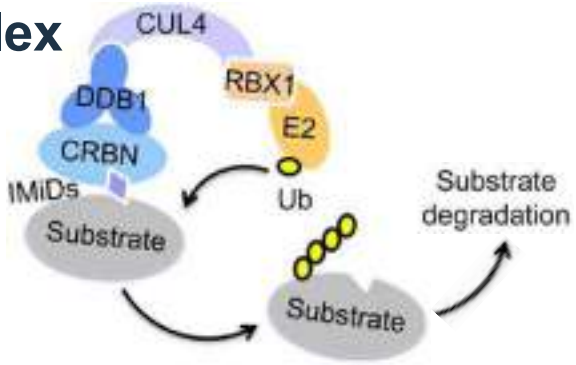
ICP-332
TYK2 inhibitor
Reversible & selective
JH1 binder

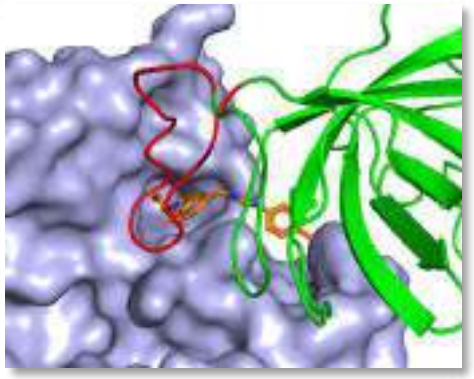


Note: structures modeled from 5P9J, 7VKO, 7VKN & 5VKN.

Targeting Undruggable Targets – Protein Degraders

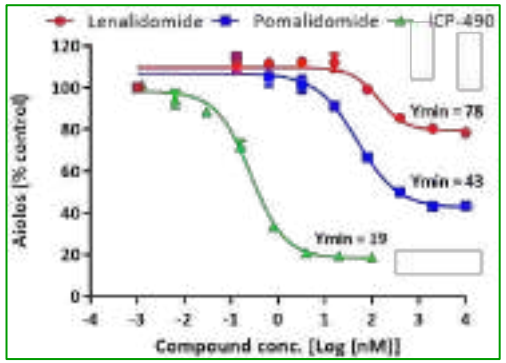
- **Utilizing CRL4^{CRBN}-E3 Ubiquitin Ligase Complex**
- **Difficult to target**
- **Class**
  - Molecular glue – monovalent molecule
  - PROTAC – heterobifunctional molecule



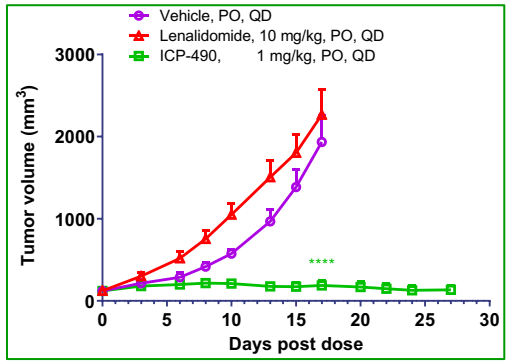


ICP-490: targeting IKZF1/3

Aiolos degradation in NCI-H929

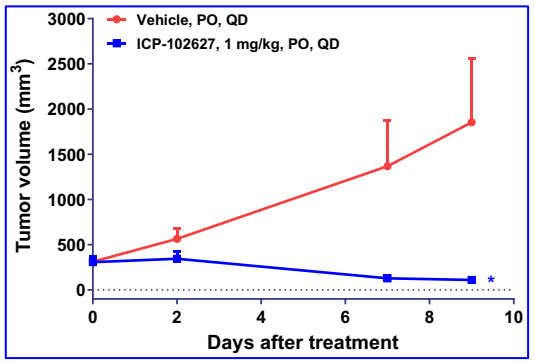


In vivo efficacy model in NCI-H929-LR

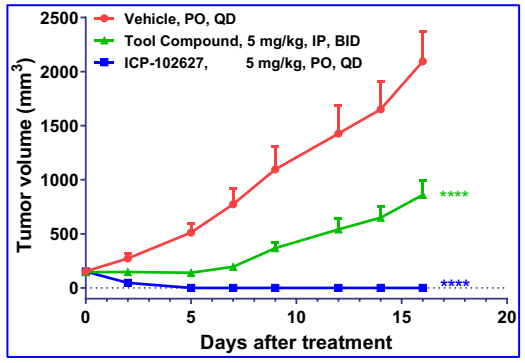


Targeting another neo-substrate

solid tumor



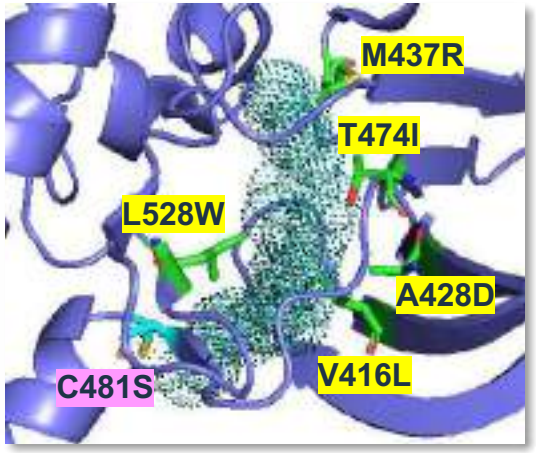
liquid cancer



Note: picture adapted from Biomarker Res. 2021, 9:43; structure from 5HXB.

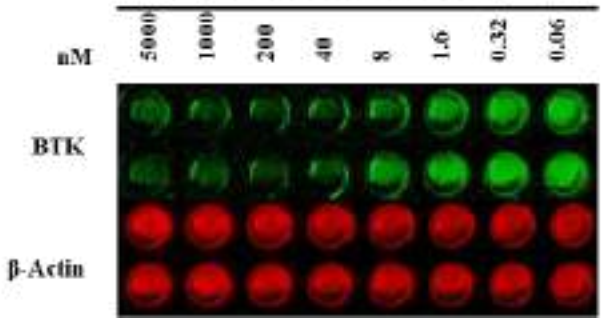
Emerging Modality – PROTACs

- **Covalent BTK inhibitor (targeting C481) – orelabrutinib**
- **Drug resistance due to mutations:**
  - Mutations at the kinase domain – C481 (covalent) and others (reversible)
  - Mutations at the SH2 domain leading to PLCγ2 overactivation (such as T316A)



PROTAC

DC_{50} = 5.5 nM
Cl: 13 mL/min/kg; F: 12%



Reversible inhibitor

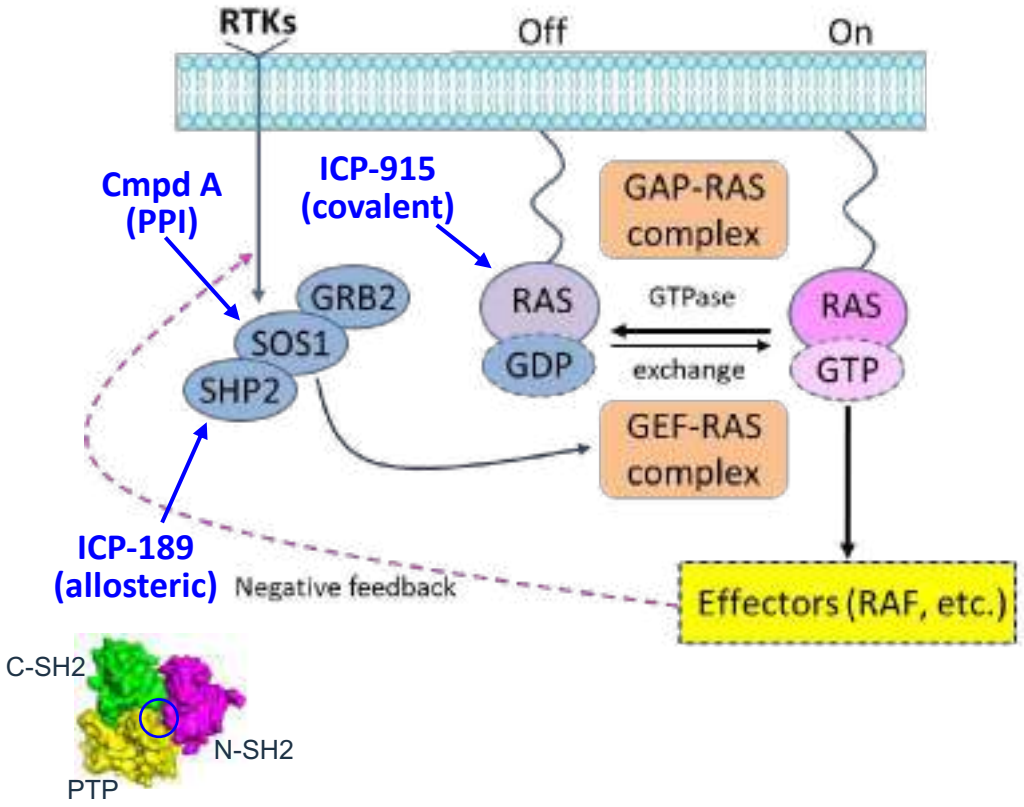
Cl: 5.9 mL/min/kg; F: 30%

Inhibitor	IC_{50} (nM)						
	BTK	BTK C481S	BMX	TEC	ITK	EGFR	A431
Ibrutinib	1.0	3.2	3.8	0.5	11	2.5	254
ARQ-531	2.2	1.5	11	6.2	773	4.5	1166
LOXO-305	0.6	0.7	3624	922	>10000	53	8047
ICP-979	1.3	1.0	1424	1659	>10000	25	>10000

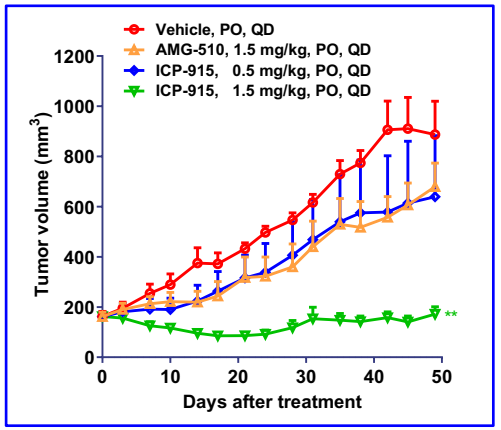
Note: N. Engl. J. Med. 2022, 386, 735; structure from 5P9J.

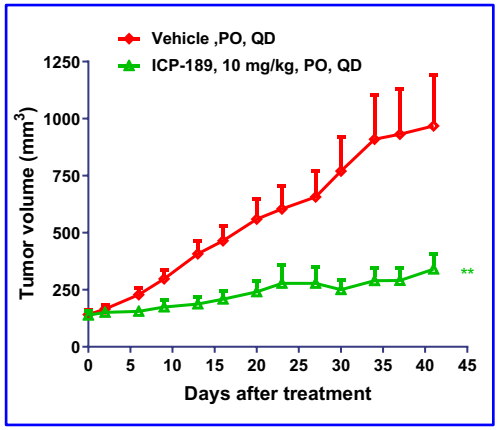
Targeting the "Undruggable" KRAS Pathway

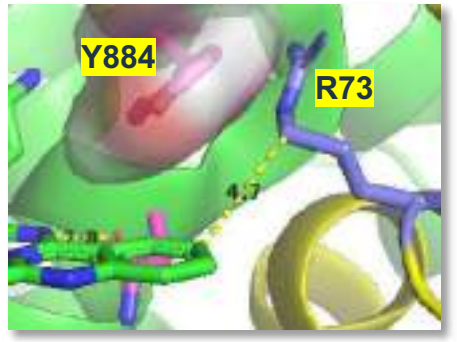
- Frequently dysregulated; difficult to target
- Multiple approaches for potential combination therapy
- ➡ Potent, selective & orally bioavailable inhibitors

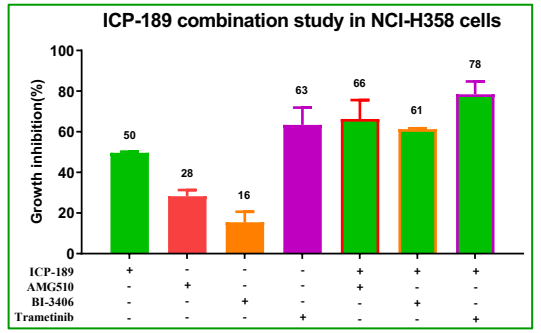


NCI-H358 xenograft models









Note: structures from 7JVM, 7AVV & 6D55.

Perspective

- **Pursue discovery programs in right competitive space**
  - Strengthen our therapeutic focus areas
  - Have synergistic effects with others in the pipeline
  - Build a balanced pipeline (best-in-class and first-in-class)
- **Develop molecules with differentiated properties**
- **Explore suitable chemical modalities/MOAs**

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科学驱动创新

诺诚健华2022研发日

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Building A Highly Innovative Biologic Pipeline

VP of Biology

- *More than 15 years of drug discovery experience*
- *Former VP of Scientific Research & Innovation at Crown Bioscience*
- *Former Asso. Principal Scientist at Merck*
- *Ph.D. in Cancer Biology from the University of Hong Kong*

Dr. Davy Ouyang

Overall Strategies for Biologics Pipeline Building

Clinical Programs

Quick wins through partnership to create crossover synergies with small molecule programs, focus on hematology-oncology

- ICP-B04 **Tafasitamab** (Effector function enhanced anti-CD19 antibody)
- ICP-B02 (**CD20 x CD3** bi-specific antibody)

Preclinical Programs

High-efficiency low-toxicity cytokine therapeutics based on pro-drug designs (**InnoKine**)

- ICP-B03 (**Pro-IL-15**) & other Pro-cytokines
- **Anti-TAA x Pro-IL-2** & other antibody-conjugated Pro-cytokines

Preclinical Programs

First-in-class mono- & bi-specific antibodies tackling immune-suppressive TME

- ICP-B05 (**CCR8**) & other T-reg targeting mono-antibodies
- First-in-class MDSC, M2 Mφ & ECM targeting agents
- Novel anti-angiogenesis agents

Highly Focused Preclinical Programs in Immuno-oncology Space

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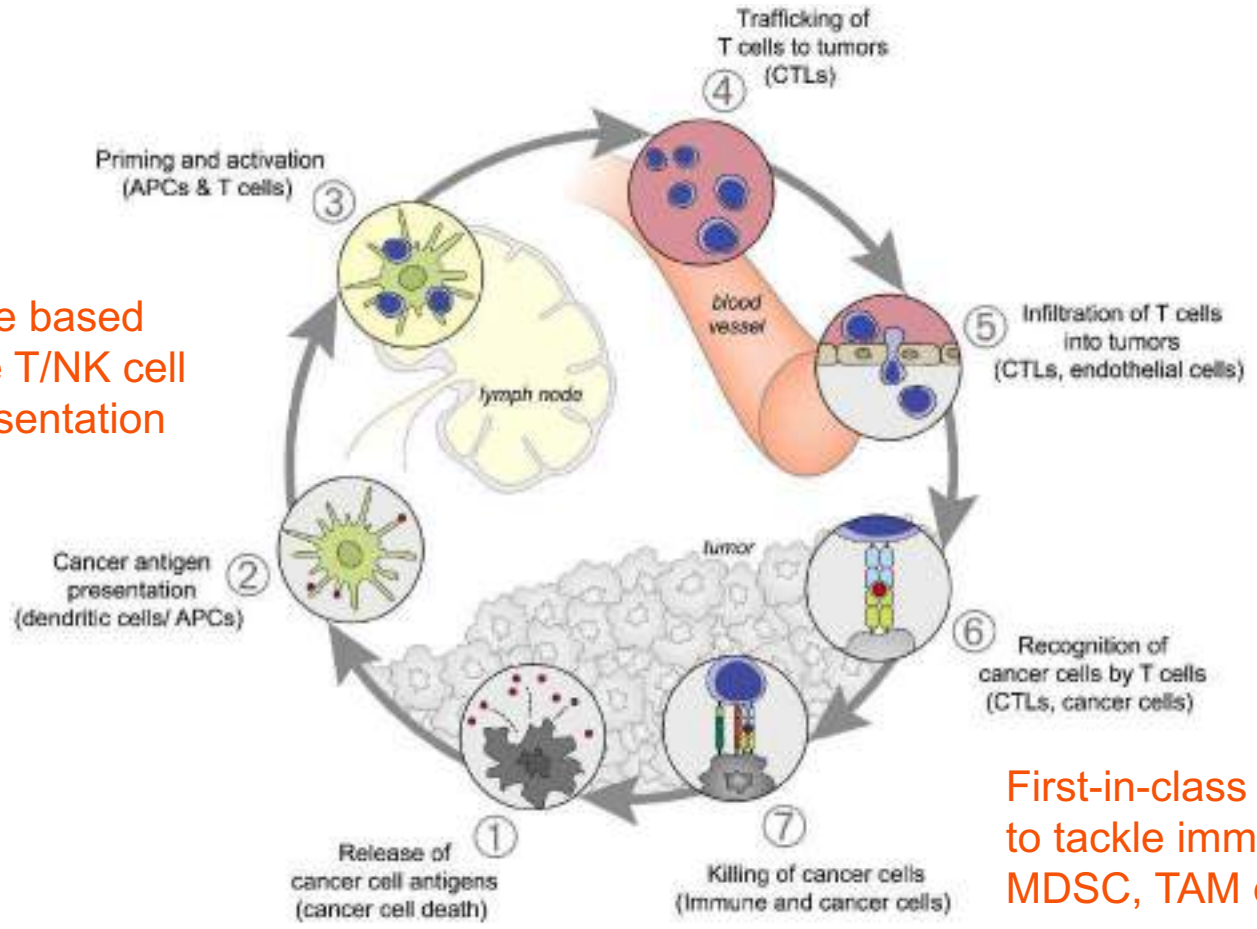
Cancer-Immunity Cycle



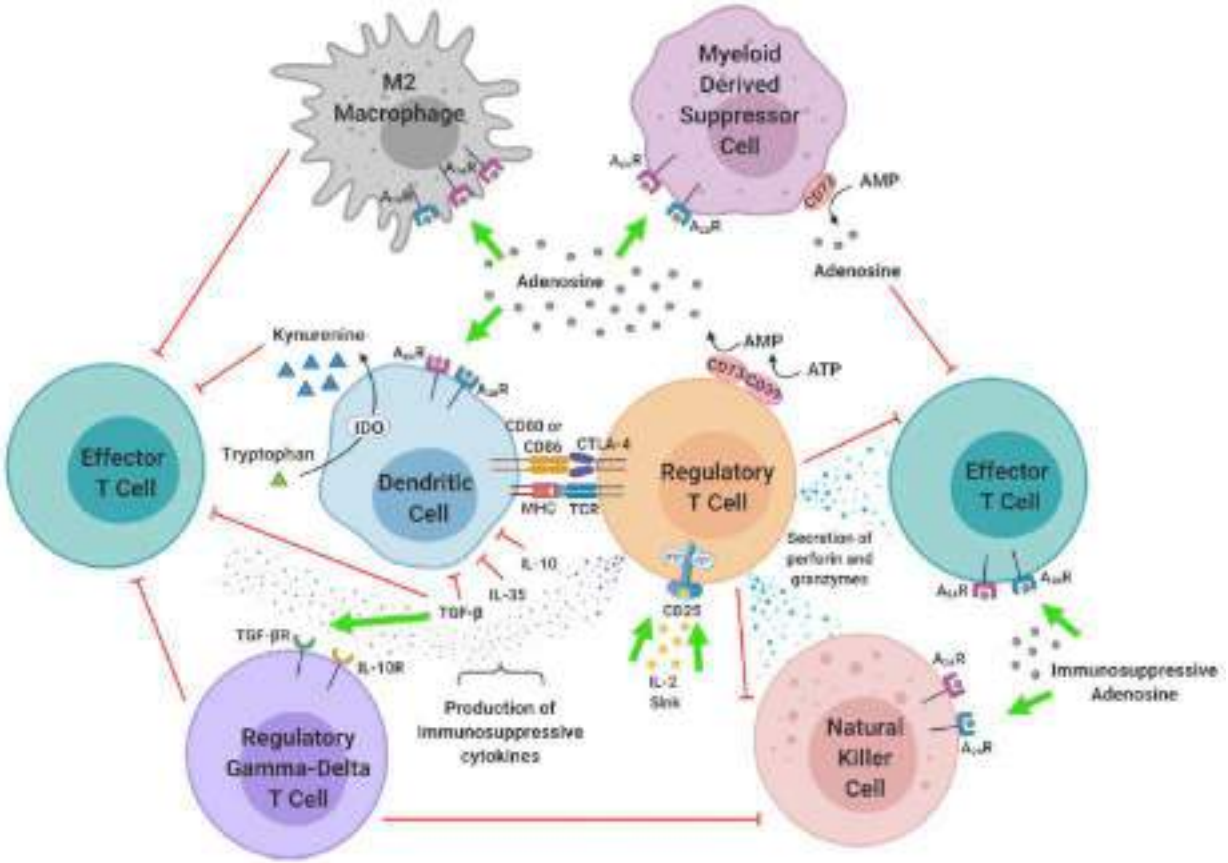
Next generation cytokine based therapeutics to enhance T/NK cell activation & antigen presentation

First-in-class antibody based therapeutics to tackle immune suppressive cells (T-reg, MDSC, TAM etc.)

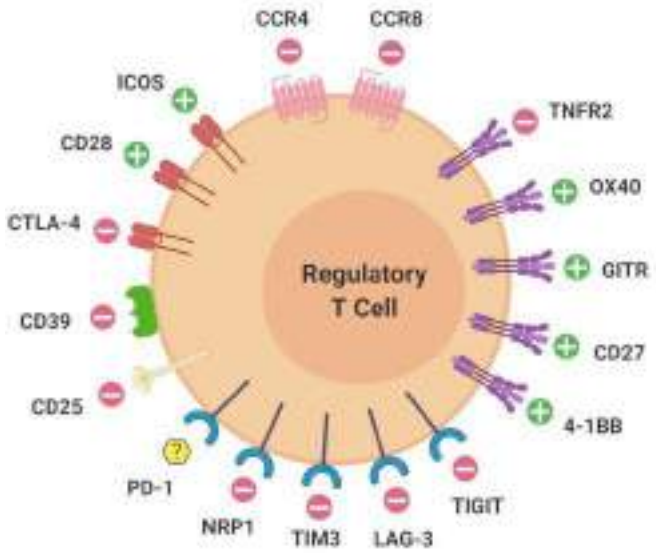
Adapted from Chen & Mellman, Immunity 39,3-11:2013

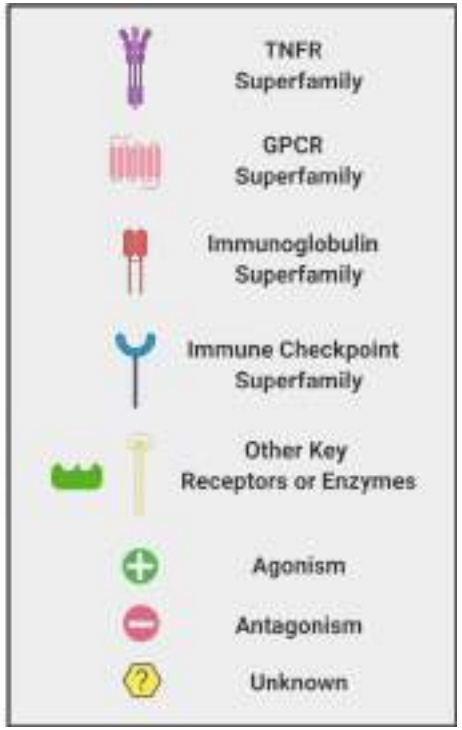
Immune Suppression Network in TME & Targeting Opportunities

Regulatory T cells play vital immune suppression roles to support tumorigenicity



Potential therapeutic approaches to target regulatory T cells





Adapted from Dees et al., Eur J Immunol, 51:280;2021

Targeting T-reg: Current Status, Challenges & Our Approaches

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❑ Currently approved therapies

- CTLA4 antibody monotherapy & PD1 combo for various indications
- LAG3 & PD1 combo for melanoma

❑ Challenges of targeting T-reg

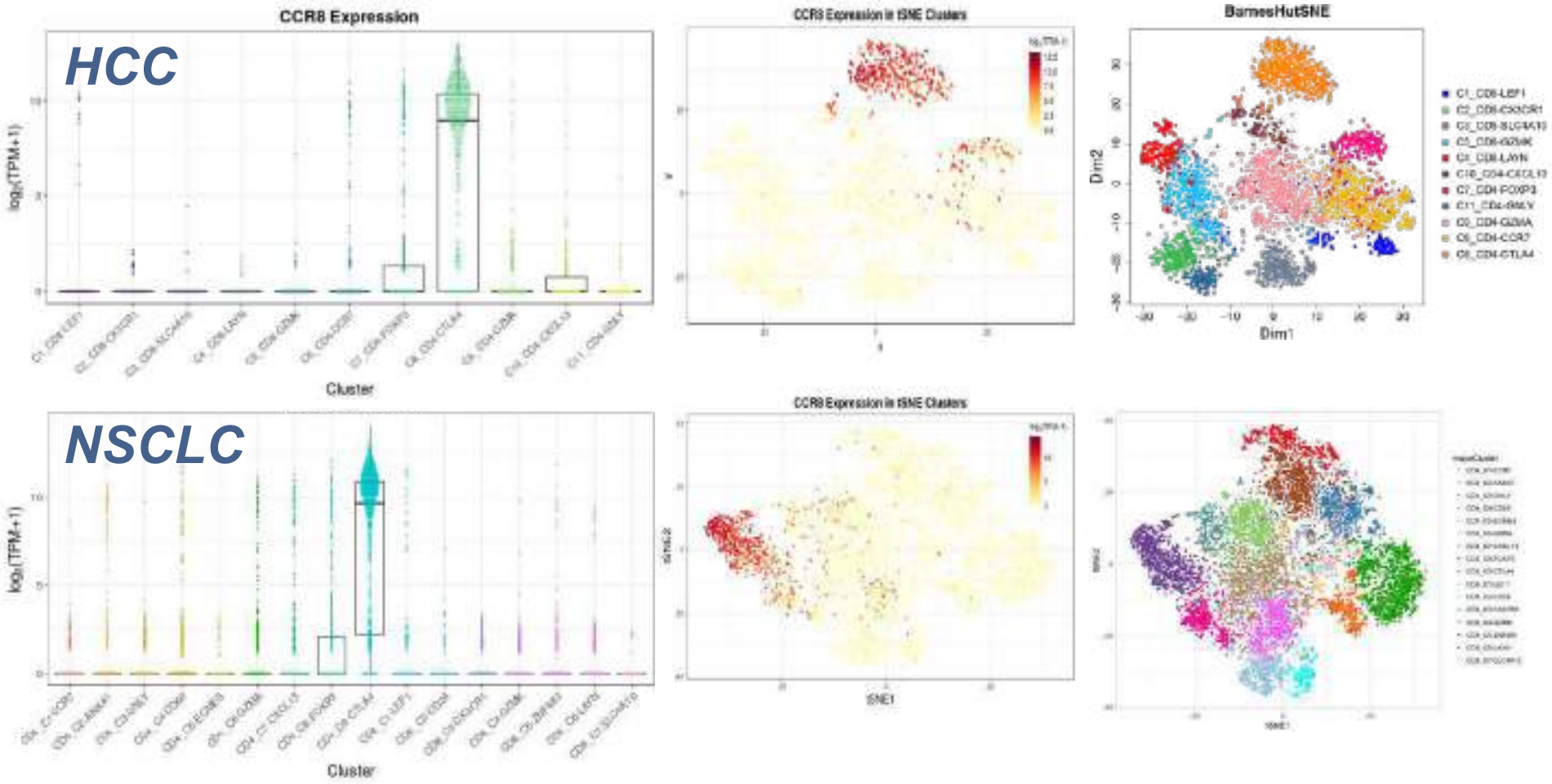
- irAE: systemic T-reg depletion caused autoimmune disorders
- Collateral damage: hitting effector T cells, helper T cells and DCs
- Inefficient depletion

❑ Our approaches

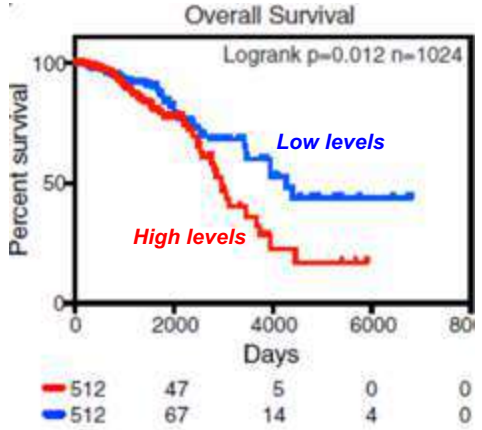
- Selectively target T-reg in TME, to solve irAE issues.
- Selectively target T-reg, without damaging other effector cells
- Improve efficiency – ADCC-enhanced high-affinity mAb, BsAb, ADC, etc.

ICP-B05* ADCC Enhanced Anti-CCR8 mAb

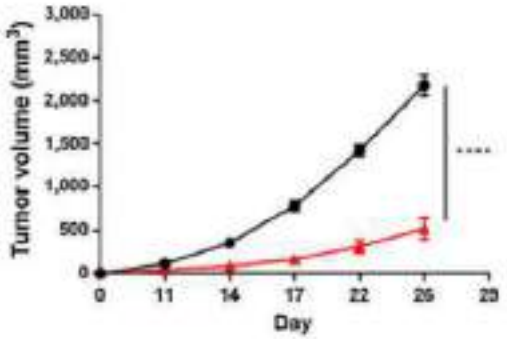
Proprietary single cell sequencing data revealed expression of CCR8 in a distinct cluster of T-reg population in various tumors



High CCR8 levels are associated with poor overall survival



Mouse surrogate antibody treatment led to significant tumor growth inhibition



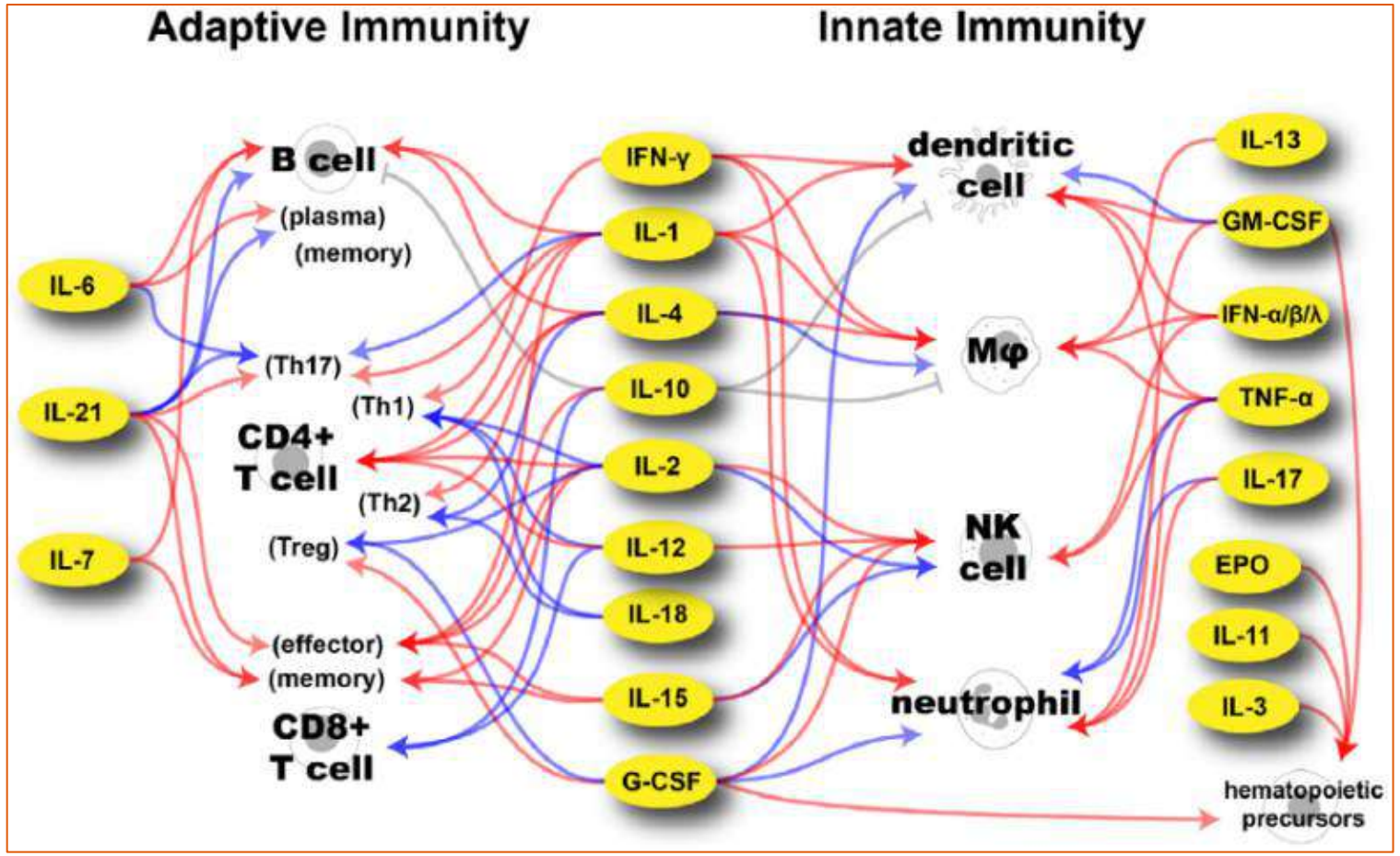
* Collaboration with Keymed Biosciences Inc.

Adapted from Plitas et al., Immunity, 45:1122;2016. Villarreal et al., Cancer Res, 78:5340;2018.

Developing Next Generation of Cytokine Therapeutics (InnoKine)

Major cytokine targets in clinical development

Dynamic & complex functions of cytokines depending on context



A bumpy journey of developing cytokine therapeutics for cancer immunotherapy

- 1st generation of cytokine therapeutics approved in the 90's didn't yield effective anti-tumor drugs
- New generation of engineered cytokines (combo with ICIs; incorporated in CAR-T, oncolytic virus, and cancer vaccines)
- Lessons learned from IL-2 and IL-15 clinical development
- Development strategies – TAA-driven and/or pro-drug approaches for tumor specific cytokine delivery & activation

Adapted from Pires et al., Adv. Therap.2021,4, 2100035

ICP-B03 Pro-IL-15
Achieving Efficacy with Much Improved Safety Profiles

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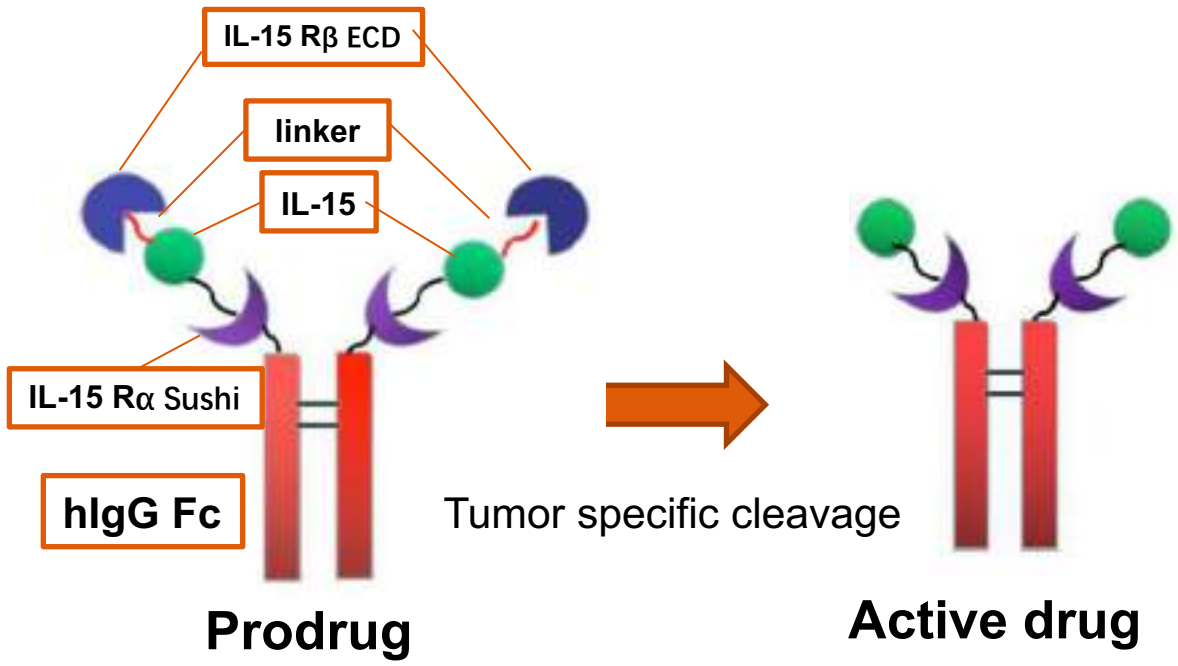
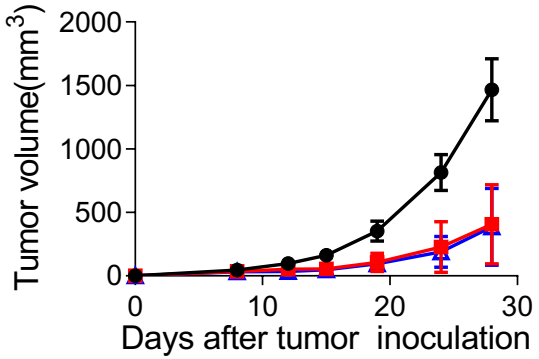
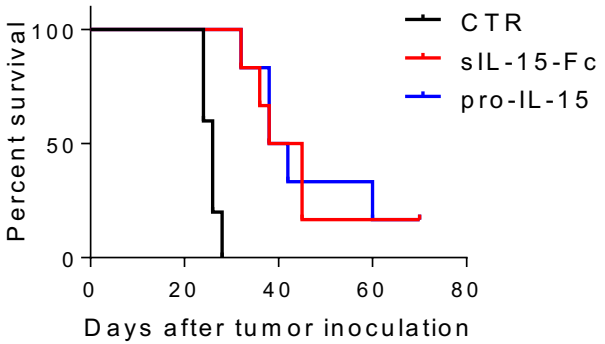
Molecule Design

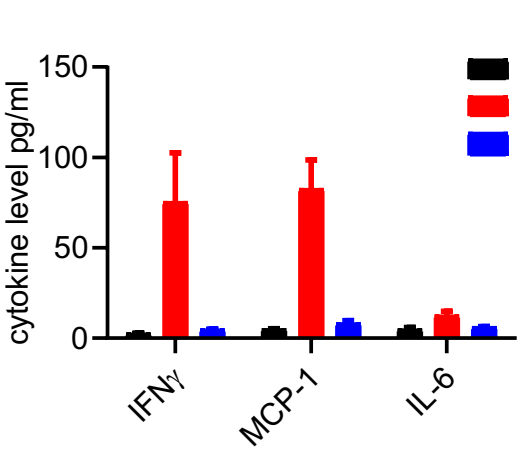


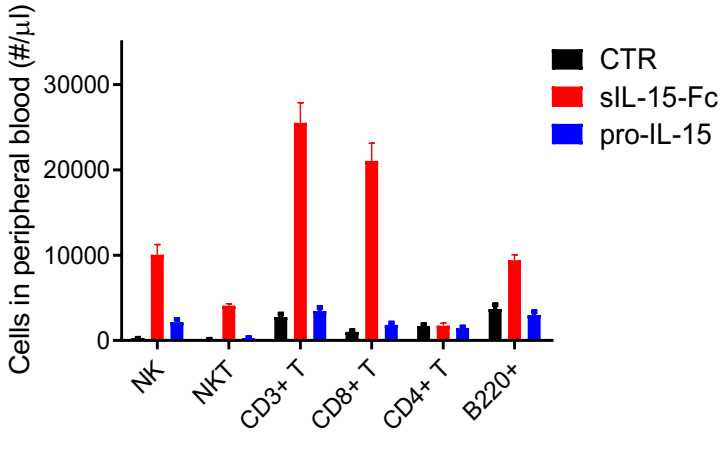
Similar Efficacy of Pro-IL-15 vs. Super-IL-15





Reduced systemic immune responses of pro-IL-15 vs. Super-IL-15





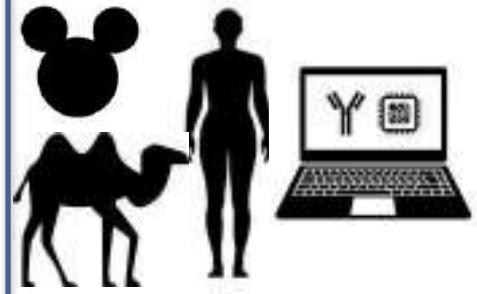
Biologics Pipeline

Drug Candidate	Target	Indication	Worldwide right	Discovery	Preclinical Research	IND	Phase I	Phase II	Phase III	Launched
ICP-B04/ Tafasitamab	CD19	DLBCL/ B cell lymphoma								
Orelabrutinib + MIL62	BTK +CD20	B cell lymphoma (Basket trial)								
ICP-B02	CD3 x CD20	B cell lymphoma								
ICP-B05 CCR8 mAb	CCR8	Solid tumors		IND expected in Q2, 2022						
ICP-B03 Pro-IL-15	IL-15	Solid tumors								
Anti-TAA x Pro-IL-2	TAA, IL-2	Solid tumors								
T-reg targeting mAb	Undisclosed	Solid tumors								
T-reg targeting BsAb	Undisclosed	Solid tumors								
T-reg targeting BsAb	Undisclosed	Solid tumors								

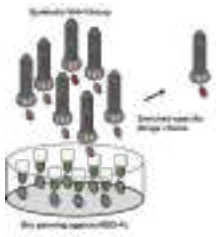
Discovery stage programs of undisclosed targets & bi-specific antibody combinations, fusion proteins targeting MDSC, Mφ, TAM, ECM, Angiogenesis

Biologics Discovery Team & Platform Building

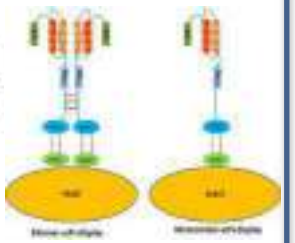
Antibody Discovery



Naïve / Immunized / Synthetic Library

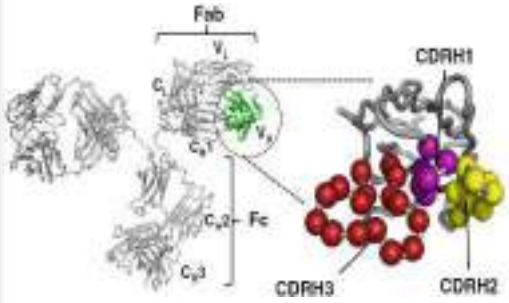


Phage display



Yeast display

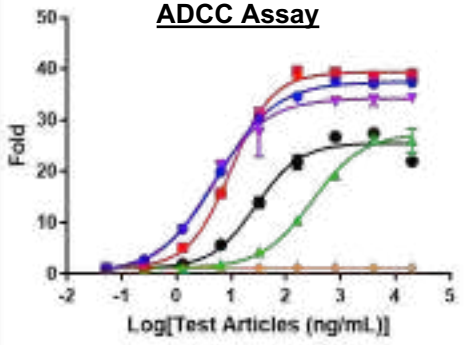
Protein Science



Protein engineering

- Druggability assessment & improvement
- BsAb & fusion protein configurations
- Pro-cytokine engineering
- Fc engineering: ADCC enhancing or silencing
- pH resistant or sensitive molecules
- Biochemical & biophysical characterization

I/O Assays



- MLR assay
- T cell/PBMC activation
- ADCC, ADCP, CDC
- Cell proliferation, cytotoxicity assays
- Multiplex cytokine analysis
- Antigen-specific T cell assessment
- Occupancy and Internalization
- Reporter assays
- PK/PD

Well-Established Functional Supports

- **Biology**
- ***In vivo* Pharmacology**
- **DMPK**
- **Translational Research**
- **Toxicology**
- **CDMO → Internal CMC capability**

Overall Capability Building for Biologics R&D

- Immuno-Oncology
  - Mab based biologic
    - Mono-specific Ab
      - Library Building
        - Naïve library
        - Immune library
        - Nanobody
        - scFv
        - Synthetic
      - Display
        - Hybridoma
        - Phage display
        - Yeast display
      - Engineering & Validation
        - Humanization
        - Affinity maturation
        - In vitro & in vivo PD/efficacy
        - Analytical capabilities
        - Expression / Yield Opt.
    - Bi-specific Ab
      - Full length
        - LC mispairing
        - HC mispairing
      - Fragment
    - Fc engineer
      - Heterodimer enhancement
      - ADCC enhancement
      - Fc silencing
    - ADC
      - ISAC
  - Cytokine based biologic
    - SuperKine
      - Conditional activation cytokines
      - Hyperactivated cytokines
    - ImmunoKine
      - Targeted cytokines

Innocare's Biologics CMC facility in construction

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Translational Research

Senior Director of Pharmacology and Translational Research

- *More than 10 years of drug discovery experience*
- *Former Director of Biomarker Development at QIAGEN*
- *Former Associate Director at WuXi AppTec*
- *Ph.D. in Pharmacology from Tsinghua University*
- *Postdoctoral research fellow at University of Pittsburgh*

Dr. Jason Zhang

Increasing Number Of New Molecular Entities (NMEs) Entering Translational Research

IND Submission	Project	Target	Modality	Therapeutic Area	2021 Q1	2021 Q2	2021 Q3	2021 Q4	2022 Q1	2022 Q2	2022 Q3	2022 Q4
2022 (Disclosed)	ICP-248	BCL-2	Small Molecule	Liquid Cancer						S	A	
	CM369 (B05)	CCR8	mAb	Solid Tumor						S	A	
	ICP-490	CRBN	Molecular Glue	Liquid Cancer						S	A	
2021	ICP-488	TYK2 JH2	Small Molecule	Auto-immune				S	A		FPI	
	ICP-189	SHP2	Small Molecule	Solid Tumor			S	A		FPI		
	CM355 (B02)	CD3XCD20	BsAb	Liquid Cancer			S+A		FPI			
	ICP-033	DDR1, VEGFR	Small Molecule	Solid Tumor		S+A			FPI			
	ICP-332	TYK2 JH1	Small Molecule	Auto-immune	S	A	FPI					

Liquid Cancer	S: IND Submission
Auto-immune	A: IND Approval
Solid Tumor	FPI: First Patient In

Translational Research: First-in-Human (FIH) → Proof-of-Concept (POC)

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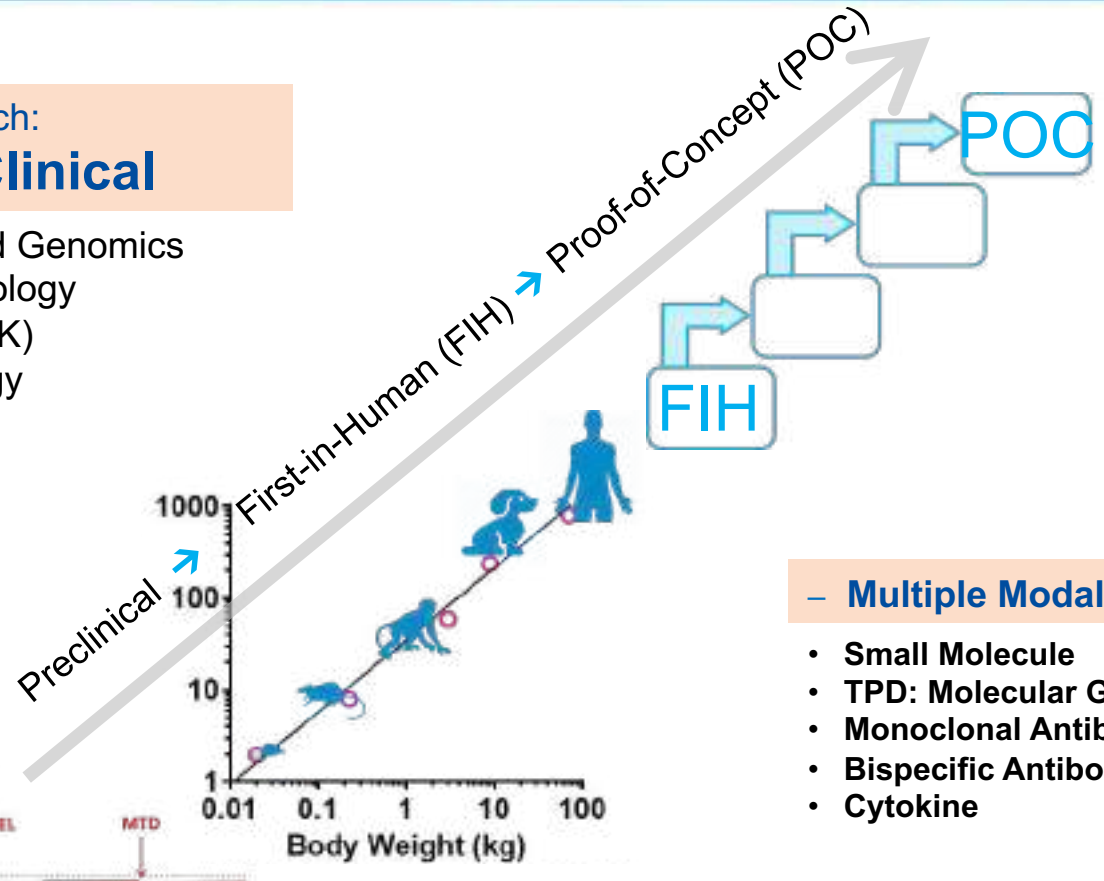
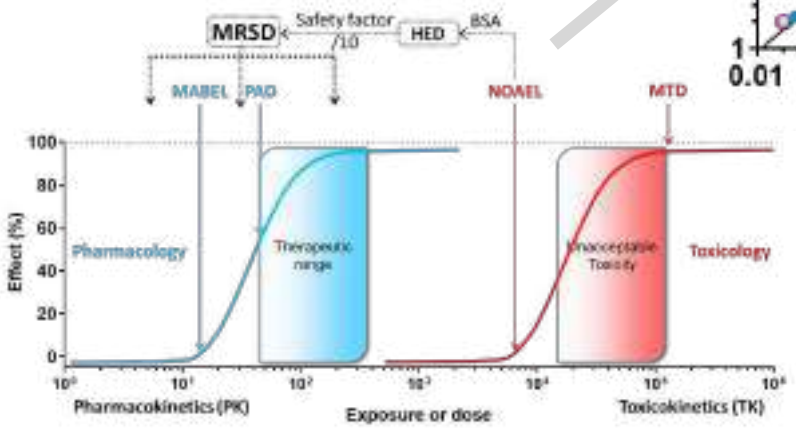
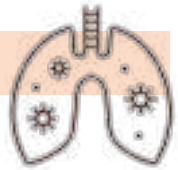
– Translational Research: Preclinical → Clinical

- Biology/Genetics and Genomics
- Pharmacology/Toxicology
- Pharmacokinetics (PK)
- Clinical Pharmacology
- Biomarker



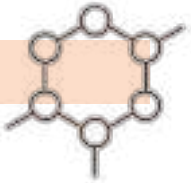


– Therapeutic Areas



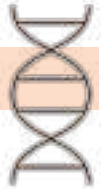
- **Liquid Cancer**
- **Solid Tumor**
- **MS**
- **SLE**
- **Psoriatic Arthritis**
- **Atopic Dermatitis**
- **Inflammatory bowel disease (IBD)**

– Multiple Modalities/Approaches



- **Small Molecule**
- **TPD: Molecular Glue/PROTAC**
- **Monoclonal Antibody**
- **Bispecific Antibody**
- **Cytokine**

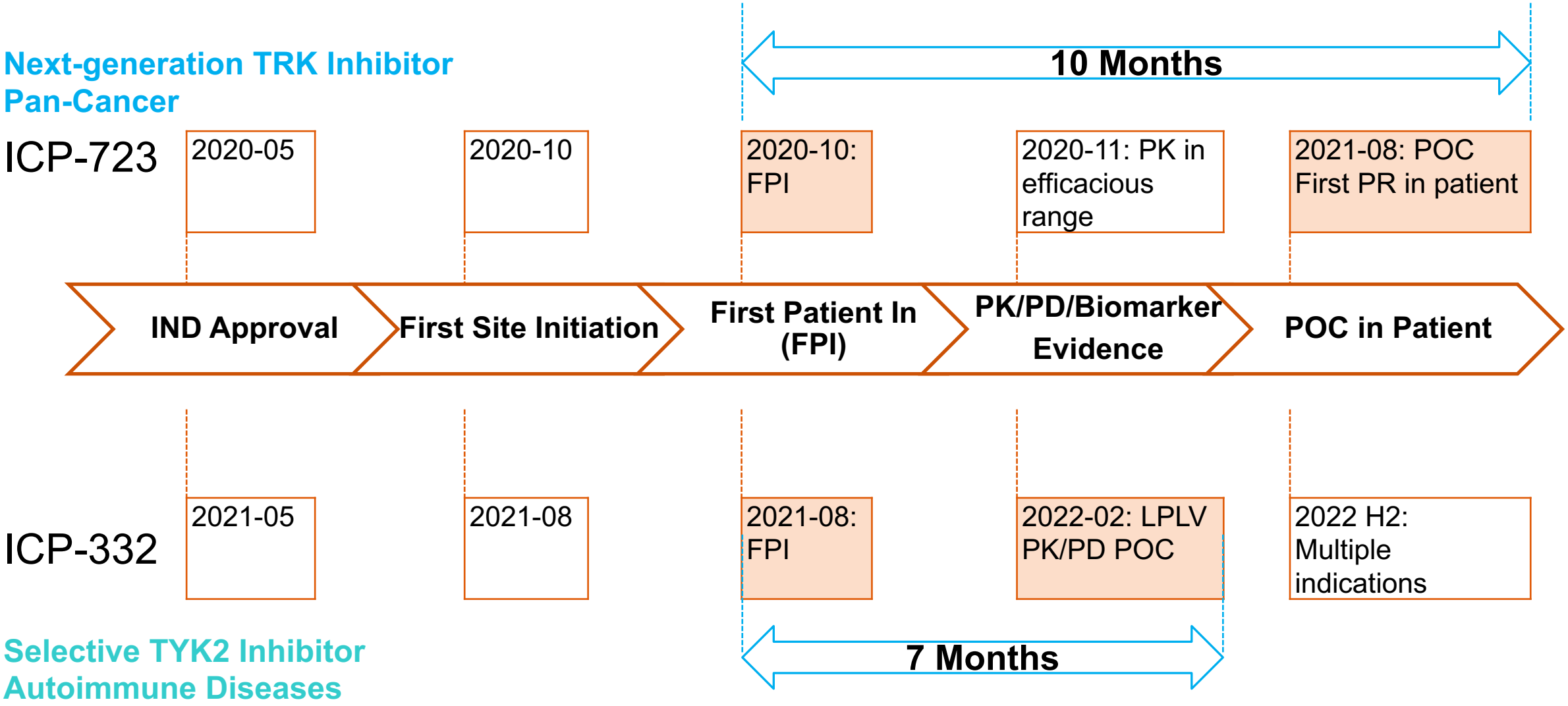
– Various Targets



- **Kinase**
- **Phosphatase**
- **Ubiquitin-Proteasome System (UPS)**
- **Immune Checkpoint**
- **Tumor Microenvironment (TME)**

MS: multiple sclerosis; PROTAC: proteolysis-targeting chimera; SLE: systemic lupus erythematosus; TPD: targeted protein degrader

Fast Achievement of POC



ICP-723: Favorable PK Profile and Encouraging Efficacy in Cancer Patients Carrying NTRK Fusion

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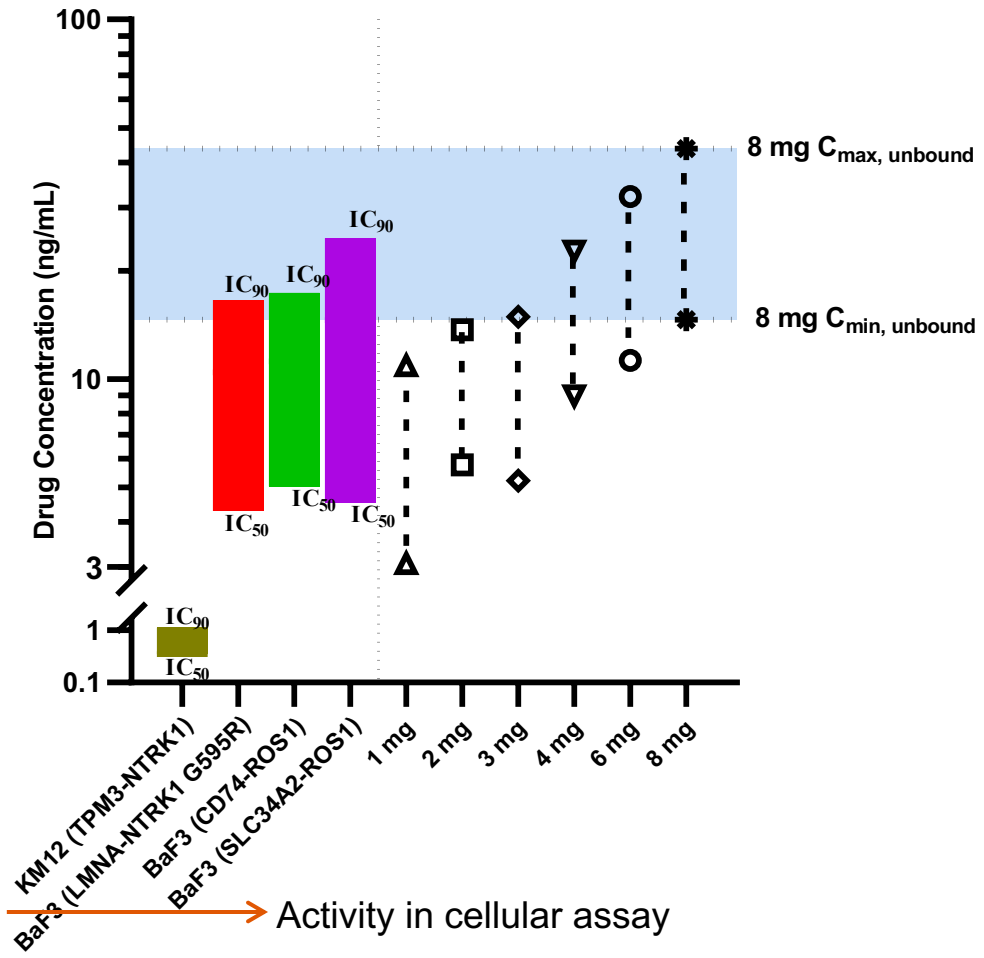
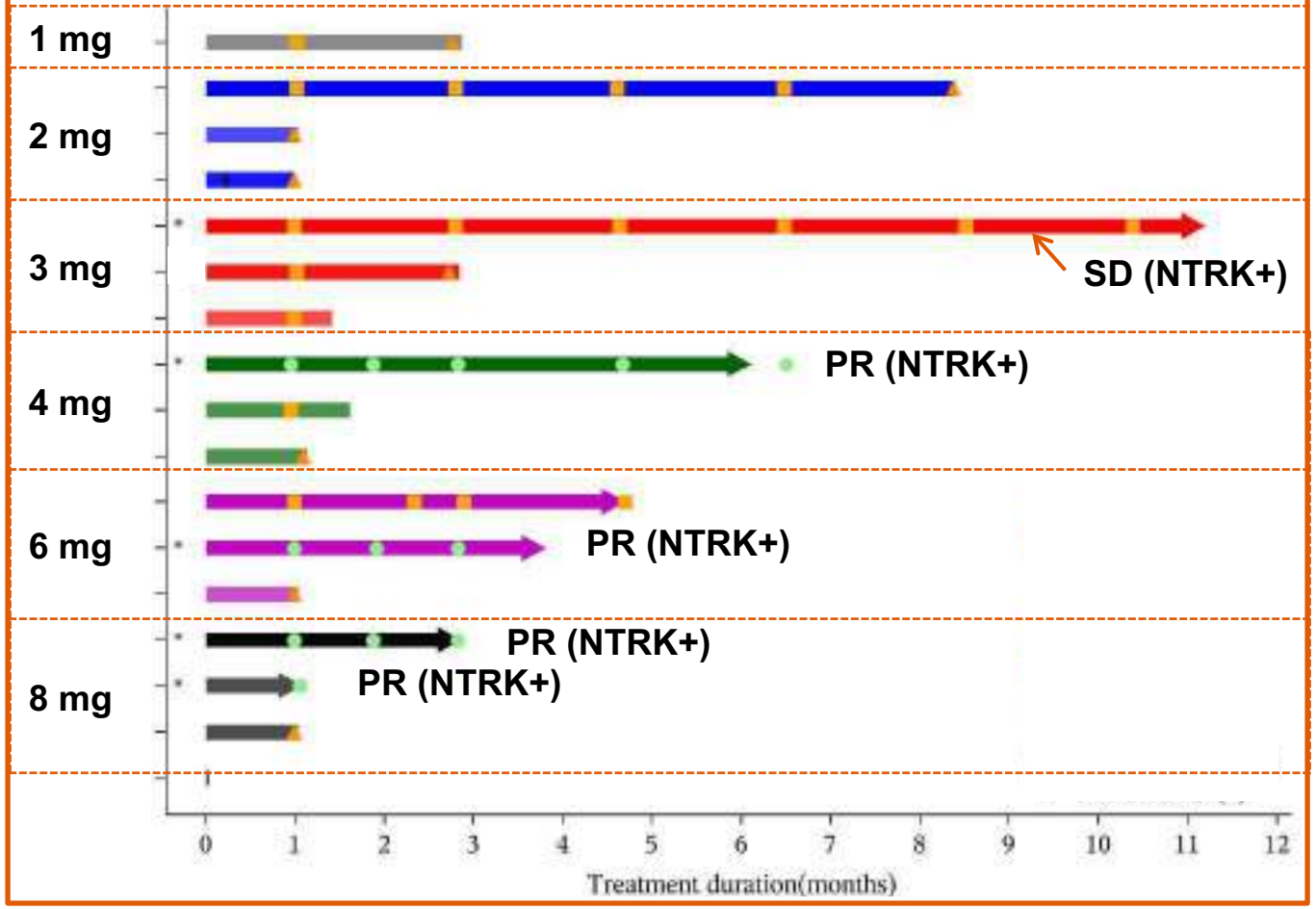
ICP-723 Clinical Exposure vs Preclinical Cellular Activity

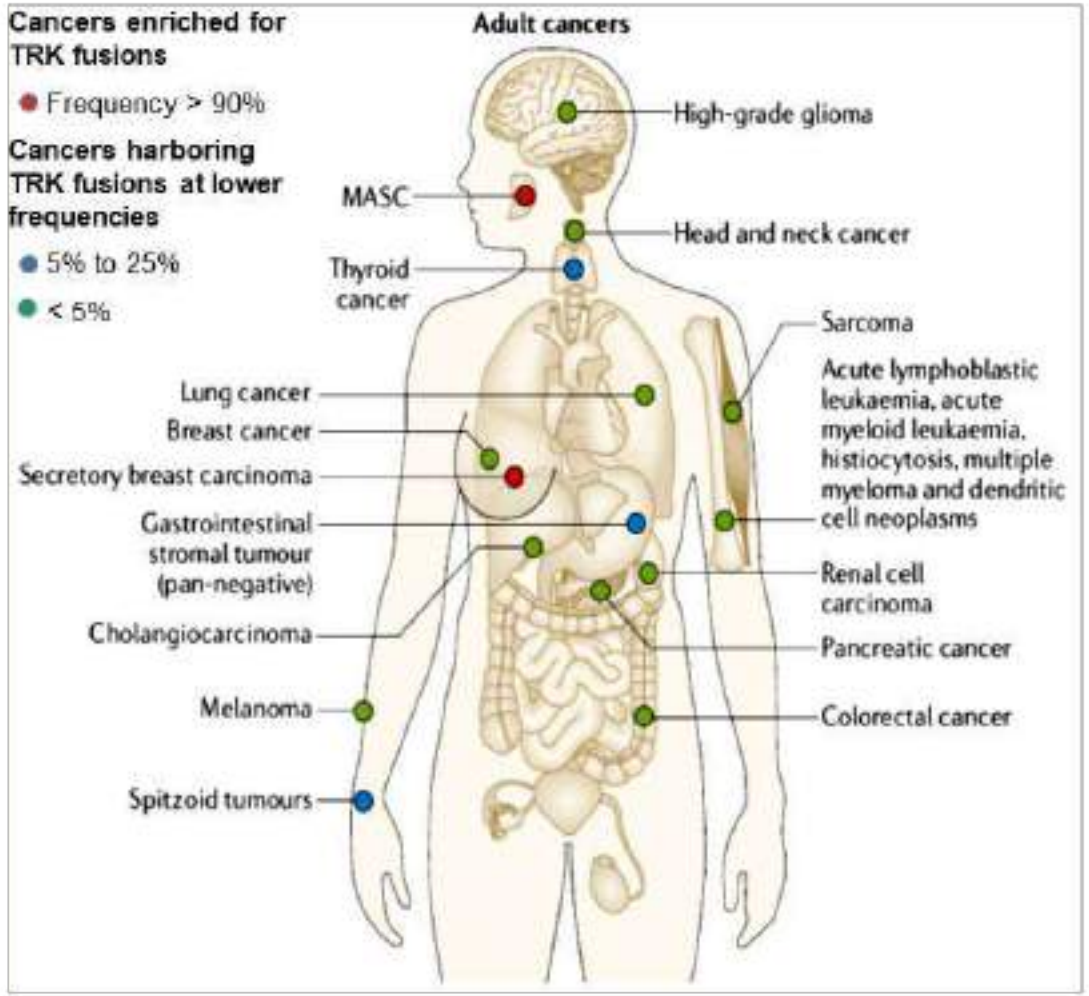


- **No DLTs observed** in 6 dosage groups (1-8 mg)
- **ORR 80% (4 PR in 5 patients with NTRK fusion), DCR 100%**
- Initiating Phase I trial in the U.S. in 2022

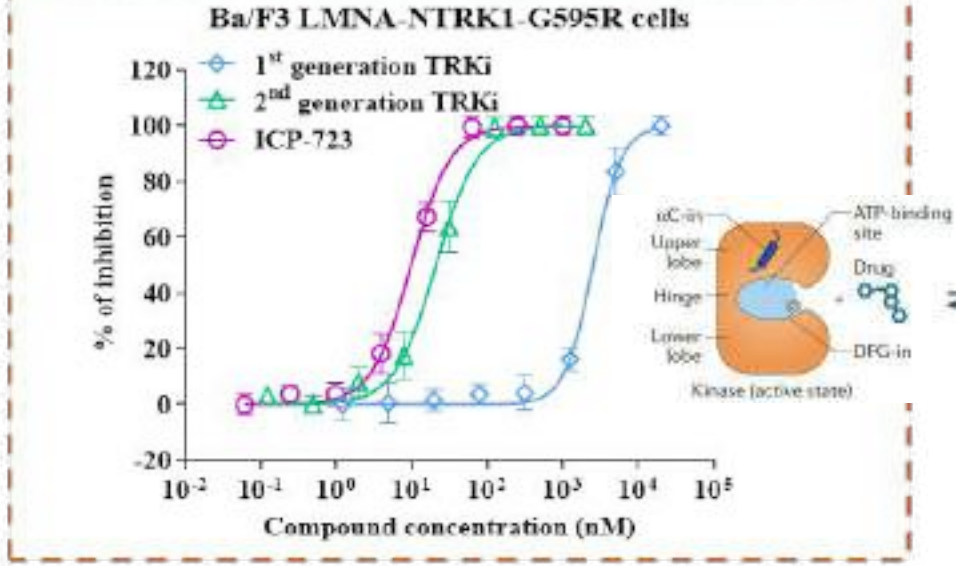


ICP-723: Next-Generation TRK inhibitor Overcoming Acquired Resistance

Distribution and frequency of *NTRK* fusions in adult[1]



Pre-clinical Results



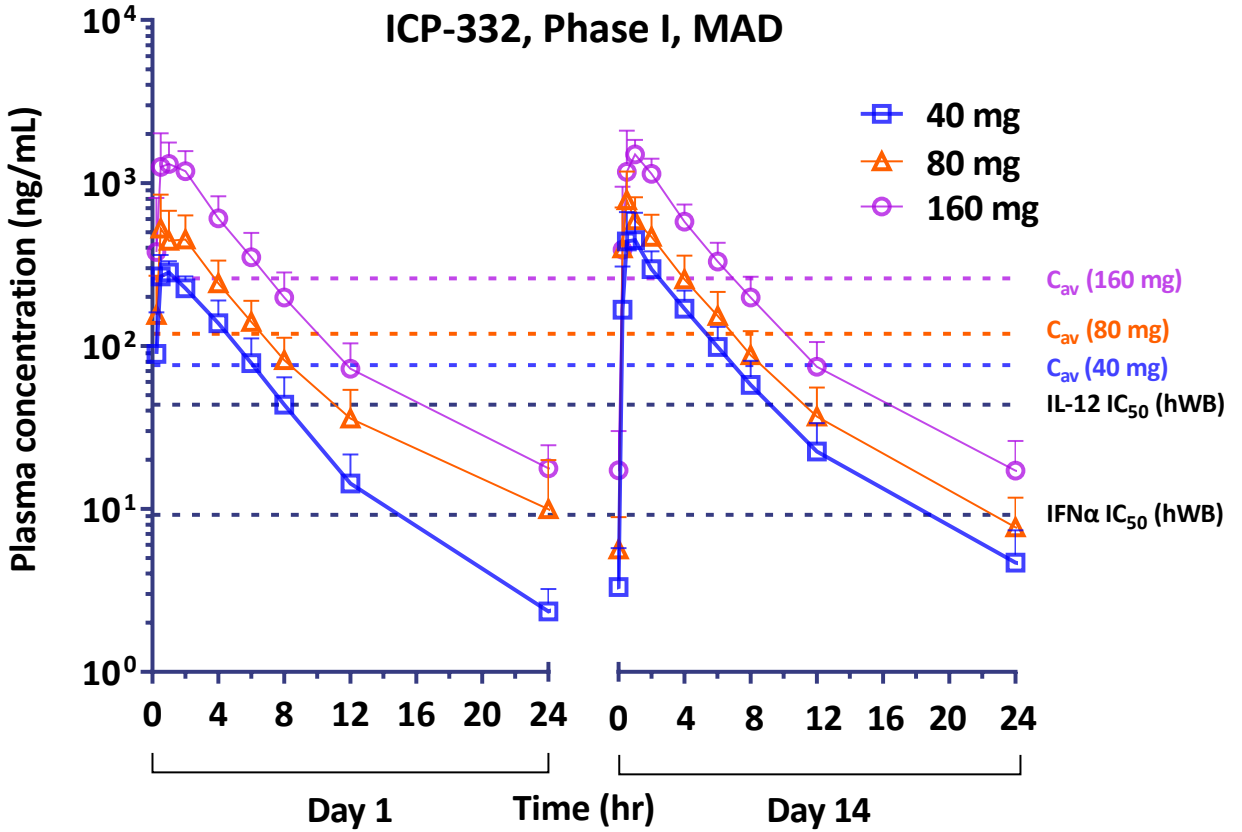
NTRKs Mutations

	TRKA	TRKB	TRKC
Solvent front	G595R	G639R	G623R/E
Gatekeeper	F589L	F633L	F617L
xDFG	G667C/A/S	G709C	G696C/A

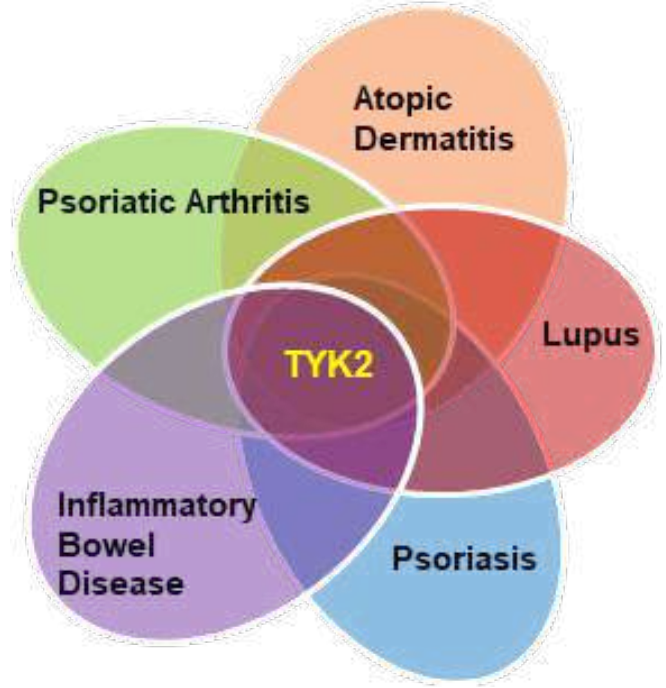
ICP-723 shows excellent activities against TRK resistance mutations including gatekeeper, xDFG and solvent front mutations.

Nat Rev Clin Oncol 15, 731-747 (2018); Nat Rev Drug Discov 20, 839-861 (2021).

ICP-332: Highly Selective TYK2 Inhibitor for Multiple Autoimmune Indications



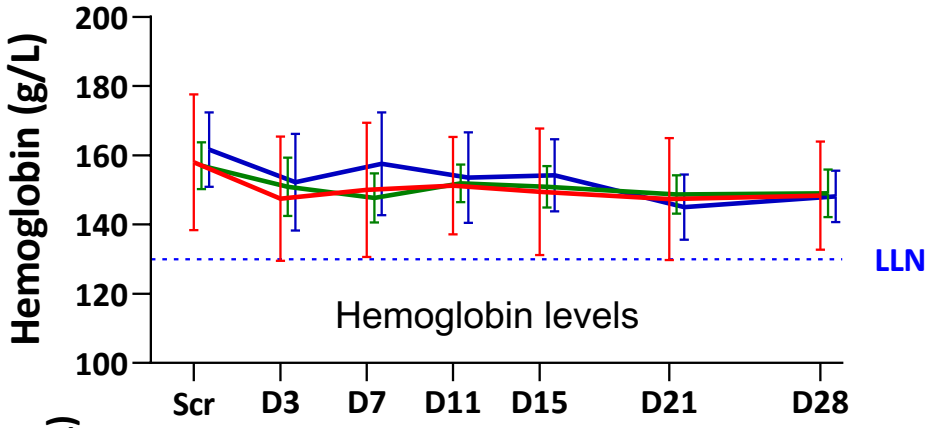
- **Phase I**: SAD (5 ~ 320 mg) and MAD (40 ~ 160 mg QD) for 14 days.
- **Safe and well tolerated** at all dose levels.
- Demonstrated **dose proportionality of the PK parameters** in the range of 5 mg ~ 320 mg.
- No drug accumulation and no significant food effect observed.

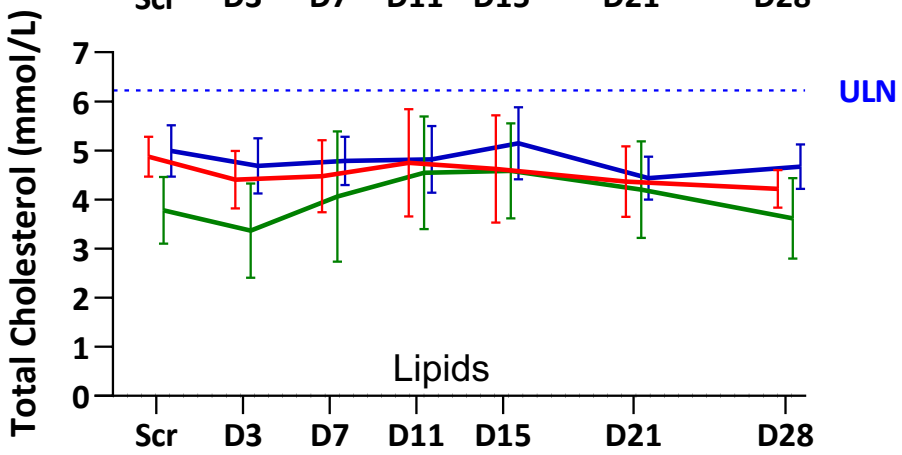


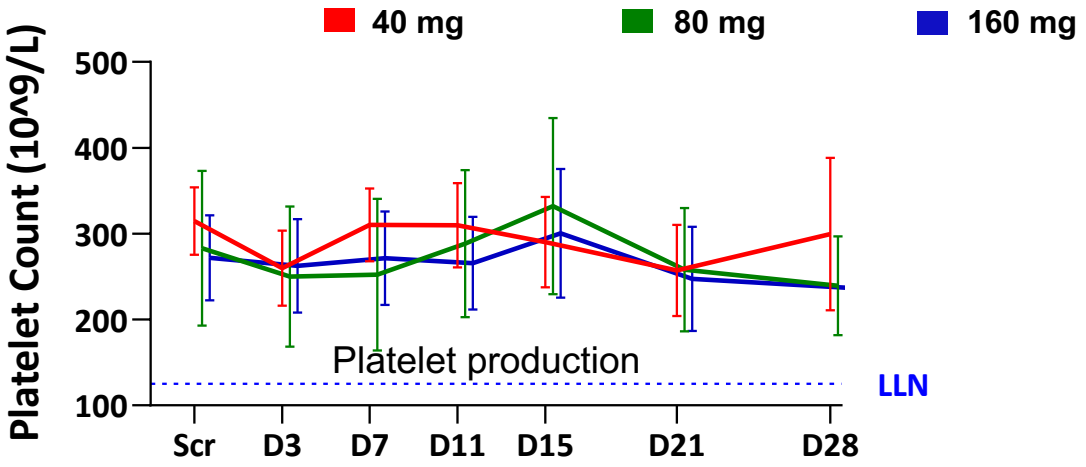
- Cav ($AUC_{\tau/\tau}$) is widely accepted as the most predictive drug-exposure measure of JAK/TYK2 inhibitor efficacy.
- The Cav at 40 mg and above were shown to be higher than the IC50s in whole blood assay, including IFNα induced p-STAT3 (JAK1/TYK2), IL-12 induced p-STAT4 (JAK2/TYK2), etc., which are implicated in multiple autoimmune diseases.

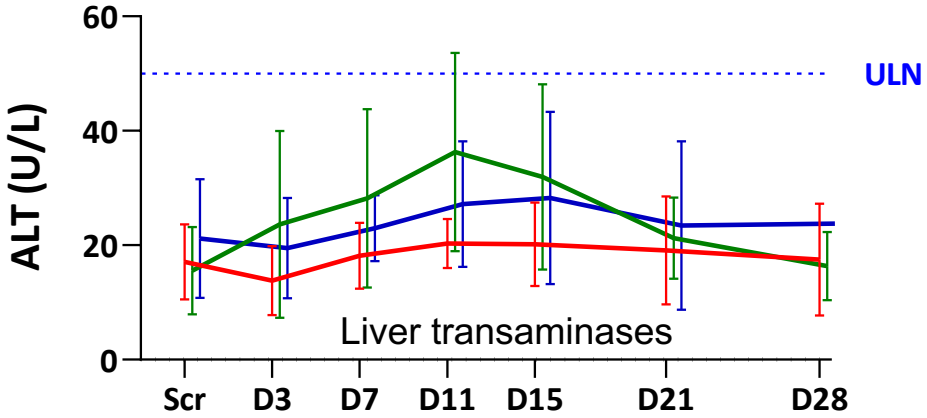
C_{av}, average plasma concentration in 24 h; IL-12, interleukin-12; IFNα, interferon α.

No Evidence of JAK2 Inhibition-mediated Changes and Other Safety Biomarkers









By selective inhibition of TYK2 **(400x folds over JAK2)**, ICP-332 may become a potential therapy for multiple autoimmune diseases with better safety profiles.

LLN: lower limit of normal; ULN: upper limit of normal

Advance More First-In-Class Drugs to Reach POC & Explore Potential Combinations to Achieve Better Efficacy

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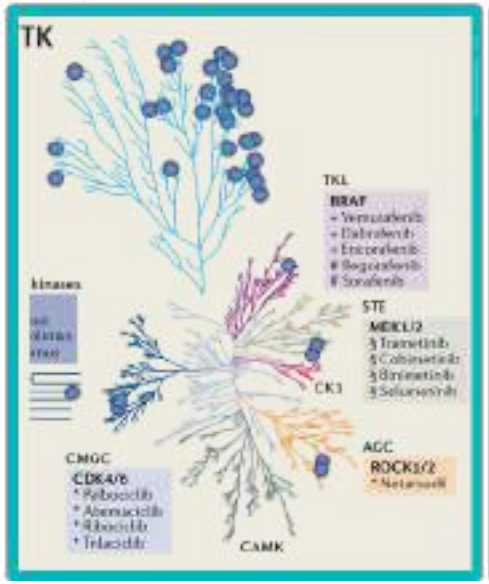
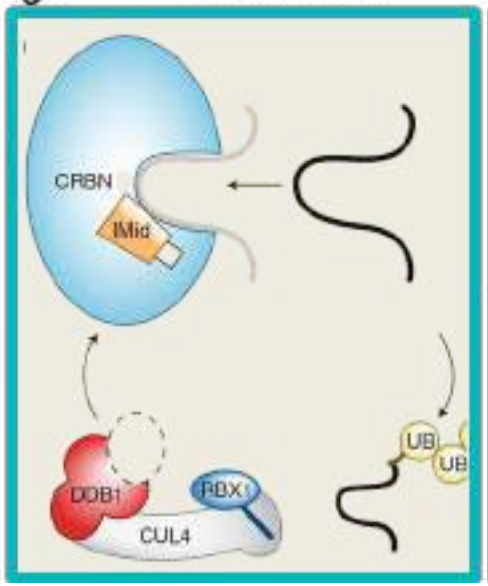
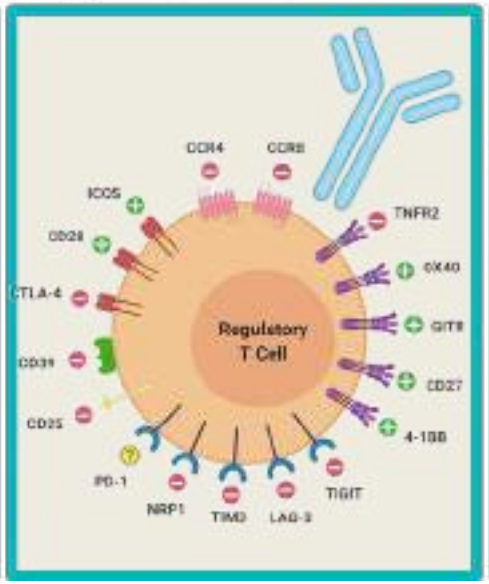
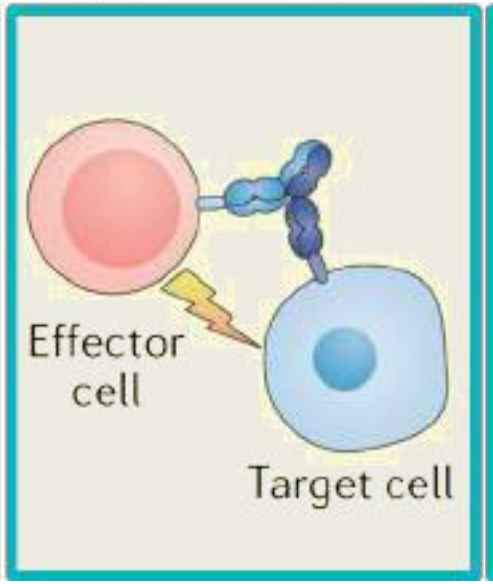
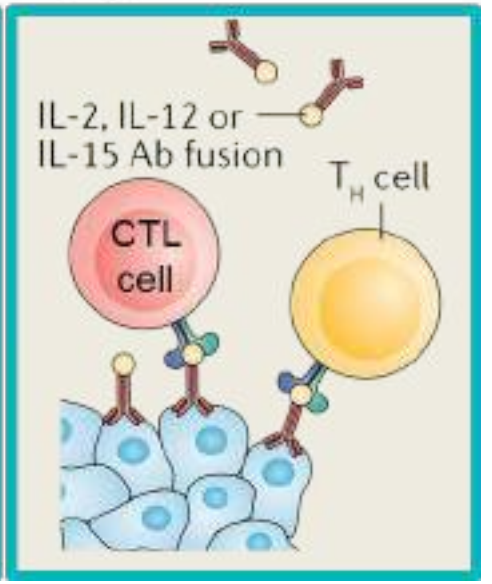
Small Molecule | Targeted Protein Degrader | Monoclonal Antibodies | Bispecific Antibodies | Cytokines











– Kinase/Phosphatase:	– Molecular Glue/PROTAC	– Direct/Indirect	– Harnessing Immune System	– Precision/Targeted

• BTK
• FGFR
• TRK
• TYK2 JH1
• **TYK2 JH2**
• **SHP2**
• **DDR1**
	• CRBN
	  • **IKZF1/IKZF3**
	  • Neo-substrates
	• Other E3 ligase
	• PROTAC
		• Direct tumor killing
		  • CD19
		• Immune-mediated
		  • **CCR8**
			• T cell-engaging
			  • **CD3xCD20 bsAb**
			• Reverse immune-suppressive TME
				• Tumor specific cleavage
				• Targeted delivery & release

Nature chemical biology 16, 2-3 (2020); Nat Rev Drug Discov 20, 839-861 (2021); Eur J Immunol 51, 280-291 (2021); Nat Rev Drug Discov 18, 585-608 (2019); Nat Rev Cancer 21, 481-499 (2021).

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科学驱动创新

诺诚健华2022研发日

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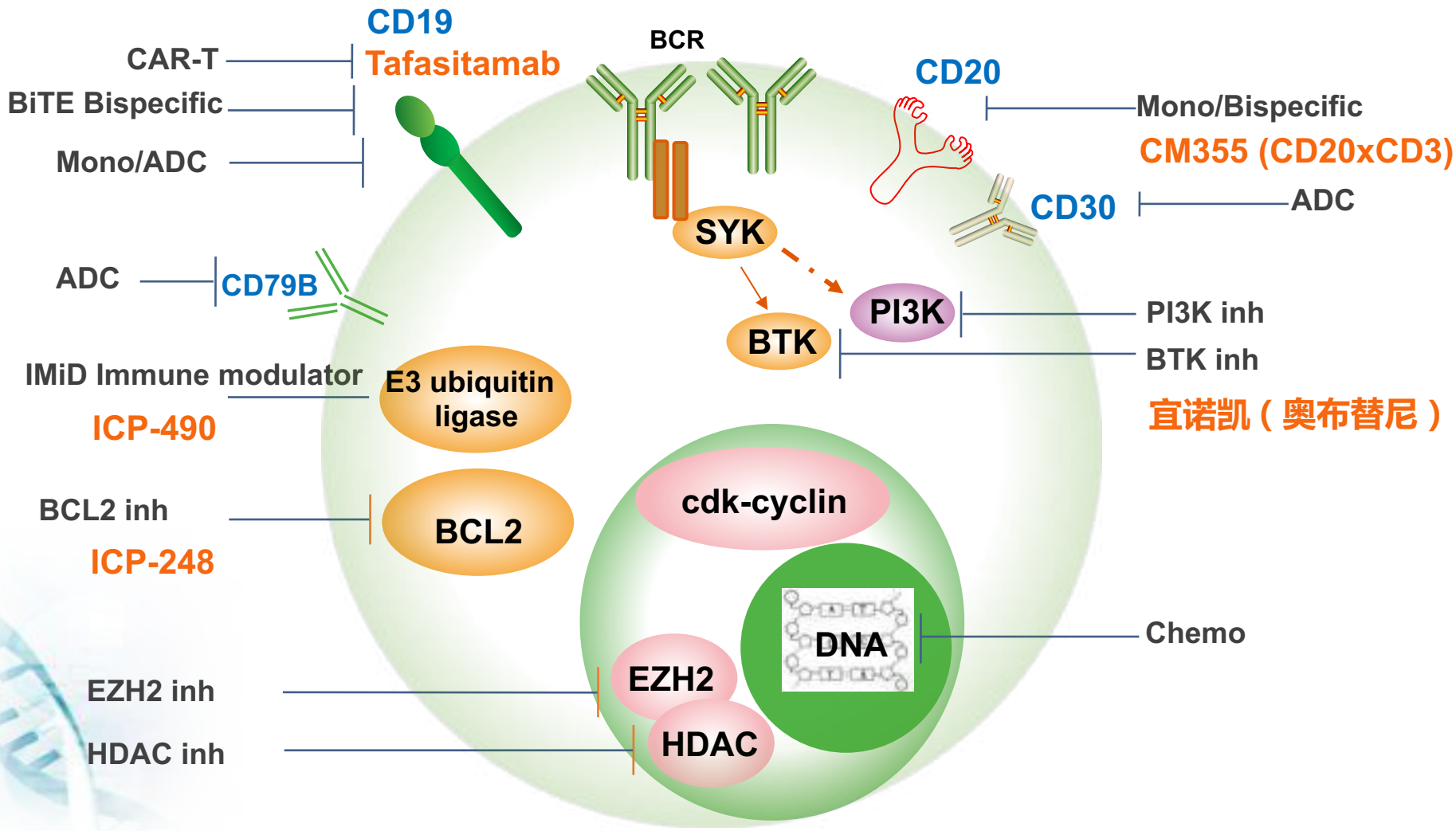
Liquid Tumor Progress

VP of Clinical Development and Regulatory Affairs

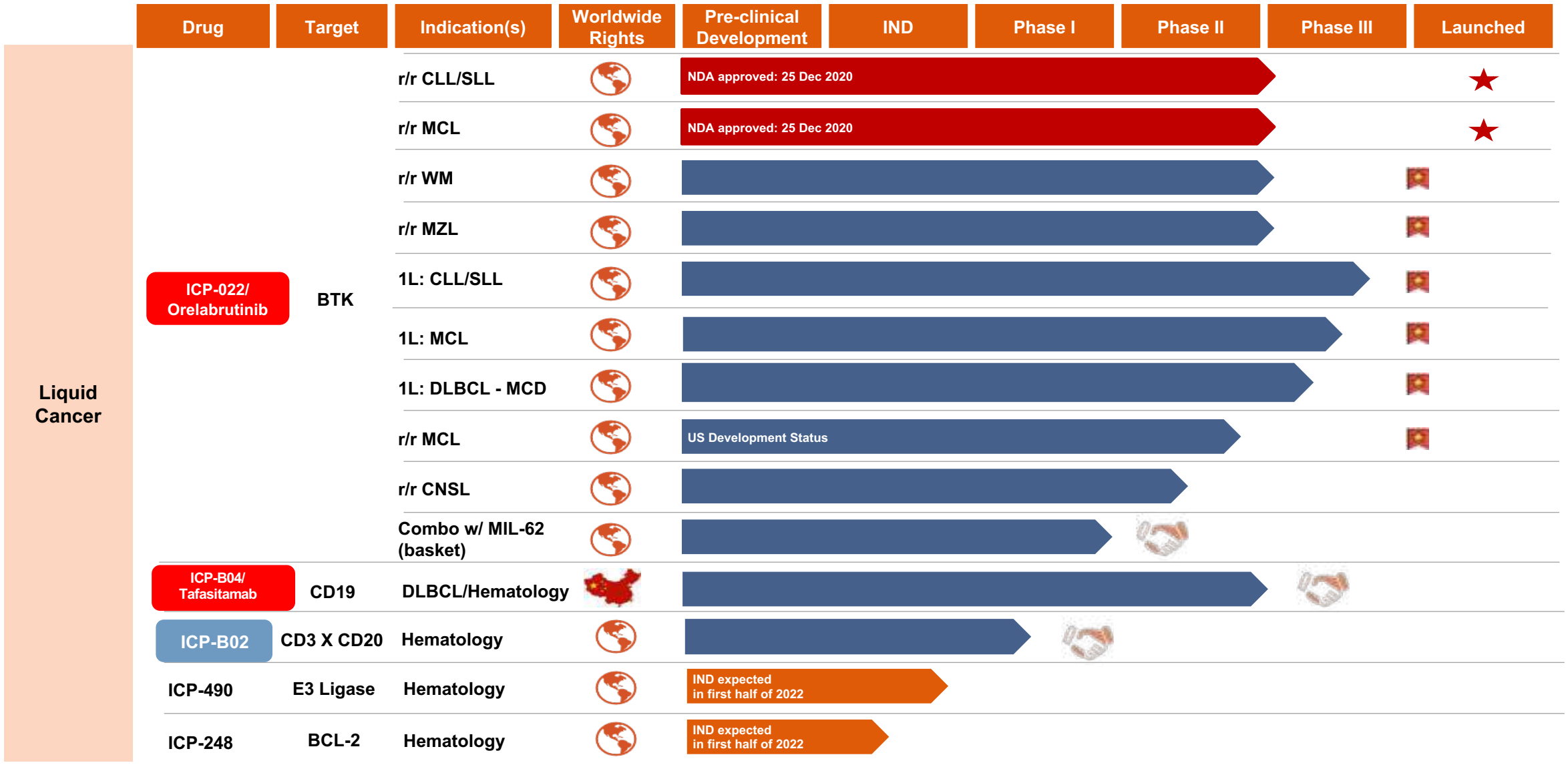
- *More than 20 years of drug discovery experience*
- *Former Director of Discovery Biology at BioDuro, a PPD company*
- *Former Principal Scientist at J&J*
- *Ph.D. from Johns Hopkins School of Medicine*

Dr. Renbin Zhao

New Mechanisms and Targets in Lymphoma



Research and & Development
Product Pipeline – Liquid Cancer



Orelabrutinib (ICP-022) : Potential Best-in-class BTKi for B-cell Malignancies

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CLL/SLL: higher CR rate improved patient survival

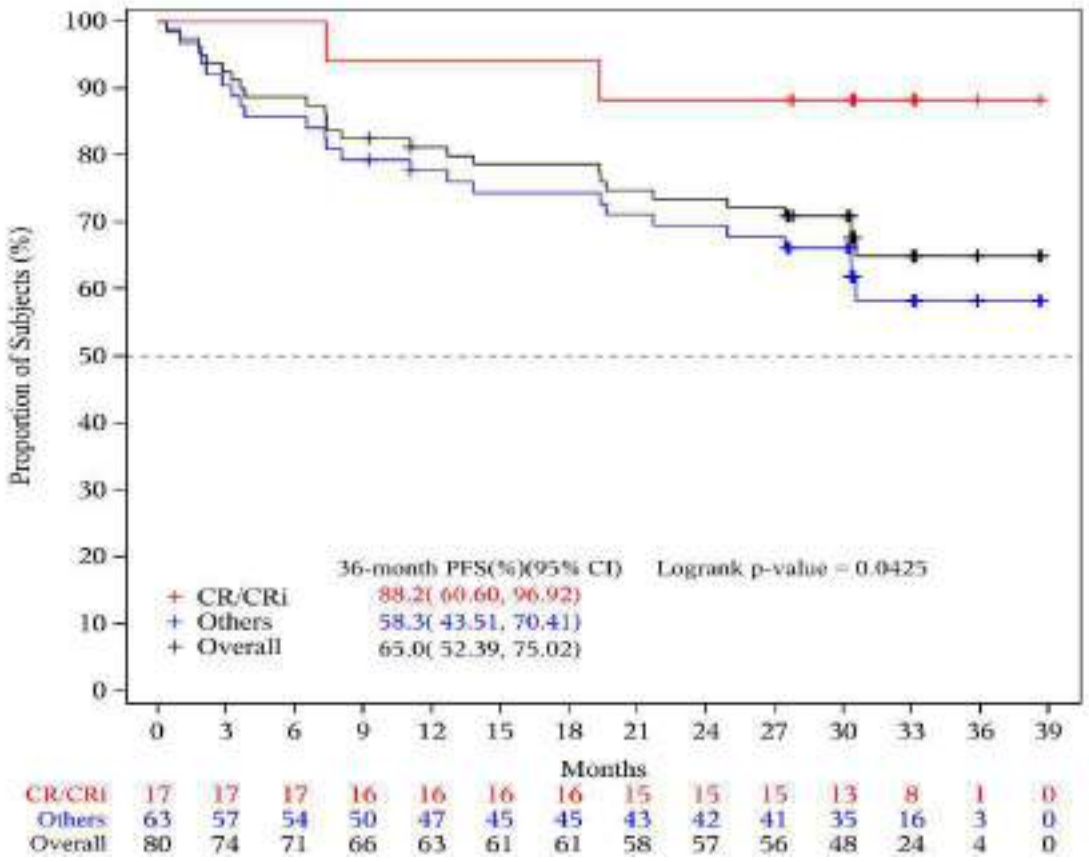
Best Overall Response by investigator

Response	Median follow-up time (N=80)		
	33.1 months	25.6 months	14.3 months
ORR	**93.8%**	**93.8%**	**90.0%**
CR+CRi	**26.3%**	**21.3%**	**8.8%**
PR/PR-L	56.3% / 11.3%	61.3% / 11.3%	65.0% / 16.3%
SD	1.3%	1.3%	5.0%
DCR	**95.0%**	**95.0%**	**95.0%**
PD	2.5%	2.5%	2.5%
UK/Other	1.3% / 1.3%	1.3% / 1.3%*	1.3% / 1.3%*

*#1 patient early withdrawal; * 1 patient early withdrawal and 1 patient can not be evaluated ; note : cutoff date 2021.8.10*

- **The updated CR/CRi rate had achieved 26.3% at 33.1 median follow-up months**

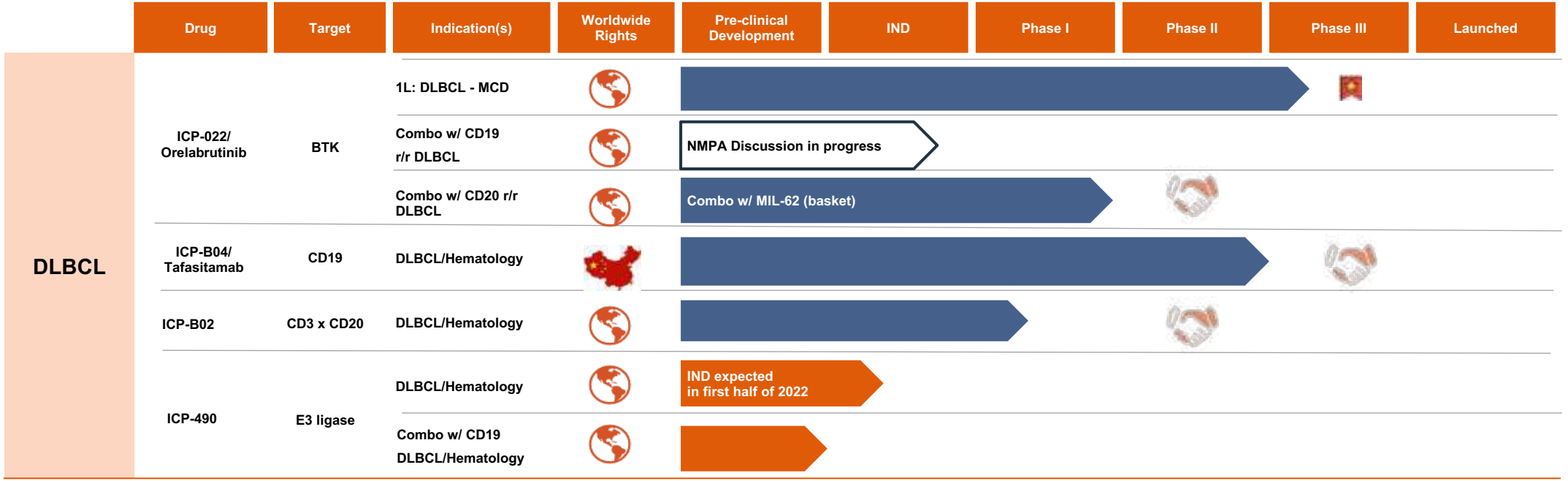
KM Curve (PFS) for CR/CRi、PR/PR-L/SD/PD subgroups(IRC) (N=80)



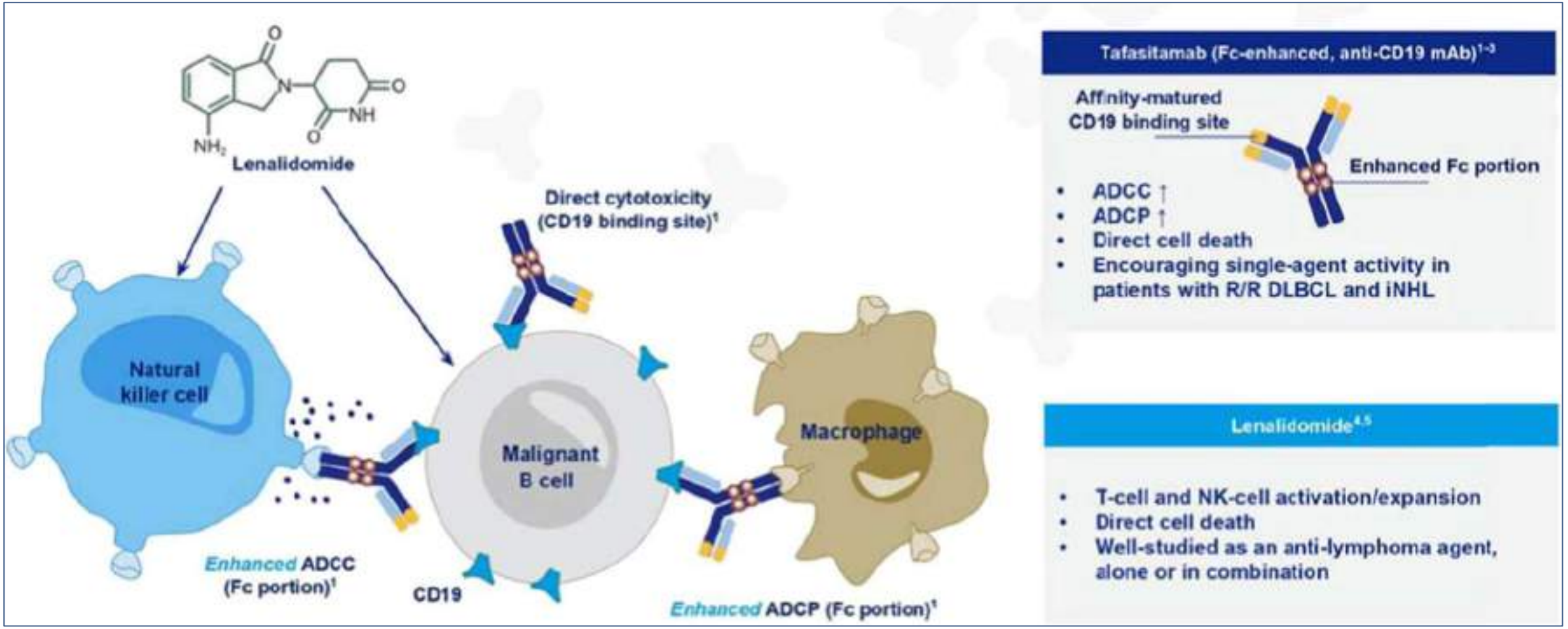
- **Patients who achieved CR/CRi showed improved survival**

DLBCL: Differentiated Approaches to 1L and r/r DLBCL

- MCD subtype DLBCL identified as a subgroup with potential high sensitivity to BTKis
- Tafasitamab/Lena combo demonstrated long term survival benefit for 2nd line DLBCL
- Orelabrutinib may be a superior BTKi when combined with other antibody drugs
- A comprehensive tool-kit including Orelabrutinib, Tafasitamab, ICP-B02 and ICP-490 offers us a unique position to tackle all stages of DLBCL patients with combination therapies



Tafasitamab – Mechanism of Action



Tafasitamab (Fc-enhanced, anti-CD19 mAb)[1-3]

- ADCC ↑
- ADCP ↑
- Direct cell death
- Encouraging single-agent activity in patients with R/R DLBCL and iNHL

Lenalidomide[4,5]

- T-cell and NK-cell activation/expansion
- Direct cell death
- Well-studied as an anti-lymphoma agent, alone or in combination

Adapted from Cheson et al. Blood Cancer Journal, 2021;11:68

Long term follow-up (35m) for L-MIND study

Table 2. Efficacy outcomes in the primary and follow-up analyses.*

	Tafasitamab plus lenalidomide (N=80)[1]	
	Primary analysis (data cut-off: Nov 30, 2018)[3]	Follow-up analysis (data cut-off: Oct 30, 2020)
Best objective response, n (%)		
Complete response	34 (42.5)	32 (40.0)
Partial response	14 (17.5)	14 (17.5)
Stable disease	11 (13.8)	13 (16.3)
Progressive disease	13 (16.3)	13 (16.3)
Not evaluable*	8 (10.0)	8 (10.0)
ORR (CR + PR), n (%) [95% CI][†]	48 (60.0) [48.4-70.9]	46 (57.5) [45.9-68.5]
Median DoR (IRC), months (95% CI)	21.7 (21.7-NR)	43.9 (26.1-NR)
Median PFS (IRC), months (95% CI)	12.1 (5.7-NR)	11.6 (6.3-45.7)
Median OS, months (95% CI)	NR (18.3-NR)	33.5 (18.3-NR)

*Non-evaluable patients had no valid post-baseline response assessments. [†]Using the two-sided 95% Clopper-Pearson exact method based on a binomial distribution. [‡]One patient received tafasitamab only. ORR: objective response rate; CR: complete response; PR: partial response; 95% CI: 95% confidence interval; DoR: duration of response; IRC: independent review committee; PFS: progression-free survival; OS: overall survival; NR: not reached.

Comparison with other approved therapy for r/r DLBCL

Name	Loncastuximab tesirine[1]	Polatuzumab vedotin +BR vs BR[2]
Target	CD19 ADC	CD79b ADC
CR (%)	24.1	40 vs 18
ORR (%)	48.3	45 vs 18
mDOR (m)	10.3	12.6 vs 7.7
mPFS	4.9	9.5 vs 3.7
mOS (m)	9.9	12.4 vs 4.7

*Duell et al._*Haematologica* 2021;106(9):2417-2426;

1.Paolo F Caimi et al. Lancet Oncol 2021; 22: 790–800

2. Laurie H. Sehn et al. Journal of Clinical Oncology Volume 38, Issue 2 155

Clinical Development of Tafa/LEN in Greater China

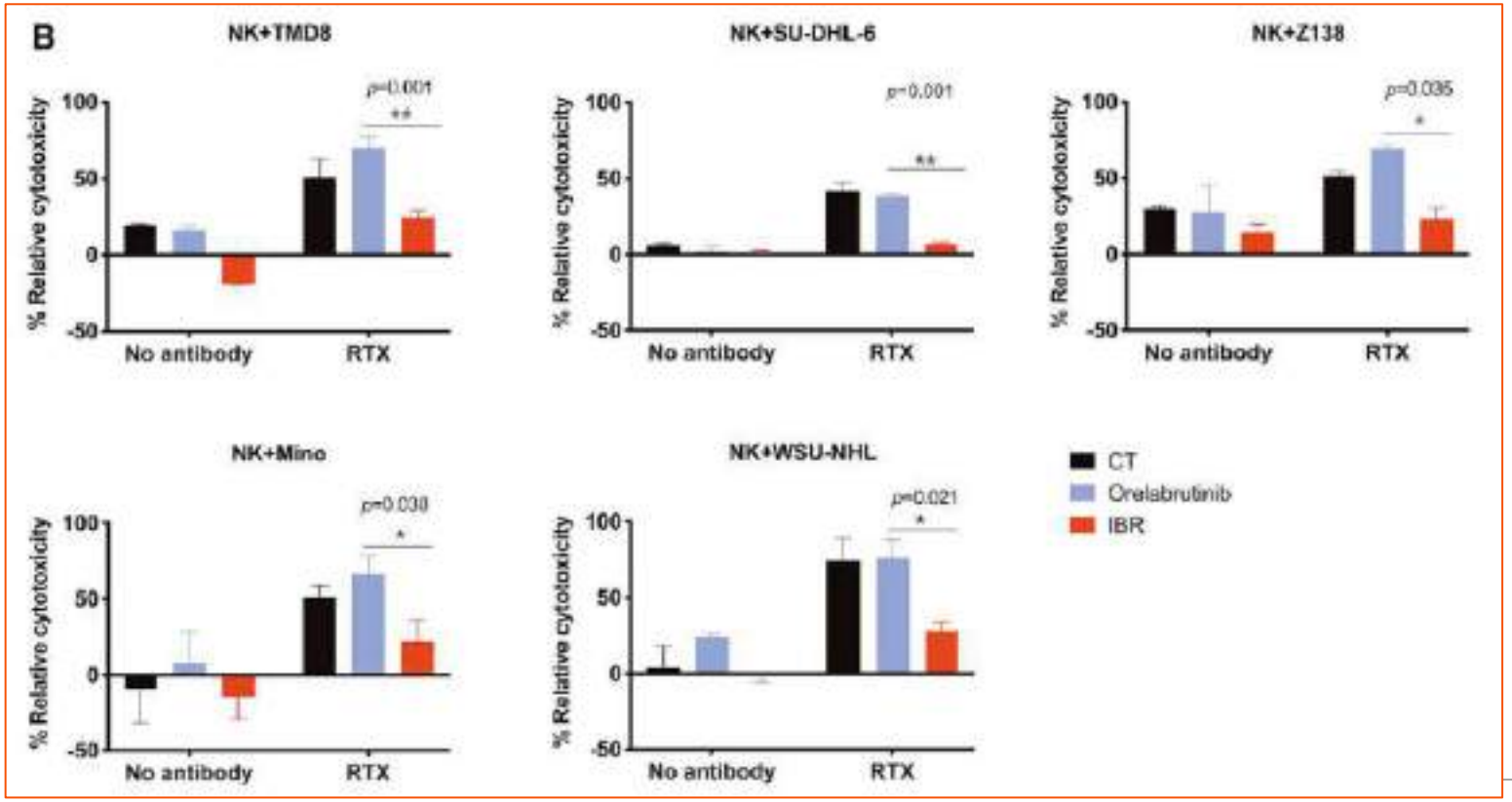
- **Hainan pilot zone: Approved for early access, launch in Q2 of 2022**
- **Macau:**
  - BLA submission in Q3 of 2022
- **HongKong:**
  - Tafa/LEN BLA submission by end of Q2
- **Great Bay area:**
  - Early access program after HK or MC approval
- **Taiwan:**
  - BSE submitted in March, BLA will be submitted by end of 2022 if BSE waived.
- **Mainland China:**
  - IND for Tafa/Len for r/rDLBCL accepted by CDE in March, FPI is planned for Q3 of 2022
  - IND for Tafa/Ore will be submitted by end of Q2 of 2022

Orelabrutinib (ICP-022) : Likely the Best BTK Inhibitor as Antibody Combo Partner

Addition of BTK inhibitor orelabrutinib to rituximab improved anti-tumor effects in B cell lymphoma

Hui Yu,[1] Xing Wang,[1] Jiao Li,[1] Yingying Ye,[1] Dedao Wang,[1] Wei Fang,[1] Lan Mi,[1] Ning Ding,[1] Xiaogan Wang,[1] Yuqin Song,[1] and Jun Zhu[1]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China

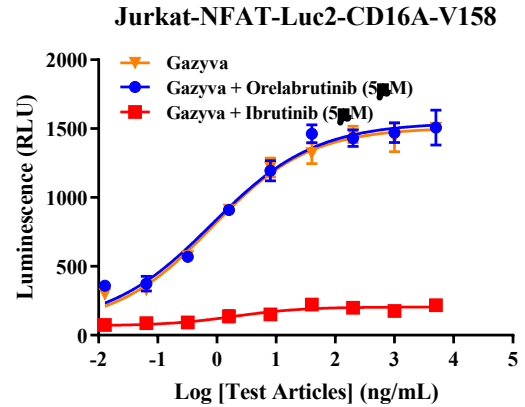


- Orelabrutinib and Ruituximab combo demonstrates improved anti-tumor effects in B-lymphomas
- ADCC and ADCP functions of CD20 antibodies are well retained by Orelabrutinib, but significantly compromised by Ibrutinib

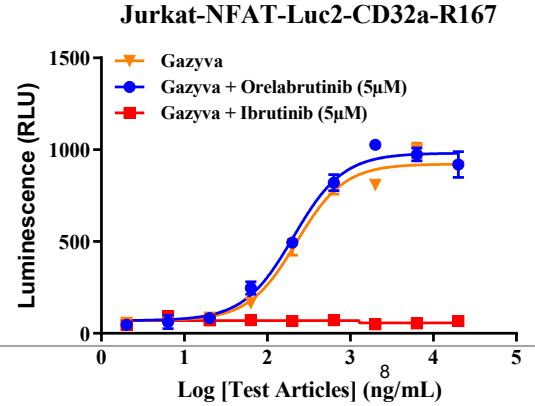
BTKi + Gazyva (Obinutuzumab)

(Reporter assays: TMD8 as target cell)

ADCC



ADCP



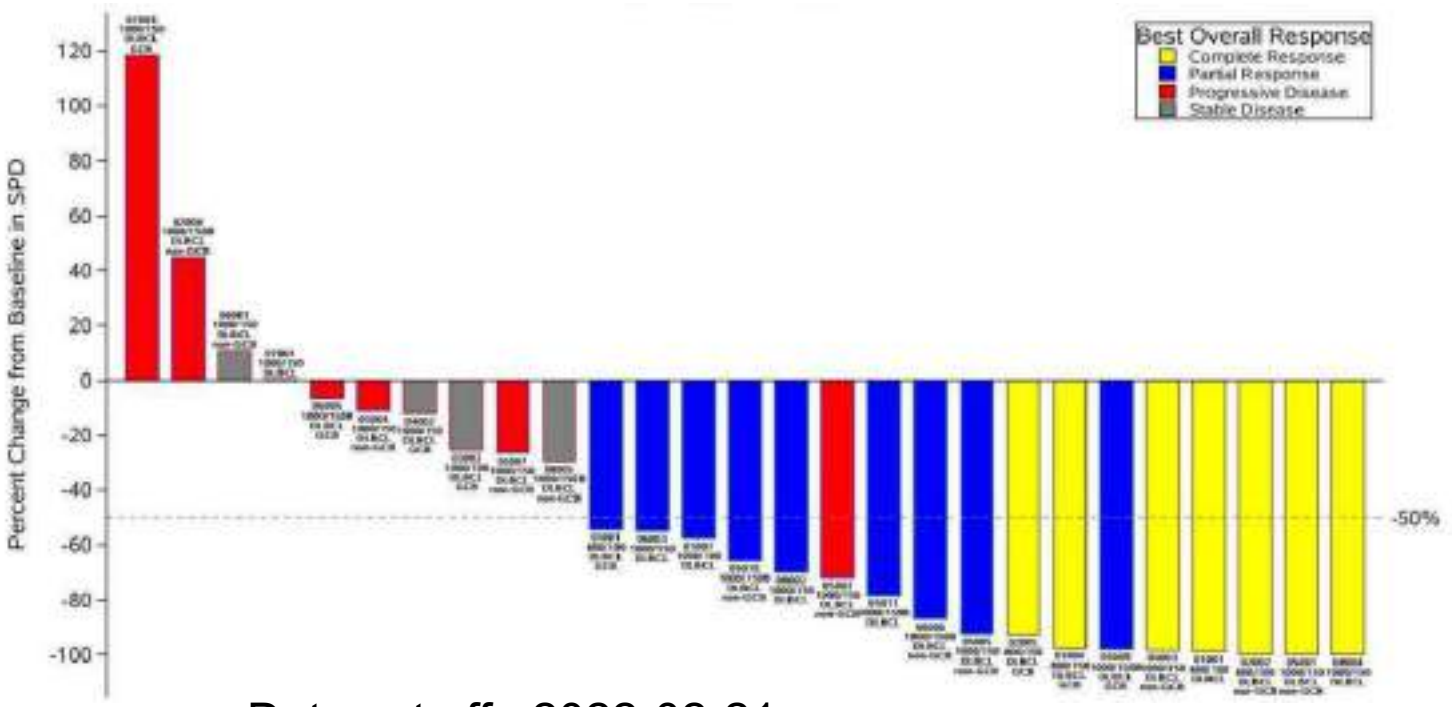
Preliminary Efficacy Data for Orelabrutinib/CD20 Type II Ab for r/r DLBCL

- Mil62 is a type II CD20 antibody with Fc modification to enhance ADCC activity
- Orelabrutinib combo with Mil62 showed promising result in treatment of r/r DLBCL patients

Best response

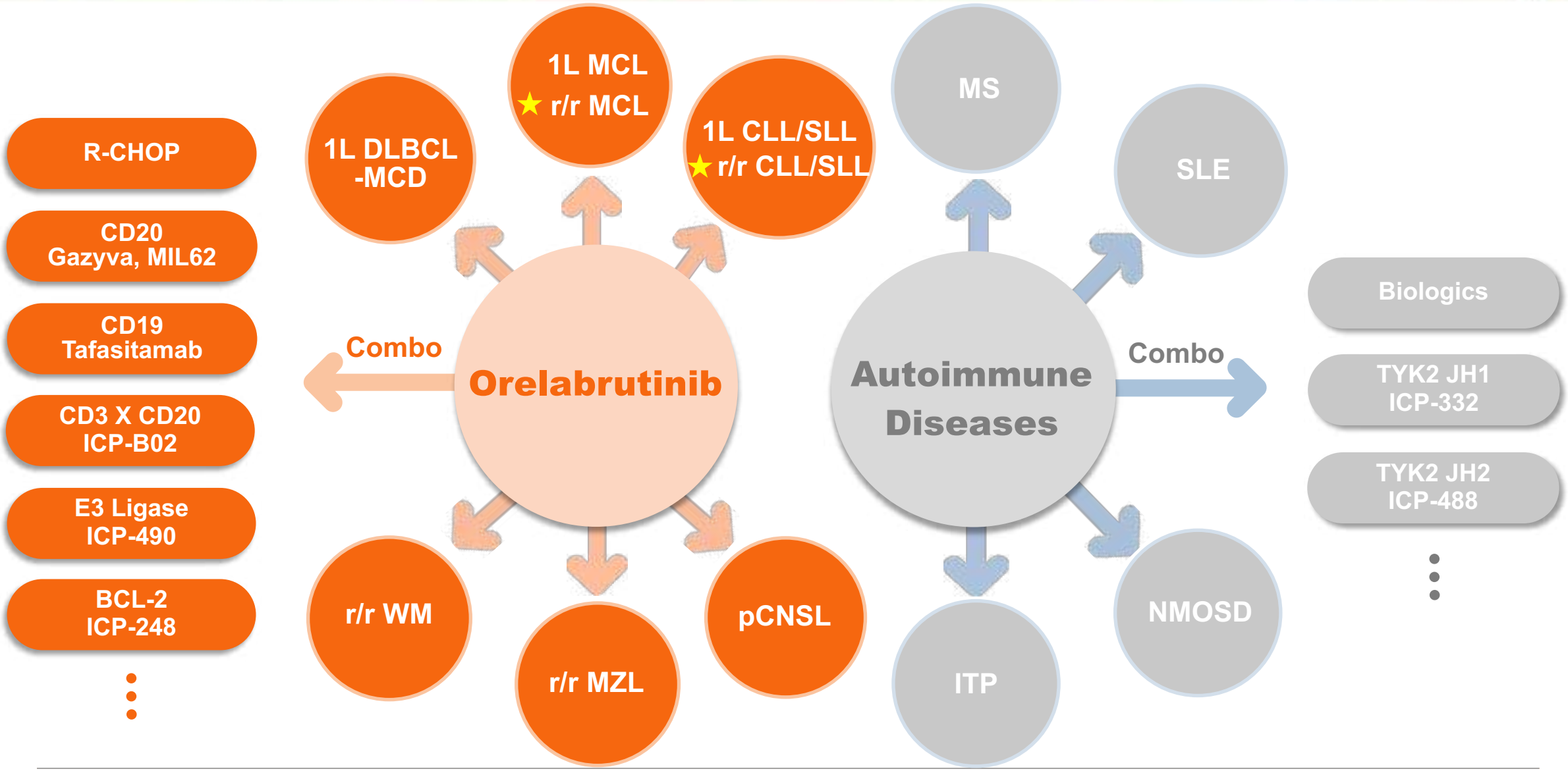
	≥3L N=19	All DLBCL (N=28)
ORR	52.6%	57.1%
PR	31.6%	32.1%
CR	21.1%	25.0%
DCR	73.7%	75.0%
3mDOR	71.4% 95%CI：25.8, 92.0	81.8 % 95%CI：44.7, 95.1
mPFS	4.5m 95%CI:2.3,NR	5.6m 95%CI:3.8,NR

Waterfall plot: Change of SPD compared to baseline



Data cut off: 2022-02-21

Indications Covered by Orelabrutinib



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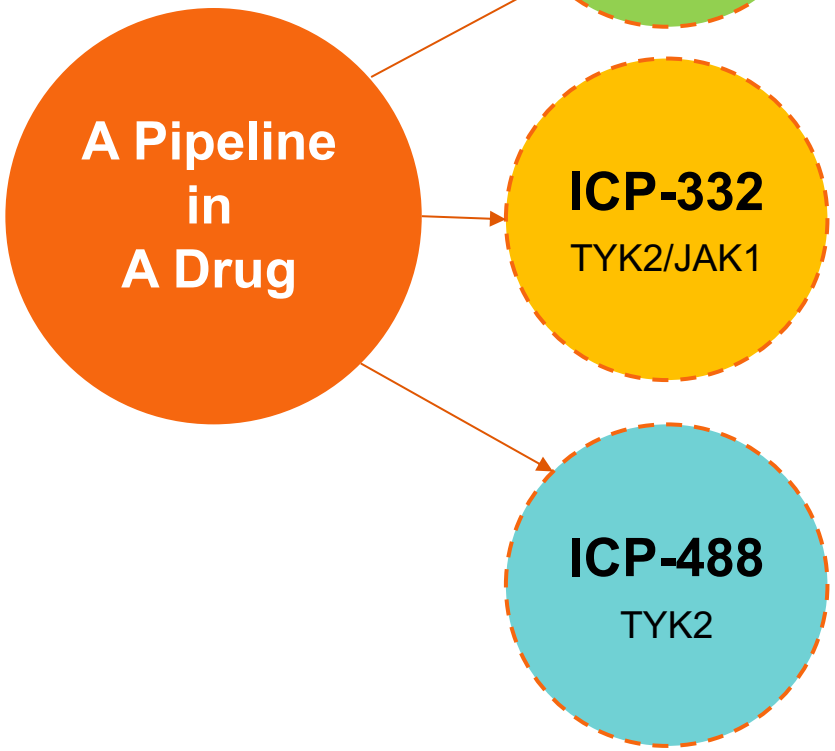
Strategy for Autoimmune Pipeline Building

VP of Medical Affairs

- *More than 15 years of new drug clincial development experience*
- *Former Non-oncology Medical Head of Hansoh*
- *Former Asia Medical Direcotr of Takeda (Immuology, Neuroscience and CVM)*
- *Ph.D. of Nephrology*
- *Master of Surgery*
- *Master of Science in Pharmaceutical Medicine*

Dr. Carrie Zhou

Overall Strategy for Autoimmune Pipeline Building



2021 Highlight

- **SLE**：Finished ph2 study
- **ITP**：Ph2 IND approval; positive pre-clinical study
- **MS**：EU/China Ph2 IND approval; recruitment ongoing

- **HV**：IND approval
- **SAD**：Finished
- **Food Effects**：Finished

- **Ph1:** IND submission

2022-2023 Highlight

- **SLE**：Promising ph2 results; start next stage study
- **ITP**：PoC + dose finding
- **MS:** Finish ph2 and initiate global ph3
- **NMOSD**：IND approval and ph2
- Explore **more indications**

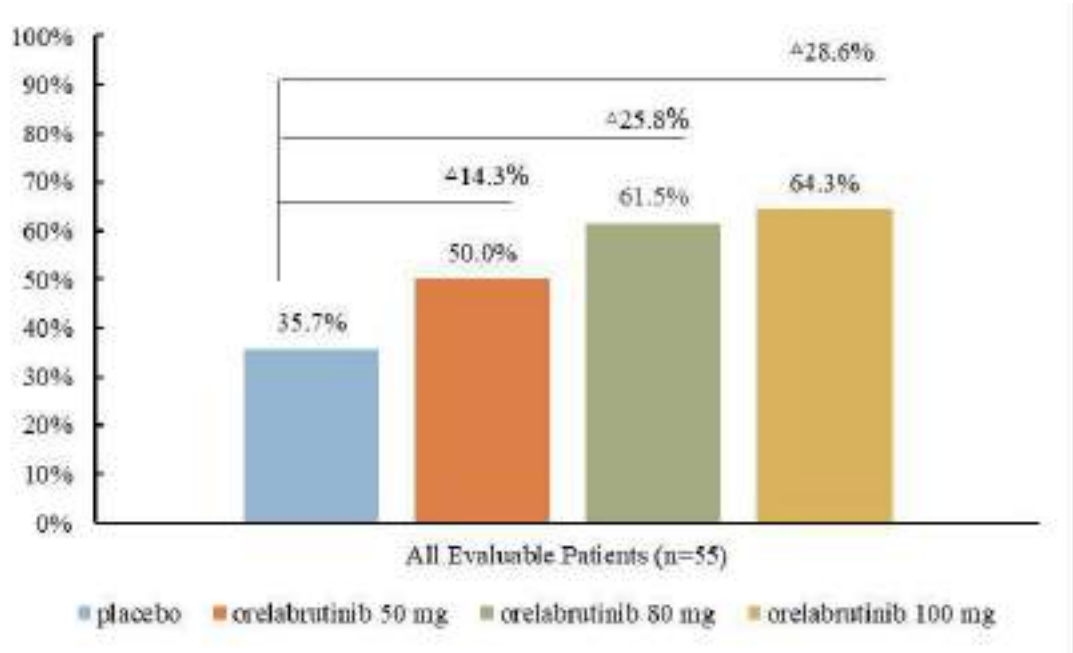
- **MAD**： Finished
- **Phase 2**： Explore two indications to deeply understand mechanism and value of drug

- **Ph1:** IND approval
- **SAD/MAD/PoC**：Innovative clinical plan and study initiation

Orelabrutinib (ICP-022): Promising SLE Study Results

- Randomized, double-blind, placebo-controlled, dose-finding, phase Ib/IIa study
- Targeted patients with mild to moderate SLE who received standard of care (SoC) therapy
- Treatment time：12 weeks

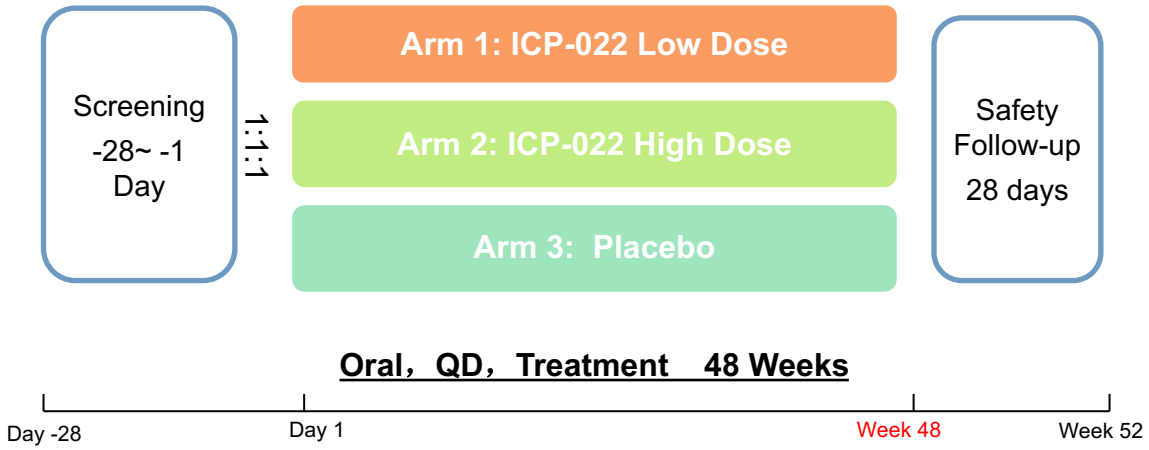
- ✓ **The Phase II trial evaluated the safety and efficacy of Orelabrutinib in patients with mild to moderate SLE**
- ✓ **Orelabrutinib was safe and well tolerated at all doses**
- ✓ **SLE Responder Index ("SRI")-4 response rates increased in a dose dependent manner**
- ✓ **Trends of reduction in level of proteinuria and improvement of immunologic bio-markers.**



Orelabrutinib (ICP-022) Development Plan for SLE

Next Step Study:

- **Study design: Randomized, Double-Blind, Placebo controlled**
- **Treatment: ICP-022 OR Placebo + SoC**
- **Primary Endpoint: SRI-4**
- **Leading Site: Beijing Renmin Hospital**
- **Leading PI: Prof. Zhanguo Li**



More regimen:

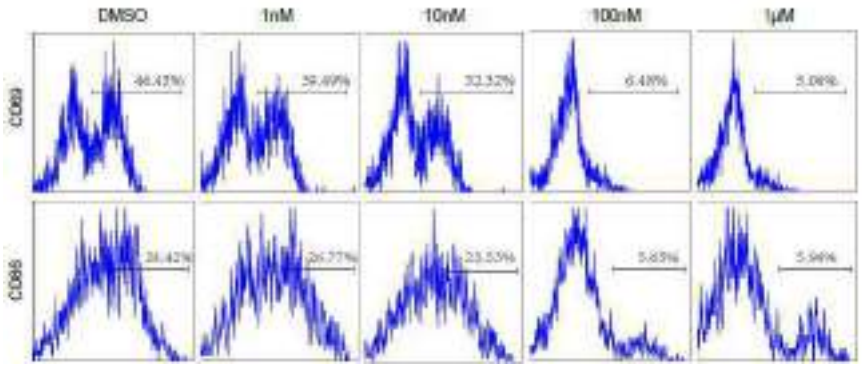
- Combination with TYK2 inhibitor
- Combination with Other internal or external Biologics

Indication Expansion:

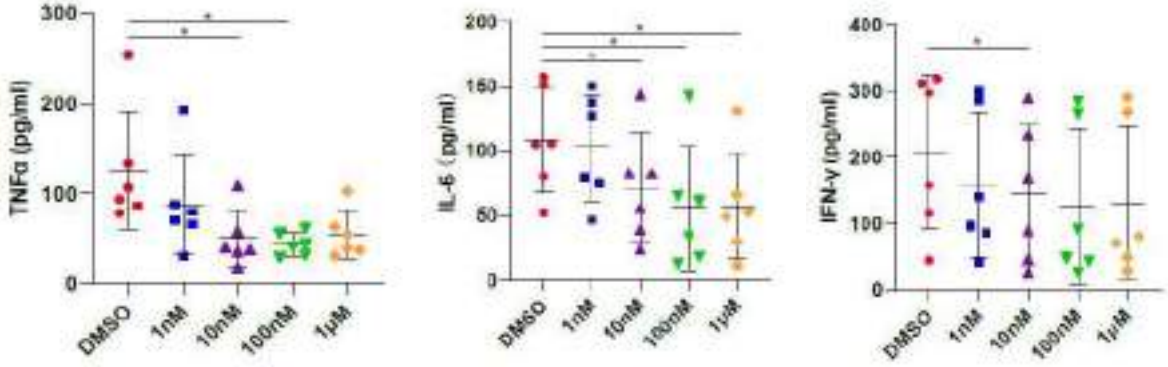
- Lupus Nephritis
- Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)

Orelabrutinib (ICP-022): Pre-clinical Study Showed MoA and Efficacy in Immune Thrombocytopenia (ITP)

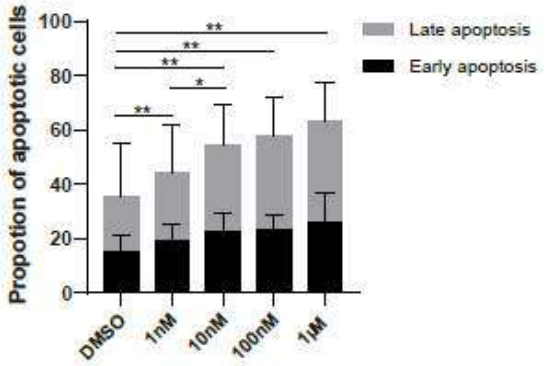
Orelabrutinib inhibited activation markers downstream of BCR pathway and co-stimulation molecules on B cells

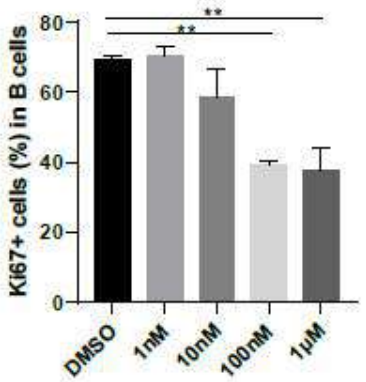


Orelabrutinib reduced the secretion of pro-inflammatory cytokines by B cells

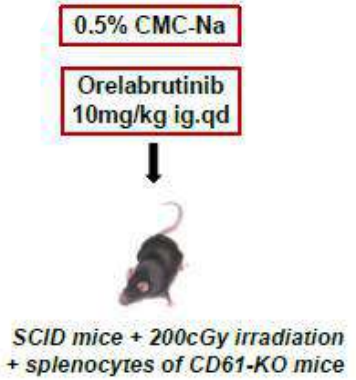


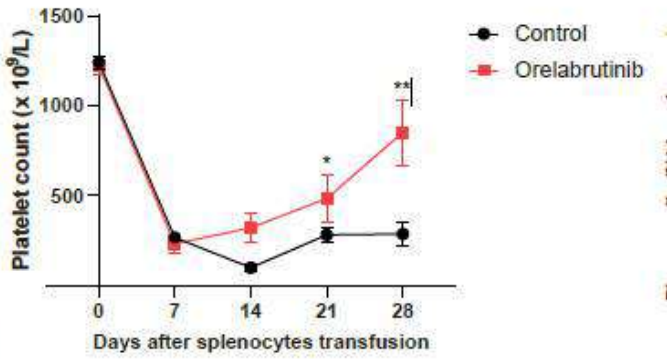
Orelabrutinib promoted B cell apoptosis and inhibited B cell proliferation





Orelabrutinib ameliorated thrombocytopenia in active ITP murine models

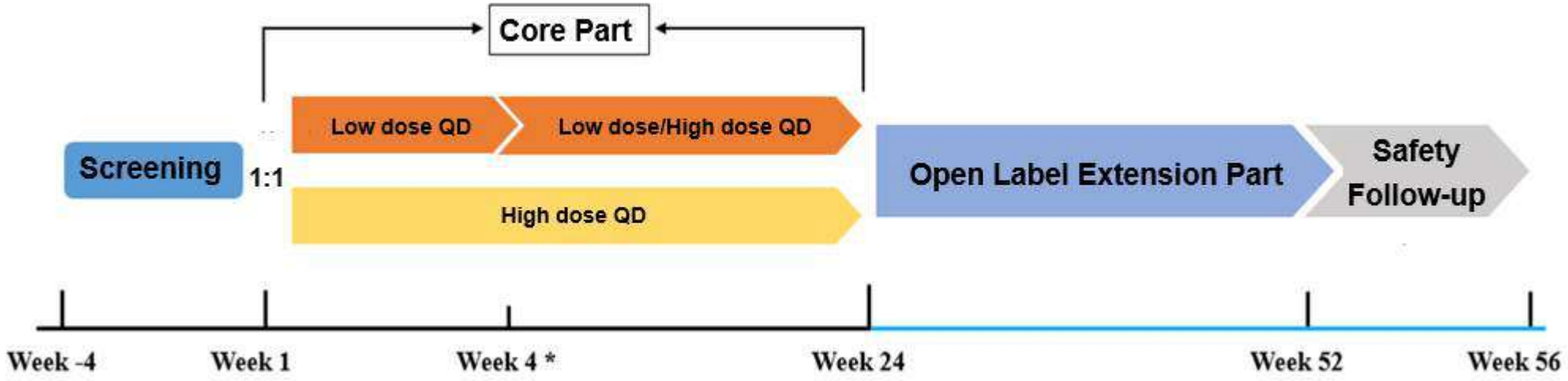




Source： ASH 2021; Yu T, Wang L, Ni X, et al. Blood (2021) 138 (Supplement 1): 3172.

Ph2 Study of Orelabrutinib in Immune Thrombocytopenia (ITP)

- **Study design**: Randomized, open-label, multicenter, phase IIa/IIb seamless adaptive trial design
- **Leading Site**: Qi Lu Hospital
- **Sites Number:** 9 sites
- **Leading PI**: Prof. Min Hou
- **FPI:** 21Feb2022



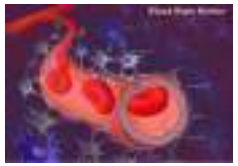
*Low dose may increase to high dose depending on safety and efficacy

Orelabrutinib (ICP-022): Steady Steps in the Development of Neurology

Orelabrutinib
Brilliant Features for Neurology Indication

Dual role in B cell and Myeloid cells

Penetration of central nervous system

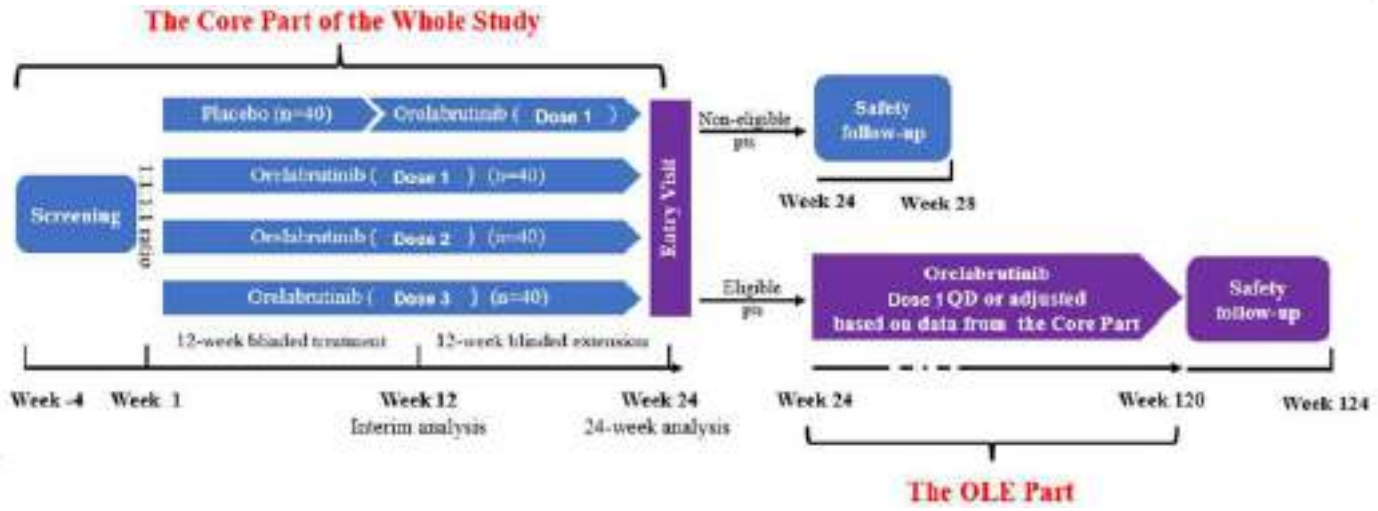


1st wave

2nd wave
TBD

- Multiple sclerosis
- NMOSD
- Myasthenia gravis
- NPSLE

ICP-CL-00112 Study: CN IND Approval



ICP-CL-00118 Study: NMOSD IND Approval

国家药品监督管理局

药物临床试验批准通知书

受理号：CXHL2101710　　通知书编号：2022LP00324

北京诺诚健华医药科技有限公司：

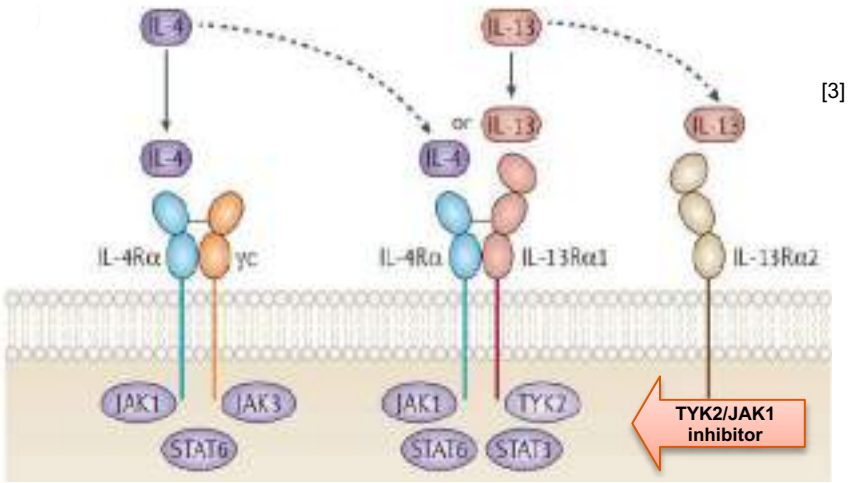
根据《中华人民共和国药品管理法》及有关规定，经审查，2021 年 12 月 2 日受理的奥布替尼片符合药品注册的有关要求，同意开展临床试验。

申请的适应症：拟用于治疗视神经脊髓炎谱系疾病(NMOSD)。

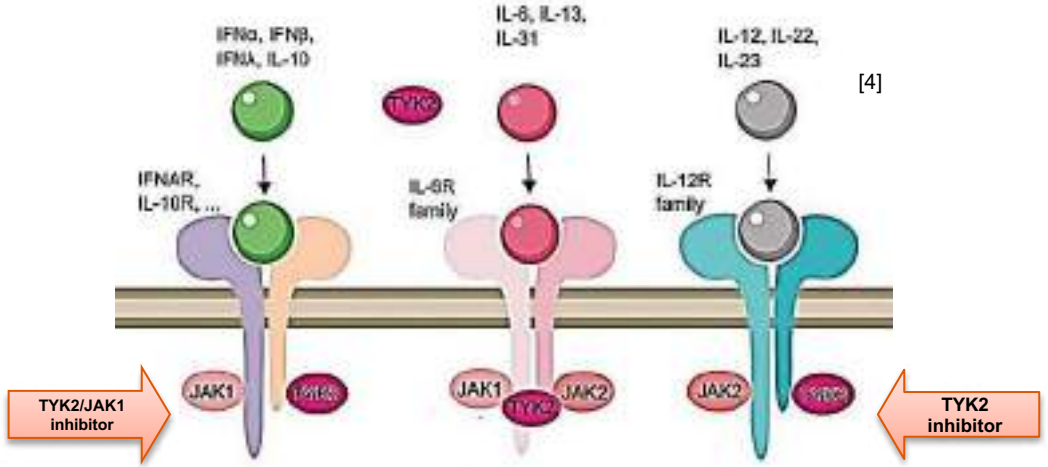
Picture source：BioVIP and Presentation at the 49th annual meeting of the European Society for Dermatological Research (ESDR), September 18-21, 2019 in Bordeaux, France: # 011

ICP-332 : Understanding the Role in the Pathways and Disease

Type	Drug	IC50(nM)				TYK2 selectivity versus JAK2 (fold)	JAK1 selectivity versus JAK2 (fold)
		JAK1	JAK2	JAK3	TYK2 (JH1)		
TYK2 Selective Inhibitor	PF-06700841[1]	17	77	6494	23	3.35	4.53
	PF-06826647[2]	383	74	>10000	17	4.35	0.19
TYK2 Selective Inhibitor	**ICP-332**	**19**	**191**	**930**	**0.49**	**389.80**	**10.05**



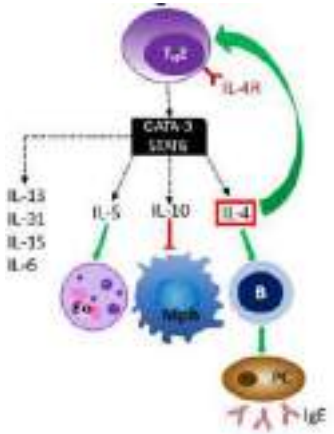
[3]



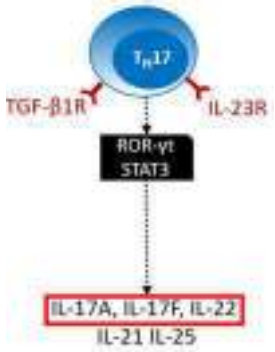
[4]

1. J Med Chem. 2018 Oct 11;61(19):8597-8612
2. J Med Chem. 2020 Nov 25;63(22):13561-13577
3. Adapted from Gandhi, N., et al. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov 15, 35–50 (2016).
4. Adapted from Dendrou, C. A., et al。 Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity. Sci Transl Med 8, 363ra149.

ICP-332: PoC of Atopic Dermatitis and Psoriasis Guide Scientific Direction

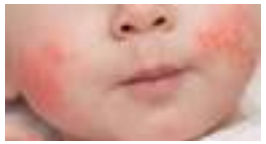


Type 2 immunity [1]



Type 3 immunity [1]

PoC study



Atopic Dermatitis
（Source: cn-healthcare）

Psoriasis
（Source: cn-healthcare）

Indication Expansion

Type 2 inflammation affecting the skin[1]

- Asthma
- Chronic Sinusitis
- Type 2 COPD
- Allergic Fungal Rhinosinusitis
- Eosinophilic Esophagitis

Type 2 inflammation in Respiratory Disease

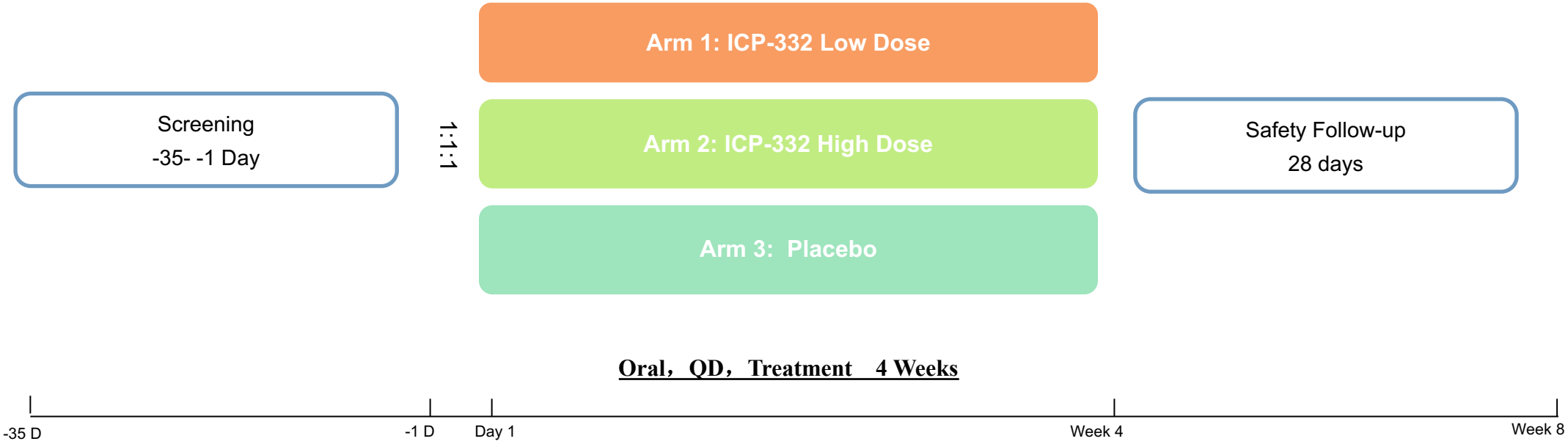
- Psoriatic arthritis
- Crohn's disease
- Systemic Lupus Erythematosus
- Ulcerative colitis
- Cutaneous Lupus
- Lupus nephritis

synergy

1. Belmesk L, Muntyanu A, Cantin E, AlHalees Z, Jack CS, Le M, Sasseville D, Iannattone L, Ben-Shoshan M, Litvinov IV, Netchiporouk E. **Prominent Role of Type 2 Immunity in Skin Diseases: Beyond Atopic Dermatitis**. J Cutan Med Surg. 2022 Jan-Feb;26(1):33-49. doi: 10.1177/12034754211027858. Epub 2021 Jul 14

Phase 2 Atopic Dermatitis Study Design

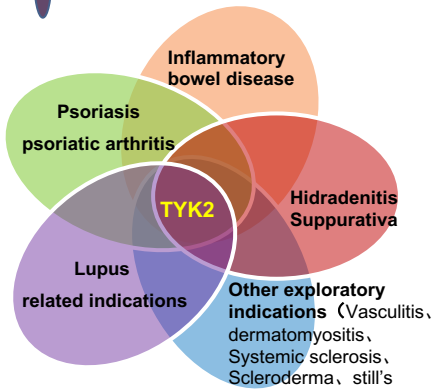
- **Study design**：Randomized, Double-Blind, Placebo controlled
- **Target Population**：Patients with moderate to severe atopic dermatitis
- **Leading Site**：Hua Shan Hospital
- **Leading PI**： Prof. JinHua Xu



ICP-488: Rapid Maximization of the Clinical Value of Potent TYK2 Inhibition

Potential to Produce Blockbuster Drugs for Multi-Indications

- Contributing to the pathogenesis of various autoimmune diseases with huge market potential
  - 8 indications under development with same class drug
  - More indications to be explored
- Developing a TYK2 inhibitor while minimizing safety issues presents a plausible strategy for non-oncology indications



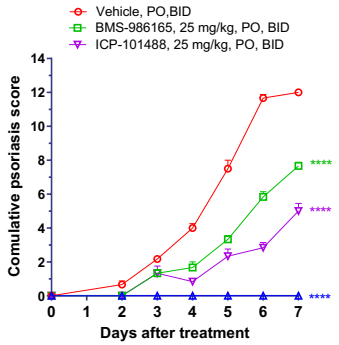
Highly Selective and Potent TYK2 Inhibitor

Highly selective TYK2 inhibitor	ICP-488 IC50 (nM)
JAK1	>10000
JAK2	>10000
JAK3	>10000
TYK2 JH1	>10000
TYK2 JH2	5.8 ± 2.0

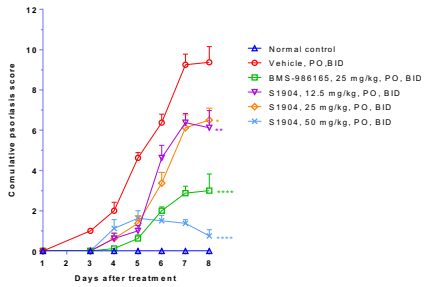
Pre-clinical Results

KINOMEscan Profiling

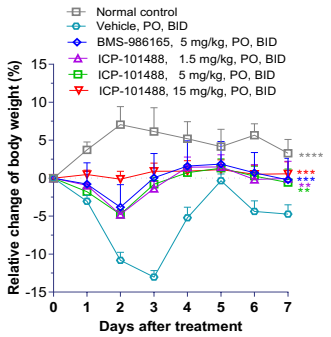
Imiquimod-induced Psoriasis Model



IL-23 induced Psoriasis-like acanthosis



Anti-CD40-induced IBD Colitis Model



Autoimmune Pipeline and Disease Area Expansion Strategy

ICP-490

Protein Degradation

ICP-332
ICP-488

Lymphocyte
T cell

ICP-022

Lymphocyte
B cell

Nephrology

Gastroenterology

Dermatology

Hematology

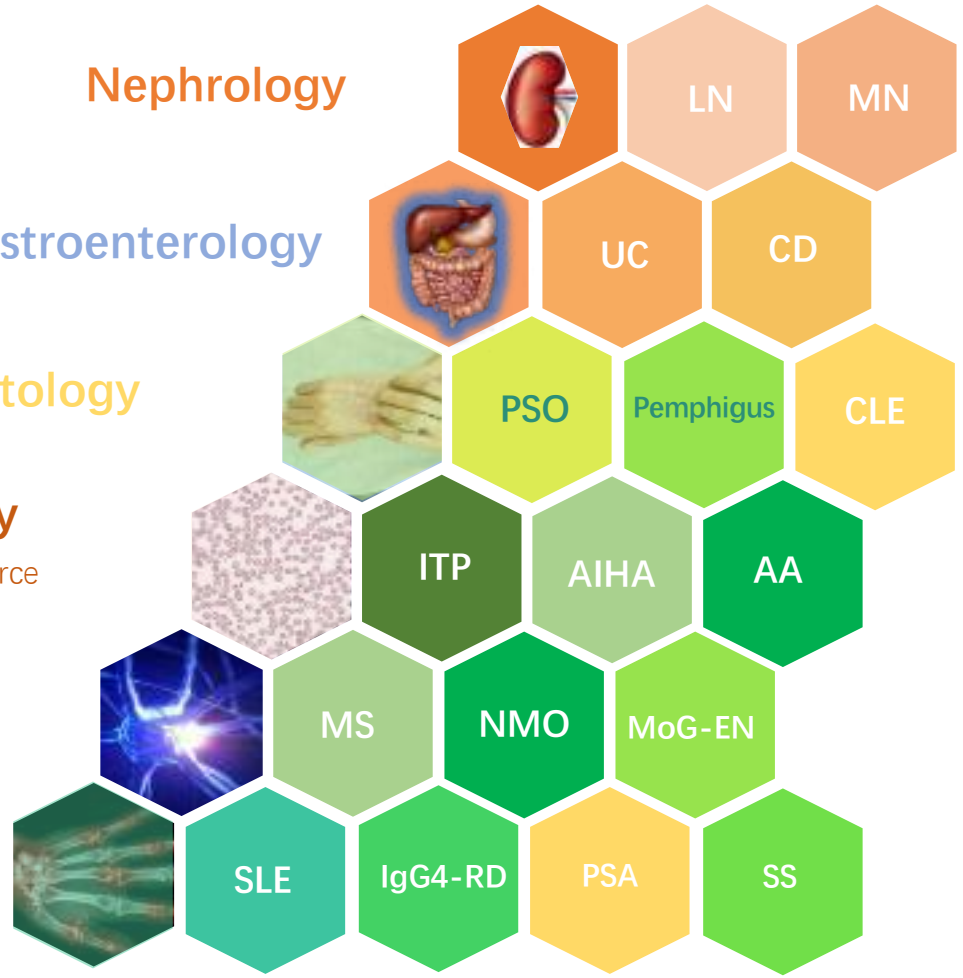
✓ Integrated Resource

Neurology

✓ Central and peripheral dual mechanism

Rheumatology

✓ Multiple compounds with multiple mechanism



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诺诚健华

科学驱动创新

诺诚健华2022研发日

INNOCARE
诺诚健华

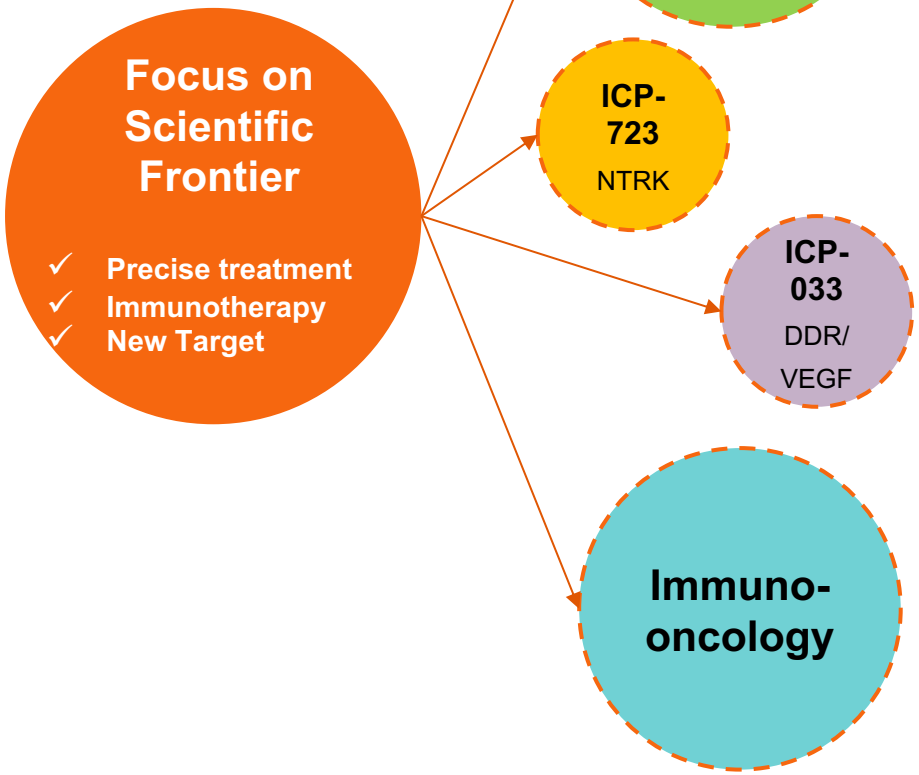
Strategy for Solid Tumor Pipeline Building

VP of Medical Affairs

- *More than 15 years of new drug clincial development experience*
- *Former Non-oncology Medical Head of Hansoh*
- *Former Asia Medical Direcotr of Takeda (Immuology, Neuroscience and CVM)*
- *Ph.D. of Nephrology*
- *Master of Surgery*
- *Master of Science in Pharmaceutical Medicine*

Dr. Carrie Zhou

Overall Strategies for Solid Tumor Pipeline Building



2021 Highlight

- **Phase 1:** Finished dose-escalation, no DLT observed and RP2D is 20mg
- **Phase 1:** Anti-tumor activity demonstrated in head & neck cancer
- **Phase 2**: Start 20mg in CCA pts
- **Phase 2:** Start 20mg in UC pts

- **Phase 1**: Progressing dose-escalation

- **Phase 1**: IND approval

- **ICP-00189 (SHP2)**: IND 2021

2022 Highlight

- **Phase 2:** preliminary efficacy in cholangiocarcinoma patients with 62.5% ORR and 100% DCR
- **Phase 2**: Start head & neck cancer dose expansion and registration study, and Solid tumor basket trial
- **Phase 2**: Start CCA registration study

- **Phase 2**: Find RP2D and start a NTRK mutation-based registrational trial

- **Phase 1**: Progressing dose-escalation and find RP2D

Preclinical Programs

- **ICP-B05 (CCR8):** IND expected in 2022
- **ICP-B03 (Pro-IL-15):** IND expected in 2023
- **Anti-TAA x Pro-IL-2:** IND expected in 2023
- **T-reg targeting antibodies**: IND expected in 2023
- **First-in-class MDSC, M2 Mφ & ECM targeting agents:** TBD

科学驱动创新 患者所需为本

Science Drives Innovation for the Benefit of Patients