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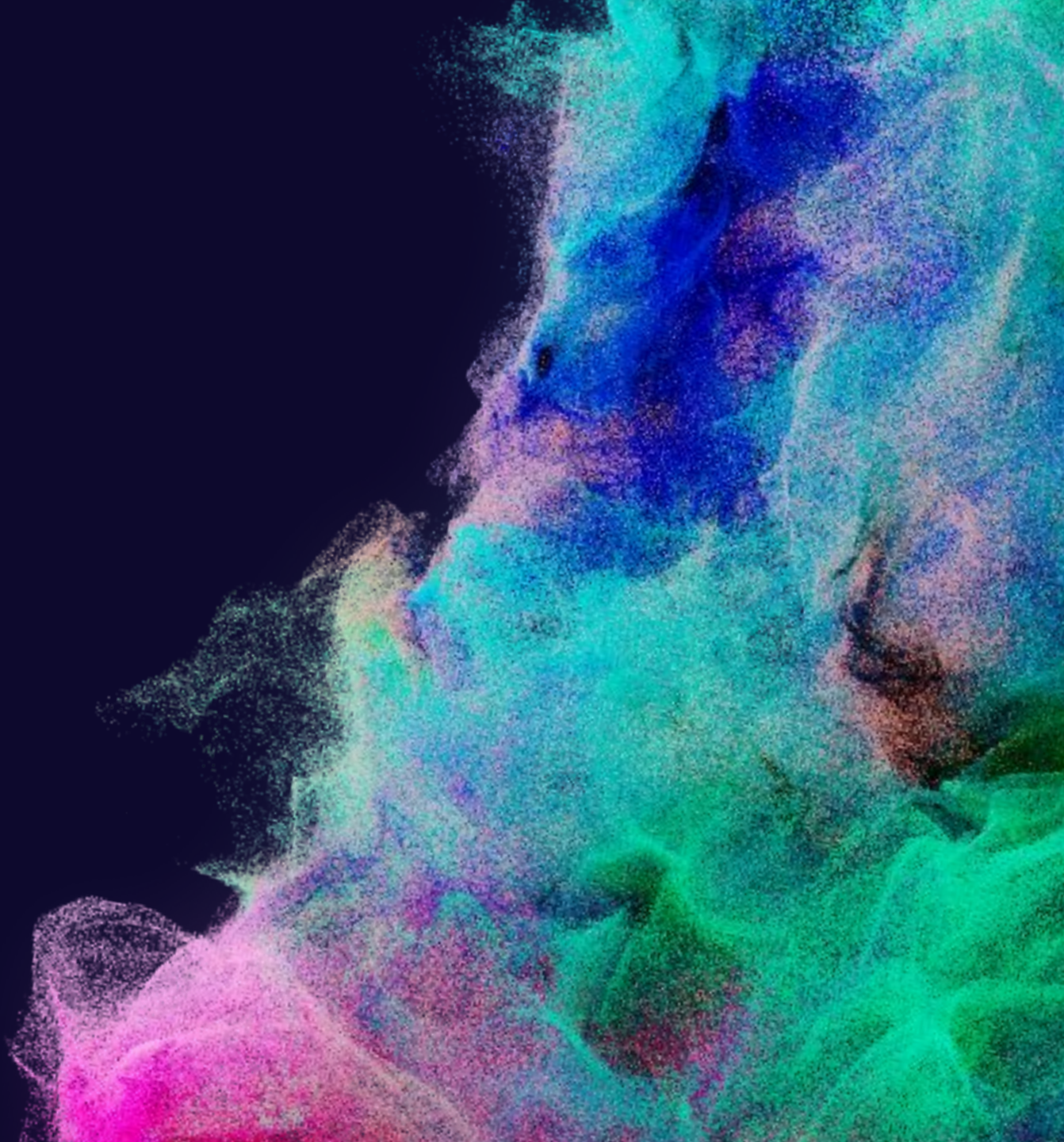
Pipeline Day

December 14, 2023



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This presentation contains certain "forward-looking statements" within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this presentation, including, without limitation, statements regarding the potential advantages of our computational platform, our research and development efforts for our proprietary drug discovery programs and our platform, the initiation, timing, progress, and results of our proprietary drug discovery programs and the drug discovery programs of our collaborators, the clinical potential and favorable properties of our molecules, including SGR-1505, SGR-2921 and SGR-3515, and other compounds discovered with our platform, the timing of potential IND applications as well as initiation of clinical trials for our proprietary drug discovery programs, the clinical potential and favorable properties of our collaborators' product candidates, including Nimbus Therapeutics and Morphic Holding, our ability to realize milestones, royalties, and other payments from our collaborative, partnered and proprietary programs, including our ability to realize returns on any of our investments in the companies we collaborate with, our plans to discover and develop product candidates and to maximize their commercial potential by advancing such product candidates ourselves or in collaboration with others, our plans to leverage the synergies between our businesses, our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our existing cash, cash equivalents, and marketable securities, and our expectations related to the key drivers of our performance, are forward-looking statements. The words "aim," "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "goal," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "will," "would" or the negative of these words or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements reflect our current views about our plans, intentions, expectations, strategies and prospects, which are based on the information currently available to us and on assumptions we have made. Actual results may differ materially from those described in the forward-looking statements and are subject to a variety of assumptions, uncertainties, risks and important factors that are beyond our control, including the demand for our software solutions, the reliance upon our third-party drug discovery collaborators, the uncertainties inherent in drug development and commercialization, such as the conduct of research activities and the timing of and our ability to initiate and complete preclinical studies and clinical trials, uncertainties associated with the regulatory review of clinical trials and applications for marketing approvals, the impacts of the ongoing COVID-19 pandemic on our business and other risks detailed under the caption "Risk Factors" and elsewhere in our Securities and Exchange Commission ("SEC") filings and reports, including our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2023, filed with the SEC on November 1, 2023, as well as future filings and reports by us. Any forward-looking statements contained in this presentation speak only as of the date hereof. Except as required by law, we undertake no duty or obligation to update any forward-looking statements contained in this presentation as a result of new information, future events, changes in expectations or otherwise.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys, and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. We have not independently verified such third-party data, and we undertake no obligation to update such data after the date of this presentation.

Today's Agenda

Introduction — Ramy Farid

Pipeline Overview and Portfolio Strategy — Karen Akinsanya

SGR-1505 (MALT1) — Karen Akinsanya, Margaret Dugan

SGR-3515 (Wee1/Myt1) — Timothy Yap, Karen Akinsanya

SGR-2921 (CDC7) — Elie Traer, Hamish Wright

New Discovery Programs — Jean Lachowicz

Capital Allocation and Value Creation — Geoff Porges

Q&A



Ramy Farid, Ph.D.
Chief Executive Officer, Board Member



Karen Akinsanya, Ph.D.
President of R&D, Therapeutics



Margaret Dugan, M.D.
Chief Medical Officer



Hamish Wright, Ph.D.
Vice President, Translational Science



Jean Lachowicz, Ph.D.
Senior Vice President,
Chief Development Scientist



Geoff Porges, MBBS
Chief Financial Officer

Today’s Guest Speakers



Timothy Yap, MBBS, Ph.D., FRCP

Principal Investigator, Professor in the Department of Investigational Cancer Therapies (Phase 1 Program) and Vice President, Head of Clinical Development in the Therapeutics Discovery Division

University of Texas MD Anderson Cancer Center



Elie Traer, M.D., Ph.D.

Associate Professor of Medicine, Division of Hematology/Medical Oncology, School of Medicine

Oregon Health & Science University

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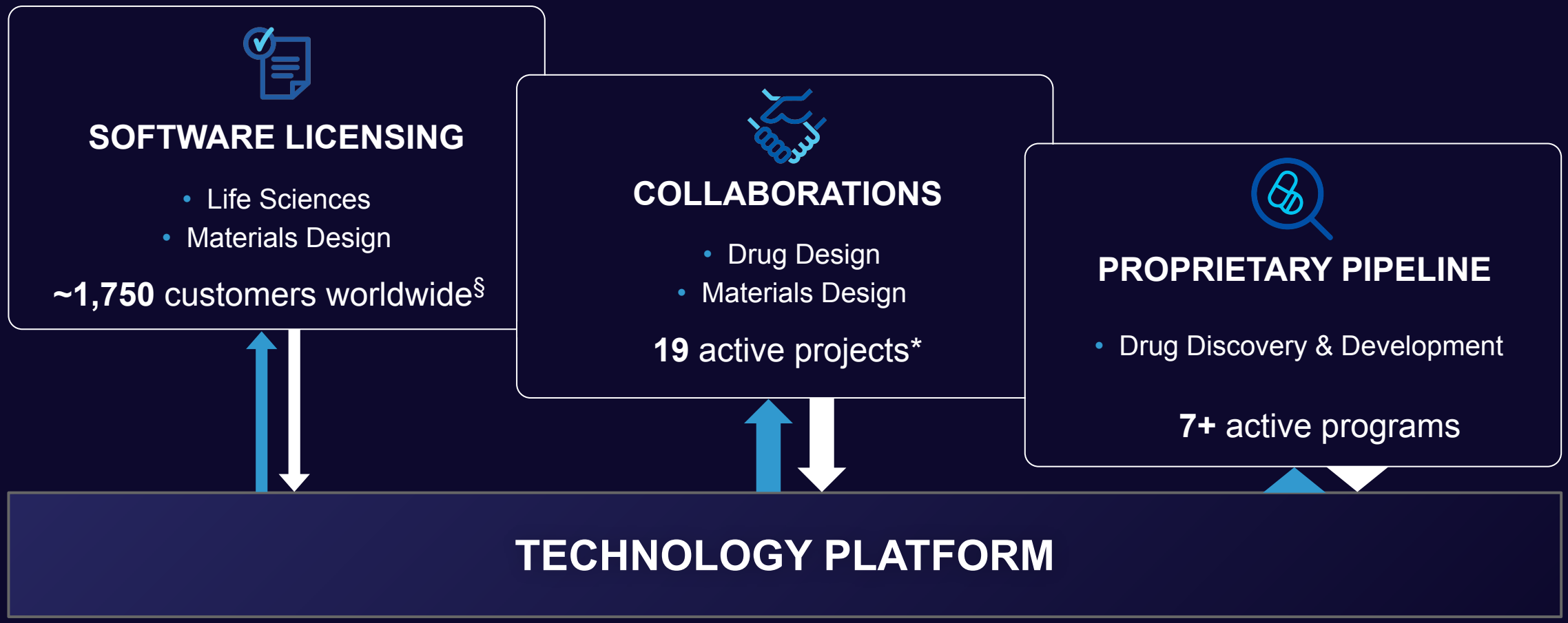
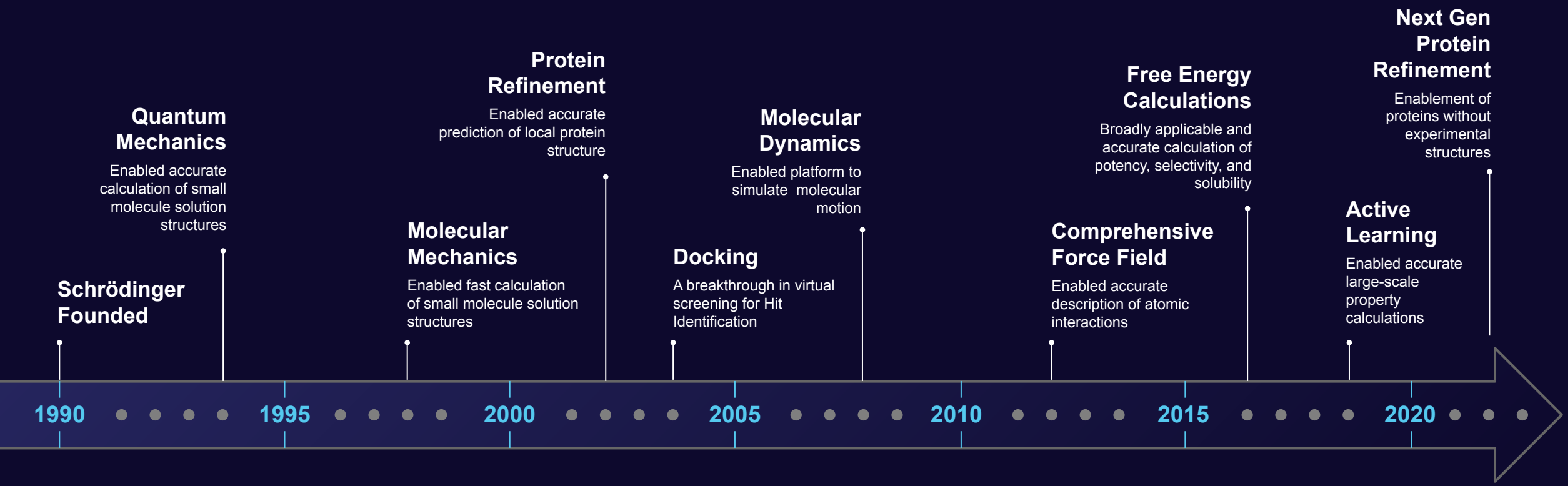
Synergistic and Balanced Business Model



§ Active Customers (# of customers who had an ACV >$1000) as of Dec. 31, 2022
* +13 additional collaboration programs in IND-enabling studies or clinical trials

A History of Scientific Innovation & Platform Advancement



Platform Validated by Advancing Collaboration Programs[1][2]

8 programs in the clinic (+ 5 in IND-enabling studies)

Phase 1

nimbus THERAPEUTICS	Immuno-oncology
STRUCTURE THERAPEUTICS	Pulmonary Arterial Hypertension
PETRA PHARMA	Oncology**
Undisclosed	Oncology
Undisclosed	Undisclosed

Phase 2

nimbus THERAPEUTICS	Autoimmune and Inflammatory Diseases****
	Metabolic Diseases***
MORPHIC	Inflammatory Bowel Diseases

FDA-Approved

agios	*TIBSOVO**
	*IDHIFA**

Additional programs in discovery and preclinical development with: Bristol Myers Squibb™, Lilly, Takeda, MORPHIC, STRUCTURE THERAPEUTICS, Ajax THERAPEUTICS, Otsuka

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[1] Based on publicly available information or information disclosed to us.
[2] All of the programs being pursued under these collaborations are owned and controlled by each respective collaborator.
*Acquired by Servier **Acquired by Lilly ***Acquired by Gilead ****Acquired by Takeda

Power of Schrödinger's Computational Platform



Power of Schrödinger's Computational Platform — Advancing Proprietary Pipeline

Computationally enable wide range of targets → Accurately assess druggability of protein target → Identify multiple, distinct chemical starting points → Rapidly and reliably optimize leads to identify development candidate with superior drug-like properties

SGR-1505 (MALT1)

- 10X more potent than existing inhibitors; low DDI potential enabling clinical combinations
- Phase 1 completed in healthy volunteers and ongoing study in advanced B-cell malignancies

SGR-2921 (CDC7)

- Potent, selective inhibitor; low predicted dose and limited DDI potential enabling combinations
- Phase 1 initiated in acute myeloid leukemia and myelodysplastic syndrome

SGR-3515 (Wee1/Myt1)

- Optimized for activity against both Wee1 and Myt1; limited DDI potential enabling combinations
- IND-enabling activities underway

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Pipeline Overview & Portfolio Strategy



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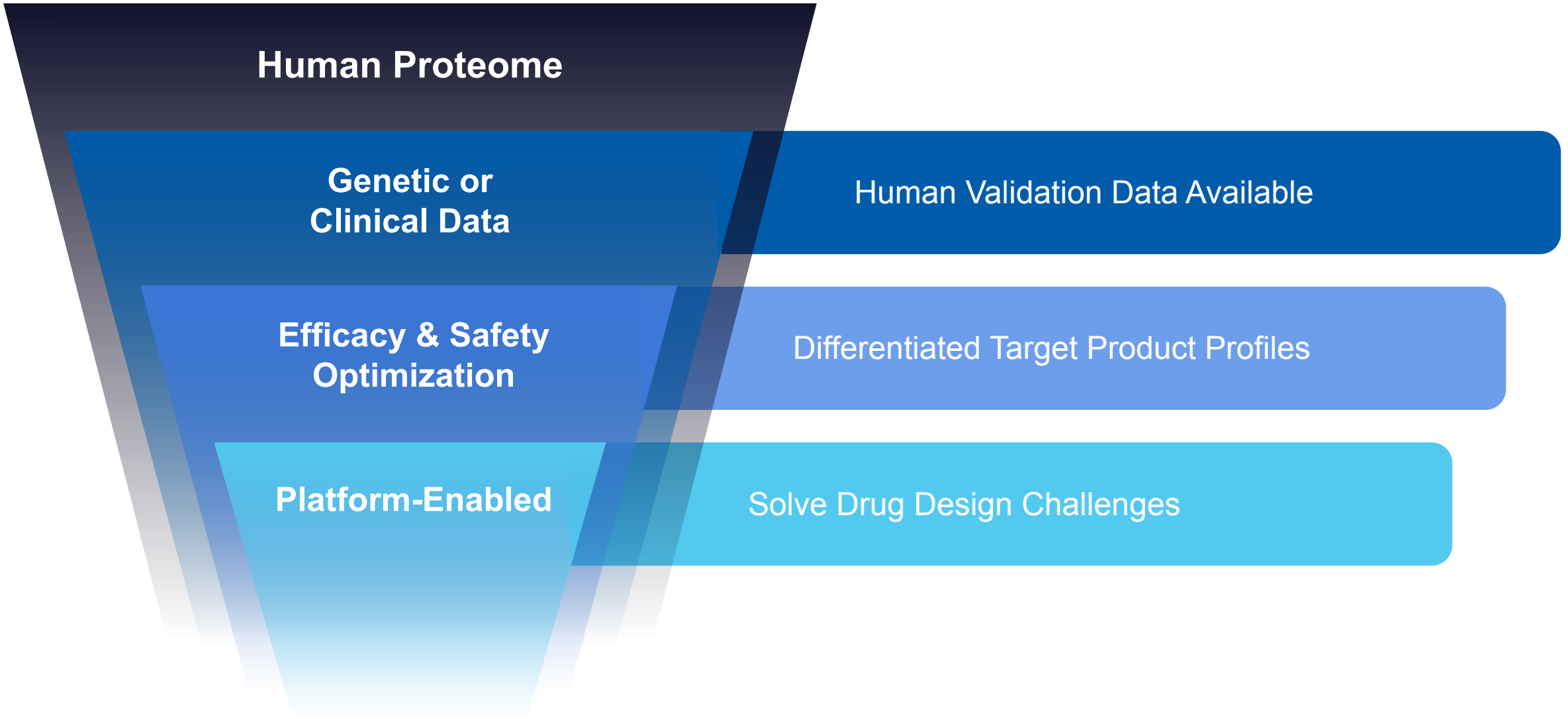
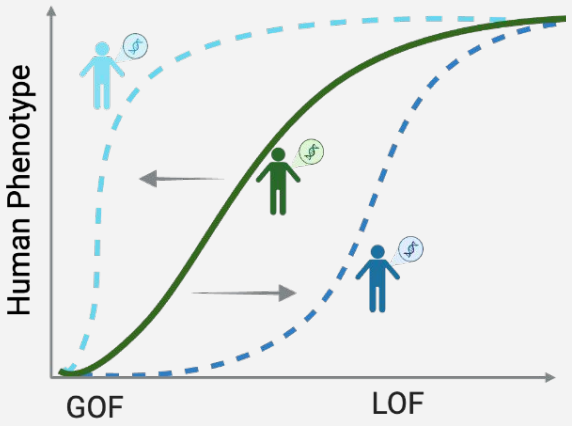
Target Prioritization and Program Selection



Genetic Validation: Key to Our Target Selection Strategy

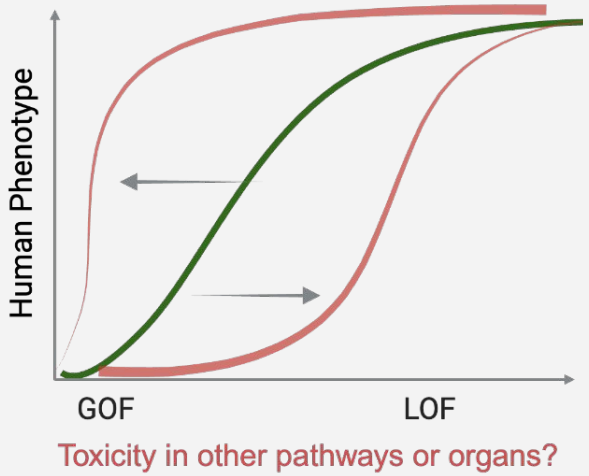
1

Genotype Phenotype Dose Response?



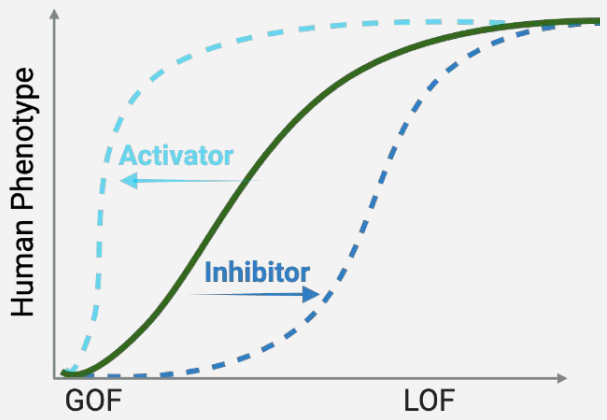
2

Therapeutic Index Insight?



3

Phenocopy Biology with a Drug?



Drug targets with bidirectional gene dose effects have an ~4-fold increased probability of success in clinical trials[1]

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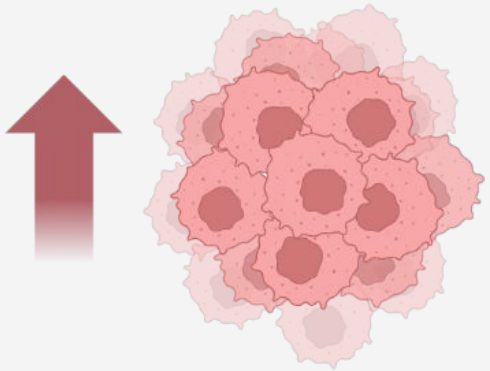
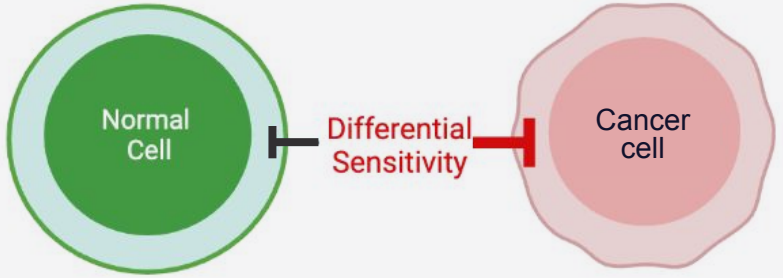
[1]Estrada et al. *Nat Commun* 12, 2224 (2021).

Targeting Cancer Cell Vulnerabilities



Cancer cell growth and survival in tumors

- Disrupt dependence on inactivation of tumor suppressors / addiction to drivers
- Escalate impact of DNA damage / insufficient repair and replication stress
- Leverage conditional synthetic lethality
- Inhibit compensation mechanisms





Cancer cell death

Portfolio Enriched in Pathways with Human Validation

Strong Human Evidence	Genetics - Genotype/ Phenotype Dose Response
	Clinical Pharmacology and Efficacy Data
Cancer Cell Intrinsic Vulnerabilities	Drivers & Resistance Mechanisms
	DNA-Damage Repair & Synthetic Lethality
Combination Opportunities to Enhance Efficacy	Combinations & Rational Sequencing with SOC
	Deeper Responses & Resilience to Resistance Mutations

Multiple Programs with Established and Emerging Clinical Validation Across Hematological Cancers and Solid Tumors



*Partnered with Bristol Myers Squibb

Combination Opportunities in Complementary Pathways to Build Upon Single Agent Efficacy

MALT1	+	**BTK** 1st 2nd & 3rd Gen, Degraders	**BCL2** 1st & 2nd Gen	**CD20** 1st & 2nd Gen
EGFR^{C797S}	+	**EGFR** 3rd Generation	**EGFR-MET** Bispecifics	**MET**
SOS1*	+	**KRAS**	**MEK**	**BRAF**
Wee1/Myt1	+	**PD-1/PDL-1**	**PARP** 1st & 2nd Gen	**KRAS**
CDC7	+	**HMA**	**BCL2** 1st & 2nd Gen	**FLT3**
PRMT5-MTA	+	**PD-1/PDL-1**	**KRAS**	**EGFR**

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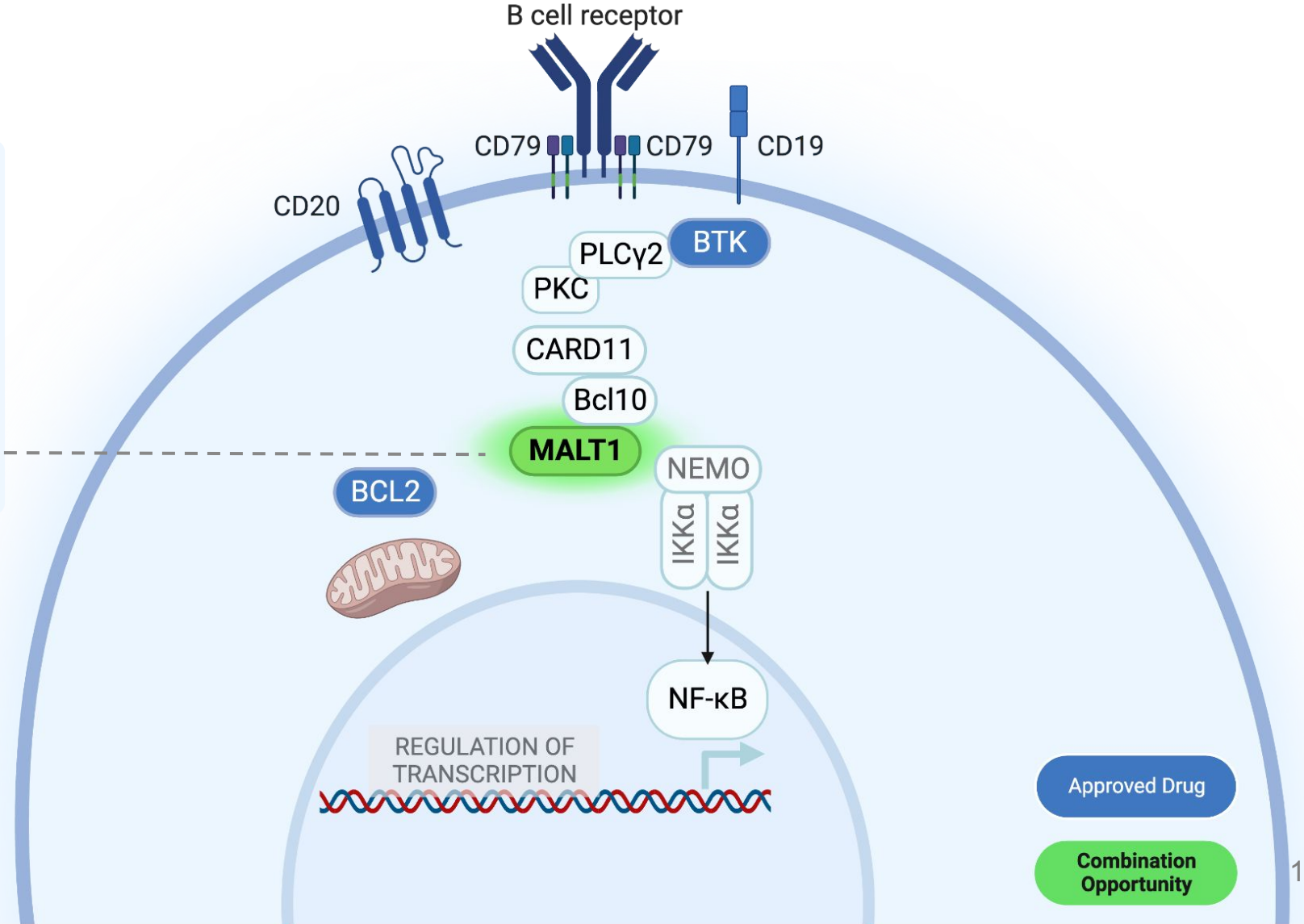
*Partnered with Bristol Myers Squibb

MALT1: An Emerging Mechanism for Novel Combinations in B-cell Malignancies

- MALT1 — drives proliferation of BCR-addicted lymphomas
- Robust anti-tumor activity in preclinical lymphoma models resistant to BTKi
- MALT1 mediates resistance to ibrutinib and venetoclax in MCL[1]



[1]Jiang et al., *J Clin Invest* 2023 Feb 1; 133(3): e165694.

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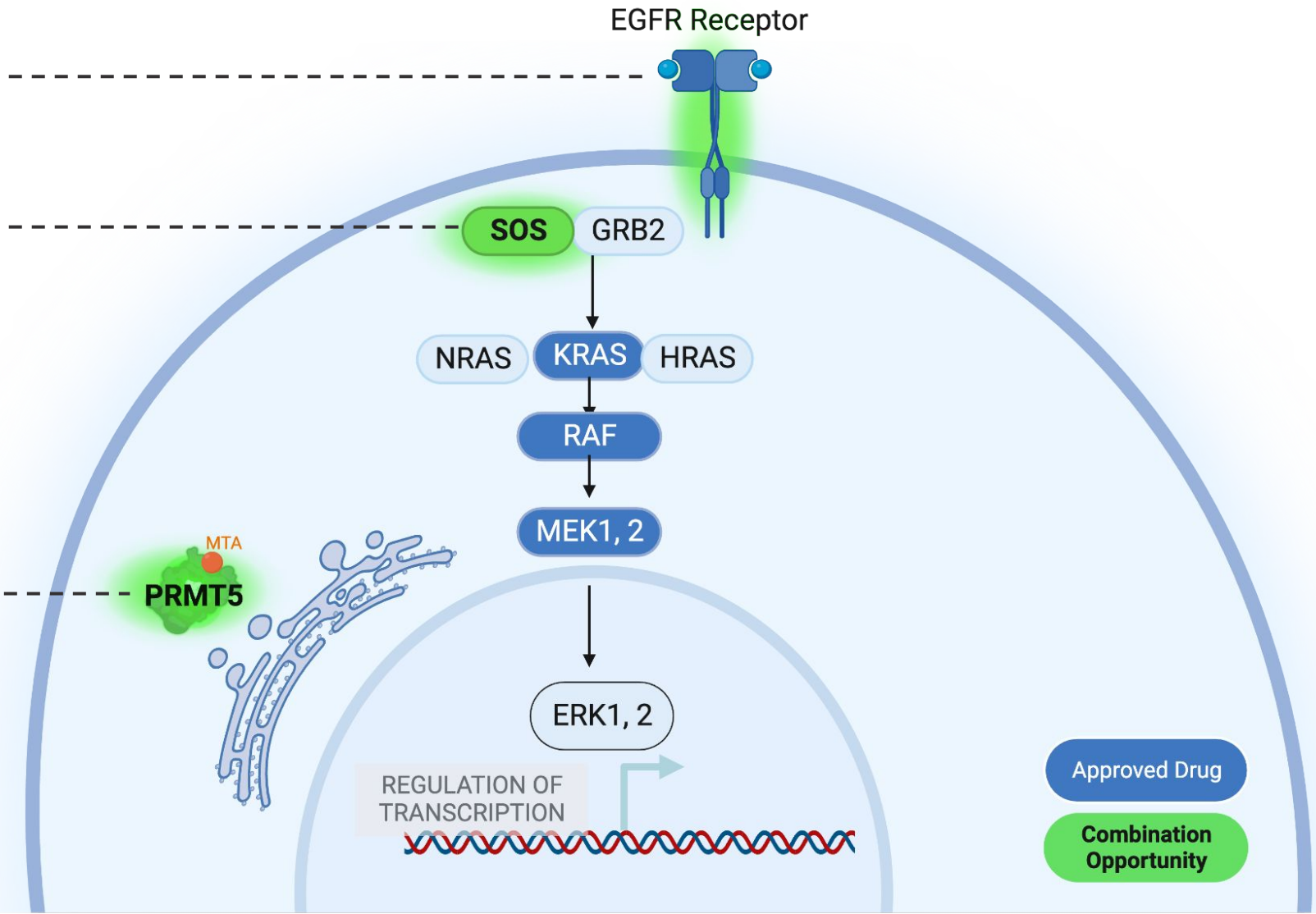
Next-Generation Small Molecule Opportunities in Lung Cancer

Limiting and treating brain metastasis — unmet need in advanced NSCLC

Acquired RAS therapy resistance — requires combinations

Inhibition of PRMT5-MTA complexes — emerging option in MTAP-deleted NSCLC (13%)[1]



[1]Graziano et al., *J Clin Oncol* 39, no. 15_suppl (May 20, 2021) 9116-9116.

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Genetic Validation: Key to Our Target Selection Strategy

GOF & LOF Phenotypes

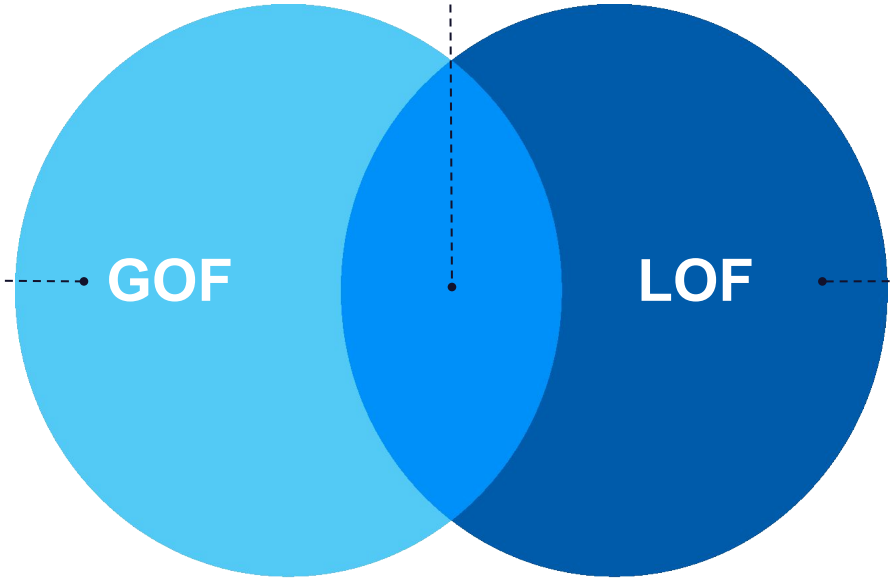
EGFR (Epithelial Proliferation)
LRRK2 (Parkinson's Risk)
MALT1 (B-cell Diseases)

BACE, PCSK9, Nav1.7, TYK2

GOF Diseases

NLRP3 (CAPS and Inflammation)

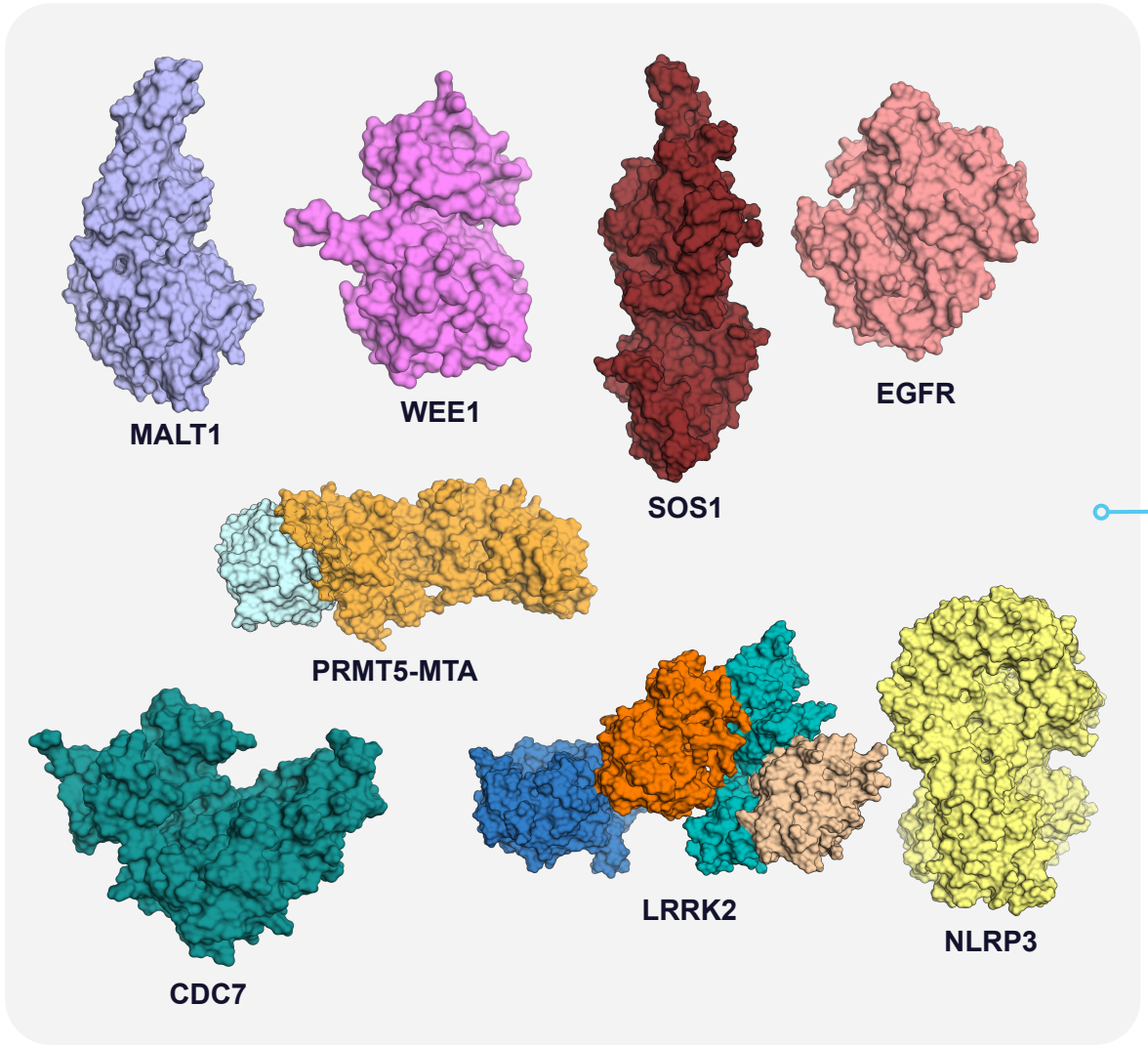
SNCA, FGFR3, LDL

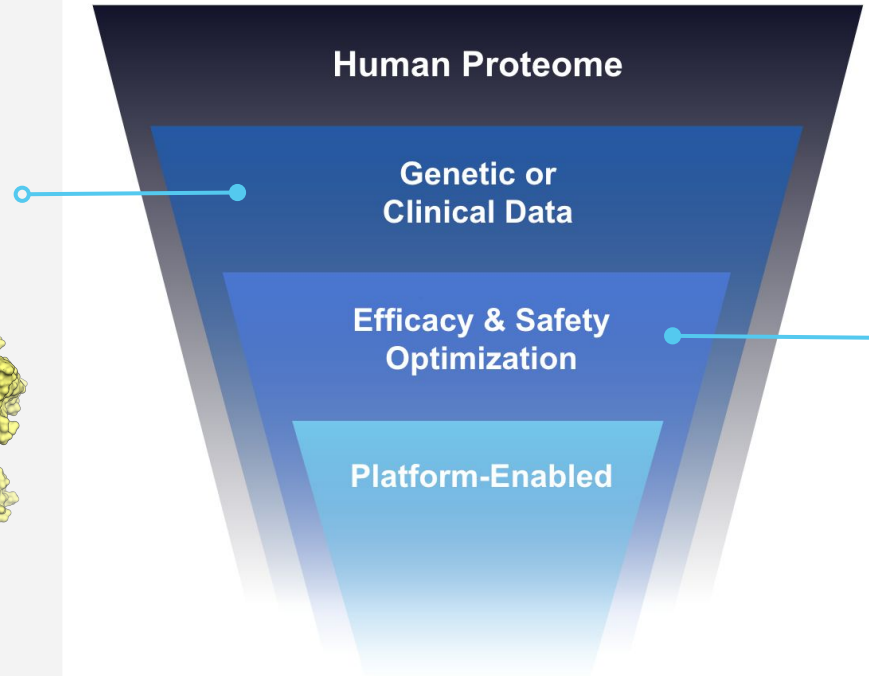


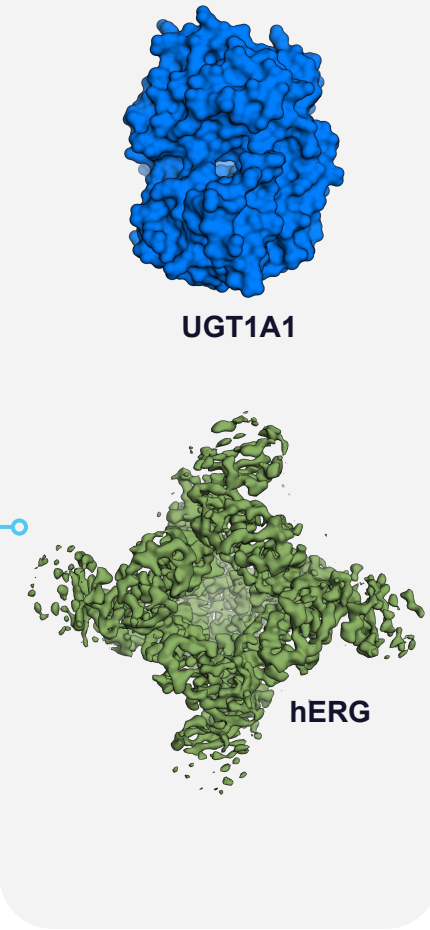
Protective LOF

APOC3, CCR5,
ZnT8, LRP5

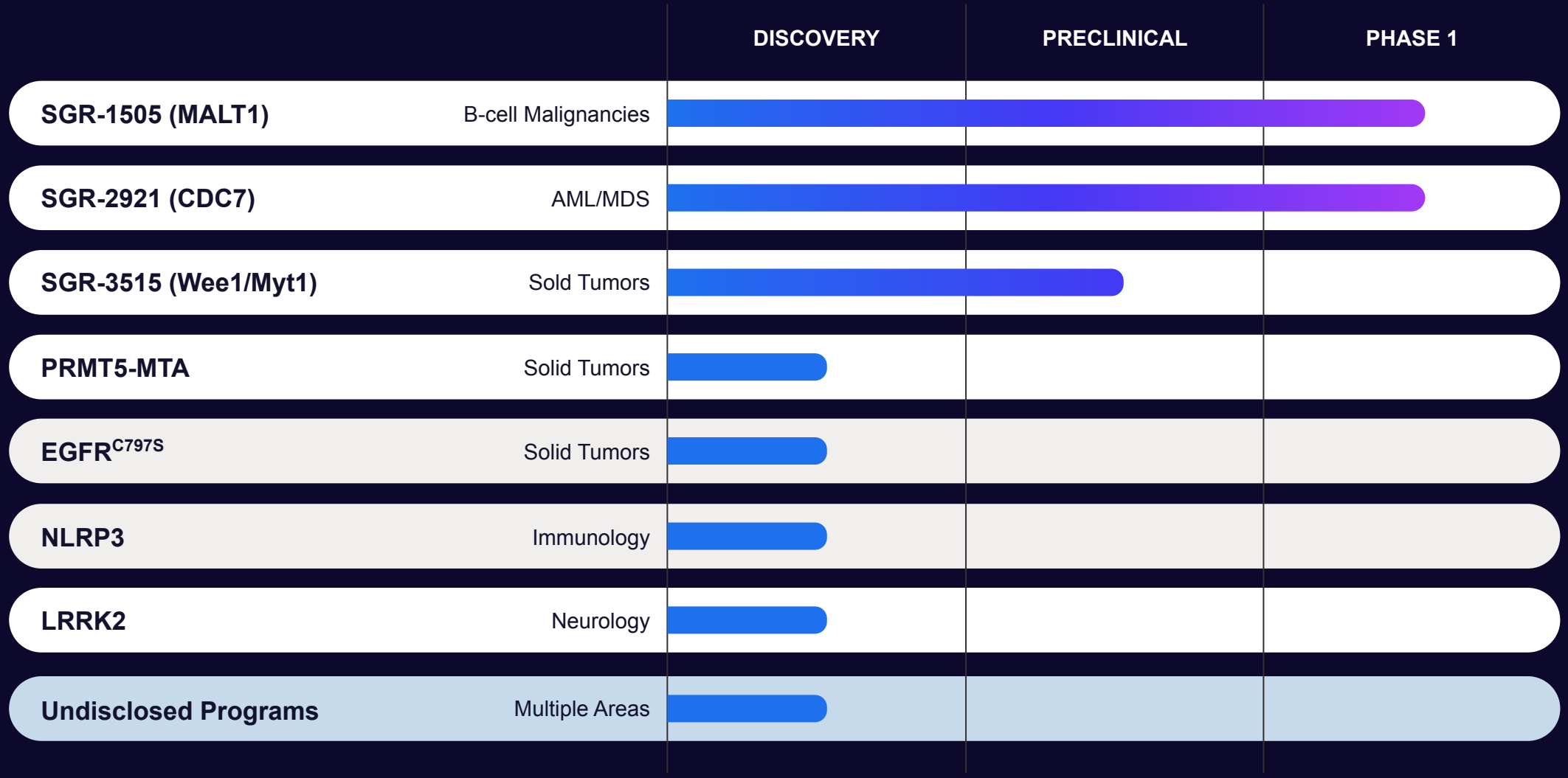
Expanding Our Access to High Quality Protein Structures







Proprietary Pipeline



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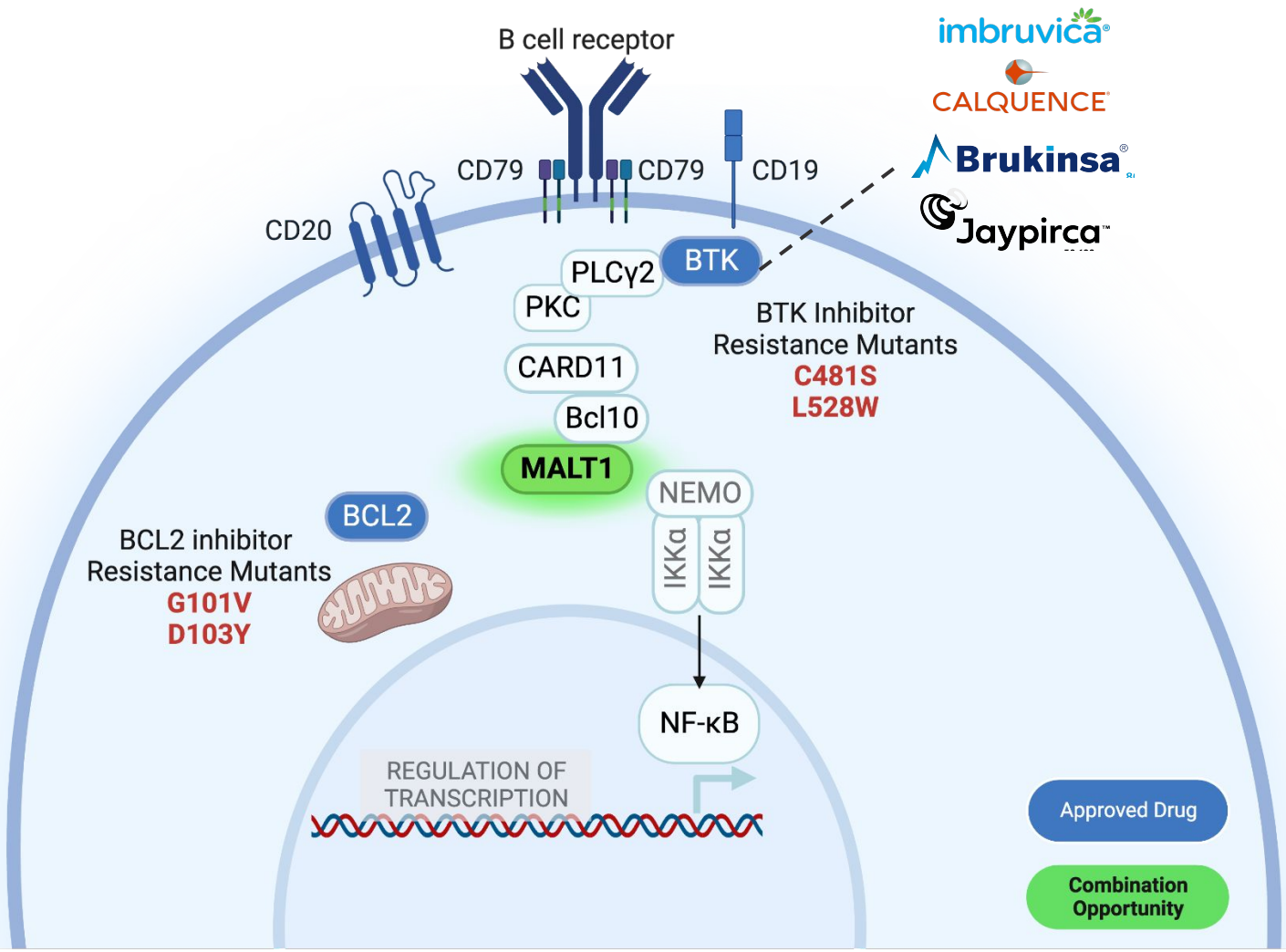
New Combination Opportunities in B-cell Malignancies



- Constitutive MALT1 — drives survival of malignant lymphomas
- C481S and L528W mutations are associated with treatment failure
- Preclinical data suggest potential role for MALT1 in combinations and fixed-duration regimens to drive deeper responses

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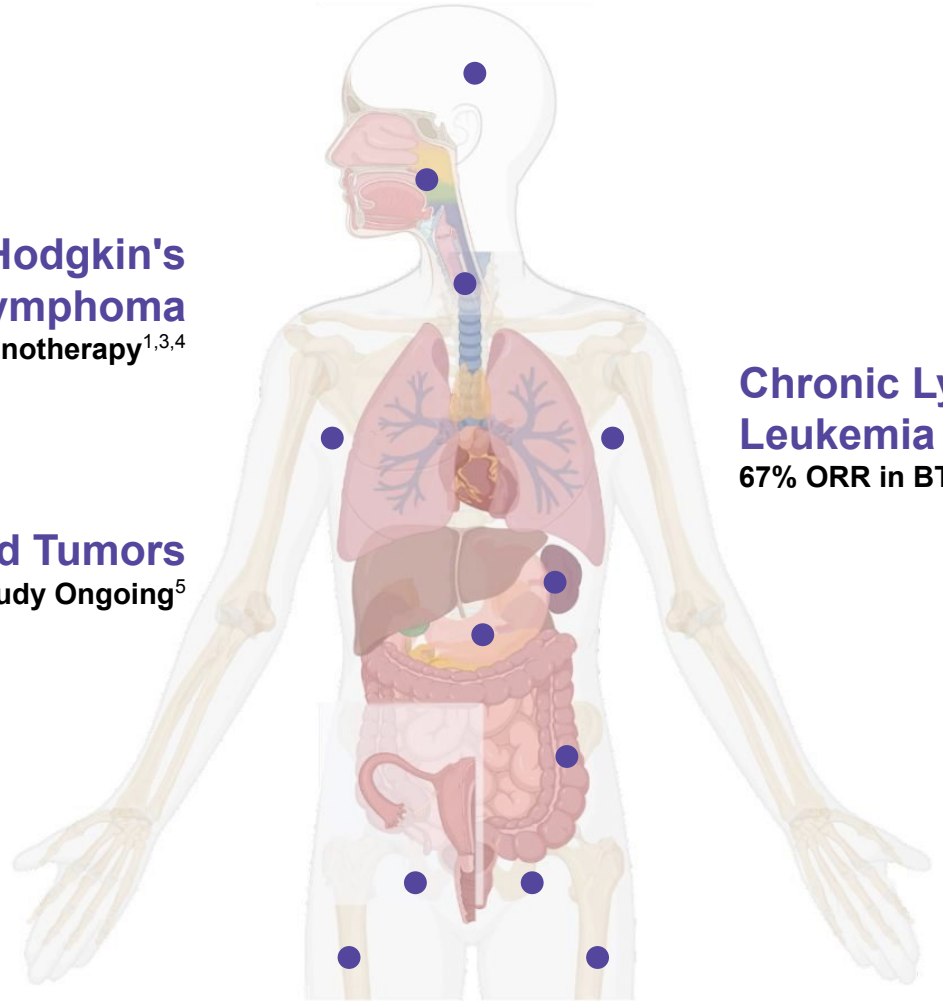
Imbruvica, Calquence, Brukinsa and Jayprica are registered trademarks of Abbvie, AstraZeneca, Beigene and Loxo@Lilly, respectively.

Blombery et al *Blood Adv* 2022 Oct 25; 6(20): 5589–5592.

MALT1 Protease Inhibitor Activity in B-cell Malignancies Confirmed by 3rd Party Clinical Data

Non-Hodgkin's Lymphoma
28% ORR monotherapy[1,3,4]

Solid Tumors
Phase 1 Study Ongoing[5]



Chronic Lymphocytic Leukemia (CLL/SLL)
67% ORR in BTK combination[2]

Allosteric Inhibition of MALT1

- JNJ-6633 proof of concept for monotherapy and combination activity in human B-cell malignancies
- Opportunity for well-tolerated, potent, optimized inhibitors with sustained target engagement in NHL and CLL
- Potential for MALT1 inhibitors in autoimmune disease based on genetic association data

[1]WO2022184716 Combination Therapy using MALT1 Inhibitor and BTK Inhibitor. [2]WO2022185097 Method of treating a condition using a therapeutically effective dose of the MALT1 inhibitor JNJ-67856633. [3]Kalac M. et. al, EHA Abstracts HemaSphere 7(S3):p e60782b9, August 2023. [4]Hertzberg et. al. *Hematological Oncol* June 2023. [5]Naing et al., *Ann Oncol* 2023, 34 (suppl_2): S619-S650.

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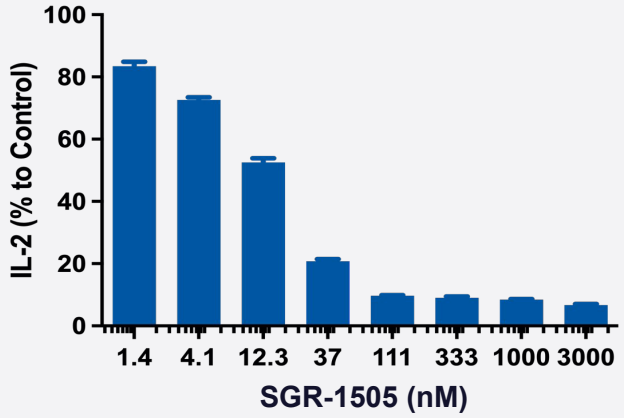
SGR-1505 Shows Excellent Potency in Biochemical and Cell-based Assays

Assay	SGR-1505		JNJ-6633	
	IC_{50} nM	IC_{90} nM	IC_{50} nM	IC_{90} nM
MALT1 Biochemical Assay	1.3	7	73	485
BCL10 Cleavage Assay — OCI-LY10 Cells	22	63	98	334
IL10 Secretion Assay — OCI-LY10 Cells	36	211	267	2,816
Antiproliferative Assay — OCI-LY10 Cells	71	181	430	5,670
Antiproliferative Assay — REC-1 Cells (MCL)	57	227	884	5,876
NF-kB Reporter Assay in Jurkat T-cell Leukaemia Cells	37	113	242	4,122
IL2 Secretion Assay — Jurkat T-cell Leukaemia Cells	15	3,800	Data pending	

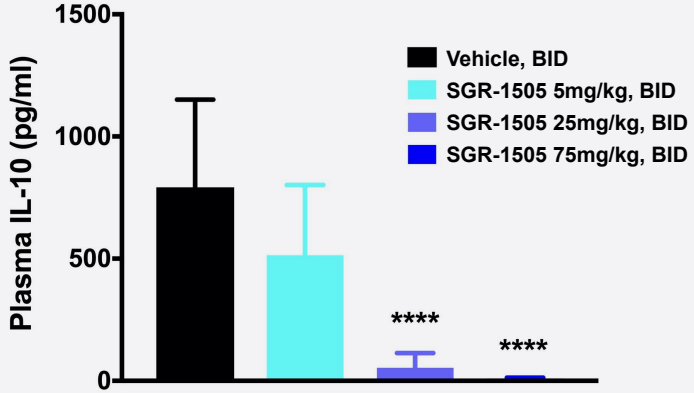
All competitor data is internally generated by contract research organizations using publicly available structure information.
Yin et al., ASH 2023.

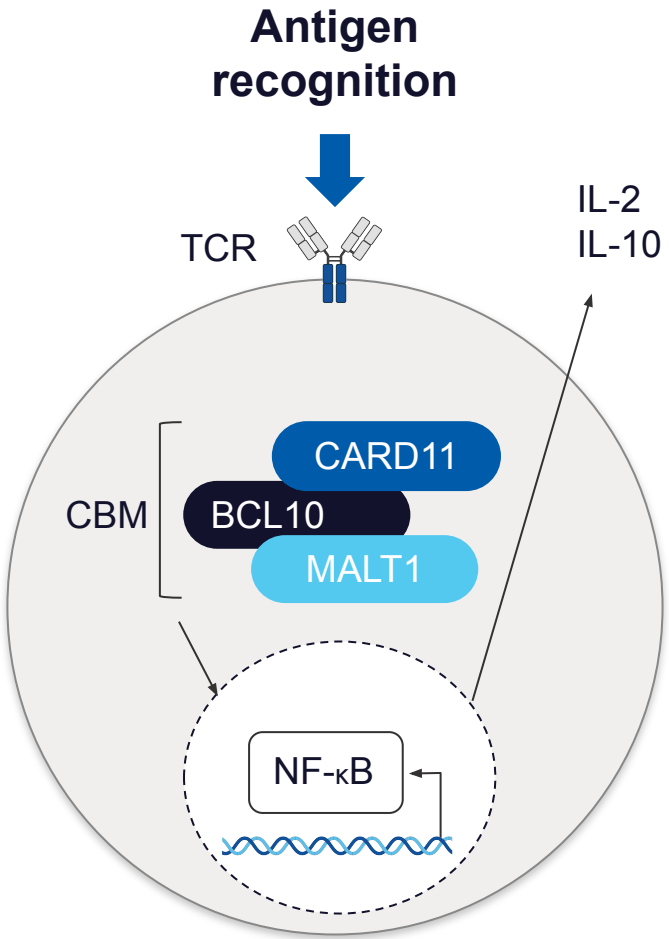
Pharmacodynamic Impact of SGR-1505 Mediated MALT1 Inhibition Established Preclinically

Inhibition of IL-2 Secretion in Jurkat Cells

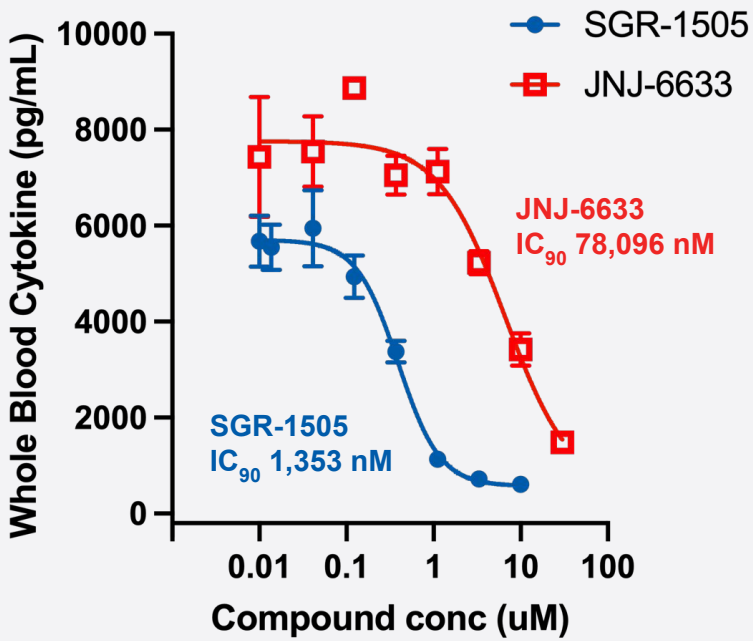


Inhibition of Plasma IL-10 Secretion[1]





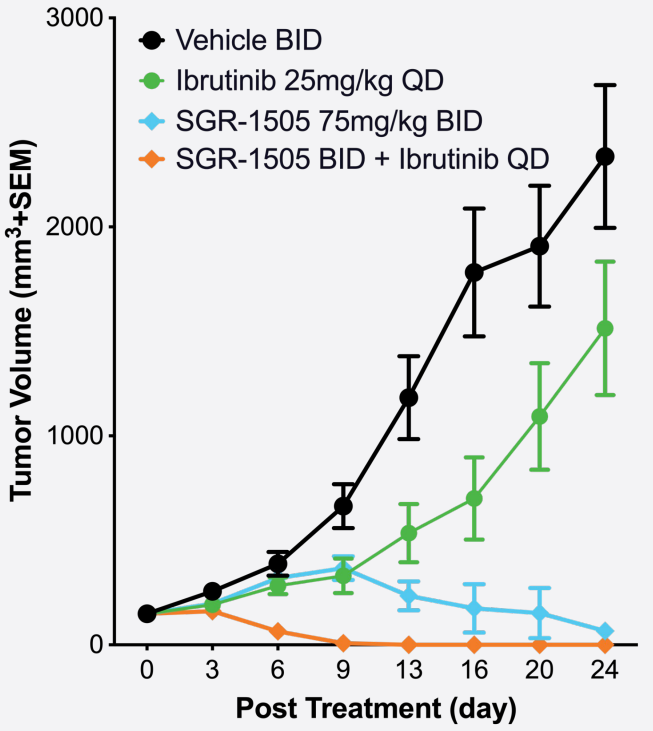
In Vitro Whole Blood Assay from Healthy Human Donors[2]



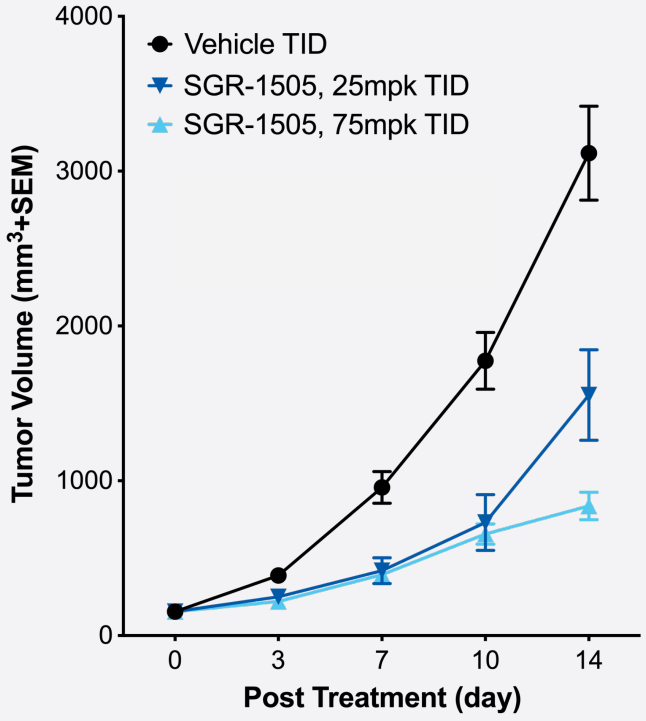
[1]Yin et al., ASH 2020; [2]Yin et al., ASH 2023.

Strong Single Agent and Combination Activity With Standard of Care Agents

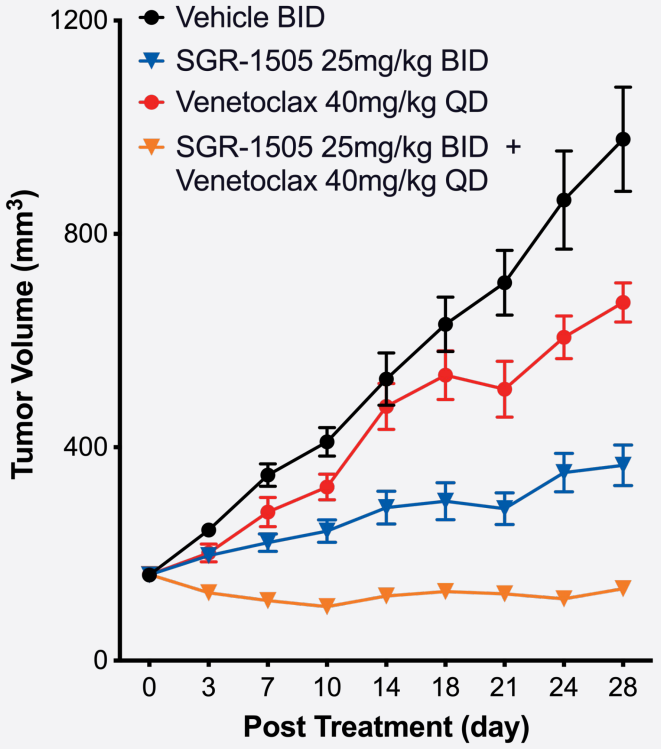
SGR-1505 + Ibrutinib in LY2298 PDX (ABC-DLBCL)



SGR-1505 Monotherapy in REC-1 (MCL)



SGR-1505 + Venetoclax in OCI-LY10 (ABC-DLBCL)



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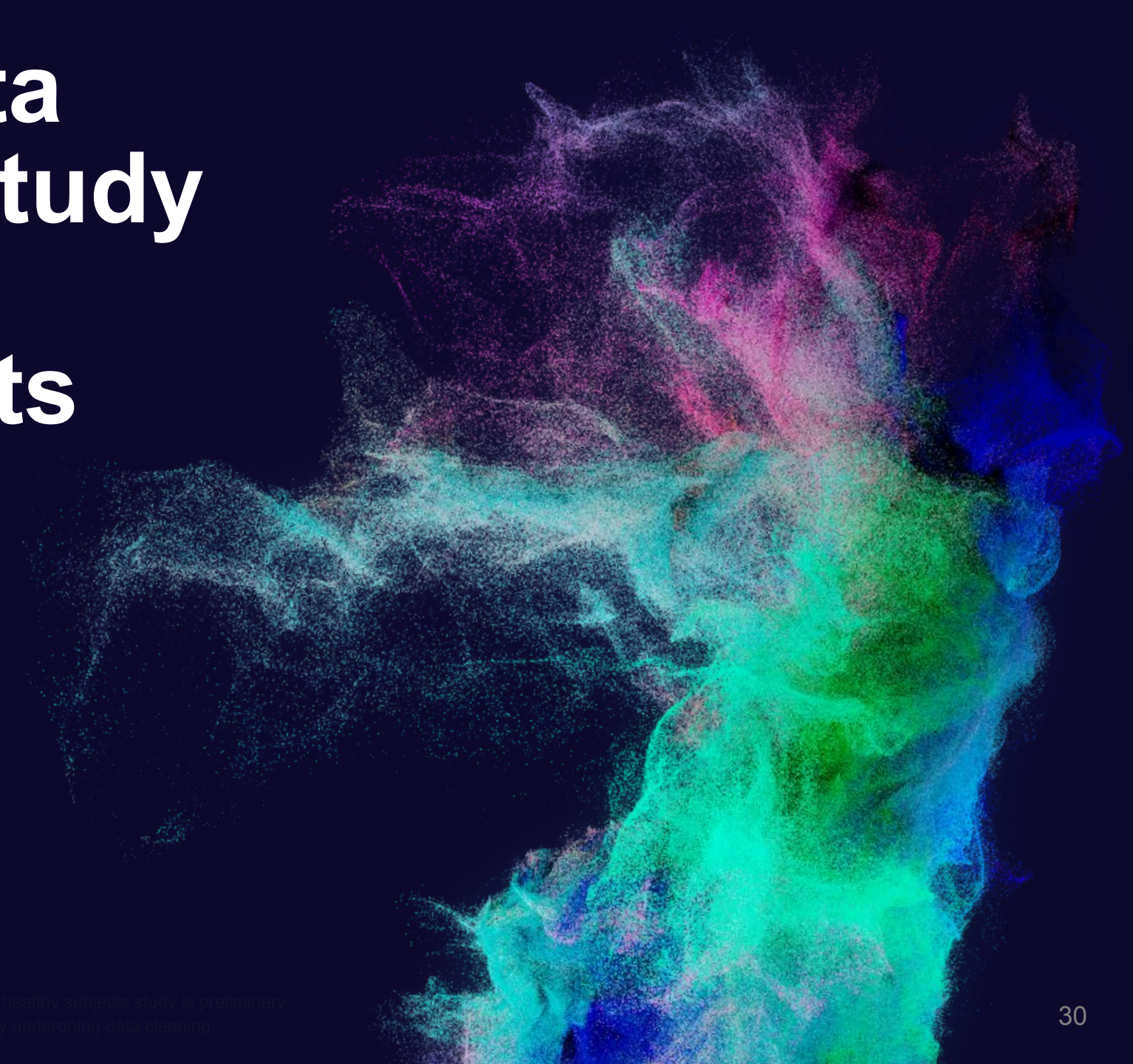
Yin et al., ASH 2021.

Preliminary Data from Phase 1 Study of SGR-1505 in Healthy Subjects



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Data presented today from the SGR-1505 102 healthy subjects study is preliminary and from an unlocked database that is currently undergoing data cleaning

SGR-1505 Study in Healthy Subjects Characterized Safety, Tolerability, and PK, and Informed the Patient Study Design

Study Objectives	
Primary	Safety and tolerability of SGR-1505
Secondary	Pharmacokinetic (PK) characterization (single and multiple doses, food effect & evaluation of CYP3A inhibition on SGR-1505 PK)
Exploratory	Pharmacodynamic (PD) characterization of blood biomarkers, PK/PD evaluation

Study Population*	
Mean age	30 years [range: 18-60 years]
Gender	62% Male; 38% Female
Race	60% White; 27% Asian; 6% American Indian or Alaskan Native; 5% Other; 1% Native Hawaiian or Other Pacific Islander

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SGR-1505 Healthy Subjects Study Design

Part A **Single Ascending Dose (SAD)** (N=30)	**25 mg QD (n=6)**	**50 mg QD (n=6)**	**100 mg QD (n=6)**	**150 mg QD (n=6)**	**225 mg QD (n=6)**
Part B **Multiple Ascending Dose (MAD)** (N=19)	**75 mg QD x 10d (n=6)**	**150 mg QD x 10d (n=6)**	**100 mg Q12H x 10d (n=7)**		
Part C **Food Effect (FE) Evaluation** (N=12 subjects)	**150 mg QD (N=12)**				
Part D **Drug-Drug Interaction (DDI) Evaluation** (N=12 subjects)	**100 mg QD (N=12)**				

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SGR-1505 Was Well-Tolerated in Healthy Subjects Across All Cohorts (N=73)

Treatment-Emergent Adverse Events (TEAE)

- 55% of subjects (40/73) experienced at least 1 TEAE
- 96% Grade 1 and 90% not treatment related
- One Grade 3 TEAE (neutropenia), not treatment-related (prior history); no Grade 4 TEAEs

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Laboratory Tests

- Bilirubin elevations occurred in 27% of subjects
  - All asymptomatic, predominantly Grade 1 (70%), and none Grade 3 or 4
  - None associated with transaminase (TA) elevations
  - All reversible upon discontinuation of SGR-1505

Data presented today from the SGR-1505-102 healthy subjects study is preliminary and from an unlocked database that is currently undergoing data cleaning. This study was conducted outside of the U.S.

SGR-1505 Was Well-Tolerated in Healthy Subjects Across All Cohorts (N=73)

Treatment-Emergent Adverse Events (TEAE)

- 55% of subjects (40/73) experienced at least 1 TEAE
- 96% Grade 1 and 90% not treatment related
- One Grade 3 TEAE (neutropenia), not treatment-related (prior history); no Grade 4 TEAEs

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Dose Interruptions and Discontinuations

- Two subjects had single dose interruption due to adverse event (nausea and H. influenza infection)
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No Serious Adverse Events

Schrödinger

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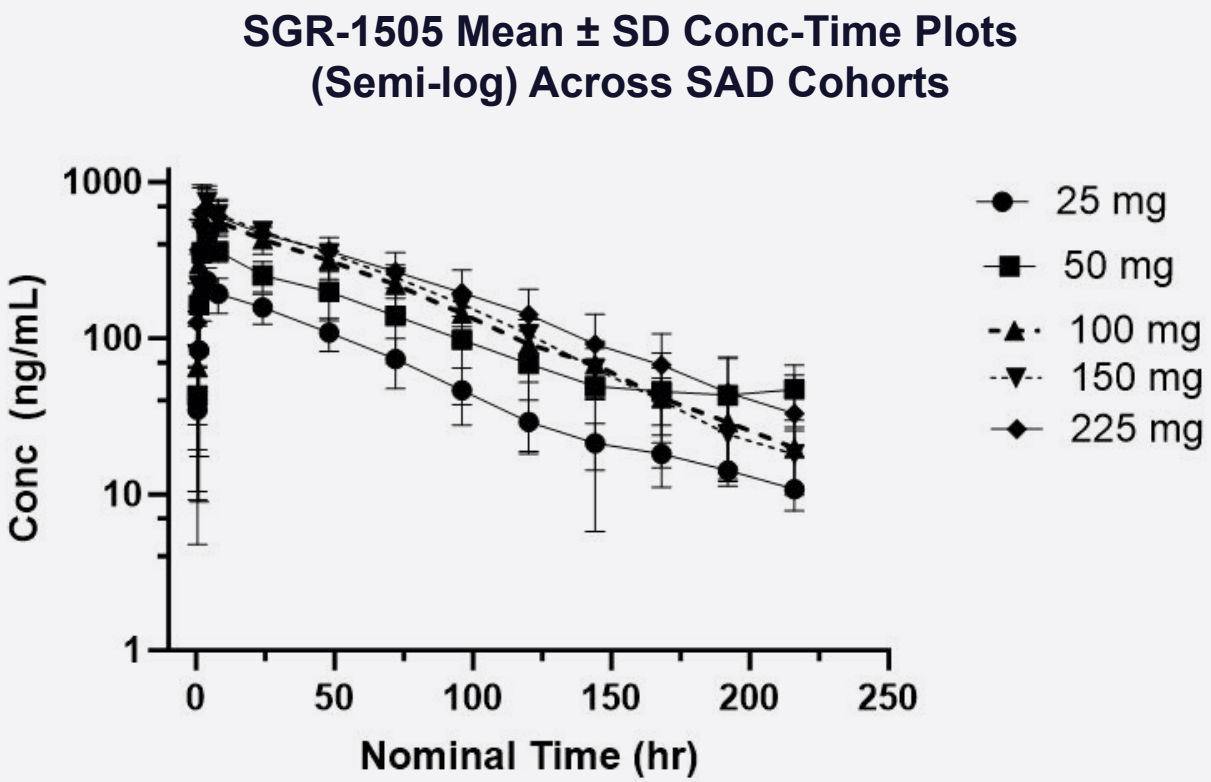
Dose Proportional SGR-1505 PK up to 100 mg in Healthy Subjects in Single Ascending Dose Cohorts

- Rapid absorption (median T_{max}: 2-4 hrs) with mean half-life range: 33-44 hrs
- Dose proportional increase in SGR-1505 exposure (C_{max} and AUC_{∞}) up to 100 mg



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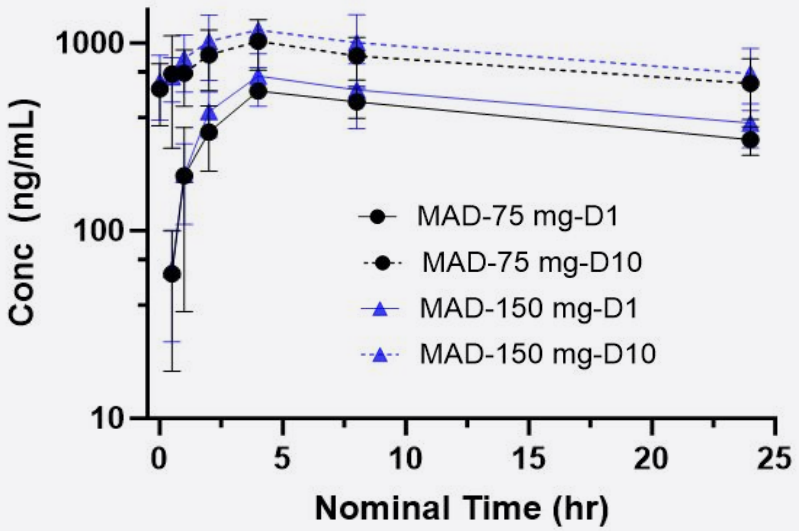
Modest Accumulation between Day 1 and Day 10 in Multiple Ascending Dose Cohorts

- ~2-fold increase in exposure on Day 10 with once daily dosing
- ~3.6-fold increase in exposure on Day 10 with Q12H dosing

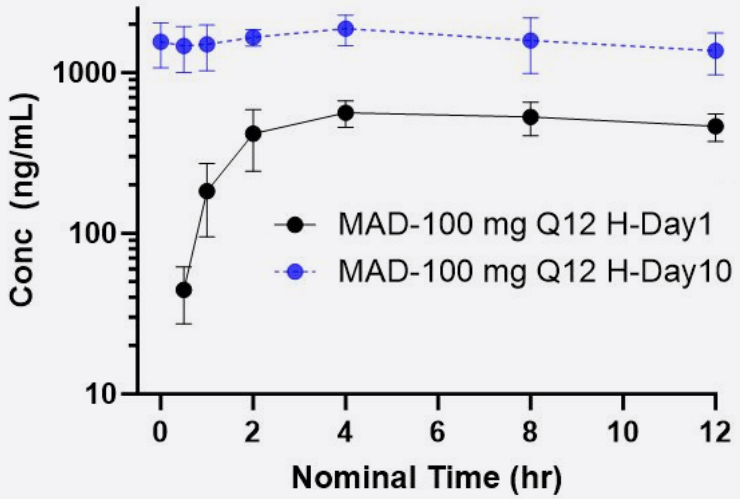
SGR-1505 Mean±SD Conc-Time Plots (Semi-log)

Across MAD (once daily) Cohorts



SGR-1505 Mean±SD Conc-Time Plots (Semi-log)

For 100 mg Q12H Cohort



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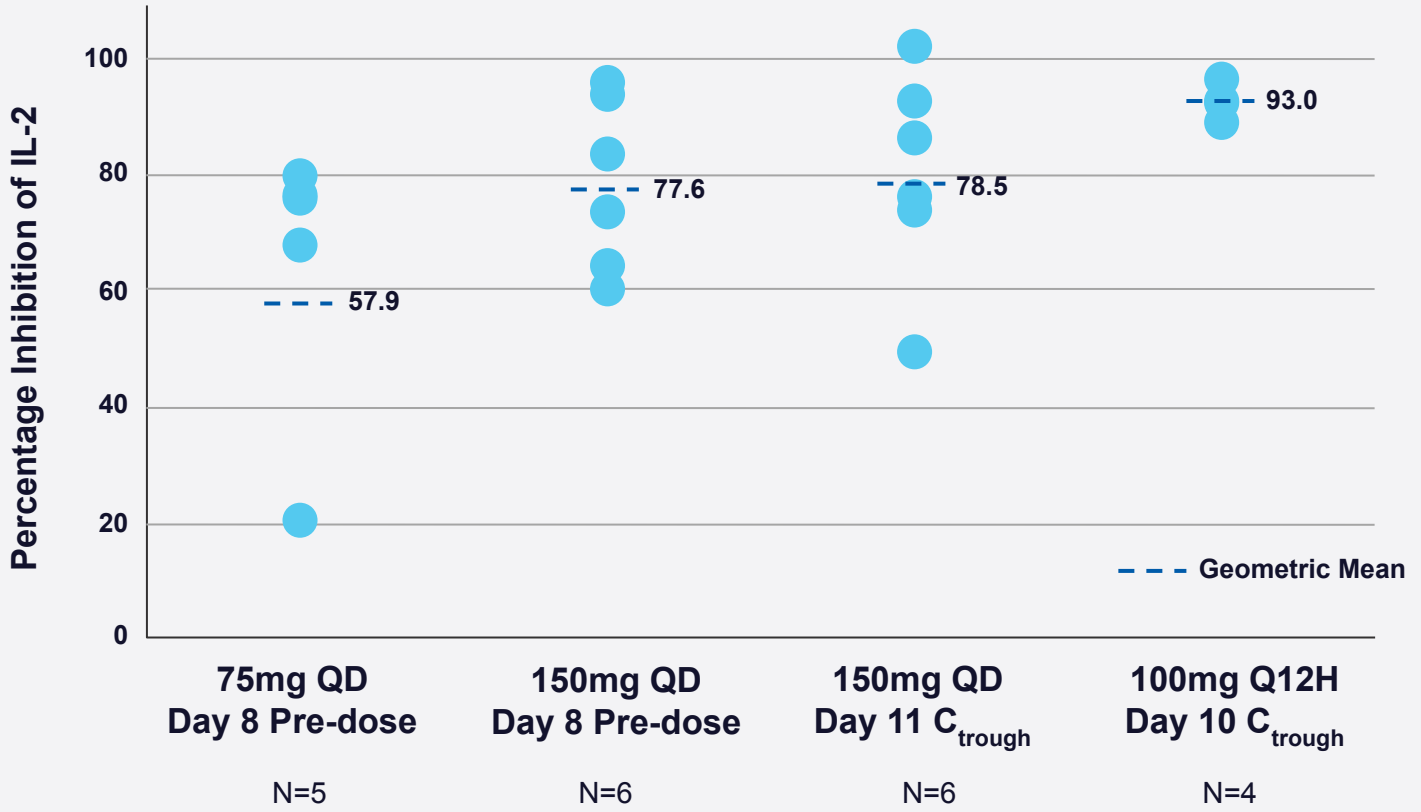
MALT1 Target Engagement Established by IL-2 Inhibition

- Steady state exposures achieved at 150 mg once daily or 100 mg Q12H demonstrate ≥75% inhibition of IL-2 secretion in activated T cells
- Maintaining >90% IL-2 inhibition at C_{trough} consistently achieved with 100 mg Q12H dosing vs. once daily



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SGR-1505 Summary and Next Steps

- SGR-1505 has a differentiated preclinical profile
- Successful healthy subject study further informs clinical development plans
- Orphan drug designation approval in mantle cell lymphoma
- Enrolling patients with relapsed or refractory B-cell malignancies at Phase 1 study sites in U.S. and EU
  - Initial data expected in late 2024 or 2025
- Combination opportunities with standard of care agents
- Additional indications under consideration

Today’s Agenda

Introduction — Ramy Farid

Pipeline Overview and Portfolio Strategy — Karen Akinsanya

SGR-1505 (MALT1) — Karen Akinsanya, Margaret Dugan

SGR-3515 (Wee1/Myt1) — Timothy Yap, Karen Akinsanya

SGR-2921 (CDC7) — Elie Traer, Hamish Wright

New Discovery Programs — Jean Lachowicz

Capital Allocation and Value Creation — Geoff Porges

Q&A



Targeting the DNA Damage Response (DDR): Focus on WEE1 inhibitors

Schrodinger Pipeline Day

December 2023

Timothy A. Yap, **MBBS, PhD, FRCP**

Professor, Department of Investigational Cancer Therapeutics (Phase I Program)

Vice President and Head of Clinical Development, Therapeutics Discovery Division

Associate Director of Translational Research, Khalifa Institute for Personalized Cancer Therapy

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

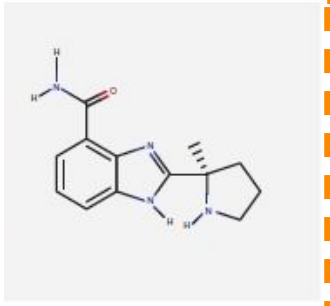
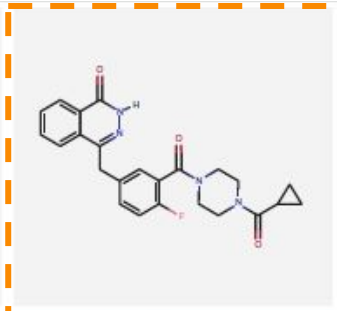
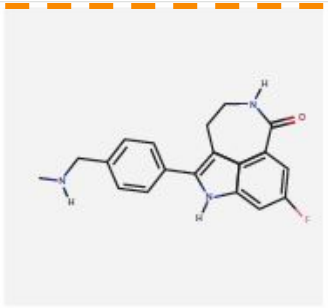
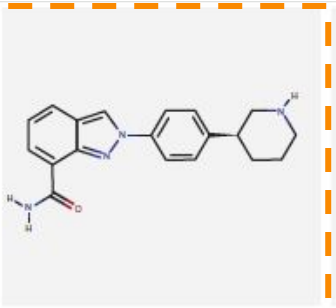
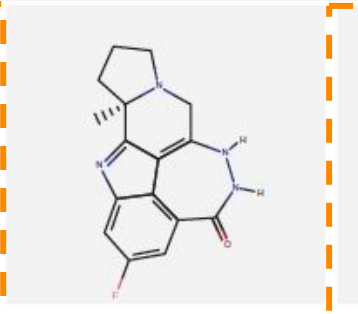
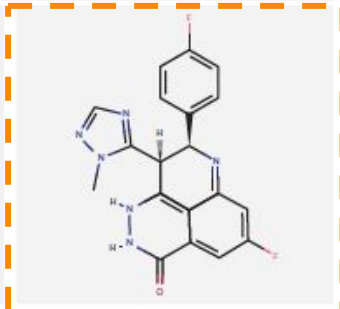
Disclosures

Timothy A. Yap

- **Employee of:** University of Texas MD Anderson Cancer Center, where I am Vice President, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)
- **Consultant for:** AbbVie, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Astex, AstraZeneca, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, BioCity Pharma, Blueprint, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis, Cybrexa, Daiichi Sankyo, Dark Blue Therapeutics, Diffusion, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos, F-Star, Genesis Therapeutics, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Prolynx, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Tolremo, Tome, Thryv Therapeutics, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi Inc, Xinthera, Zai Labs and ZielBio
- **Grant/Research support from:** Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Boundless Bio, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbius, F-Star, GlaxoSmithKline, Genentech, Haihe, Ideaya ImmuneSensor, Insilico Medicine, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tango, Tesaro, Vivace and Zenith
- **Stockholder in:** Seagen

Overview

1. **Targeting DDR: Going back to the beginning**
2. Navigating a post-PARP inhibitor world
3. Targeting WEE1: Potential registration strategies

						
	Veliparib	**Olaparib**	**Rucaparib**	**Niraparib**	**Pamiparib**	**Talazoparib**
Relative PARP-trapping capacity (nM)	-	++	++	++	++	+++
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Toxicities Most frequent	nausea (30%) fatigue (25%) lymphopenia (16%)	nausea (58-76%) fatigue (29-66%) vomiting (30-37%) diarrhea (21-33%) dysgeusia (27%) headache (20-25%)	nausea (75%) fatigue (69%) diarrhea (32%) dysgeusia (39%) LFT elevation (34%)	nausea (74%) fatigue (59%) LFT elevation (36%) vomiting (34%) headache (26%)	Limited early-phase trial data from abstracts only: nausea (56%) fatigue (40%)	nausea (49%) fatigue (50%) headache (33%) vomiting (25%) alopecia (25%) diarrhea (22%)
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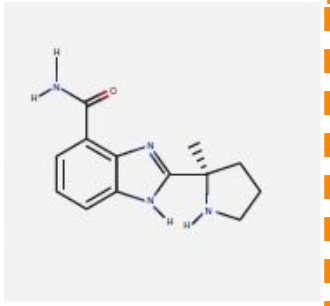
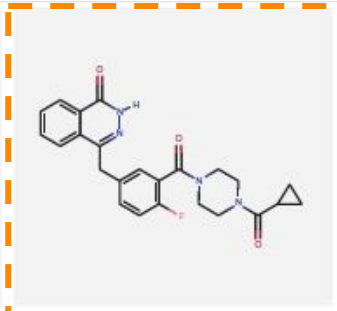
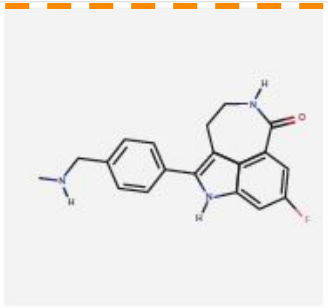
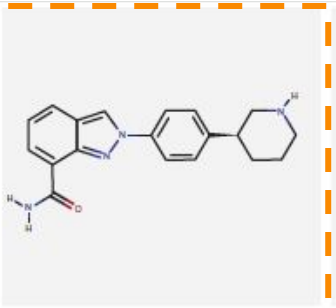
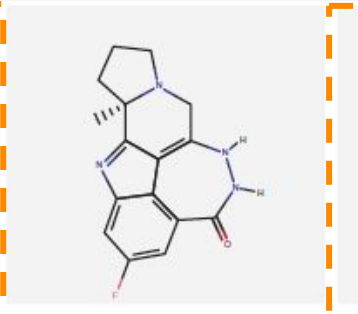
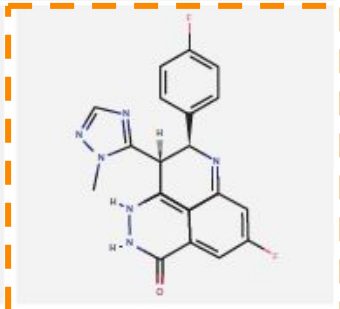
Adapted from Pilie et al, CCR (2019)

Proof of concept for a synthetic lethal approach in oncology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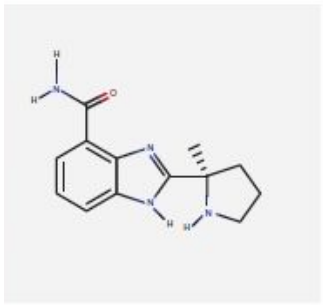
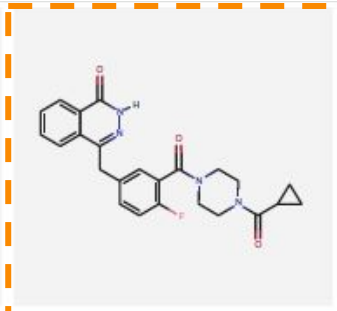
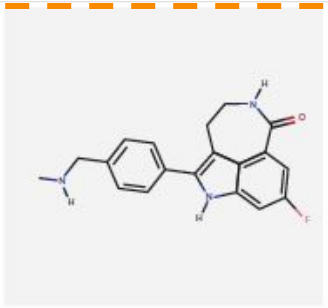
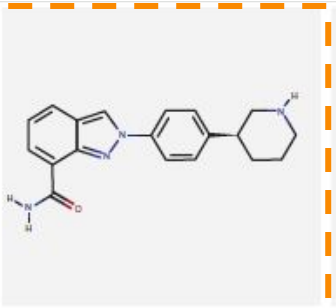
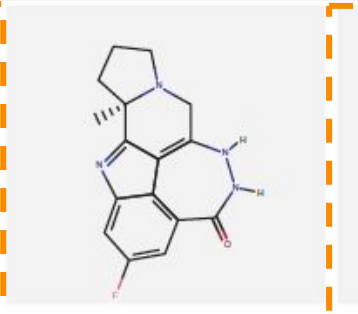
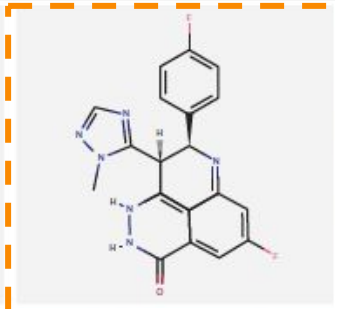
	 Veliparib	 Olaparib	 Rucaparib	 Niraparib	 Pamiparib	 Talazoparib
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- **1st generation PARP inhibitors are associated with and are limited by toxicities**
- **Not all patients with *BRCA1/2* mutated cancers will respond**
- **Drug resistance is nearly inevitable**
- **Potential to deepen responses and to increase durability of response**
- **Potential to widen the application of PARP and other DDR inhibitors**

Overview

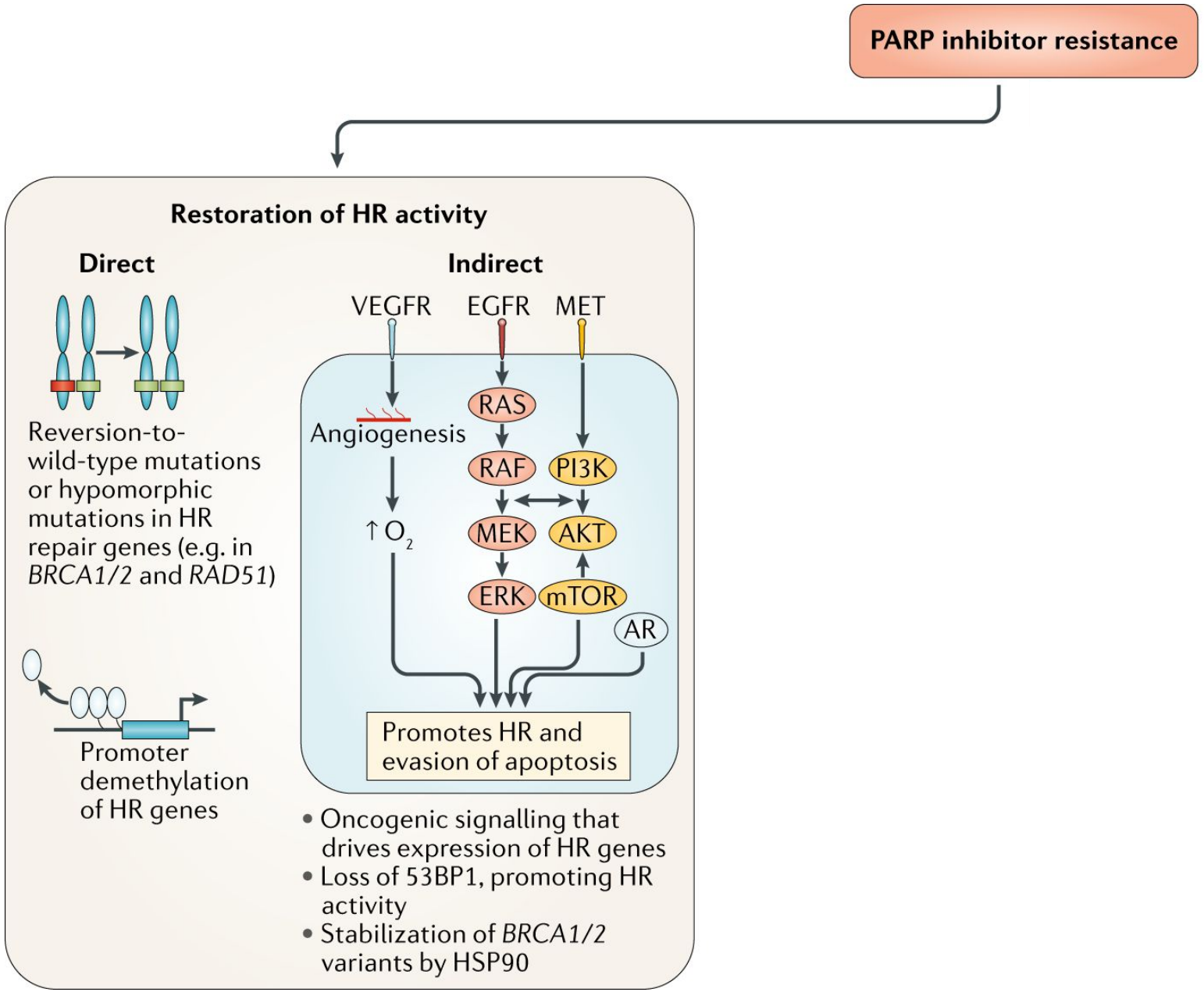
1. Targeting DDR: Going back to the beginning
2. Navigating a post-PARP inhibitor world
3. Targeting WEE1: Potential registration strategies



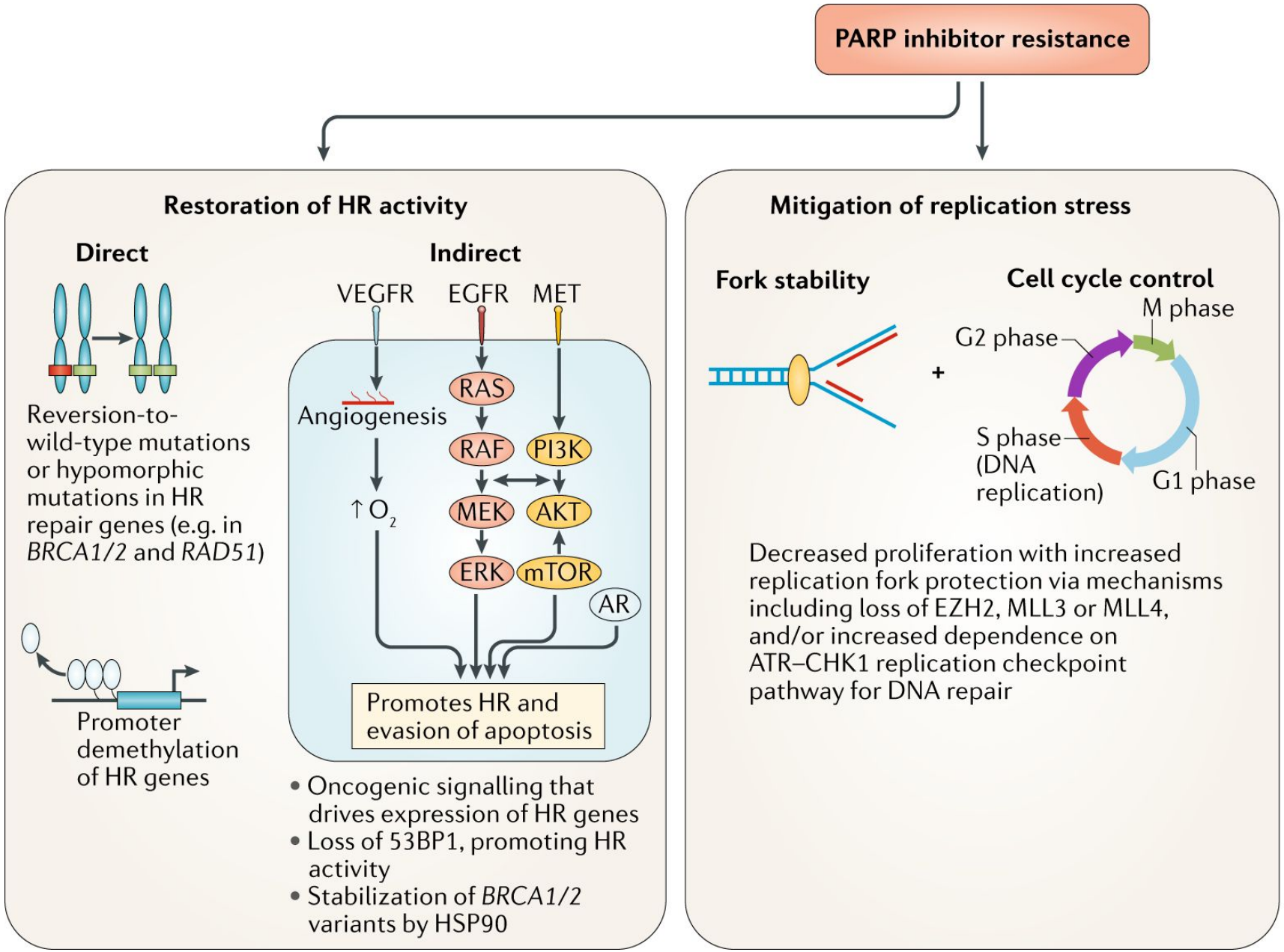
Navigating a post PARP inhibitor world

- **Resistance is complex and multifactorial: Need to better understand mechanisms involved**

- **Treatment strategies to overcome resistance will depend on underlying mechanisms**
  - New targets beyond PARP to develop new drugs
  - New predictive biomarkers to target
  - Rational combination strategies



Pilie, Tang, Mills and Yap. Nat Rev Clin Onc 2019



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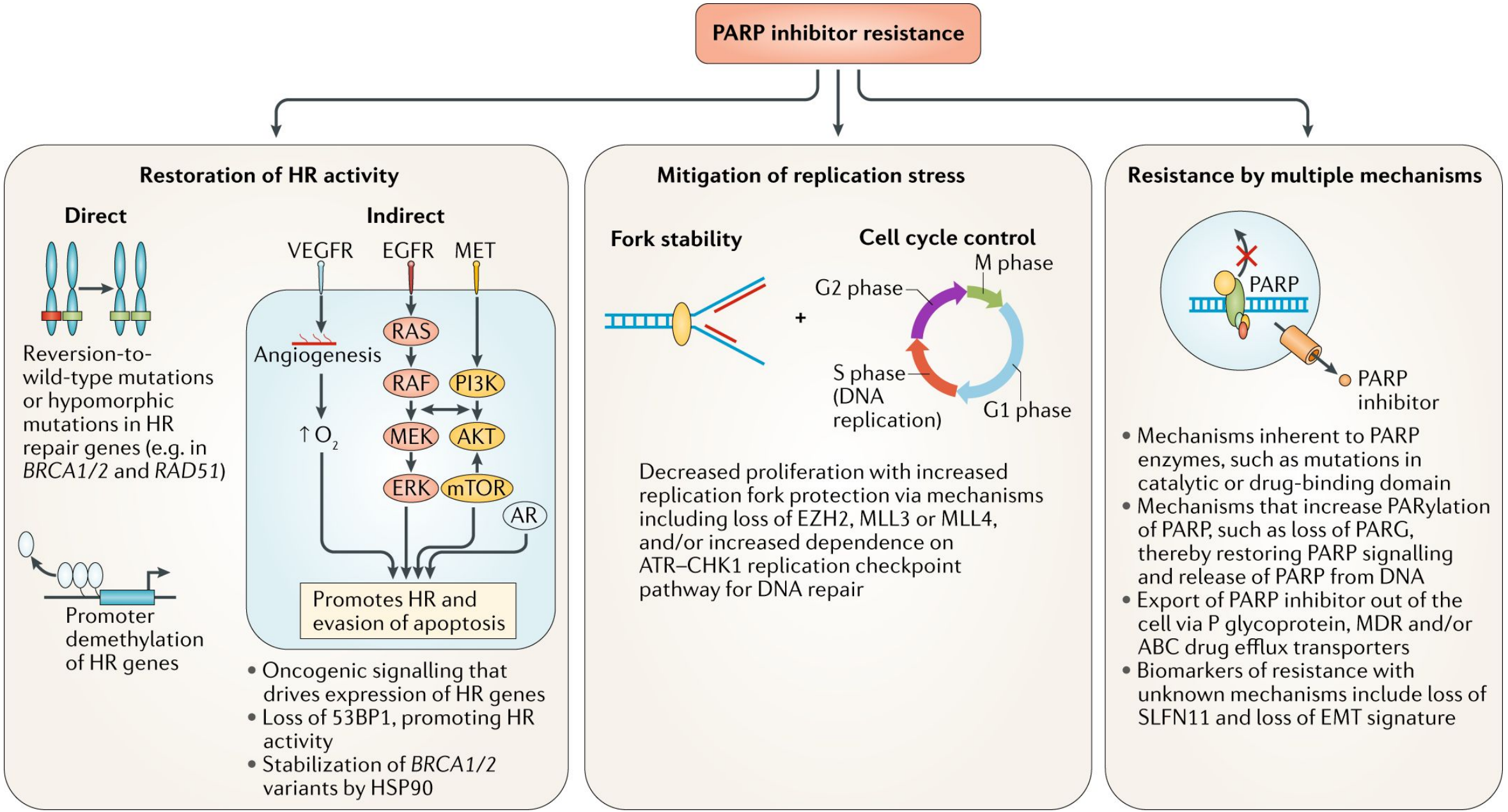
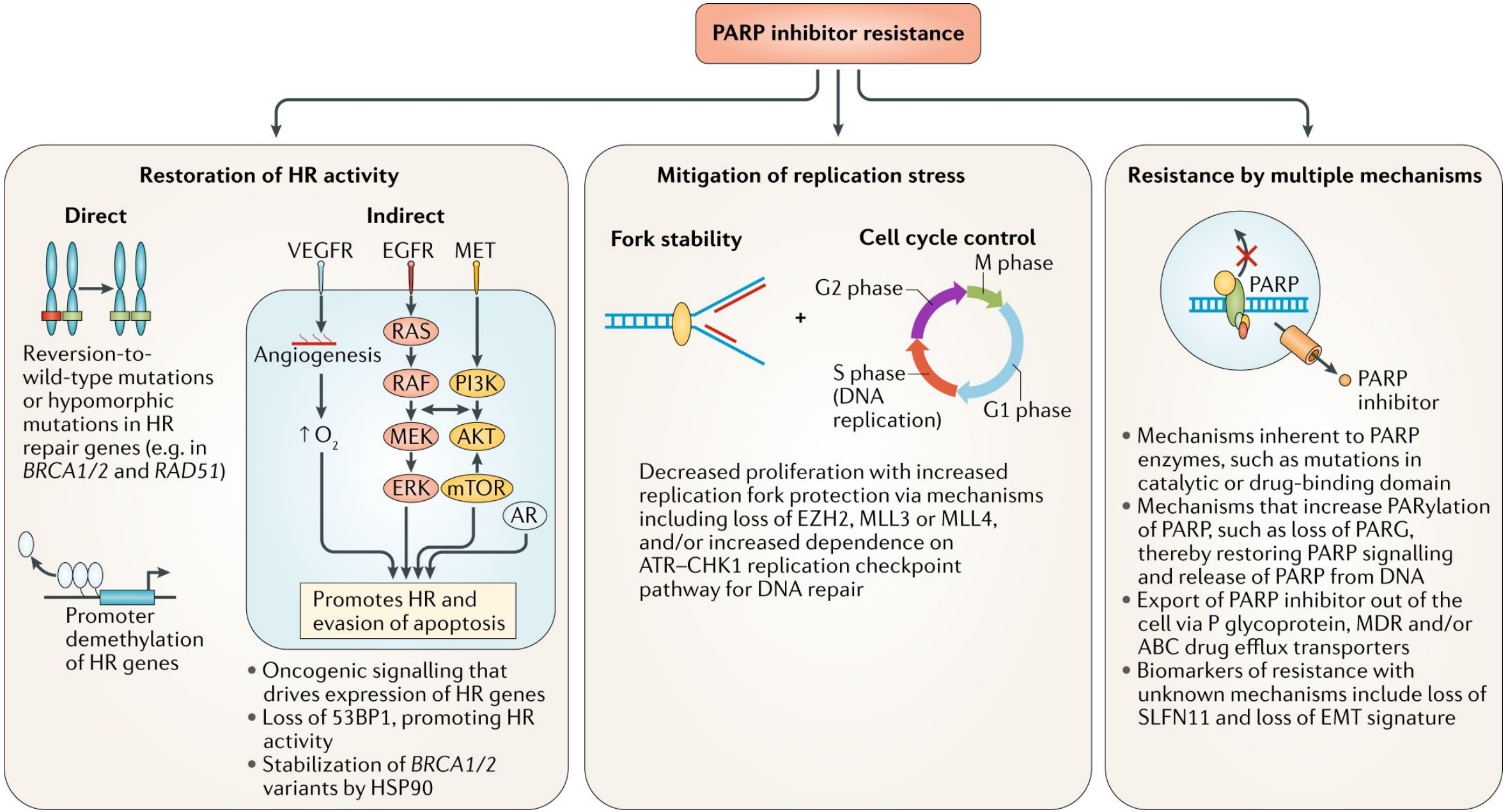


Pilie, Tang, Mills and Yap. Nat Rev Clin Onc 2019



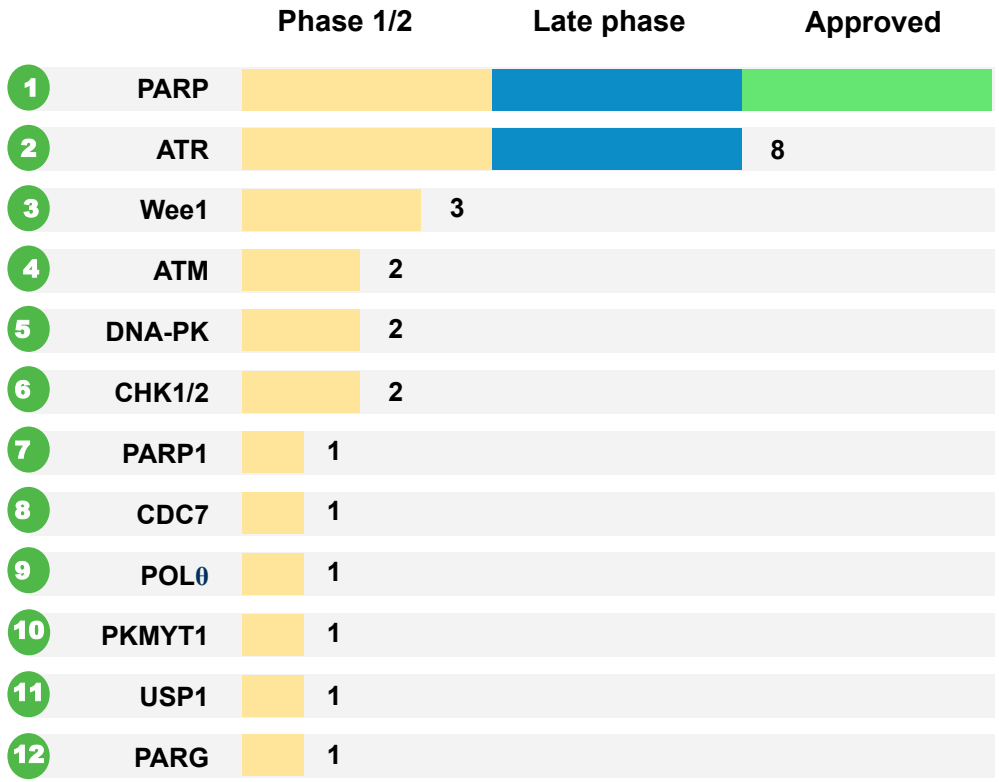
What do we currently have in our armamentarium?

Pilie, Tang, Mills and Yap. Nat Rev Clin Onc 2019

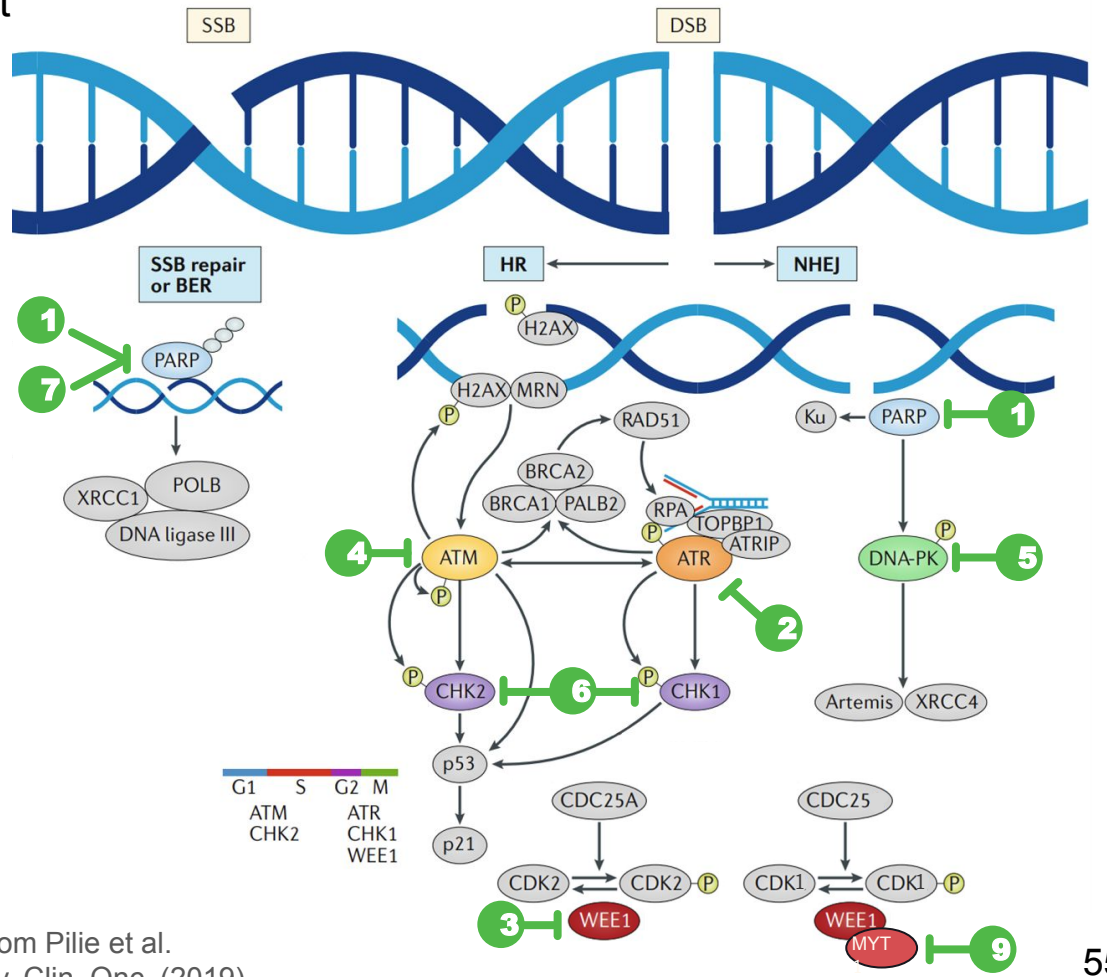
Beyond PARP: synthetic lethal interactions across DDR landscape

- The DNA damage response (DDR) therapeutic landscape is rapidly expanding beyond PARP inhibitors
- Discovery of novel, precision targets enabled by cancer genome sequencing and CRISPR
- Biomarker-driven patient selection to guide clinical development

Number of clinical assets by target



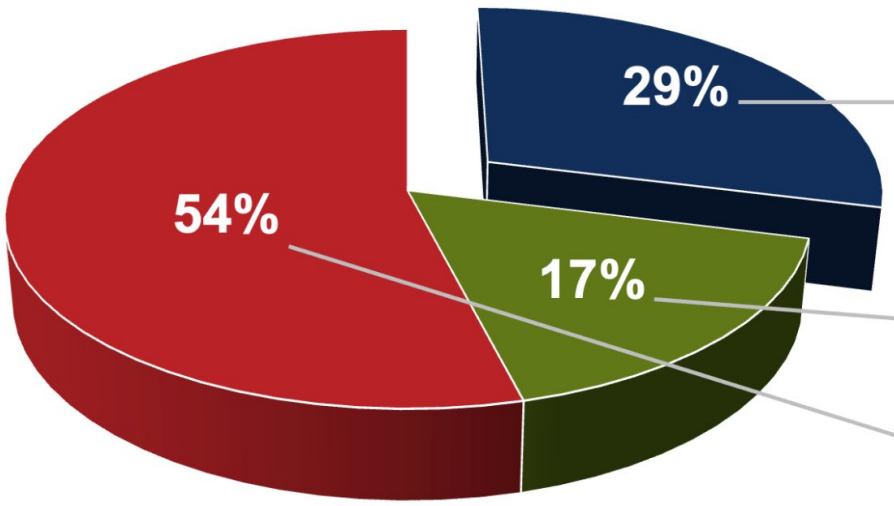
DDR inhibitors in preclinical studies: ALC1, FEN1, MRN, MLH1/2, APEX2, CIP2A, DNA Nucleases and many others



Adapted from Pilie et al.
Nature Rev. Clin. Onc. (2019)

Targeting synthetic lethality in precision oncology for untapped cancer lesions

Tapped and untapped cancer lesions



Focus of precision oncology for 20 years:
Gain of function (targetable, e.g. *EGFR*)

Gain of function (untargetable, e.g. CCNE1)

Loss of function (no known driver, e.g. going beyond *BRCA1/2*)

Untapped space (71%)

Courtesy of Dr. Mike Zinda

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 380;25 NEJM.ORG JUNE 20, 2019

"…known cancer targets represent a small minority of strong cancer dependencies … synthetic lethal targets are particularly attractive as new targets…"

William C. Hahn, NEJM 2019

Overview

1. Targeting DDR: Going back to the beginning
2. Navigating a post-PARP inhibitor world
3. **Targeting WEE1: Potential registration strategies**

Current Wee-1 kinase inhibitors in development[1]

ATRN-1051:
IND submission by end of 2023

SC0191:
1 Clinical Trial

DEBIO 0123:
4 Clinical Trials

IMP7068:
1 Clinical Trial

NUV 569:
No ongoing trials following 2022 deprioritization

SGR3515:
IND-enabling studies ongoing for 2024 submission

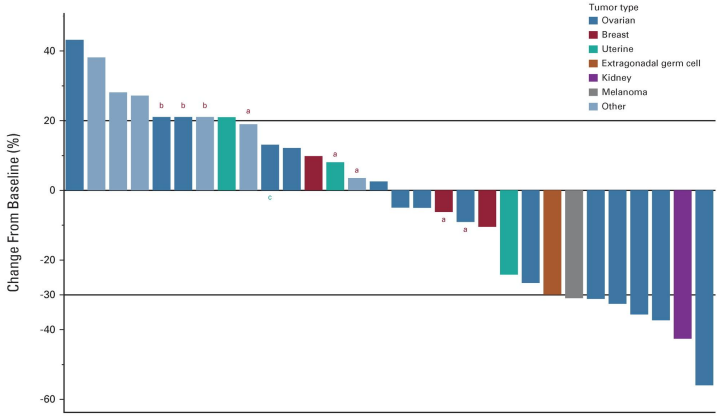
Zn-c3:
19 Clinical Trials

[1]Based on publicly available information.

Multiple registration strategies for WEE1 inhibitors

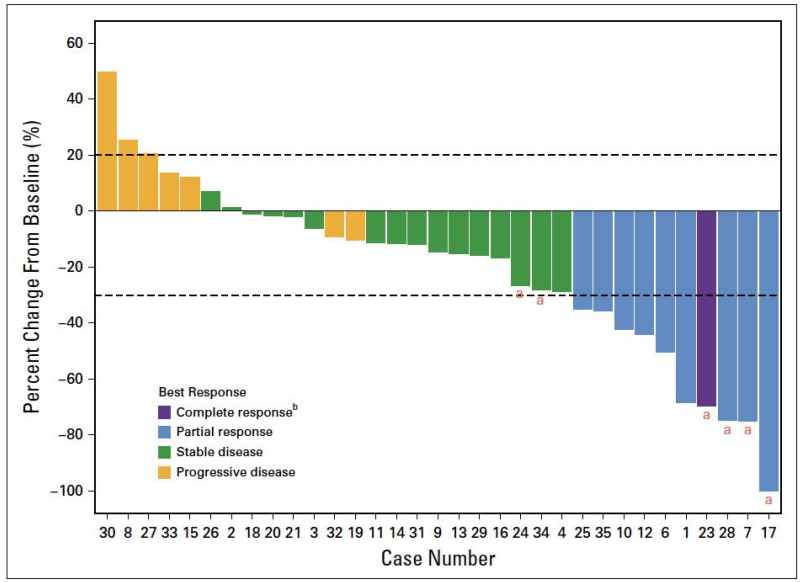
Monotherapy approaches

1. Moving DDR label beyond *BRCAm* cancers
e.g. CCNE1 amplified or cyclin overexpressed tumors



Fu et al, JCO (2023)

2. Targeting Uterine Serous Carcinoma

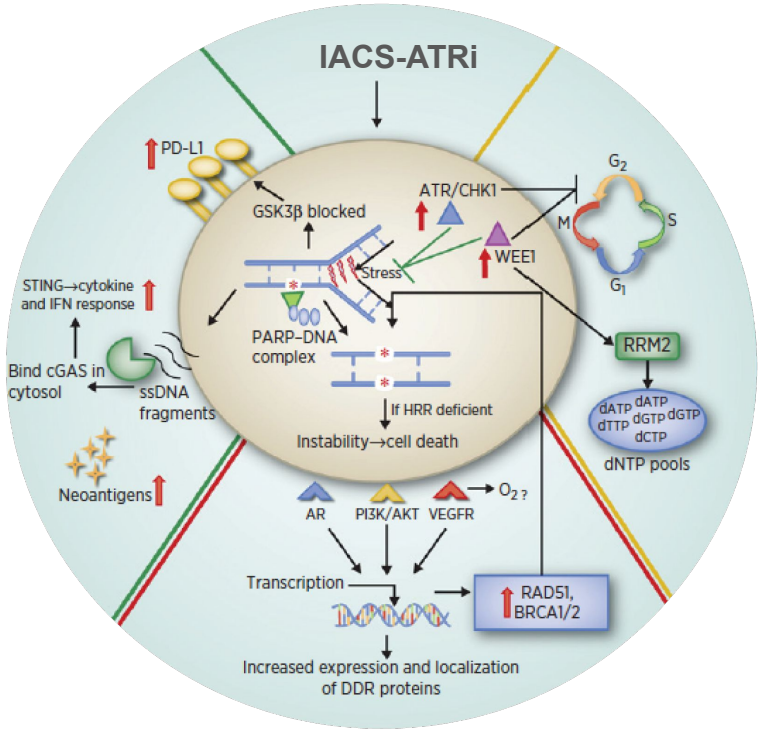


Liu et al, JCO (2021)

Combination approaches

ADC combos
e.g. ADC + WEE1i

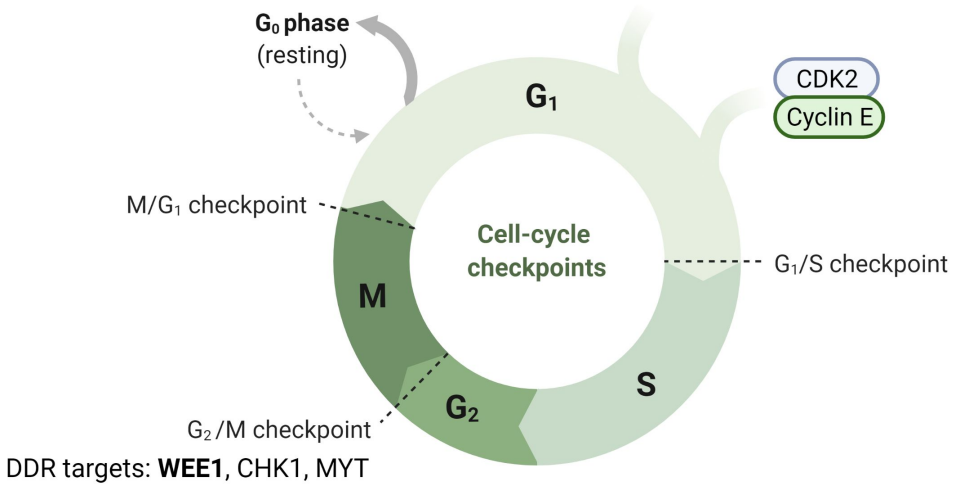
IO combos
e.g. PD-1/L1i + WEEi



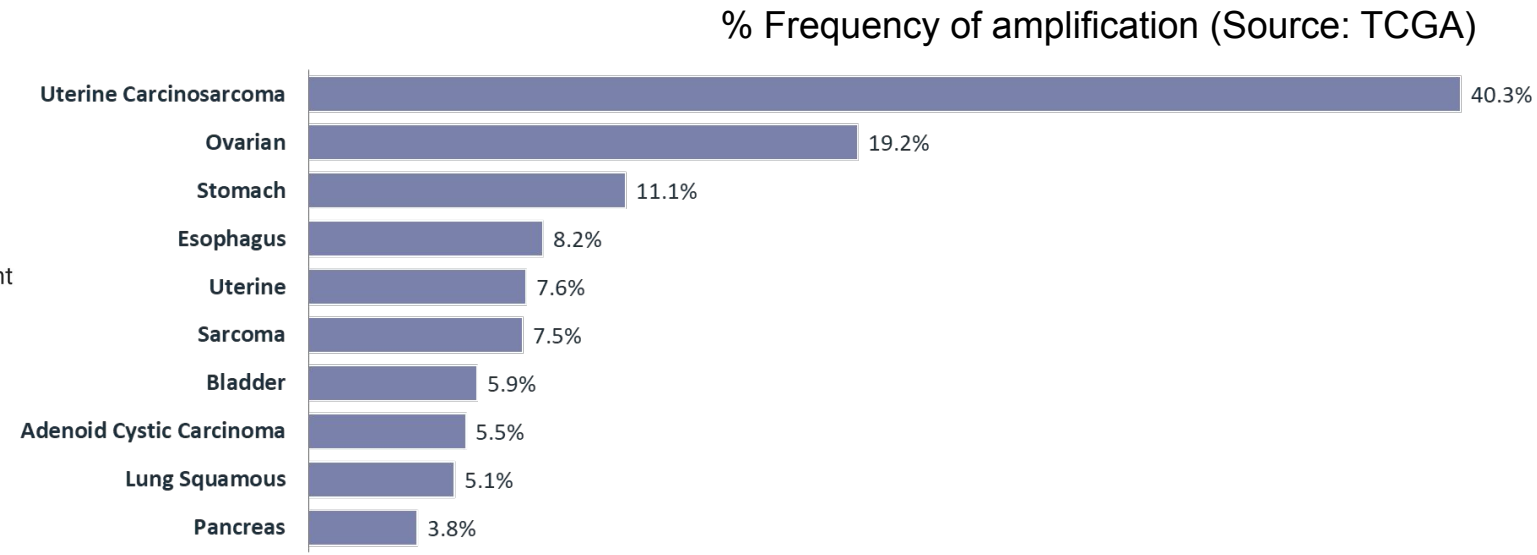
DDR combos
e.g. PARPi + WEE1i in 'PARP after PARP' resistance setting

Chemical BRCAness combos
e.g. Targeted agents to induce BRCAness phenotype in HR proficient tumors to synergize with WEE1i

Targeting CCNE high tumors



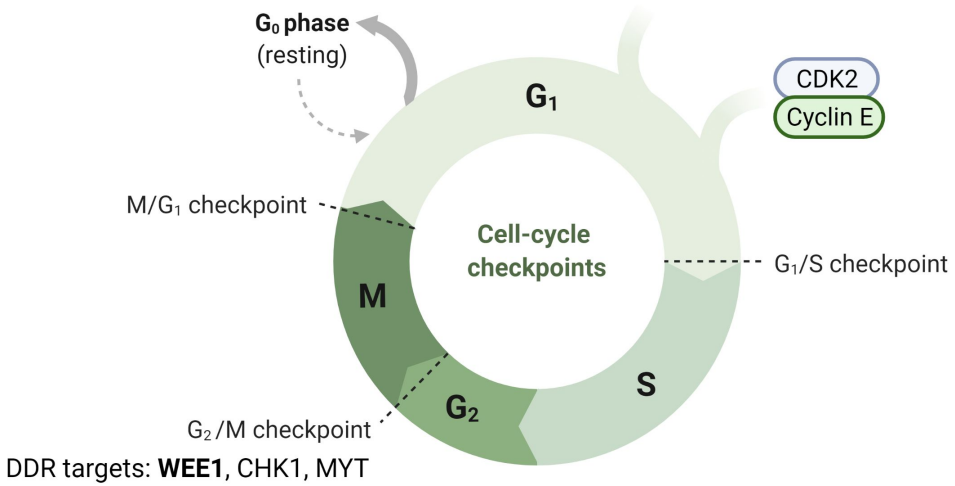
Top 10 tumor types with highest frequency of CCNE1 amplification



Fu et al, AACR 2020

- Cyclin E1 amplification, causing over-expression, is found in 2-40% of human tumors
- Promotes genetic instability
- Correlates with worse overall survival

Targeting CCNE high tumors



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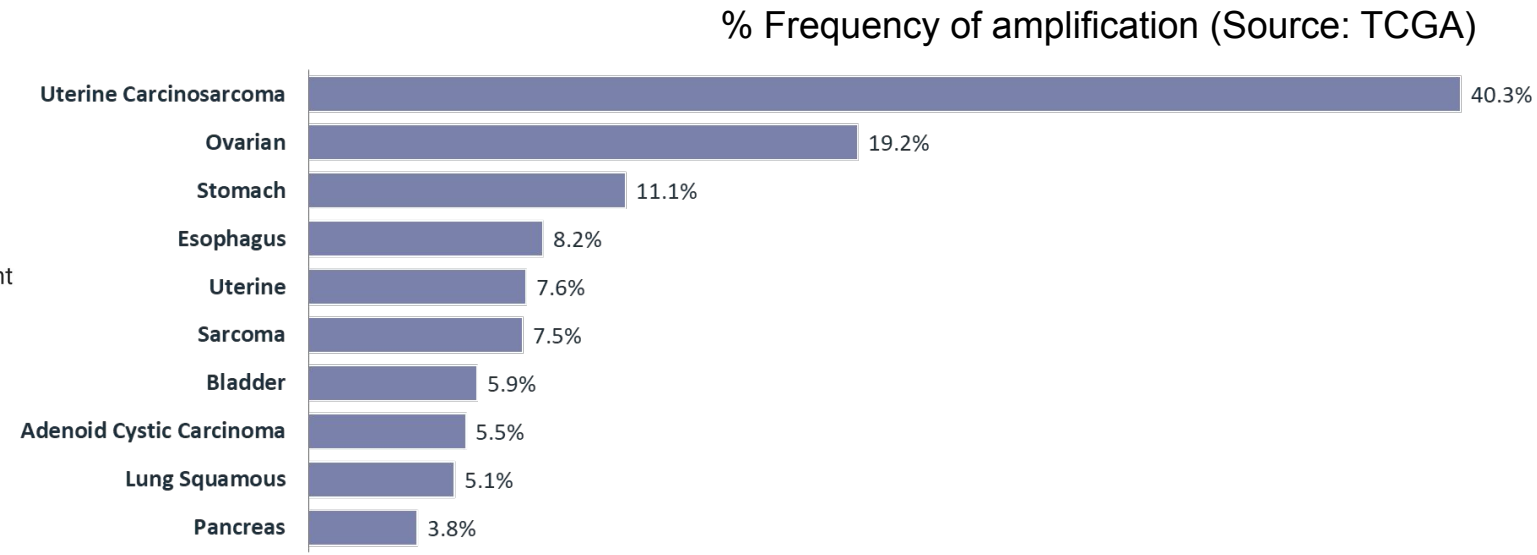

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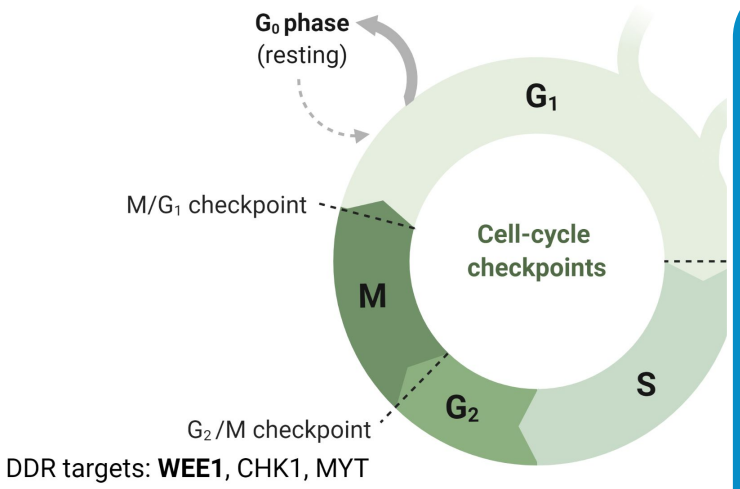
Hypothesis: Cancers harboring *CCNE1* amplification will be highly sensitive to WEE1 inhibition

Targeting CCNE high tumors



Top 10 tumor types with highest frequency of CCNE1 amplification

ency of amplification (Source: TCGA)



Fu et al, AACR 2020

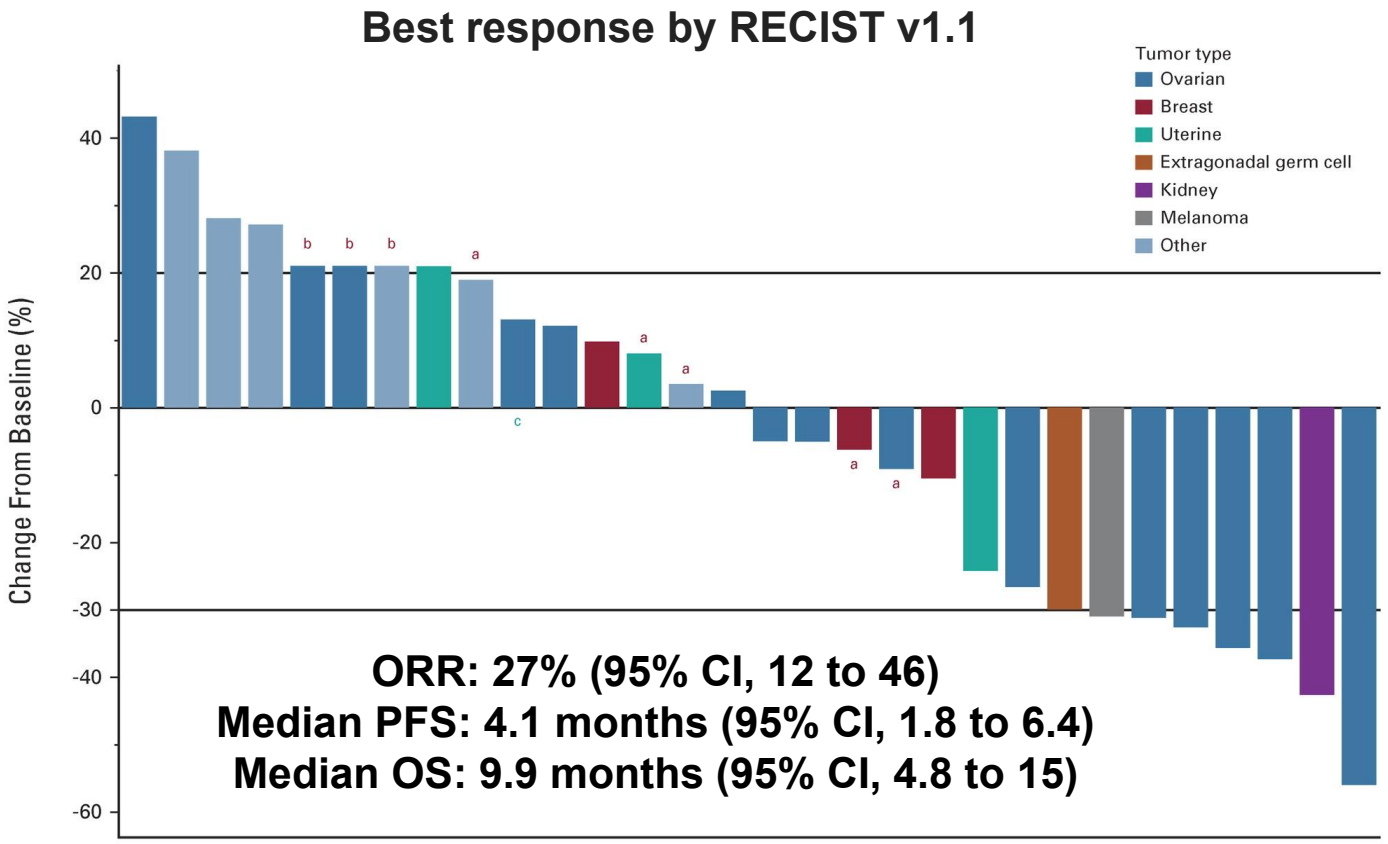
Opportunity in CCNE1-high tumors

- Monotherapy opportunity with clear biomarker
- CCNE1 amplification estimated to be ~20% of HGSOC, protein overexpression 50-80%
- CCNE1-amp associated with Pt resistance and mutually exclusive to BRCAm
- Potential expansion into other CCNE-high settings eg uterine, TNBC, gastroesophageal, bladder

- Cyclin E1 amplification, c … human tumors
- Promotes genetic instabi …
- Correlates with worse ove …

Hypothesis: Cancers harboring *CCNE1* amplification will be highly sensitive to WEE1 inhibition

Antitumor activity of adavosertib in patients with *CCNE1* amplification



TEAEs in ≥ 20% of patients

TEAE	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	All Grades, No. (%)
Diarrhea	21 (70)	4 (13.3)	5 (16.7)	0 (0)	30 (100)
Anemia	8 (26.7)	9 (30)	9 (30)	0 (0)	26 (86.7)
Nausea	14 (46.7)	7 (23.3)	5 (16.7)	0 (0)	26 (86.7)
Platelet count decreased	11 (36.7)	8 (26.7)	3 (10)	3 (10)	25 (83.3)
Fatigue	11 (36.7)	8 (26.7)	3 (10)	0 (0)	22 (73.3)
Hypoalbuminemia	11 (36.7)	8 (26.7)	1 (3.3)	0 (0)	20 (66.7)
Abdominal pain	7 (23.3)	6 (20)	5 (16.7)	0 (0)	18 (60)
Edema limbs	13 (43.3)	2 (6.7)	0 (0)	0 (0)	15 (50)
Hyponatremia	11 (36.7)	1 (3.3)	2 (6.7)	0 (0)	14 (46.7)
Vomiting	8 (26.7)	3 (10)	3 (10)	0 (0)	14 (46.7)
Back pain	8 (26.7)	3 (10)	2 (6.7)	0 (0)	13 (43.3)
WBC decreased	6 (20)	4 (13.3)	2 (6.7)	1 (3.3)	13 (43.3)
Constipation	11 (36.7)	1 (3.3)	0 (0)	0 (0)	12 (40)
Lymphocyte count decreased	5 (16.7)	5 (16.7)	2 (6.7)	0 (0)	12 (40)
Hypocalcemia	7 (23.3)	2 (6.7)	1 (3.3)	0 (0)	10 (33.3)
Neutrophil count decreased	2 (6.7)	2 (6.7)	1 (3.3)	5 (16.7)	10 (33.3)
ALP increased	6 (20)	2 (6.7)	1 (3.3)	0 (0)	9 (30)
Anorexia	4 (13.3)	5 (16.7)	0 (0)	0 (0)	9 (30)
Dyspnea	9 (30)	0 (0)	0 (0)	0 (0)	9 (30)
Dehydration	1 (3.3)	3 (10)	4 (13.3)	0 (0)	8 (26.7)
Dizziness	6 (20)	2 (6.7)	0 (0)	0 (0)	8 (26.7)
ALT increased	6 (20)	1 (3.3)	0 (0)	0 (0)	7 (23.3)
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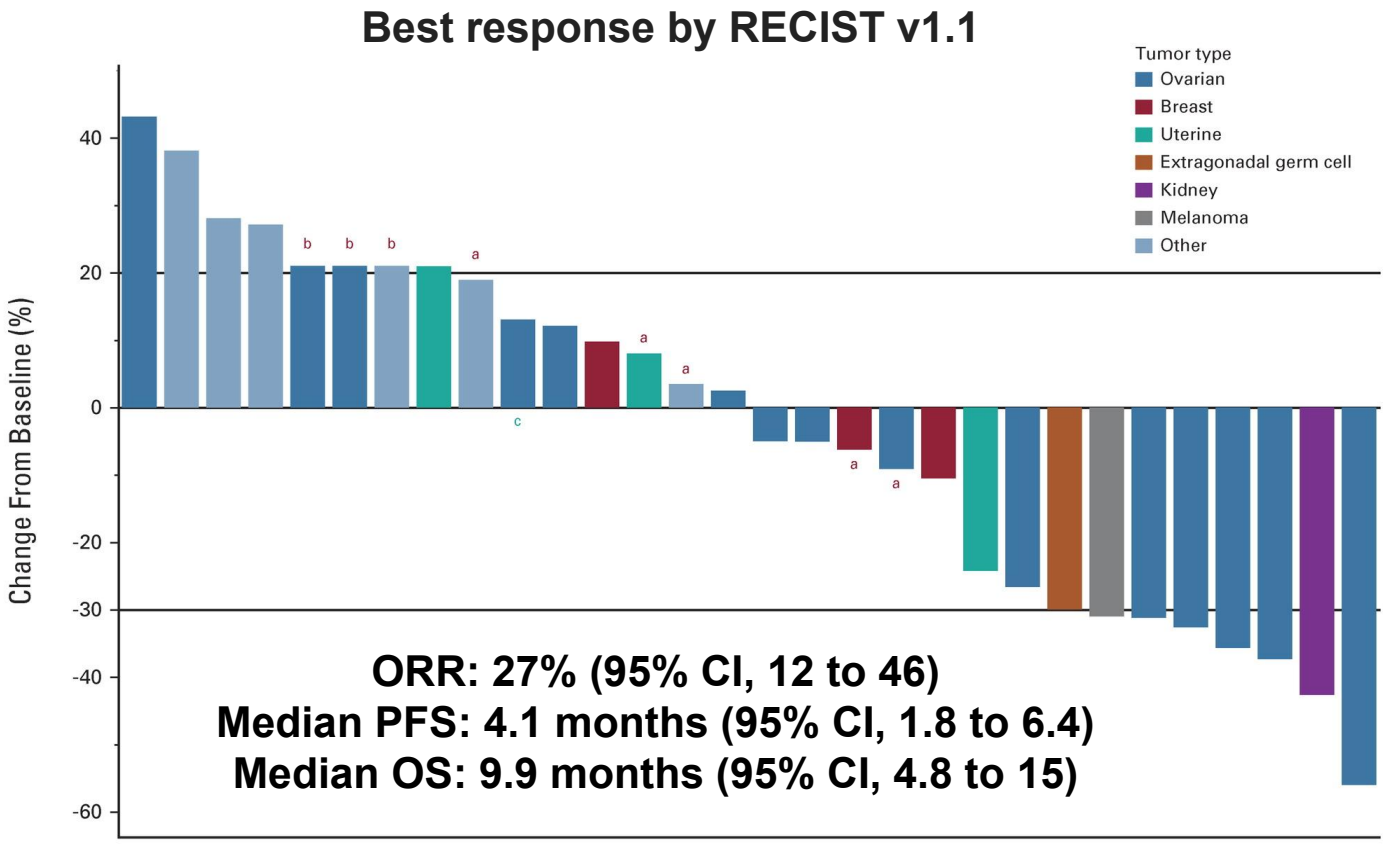
Headache	6 (20)	1 (3.3)	0 (0)	0 (0)	7 (23.3)
Pain in extremity	3 (10)	4 (13.3)	0 (0)	0 (0)	7 (23.3)
Creatinine increased	3 (10)	2 (6.7)	1 (3.3)	0 (0)	6 (20)
Hyperglycemia	3 (10)	2 (6.7)	1 (3.3)	0 (0)	6 (20)

Abbreviations: ALP, alkaline phosphatase; TEAE, treatment-emergent adverse event.

Fu S. et al, Journal of Clinical Oncology, 2022

Antitumor activity of adavosertib in patients with *CCNE1* amplification



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Fu S. et al, Journal of Clinical Oncology, 2022

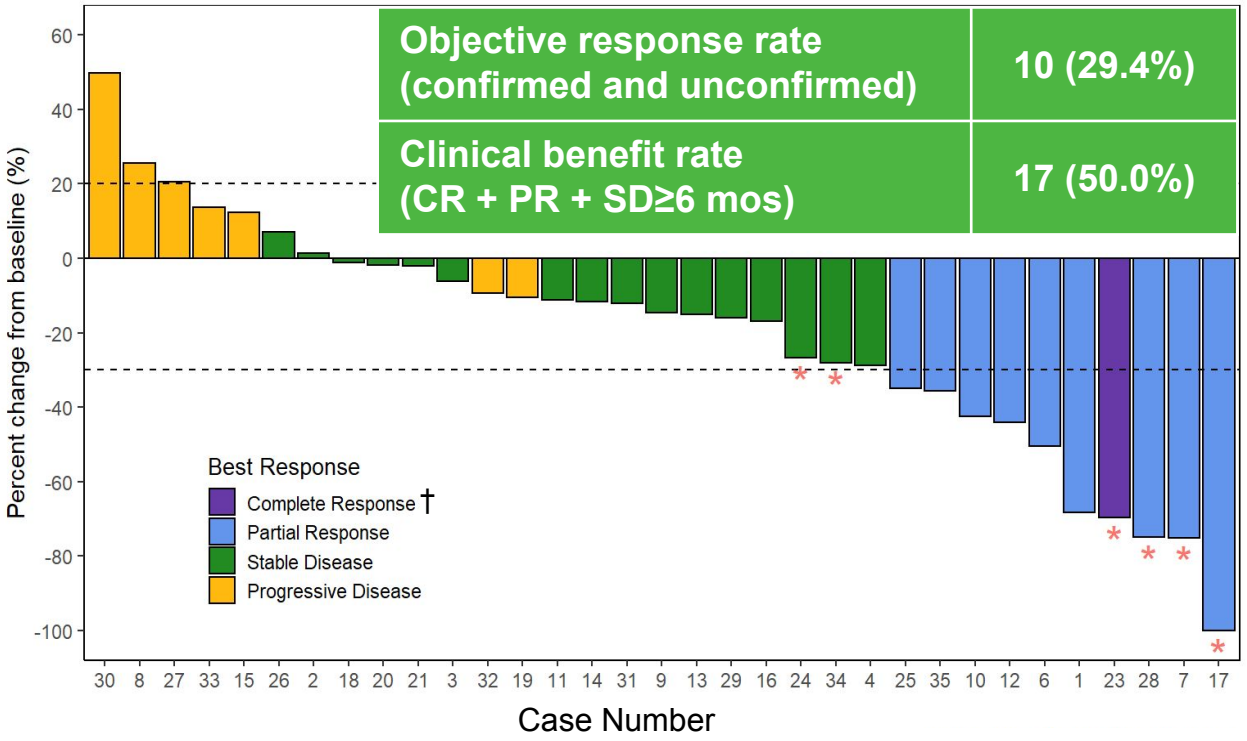
- Will other WEE1 inhibitors widen therapeutic window, e.g. Zn-c3? SGR-3515?
- How about PKMYT1 inhibitors and CDK2 inhibitors?

WEE1 inhibitor monotherapy activity

Phase 2 trial of adavosertib in recurrent uterine serous carcinoma

Hypothesis: Presence of concomitant cell-cycle dysregulation and high RS in USC will predict for increased sensitivity to WEE1 inhibition.

Median duration of response: 9 months (95% CI 5.29-NA)



Liu et al, ASCO 2020

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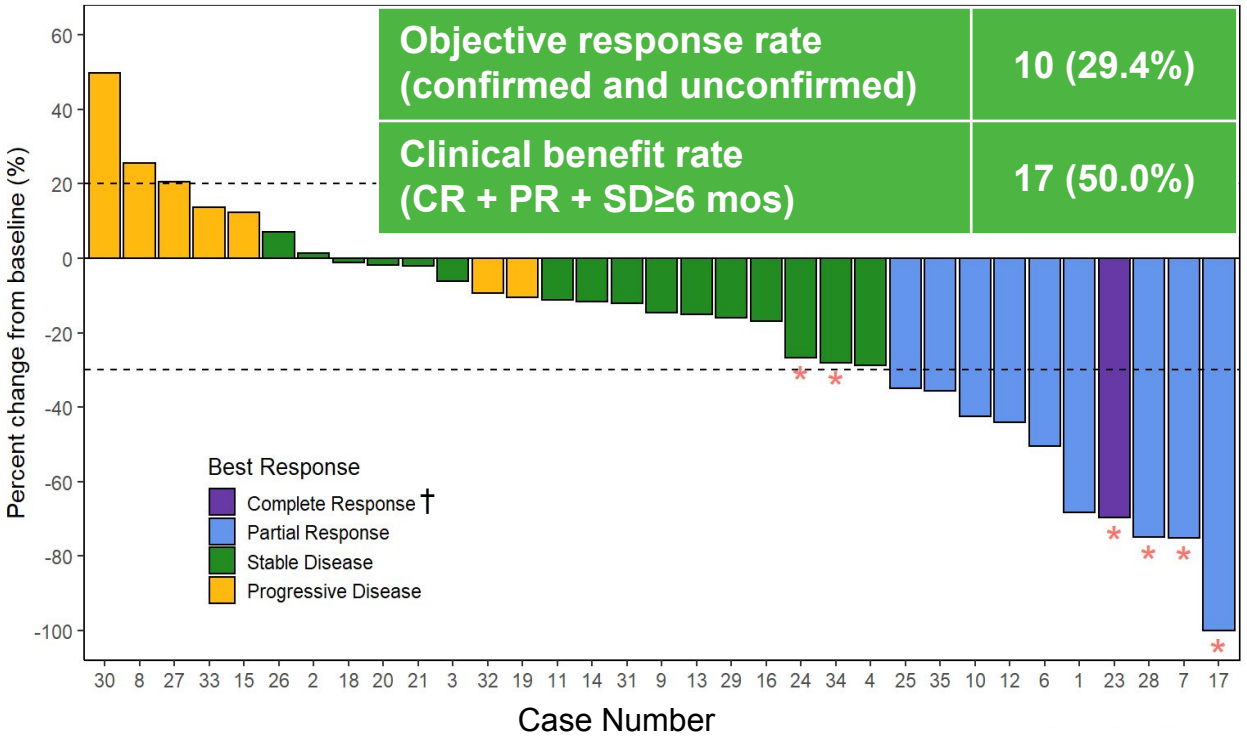
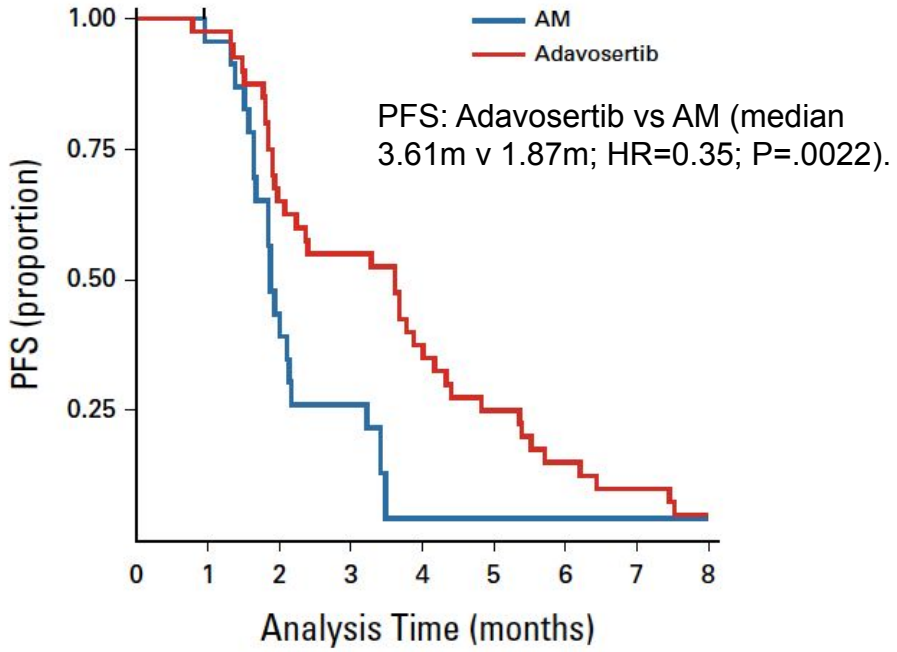


Liu et al, ASCO 2020

Focus4 Ph 2 Trial: Newly dx TP53+KRAS mCRC stable or responding after 16 weeks of chemo randomized 2:1 adavosertib vs AM

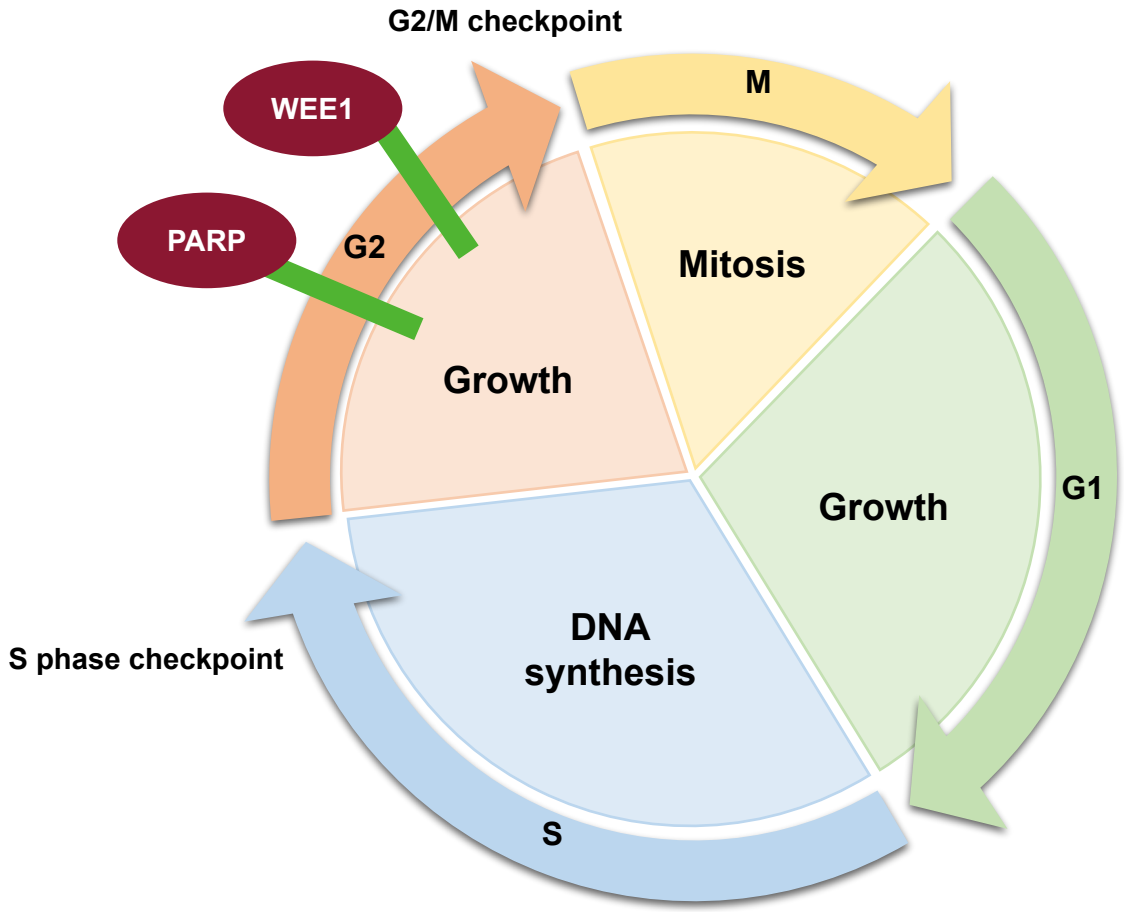
Hypothesis: Aberrations in DNA replication seen in mCRC with RAS+TP53 mutations will sensitize tumors to WEE1 inhibition



Seligmann et al, JCO 2021

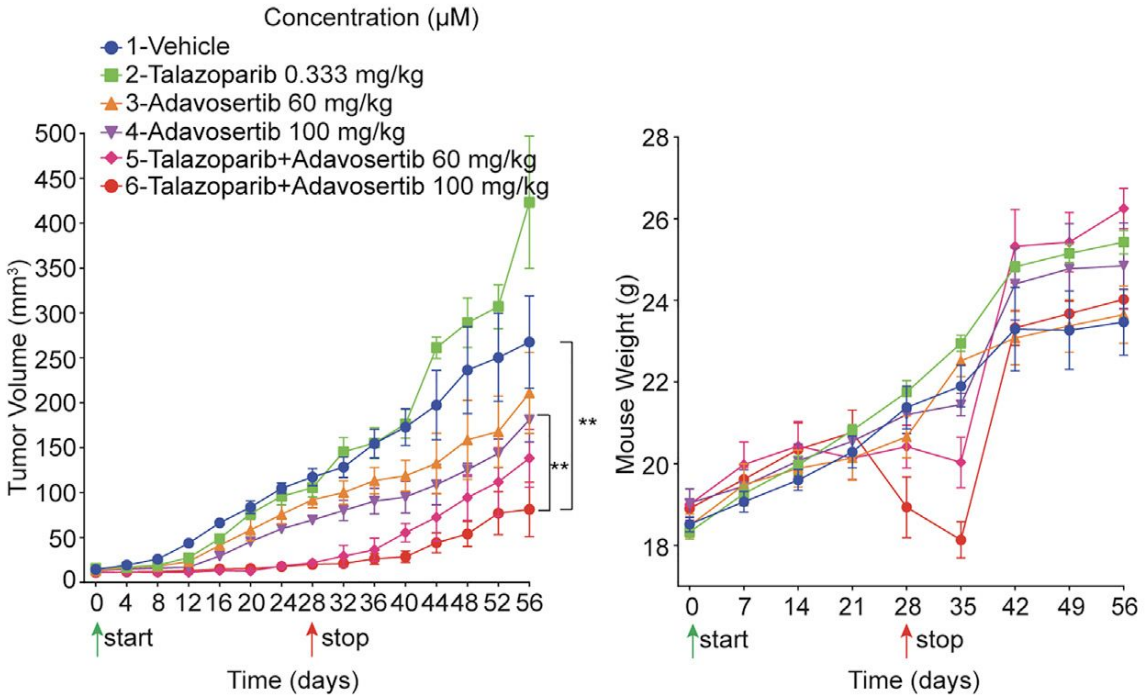
Development of PARP and WEE1 inhibitor combinations

- Aberrant DNA Damage Response (DDR) and replication stress (RS) result in accumulation of DNA damage, contributing to tumor progression
- PARP inhibitors induce DDR and RS resulting in G2 arrest
- WEE1 inhibitors abrogate G2 arrest, allowing cells with unrepaired DNA damage to enter mitosis and undergo mitotic catastrophe



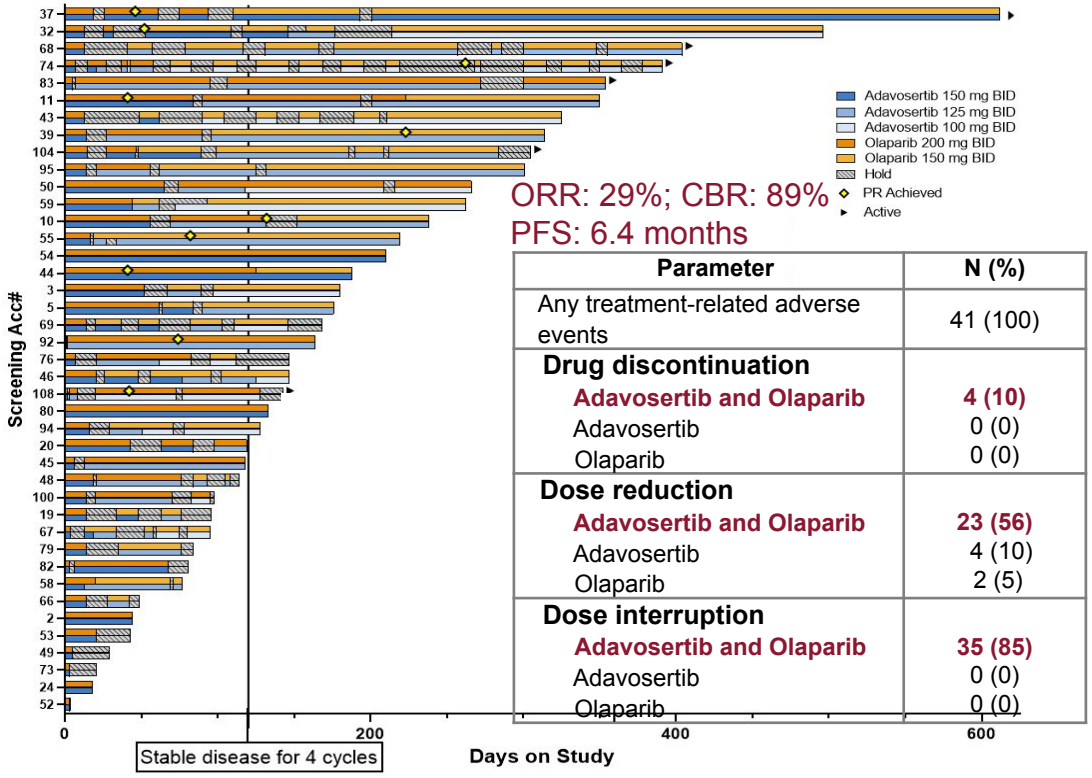
Fang et al, Cancer Cell 2019

The combination of olaparib and adavosertib has demonstrated promising antitumor activity



OVCAR8 were injected subcutaneously and grown for 2 weeks in nude mice. p value: one-way ANOVA. **p < 0.01.

Fang et al, Cancer Cell 2019



ORR: 29%; CBR: 89%
PFS: 6.4 months

Parameter	N (%)
Any treatment-related adverse events	41 (100)
Drug discontinuation	
Adavosertib and Olaparib	**4 (10)**
Adavosertib	0 (0)
Olaparib	0 (0)
Dose reduction	
Adavosertib and Olaparib	**23 (56)**
Adavosertib	4 (10)
Olaparib	2 (5)
Dose interruption	
Adavosertib and Olaparib	**35 (85)**
Adavosertib	0 (0)
Olaparib	0 (0)

Phase II study of concurrent adavosertib + olaparib in PARPi-resistant ovarian cancer patients

Westin et al, ASCO 2021

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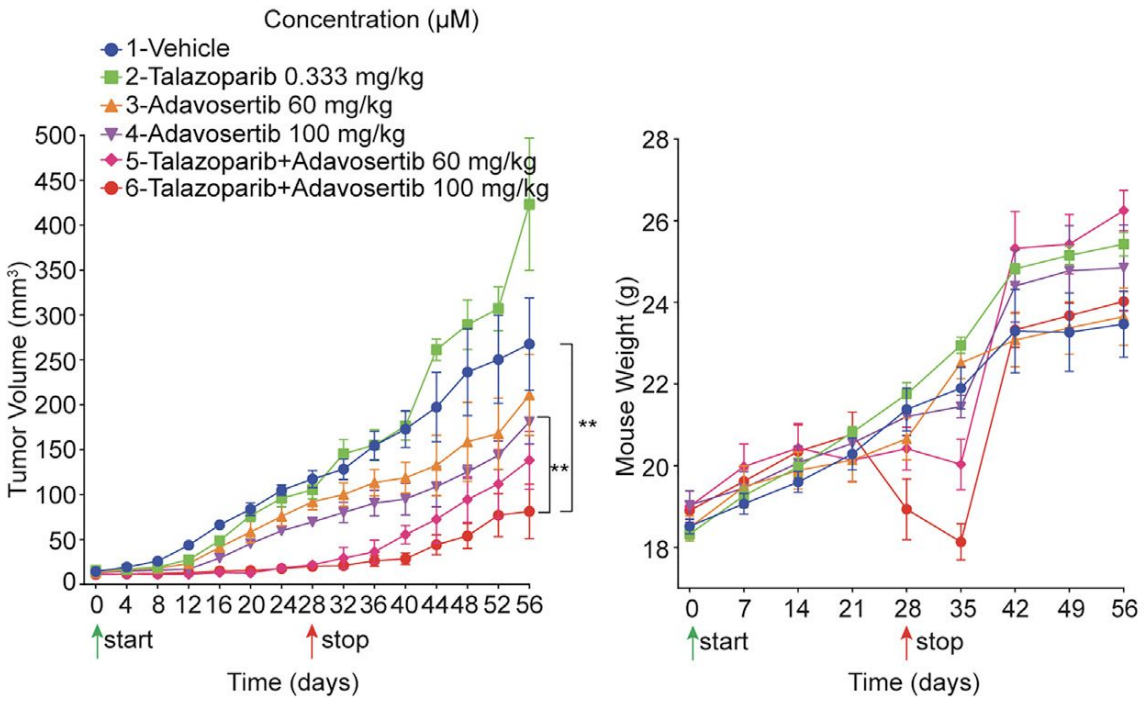

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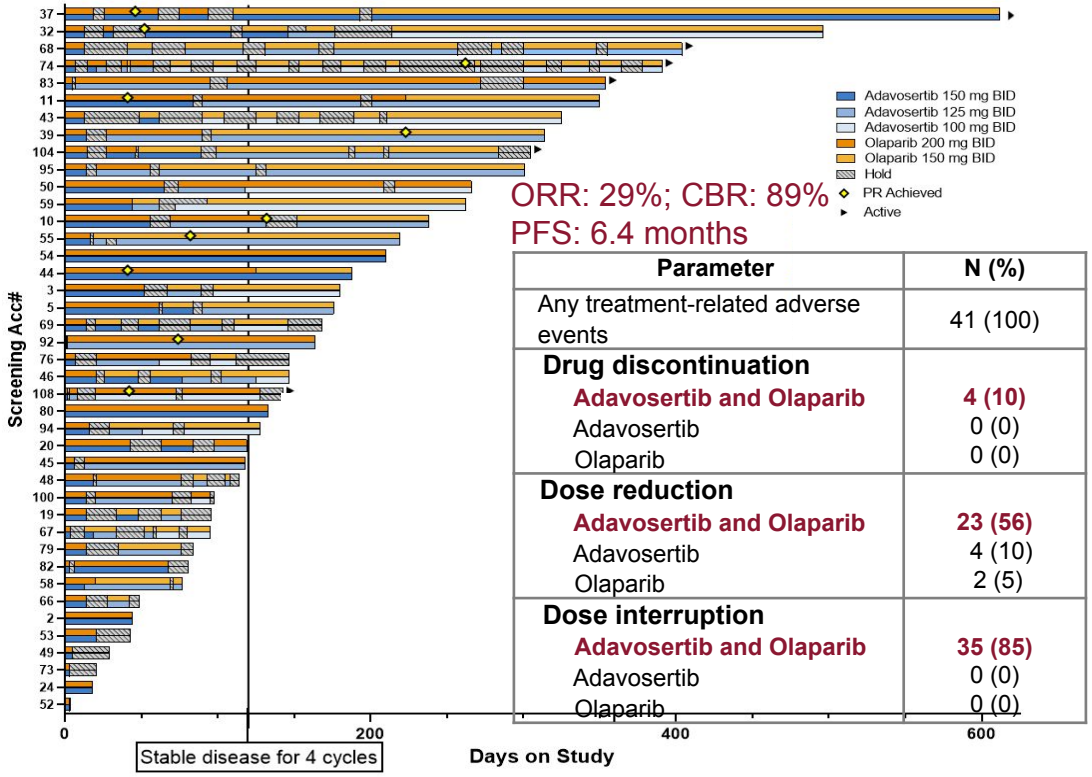

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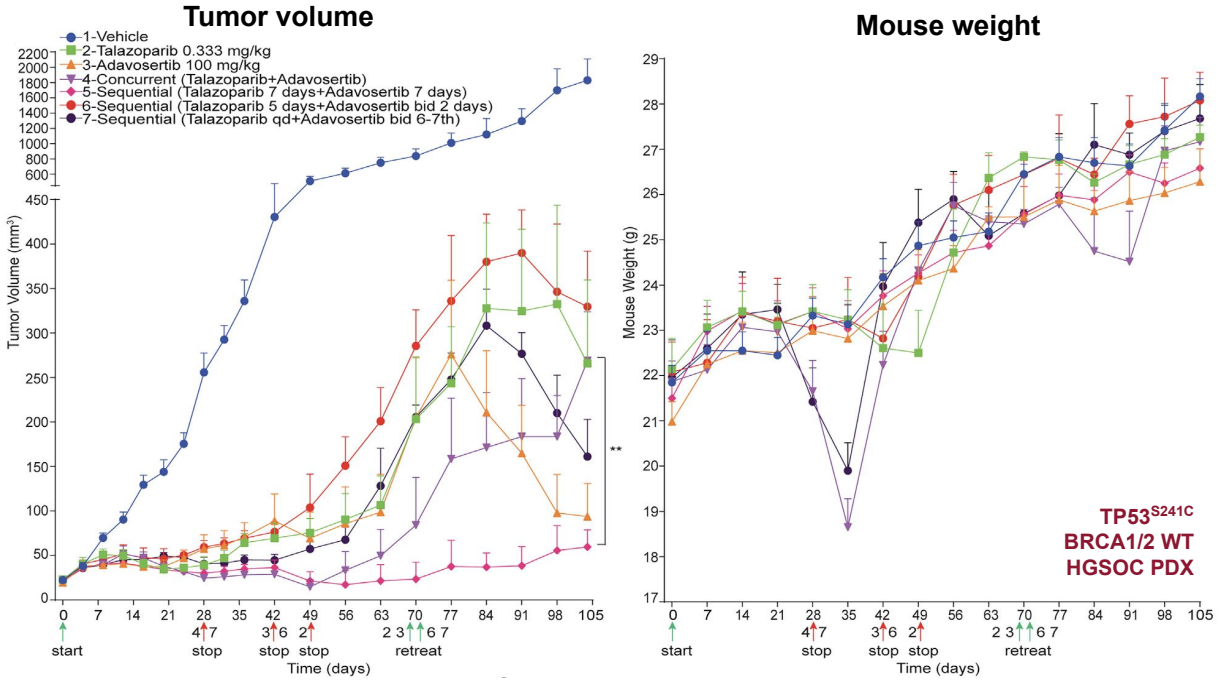
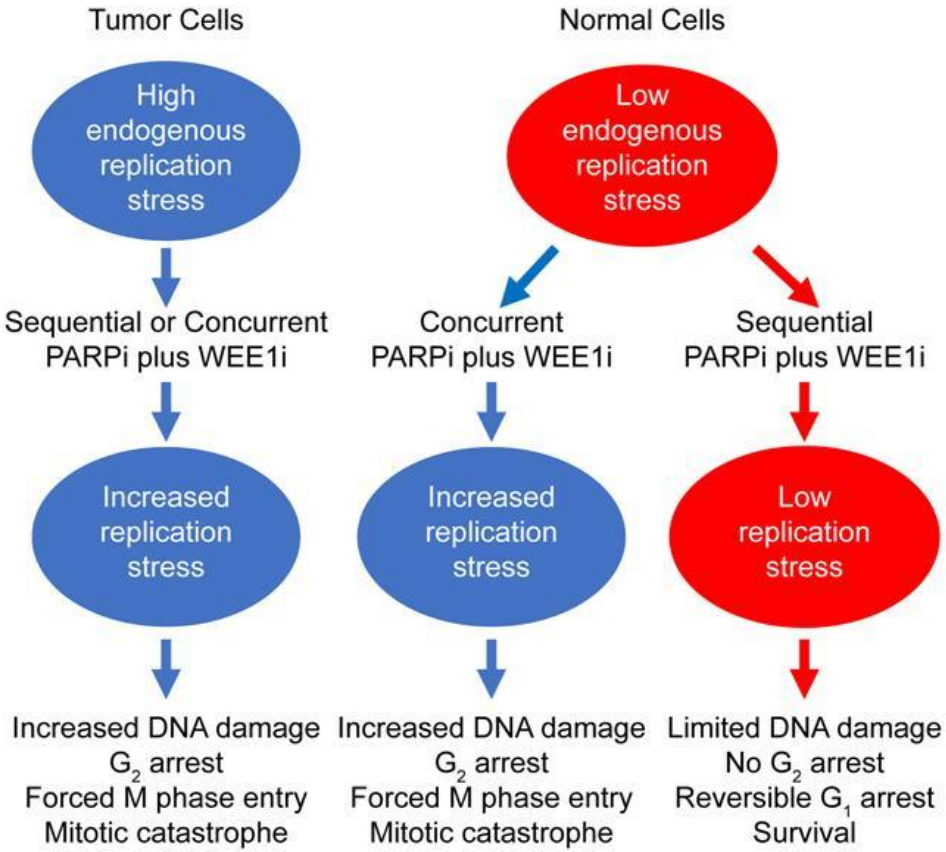
Westin et al, ASCO 2021

While promising antitumor activity has been observed, overlapping PARP and WEE1 inhibitor toxicities have made it challenging to develop well tolerated concurrent combinations of olaparib + adavosertib

Sequential PARPi + WEE1i combination minimizes toxicity while preserving efficacy

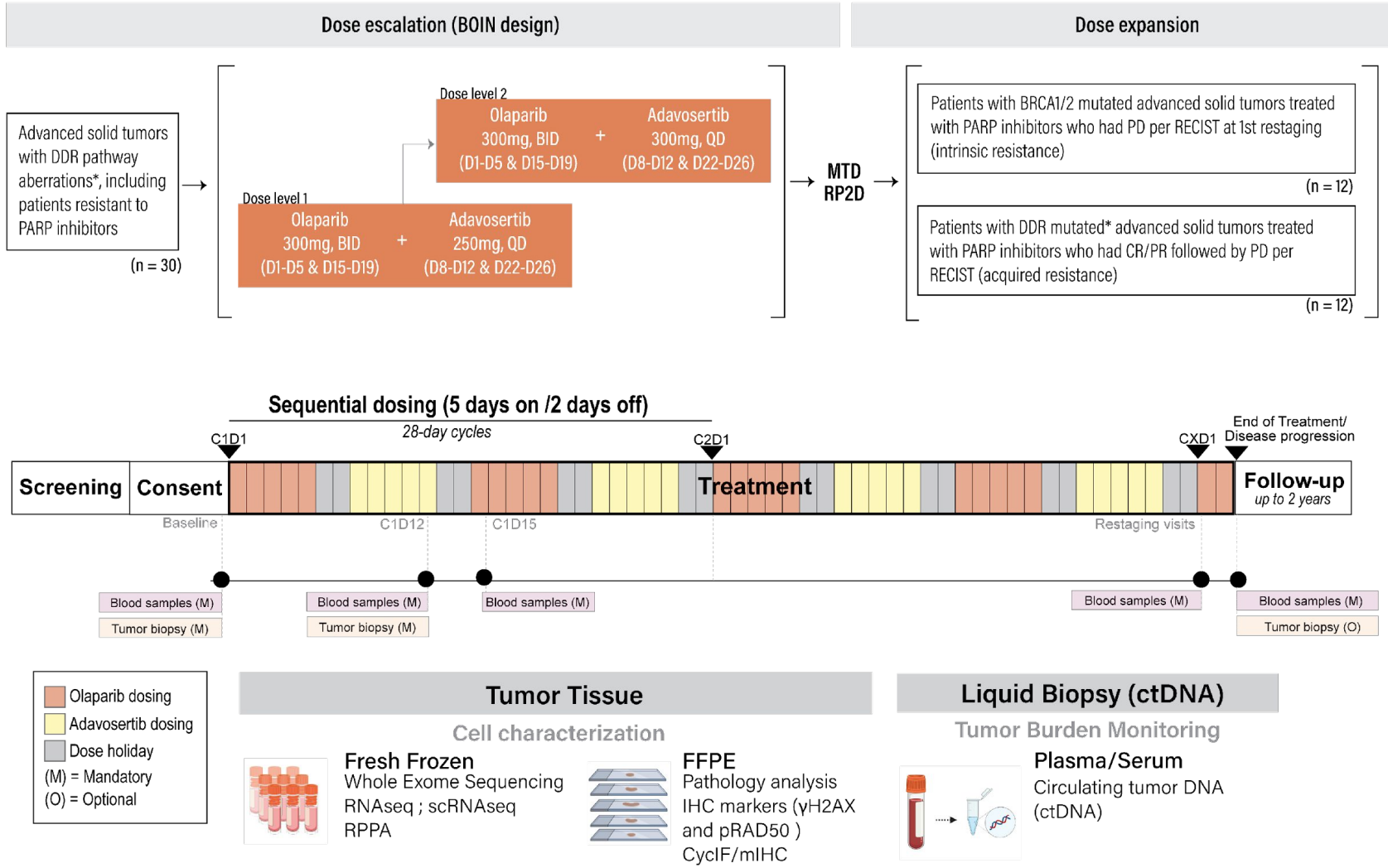




- **Concurrent PARPi + WEE1i:**
  - Effective, but poorly tolerated
  - Induces replication stress (RS) and DNA damage in both normal and malignant cells
- **Sequential PARPi + WEE1i:**
  - Following cessation of PARPi or WEE1i monotherapy, drug effects persist
  - Efficacy mirrored concurrent therapy in cancer cells with high basal RS
  - Low basal RS in normal cells protected them from DNA damage and toxicity
  - Improves tolerability while preserving efficacy *in vivo* in PDX models

Fang et al, Cancer Cell 2019

NCI10329 - Phase Ib Sequential Trial of Agents Against DNA Repair (STAR): Sequential olaparib + adavosertib in patients with molecularly-selected solid tumors



Primary
- Safety and tolerability
- Maximum Tolerated Dose
- Recommended Phase 2 Dose

Secondary
- Preliminary antitumor activity (OR [CR+PR], PFS, OS & Clinical Benefit Rate [OR+SD>6 months])
- Predictive biomarkers of response and resistance to sequential combination

- Paired tumor tissue biopsies were collected in 85% (11/13) of patients
- 90 Liquid biopsy samples were collected (average of 3 samples per patient)

Yap at al, EORTC-NCI-AACR 2022

Safety and tolerability

Treatment related adverse events (TRAEs)

Patients with an AE, n (%)	N = 13	
	Any grade	Grade ≥ 3
Nausea	10 (77)	0
Anemia	9 (69)	0
Fatigue	8 (62)	0
Vomiting	6 (46)	0
Diarrhea	5 (42)	1 (8)
Neutrophil count decrease	3 (23)	1 (8)
Platelet count decrease	3 (23)	1 (8)
White blood cell count decrease	3 (23)	1 (8)
Anorexia	3 (23)	0
Lipase increase	2 (15)	1 (8)
Abdominal pain	2 (15)	0
Creatinine increase	1 (8)	0
Dyspepsia	1 (8)	0
Fever	1 (8)	0
Headache	1 (8)	0
Serum amylase increase	1 (8)	0

No DLTs observed

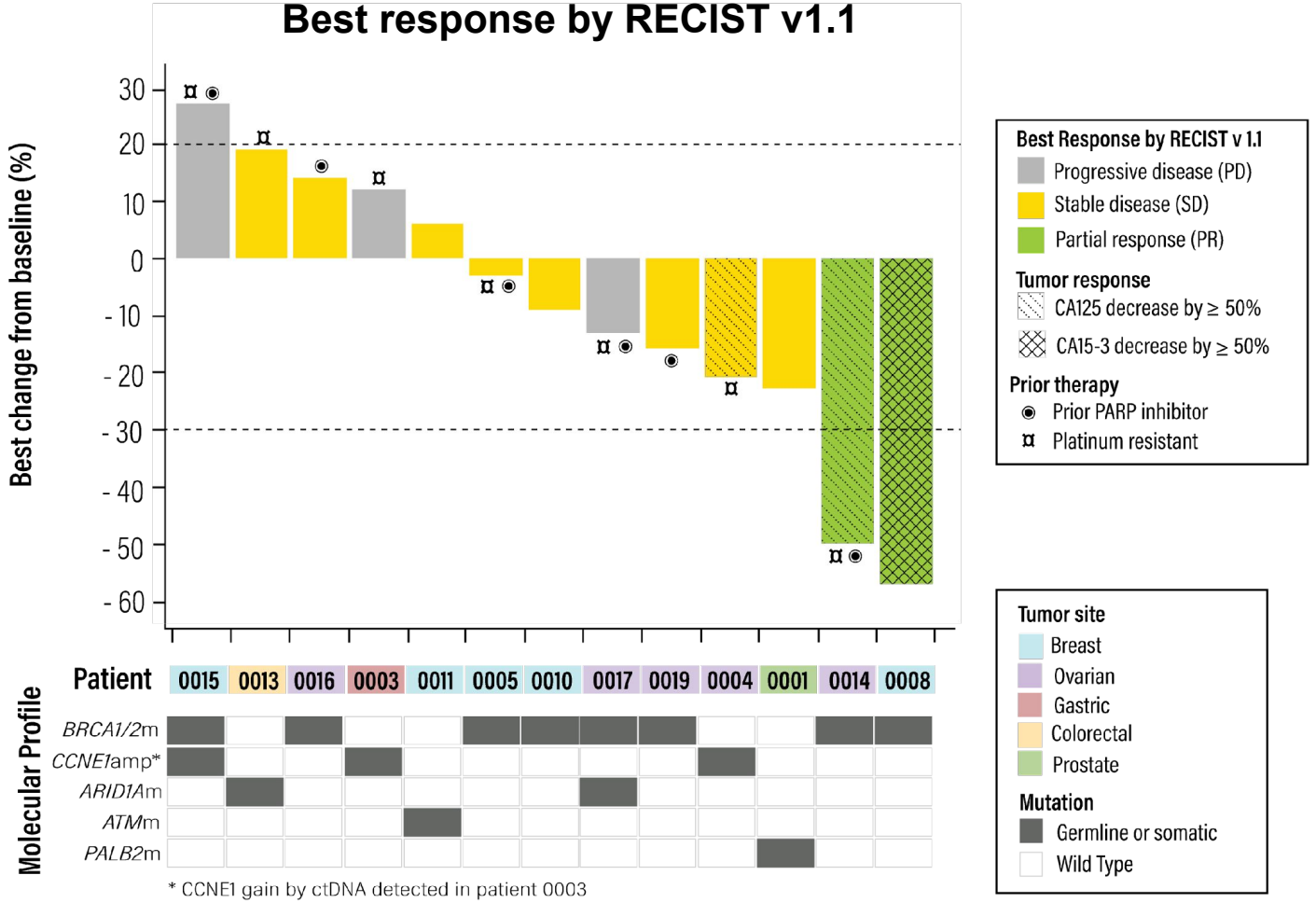
Sequential combination was well tolerated with mainly G1-2 TRAEs observed beyond DLT period

Dose reduction and non-DLT ≥ G3 myelosuppression occurred in only 2/13 (15%) patients who were heavily pre-treated

STAR: Preliminary efficacy

Antitumor activity

- **Confirmed RECIST v1.1 PRs:**
  - *BRCA2*m ER+ breast cancer (-57%; 6 months on study)
  - *BRCA2*m platinum and PARPi resistant ovarian cancer patient with *BRCA2*m reversion at baseline (-50%; 10 months on study) and GCIG CA125 response
- A *CCNE1* amplified ovarian cancer patient had GCIG CA125 response and RECIST v1.1 SD for 20 weeks; resolution of ascites
- 5/12 patients achieved RECIST v1.1 SD ≥4 months: 66.7% (8/12) disease control rate
- 4 of these 8 patients with disease control had progressed on prior PARPi



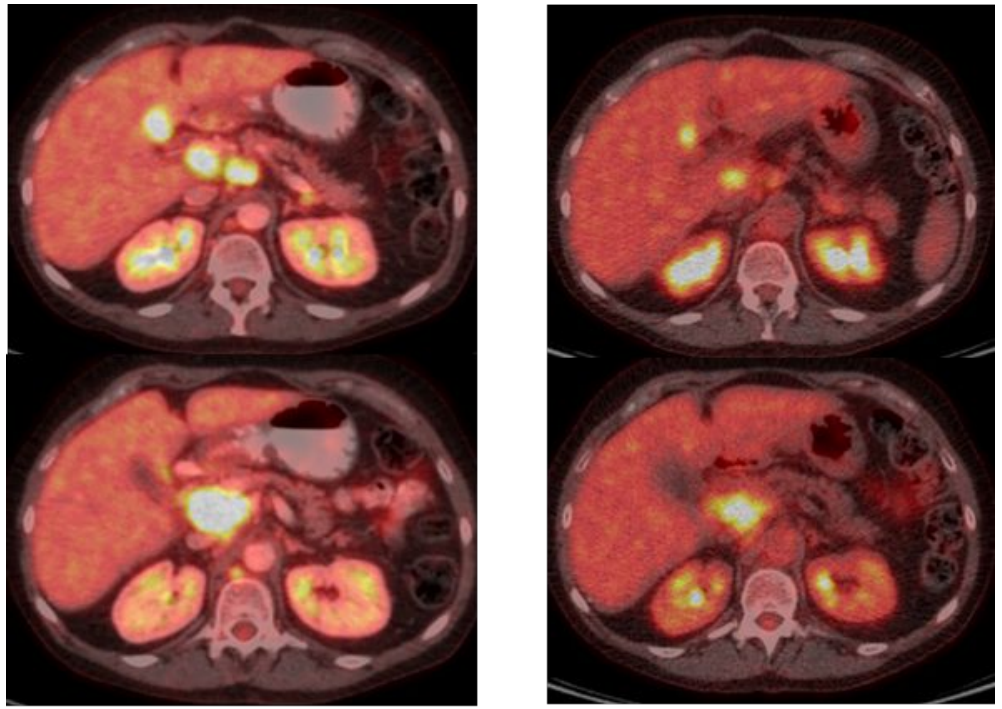
Yap at al, EORTC-NCI-AACR 2022

STAR: Preliminary antitumor activity case study

53 y/o ovarian cancer patient
DL2 (Sequential, 5 days on/ 2 days off, 300 mg olaparib BID and 300 mg adavosertib QD)
Inactivating *BRCA2* mutation and *BRCA2* reversion mutation at baseline
2 prior PARP inhibitors

Prior therapies

- Stage IIIC HGSOC: Debulking surgery → Carbo/taxol 6 cycles with NED → maintenance Bevacizumab + cyclophosphamide but stopped due to poor tolerance
- Disease relapse. Carbo/Gem/Bev x 9 cycles with complete metabolic response
- Disease relapse. Carbo/paclitaxel 6 cycles with CR → maintenance immunotherapy on trial
- Disease relapse. PLD 6 cycles with CR → **maintenance rucaparib**
- Disease relapse. Topotecan/bevacizumab
- PI3K inhibitor + **olaparib** → Disease progression.



RECIST sustained PR (-50%)
GCIG CA 125 response
On treatment for 10 months
G1 myelosuppression and GI toxicity and G1-2 fatigue

Yap at al, EORTC-NCI-AACR 2022

Take home points

Targeting DDR: Progress, Pitfalls and Promise

- **Need to build on success of PARP inhibitor monotherapy**
  - Multiple inhibitors against WEE1, ATR and beyond
    - Different patient populations: tumor types and molecular subtypes
    - Different pharmacological profiles
    - Different stages
- **Optimizing pharmacology, patient selection and therapeutic index are key priorities for monotherapy DDR inhibitor development**
- **Multiple rational DDR inhibitor combination strategies are ongoing**

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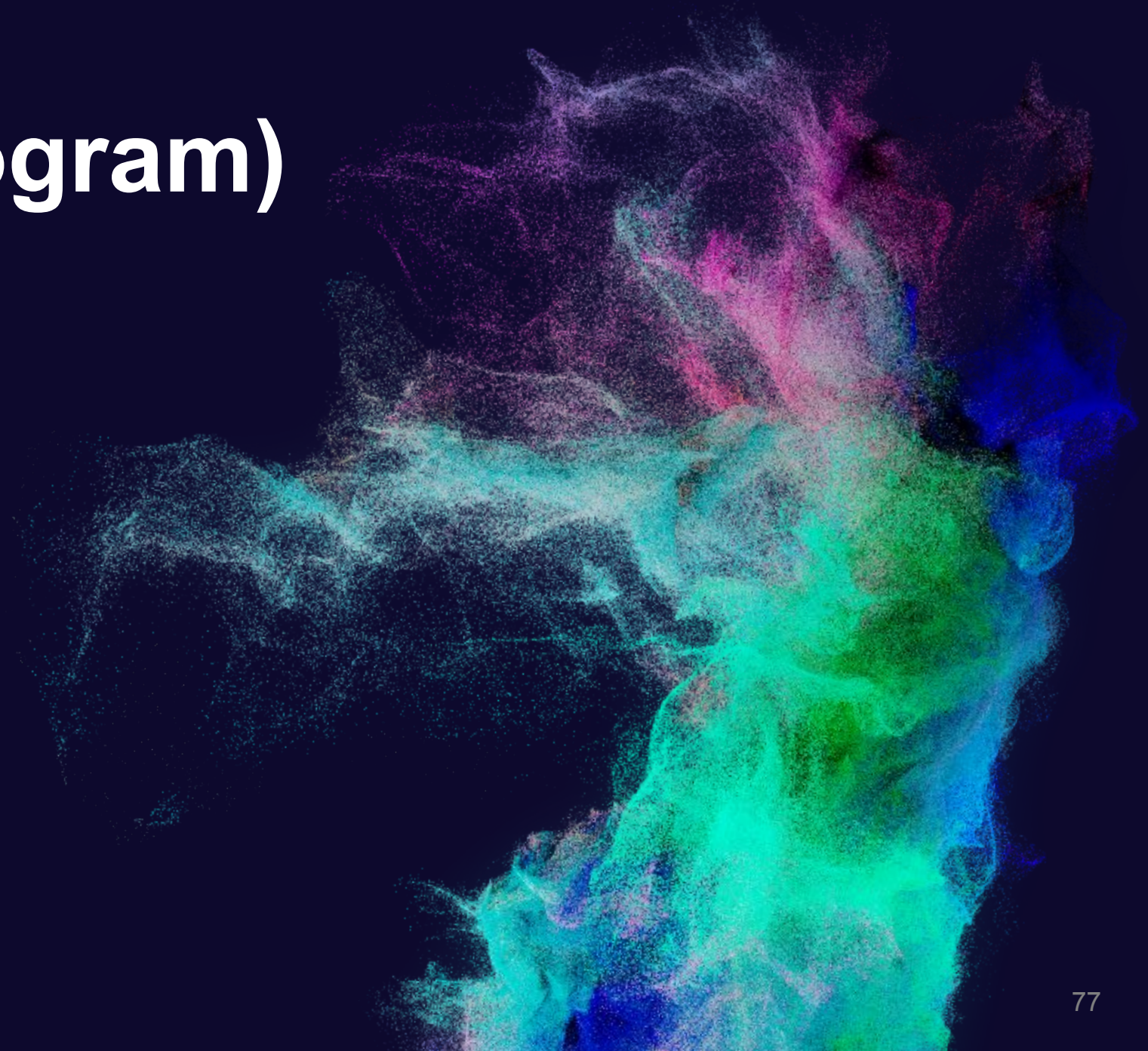
Bianca Gonzalez

SGR-3515 (Wee1/Myt1 Program)

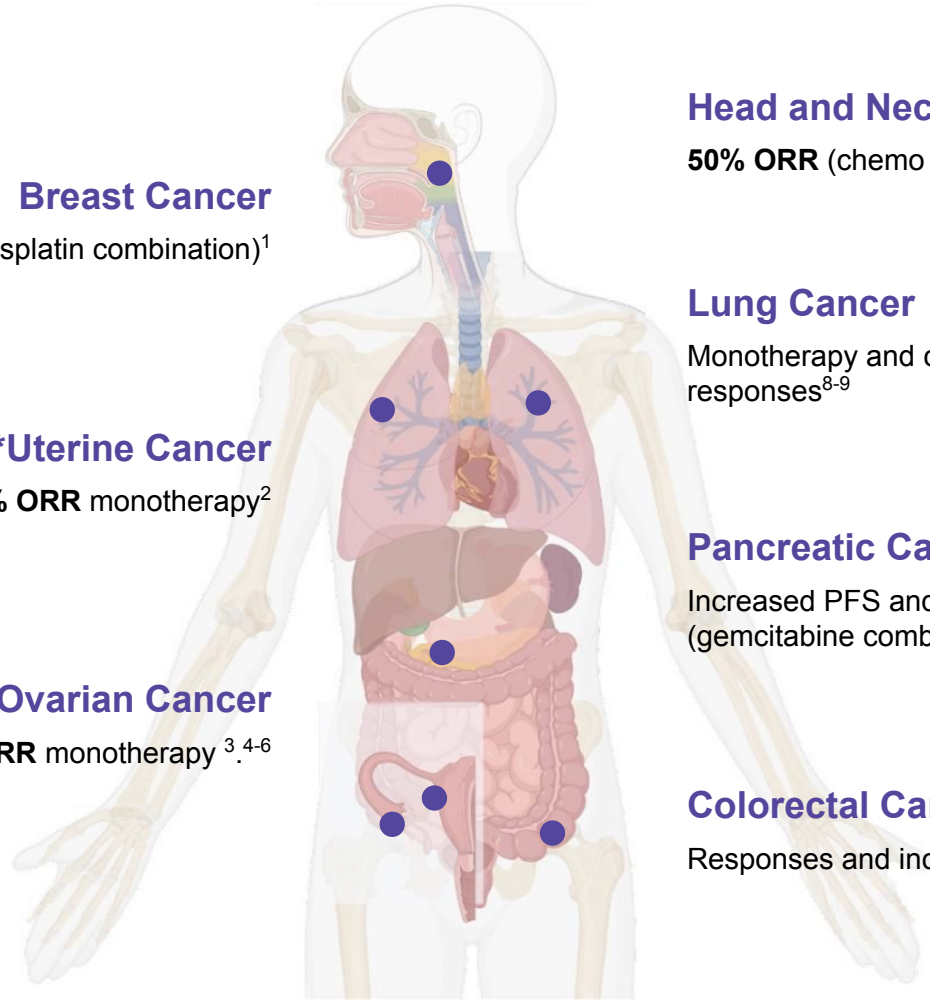


Schrödinger

Targeting Cancer Cell Vulnerabilities in Sensitive Tumors

Vulnerability	DNA Damage	Conditional Synthetic Lethality	
Mechanism	• Elevated replication stress confers sensitivity to CDC7 inhibition • CDC7 activates BRCA1-A and cohesin complexes in response to replication stress	• Inhibiting **Wee1** and **Myt1** exacerbates mitotic catastrophe • Counteracts Myt1-induced resistance to Wee1 inhibition	• MTAP deletion drives accumulation of MTA and PRMT5-MTA complexes • Stabilizing catalytically inactive PRMT5/MTA is lethal in MTAP-deleted cancer cells
Patient Population	High Replication Stress Tumors	High Replication Stress Tumors	MTAP-deleted Tumors

Wee1 Data Demonstrate Clinical Opportunity in 3rd Party Studies



Breast Cancer
26% ORR (cisplatin combination)[1]

*Uterine Cancer
30% ORR monotherapy[2]

*Ovarian Cancer
Up to 50% ORR monotherapy [3].[4-6]

Head and Neck Cancer
50% ORR (chemo combination)[7]

Lung Cancer
Monotherapy and combo responses[8-9]

Pancreatic Cancer
Increased PFS and OS (gemcitabine combination)[10]

Colorectal Cancer
Responses and increased PFS[8,11,12]

SGR-3515 Combines Wee1/Myt1 Activity

- Opportunity for improved therapeutic index
- Demonstrates durable activity from intermittent dosing in preclinical models[13]
- Myt1 activity offers opportunity to benefit from synthetic lethal relationship

*Strongest monotherapy effect in POC studies

[1]*Clin Cancer Res* 2021: 27(4). [2]*J Clin Oncol* 2021: 39(14):1531-1539. [3]*J Clin Oncol* 40, no. 16_suppl (June 01, 2022) 5515. [4]*Lancet* 2021: 398:281-92. [5]*J Clin Oncol* 2016: 34:4354-4361. [6]*Clin Cancer Res* 2018: 24(120): 2740-8. [7]*Clin Cancer Res* 2018: 15;24(12):2740-2748. [8]Zentalis investor deck. [9]*Ann Oncol* 2020: 31 (suppl_4). [10]*J Clin Oncol* 2019 Oct 10;37(29). [11]*Cancer Res* (2019) 79 (13_Supplement): CT02. [12]*J Clin Oncol* 2021 Nov 20;39(33). [13]Sun et al., AACR 2022.

Schrödinger

SGR-3515 Demonstrates Superior Wee1/Myt1 Potency, Kinase Selectivity and Lower DDI Liability

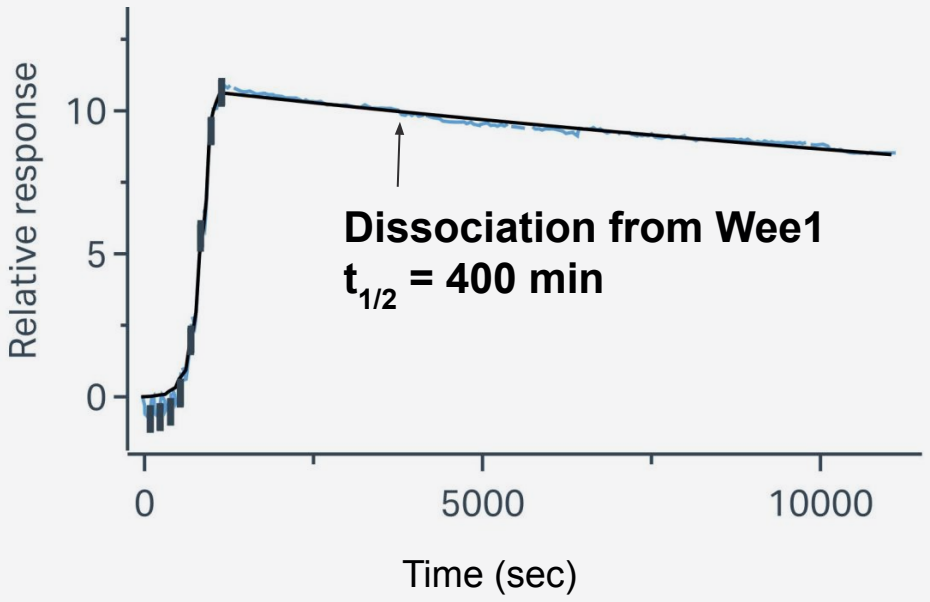
		AZD-1775	ZN-c3	SGR-3515
Binding affinity K_D, nM	Wee1	2.3	1.2	0.06
	Myt1	170	300	15
Cell target engagement IC_{50}, nM (A427 cell line)	Wee1 (pCDK1 Y15)	140	280	65
	Myt1 (pCDK1 T14)	1400	4600	230
Selectivity against PLK1, fold (PLK1 K_i / Wee1 K_D)		25x	250x	>83,000
Drug Drug Interaction (DDI) liability		Medium Potential for CYP3A4 TDI	Medium Potential for CYP3A4 TDI	Low Potential for CYP3A4 TDI

TDI: Time dependent inhibition

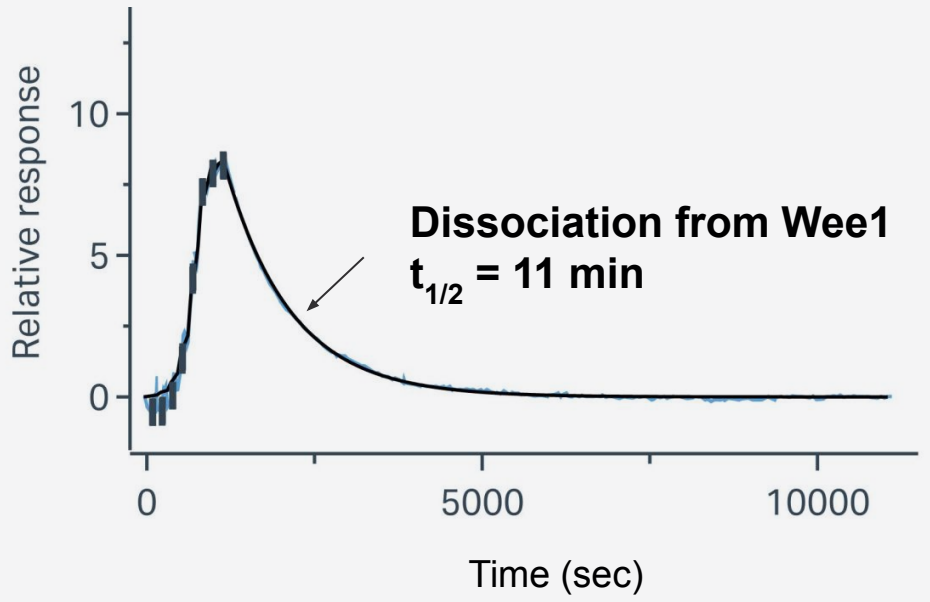
All competitor data is internally generated by contract research organizations using publicly available structure information.

SGR-3515 Has Extended Target Residence Time Which Prolongs the Pharmacological Response

SGR-3515
K_D = 0.06 nM



ZN-c3
K_D = 1.2 nM

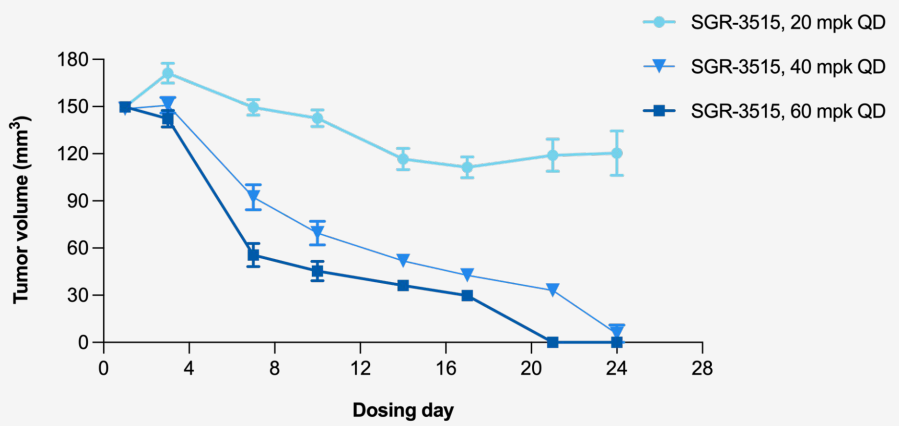


Intermittent Dosing of SGR-3515 Achieves Anti-tumor Activity Equivalent to Continuous Dosing with Full Recovery of Bone Marrow Toxicity

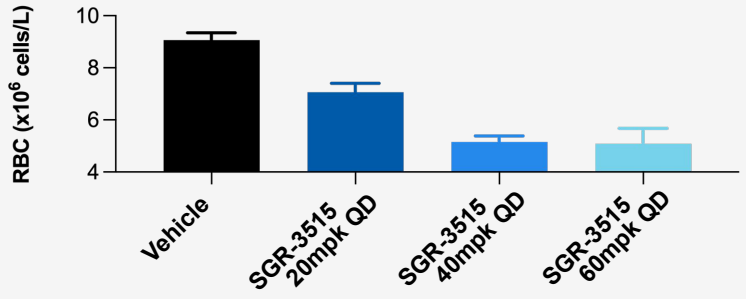
28 Day Tumor Growth Inhibition in the A427 Non-Small Cell Lung Cancer Model

Continuous daily dosing

Tumor Growth Inhibition

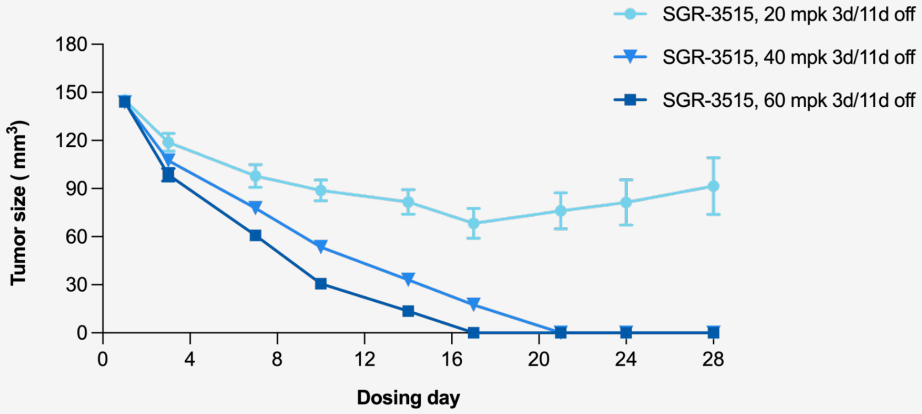


Red Blood Counts



3 days of dosing in 2-week cycle

Tumor Growth Inhibition



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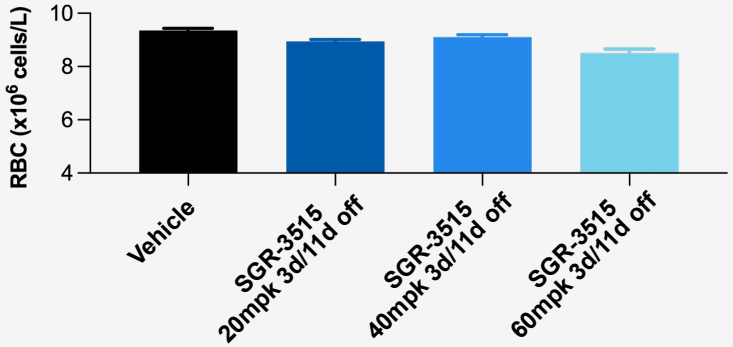
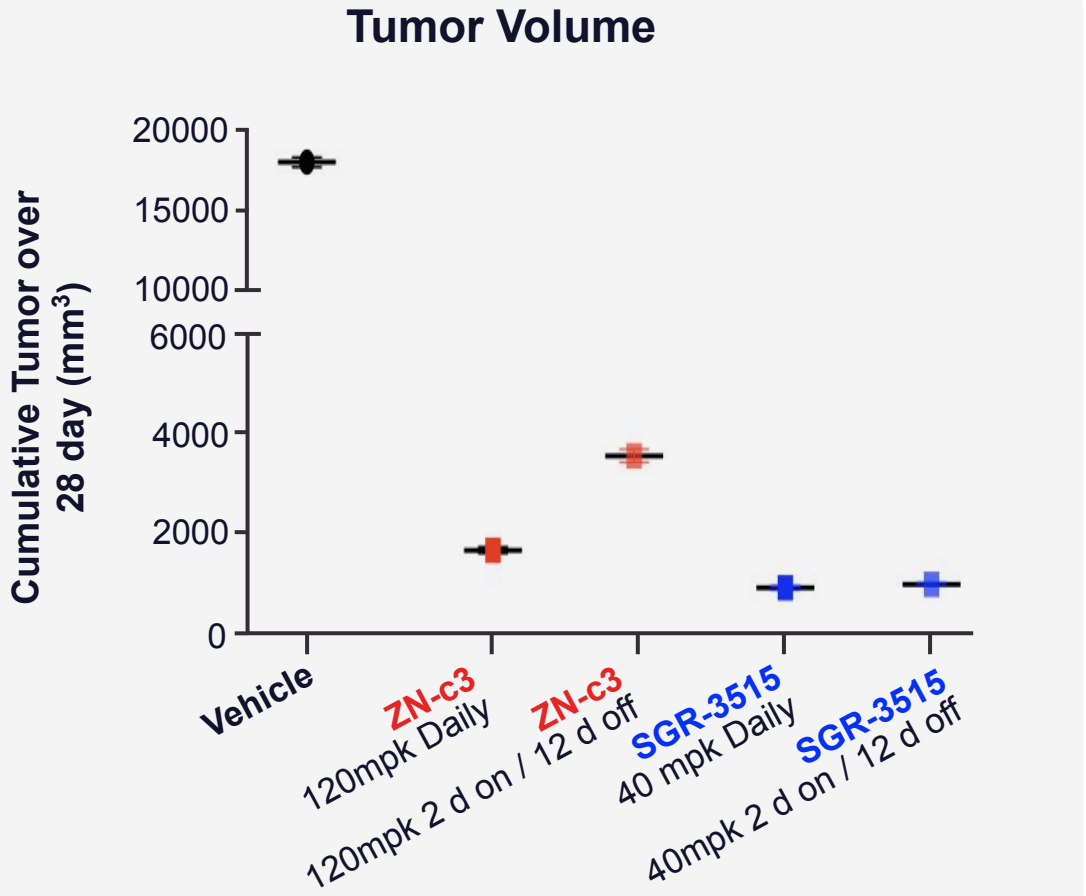
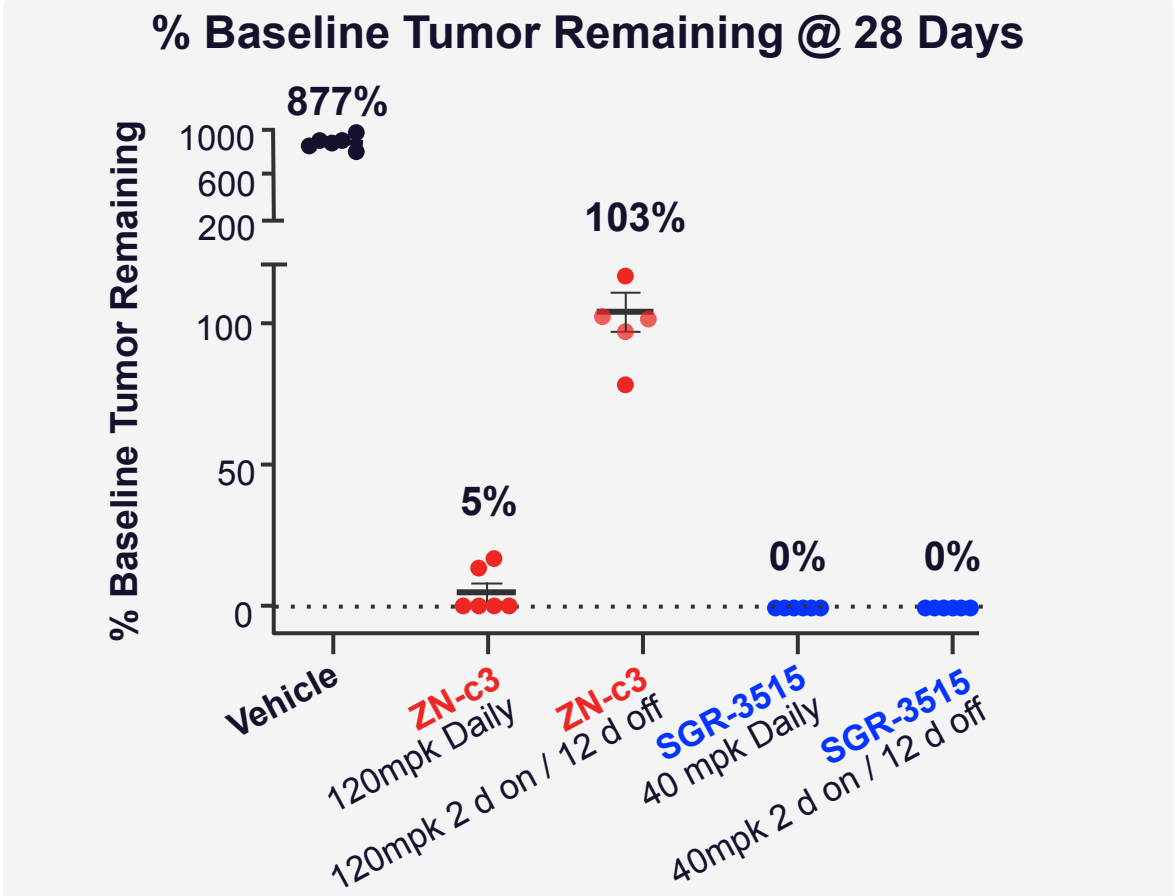


n=6/group, mean ± SEM

SGR-3515 Maintains Maximal Tumor Growth Inhibition with Intermittent Dosing Schedule

28 Day Tumor Growth Inhibition in the A427 Non-Small Cell Lung Cancer Model



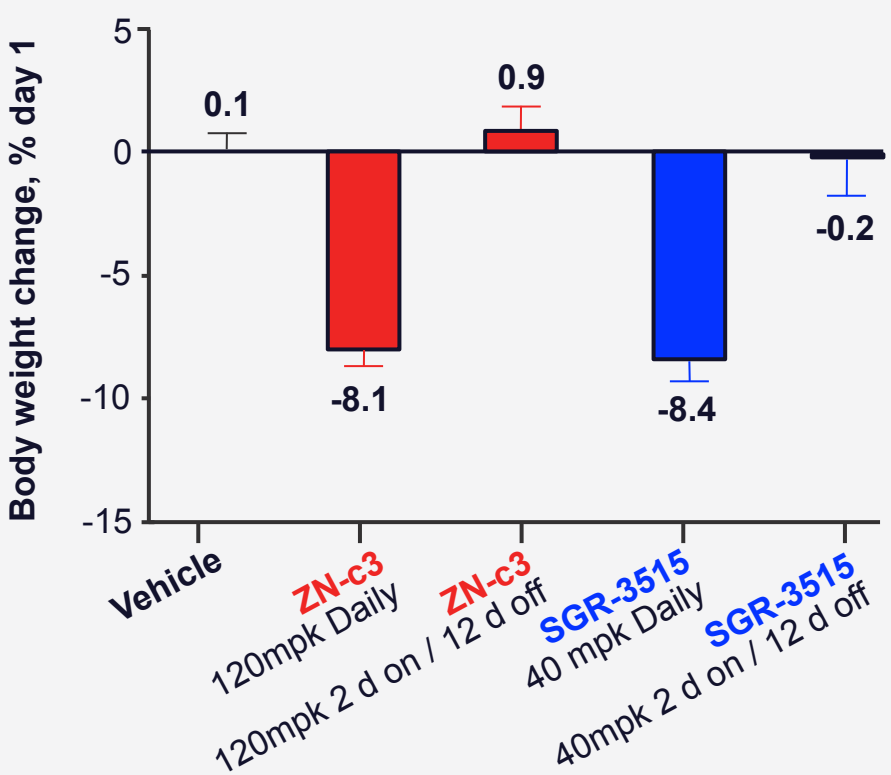


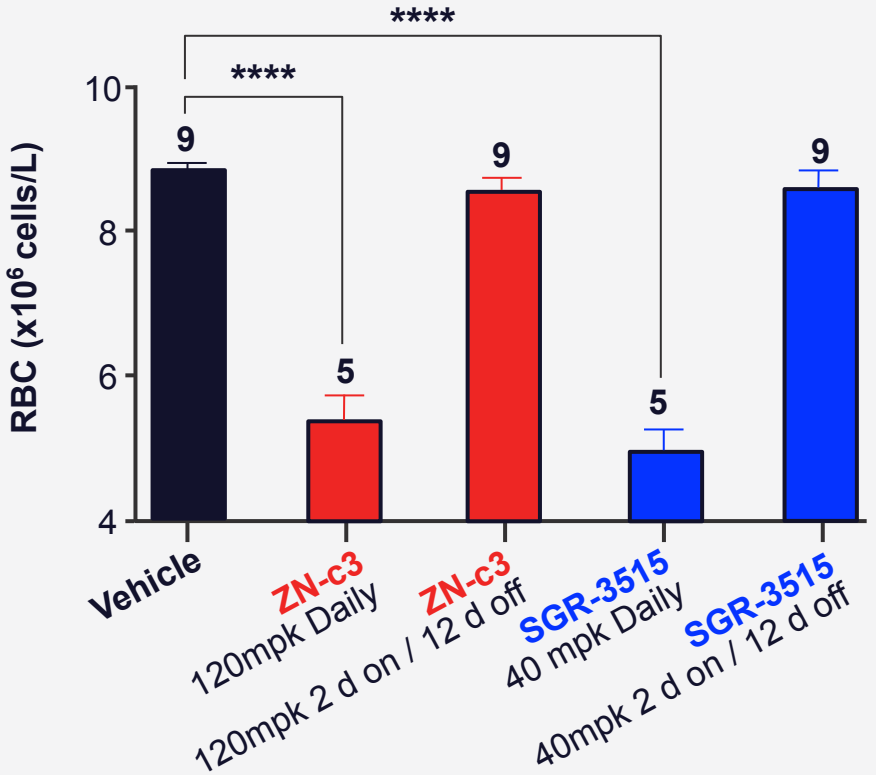
n=6/group, mean ± SEM

SGR-3515 Maintains Maximal Tumor Growth Inhibition with Intermittent Dosing Schedule

28 Day Tumor Growth Inhibition in the A427 Non-Small Cell Lung Cancer Model

Body Weight & Hematological Recovery



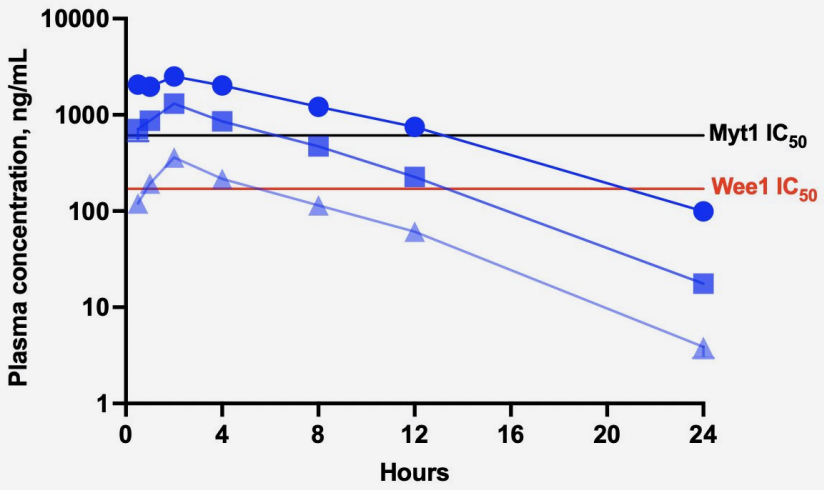


n=6/group, mean ± SEM

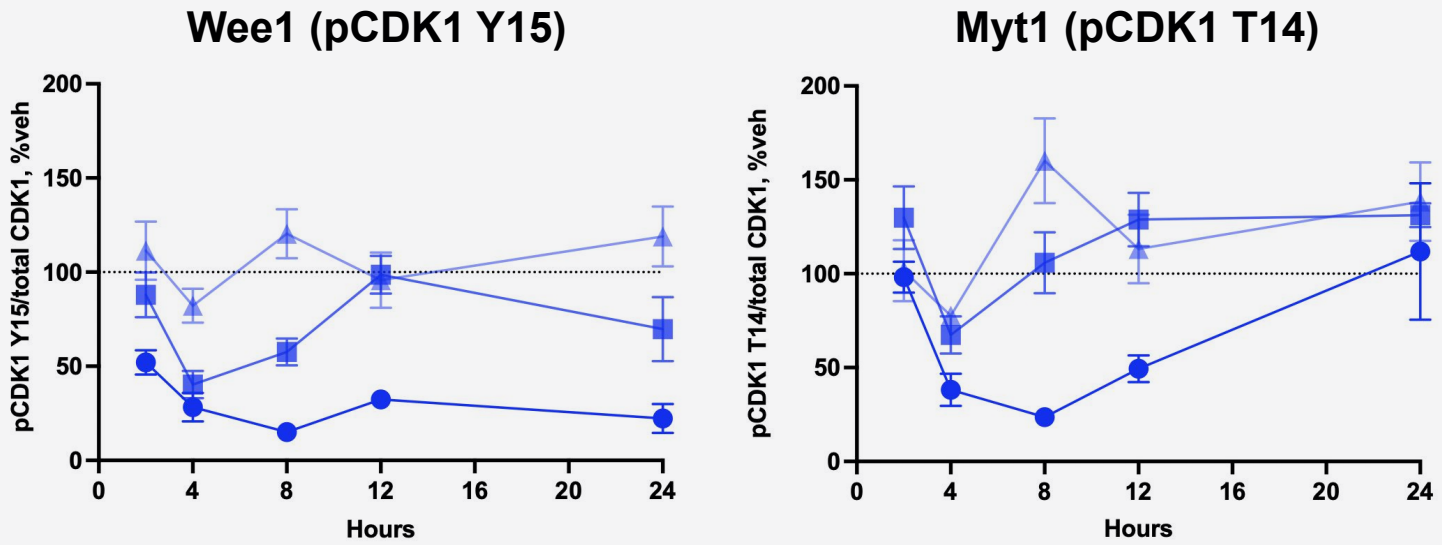
Single Dose of SGR-3515 Achieves Extended Intratumoral Wee1 and Myt1 Inhibition and Target Engagement

28 day Tumor Growth Inhibition in the A427 Non-Small Cell Lung Cancer Model

Plasma PK



Target Engagement in Tumors



SGR-3515, 40 mpk SGR-3515, 15 mpk SGR-3515, 5 mpk

n=5/group, mean ± SEM

SGR-3515 Summary and Next Steps

- SGR-3515 exhibits differentiated profile vs. other Wee1 inhibitors
  - Potent Wee1/Myt1 inhibition and long residence time in tumors
  - Profile enables optimized dosing schedule to maintain anti-tumor activity and limit hematological toxicity
  - Myt1 co-inhibition demonstrates greater activity and leverages synthetic lethality
- IND submission planned 1H24; Phase 1 study initiation in 2024

Today’s Agenda

Introduction — Ramy Farid

Pipeline Overview and Portfolio Strategy — Karen Akinsanya

SGR-1505 (MALT1) — Karen Akinsanya, Margaret Dugan

SGR-3515 (Wee1/Myt1) — Timothy Yap, Karen Akinsanya

SGR-2921 (CDC7) — Elie Traer, Hamish Wright

New Discovery Programs — Jean Lachowicz

Capital Allocation and Value Creation — Geoff Porges

Q&A

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

Elie Traer, MD PhD
Associate Professor
OHSU Knight Cancer Institute

What is AML?

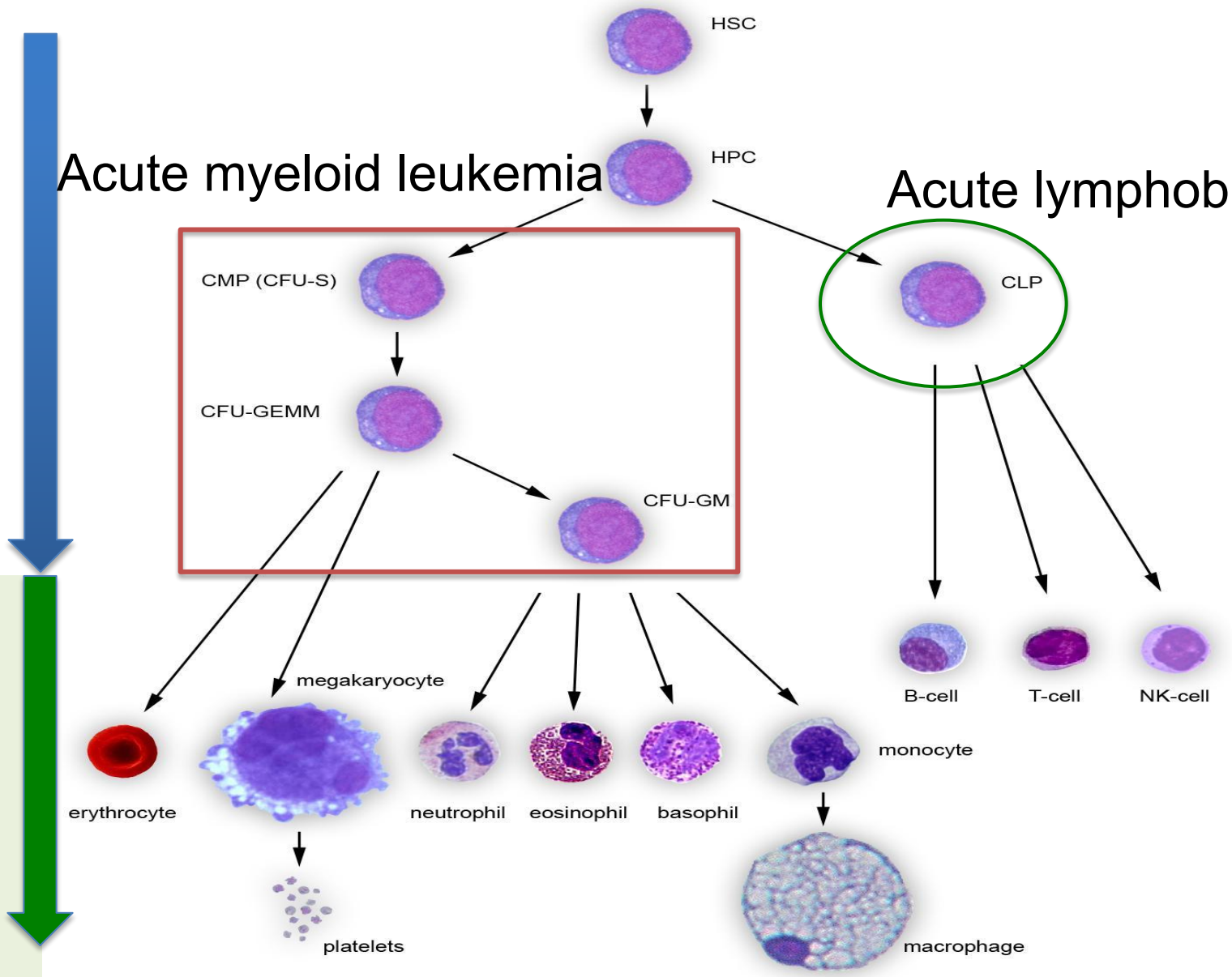
- AML is a blood cancer characterized by:
  - Block in normal white blood cell development (blasts)
  - Uncontrolled growth

- Too many leukemia blasts reduces normal marrow function
  - Decreased white blood cells, red blood cells, and platelets
  - Increased risk of infection, anemia/fatigue, and increased bleeding risk

AML is cancer of progenitor cells (blasts)

Stem and progenitor cells (ability to regenerate)

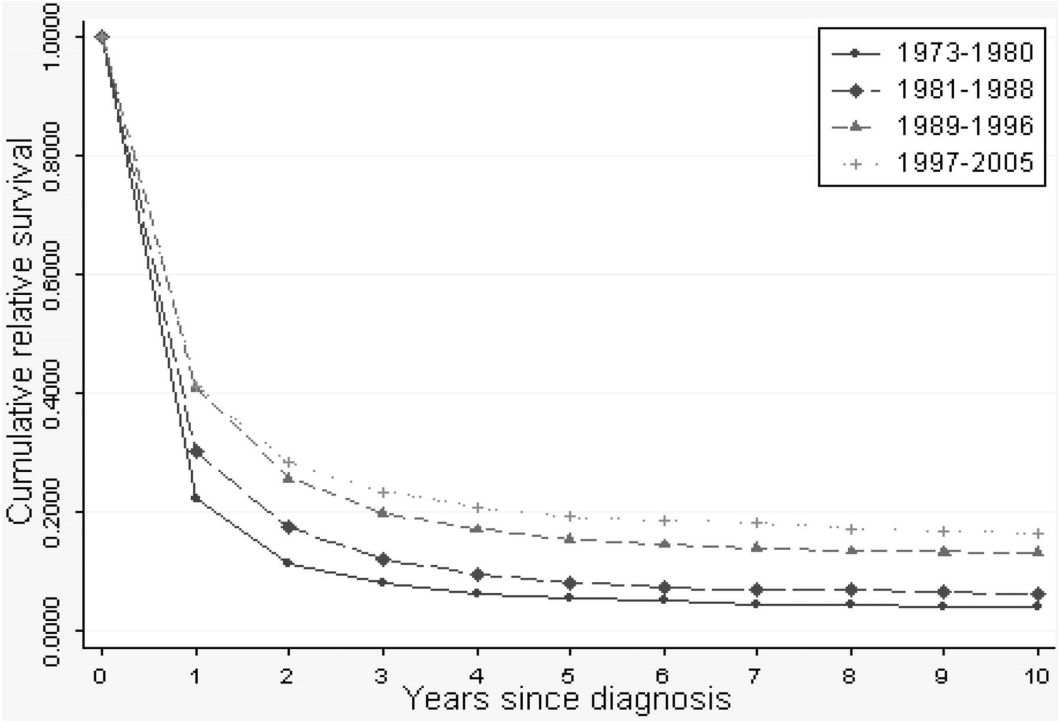
Mature cells (terminally differentiated)



http://daley.med.harvard.edu/assets/Willy/hematopoiesis.jpg

Epidemiology

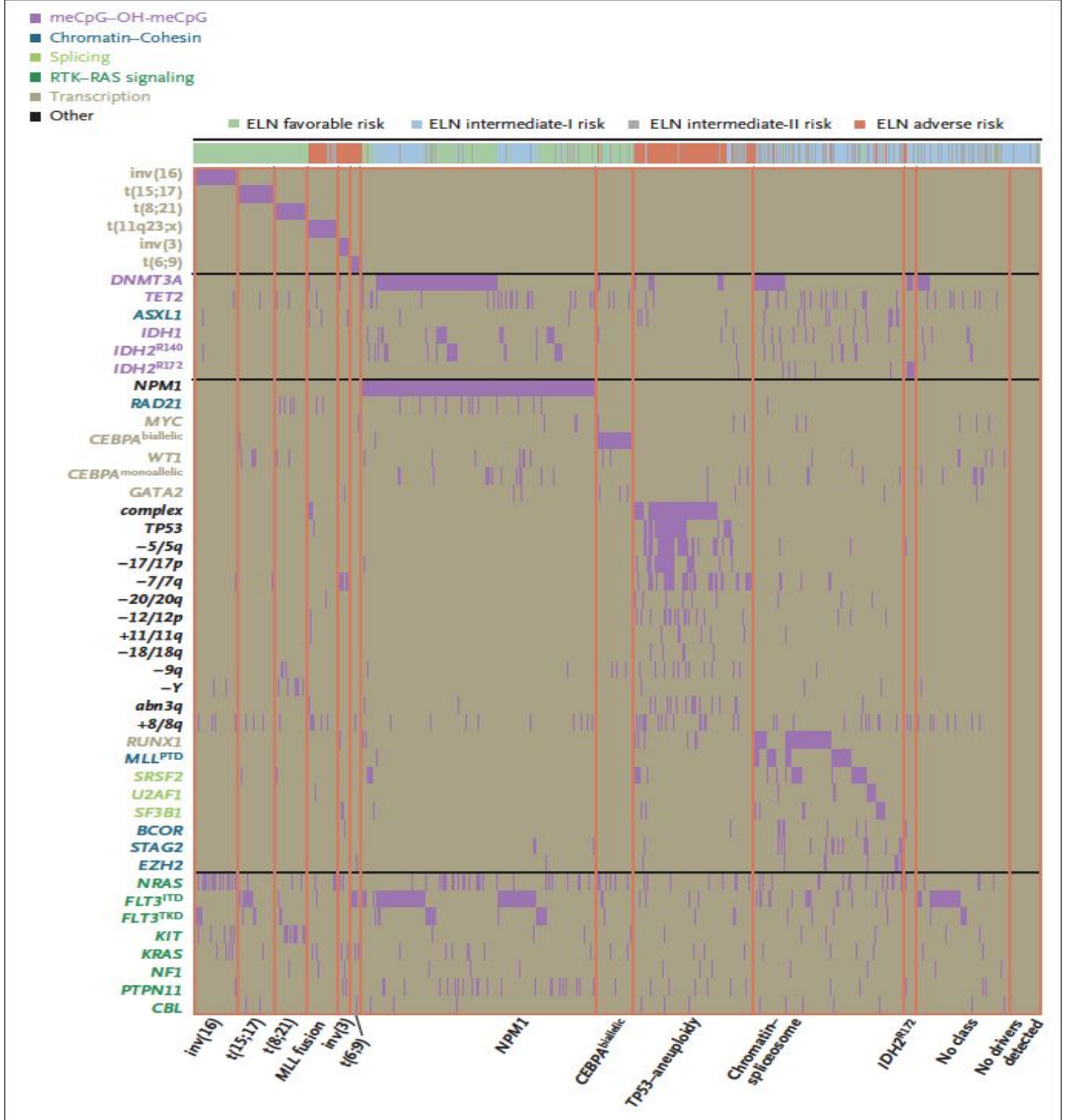
- Blood cancers: 5th most common, 4th highest cancer-related mortality
- AML one of the most common heme malignancy
- 21,000 diagnoses; 10,000 deaths per year in U.S.
- AML has a high mortality
- Need new drugs and combinations



Derolf ÅR, et al. *Blood* 2009;**113**:3666-72.

Mutations in AML

- Multiple subtypes of AML based upon recurring mutations
- Many mutations help predict response to therapy (prognostic)
- Some mutations can be targeted by drugs
  - FLT3, IDH1, IDH2



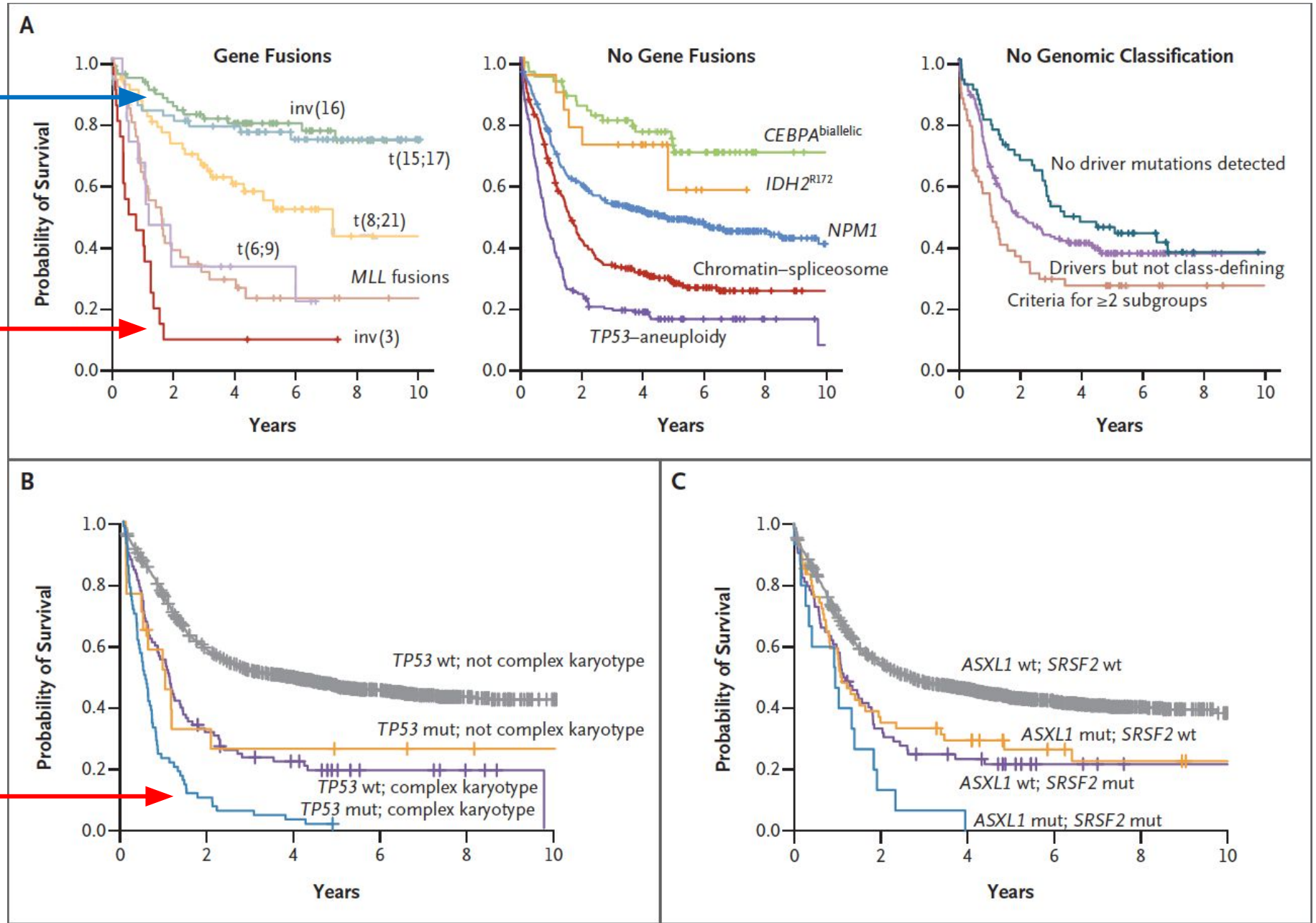
Pappaemmanuil et al. NEJM 2016

Prognostic impact of mutations (mostly with chemo)

Favorable

Adverse

TP53 mutations and complex karyotype are poor risk, and have no good therapies



Pappaemmanuil et al. NEJM 2016

Mutations define AML treatment

Table 6. 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis[a]

Risk Category[b]	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[b,c] • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[b,c] • Mutated *NPM1*[b,d] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*[e]
Intermediate	• Mutated *NPM1*[b,d] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[b,f] • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype,[h] monosomal karyotype[i] • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*[j] • Mutated *TP53*[k]

- Chance of cure with chemotherapy alone
- 20% of AML patients

- Allogeneic stem cell transplant needed for cure
- 80% of AML patients

What is MDS?

- MDS is a blood cancer characterized by:
  - Abnormal normal white blood cell development
    - blasts (<20%) and dysplastic (abnormal) white blood cells

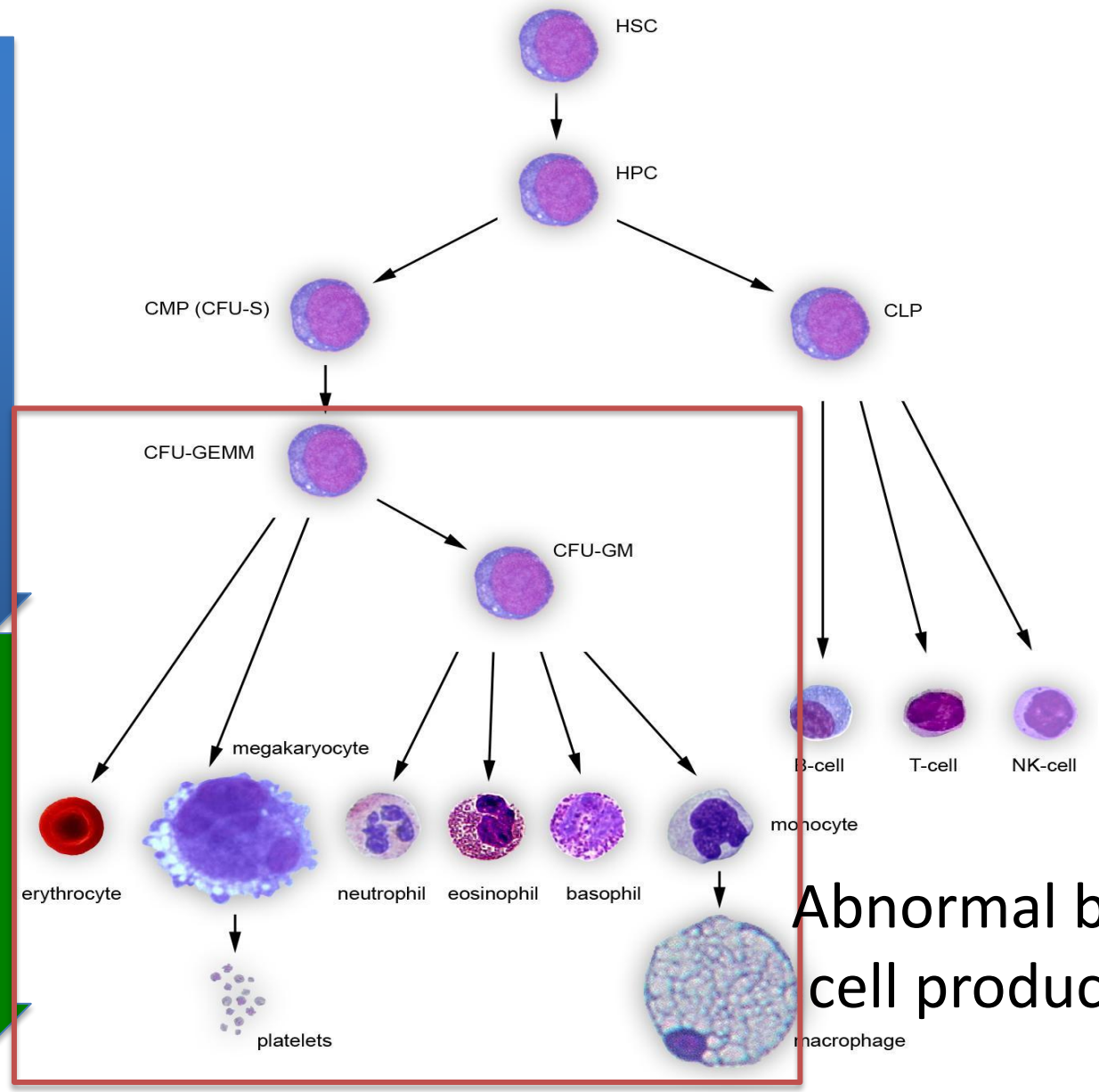
- MDS also blocks production of normal bone marrow cells
  - Decreased white blood cells, red blood cells, and platelets
  - Increased risk of infection, anemia/fatigue, and increased bleeding risk

- MDS was previously called pre-leukemia because blasts increase over time and when >20% it becomes AML

MDS affects more mature cells than blasts

Stem and progenitor cells (ability to regenerate)

Mature cells (terminally differentiated)



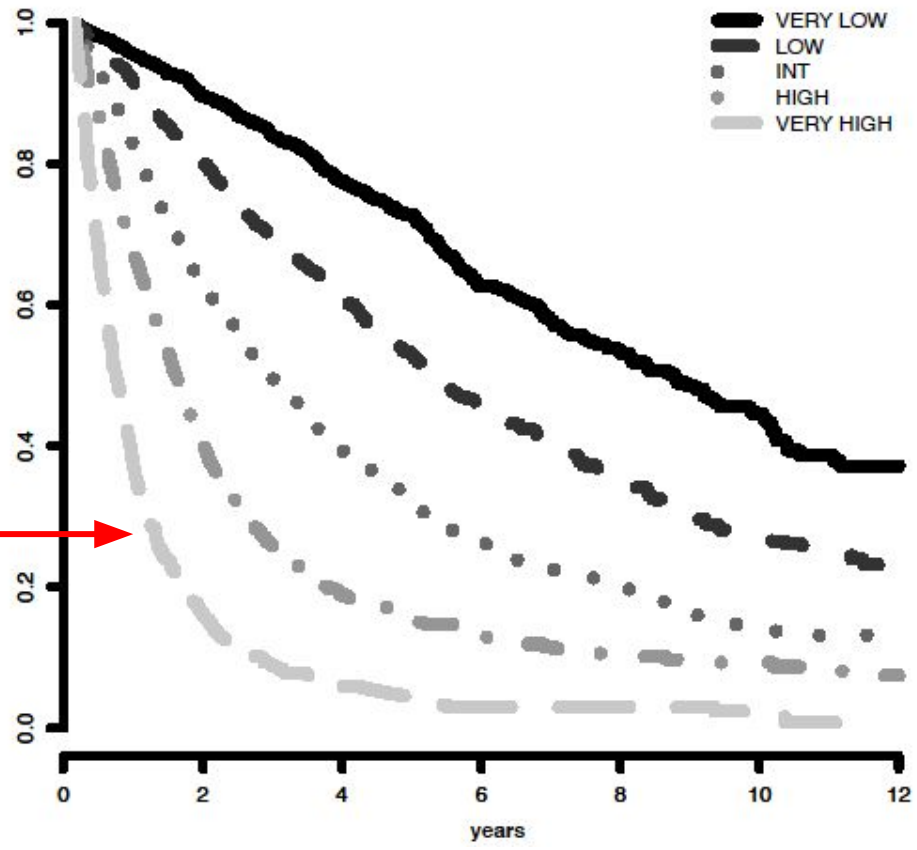
Abnormal blood cell production

http://daley.med.harvard.edu/assets/Willy/hematopoiesis.jpg

MDS also characterized by recurrent genetic mutations
Mutations affect risk of progression to AML

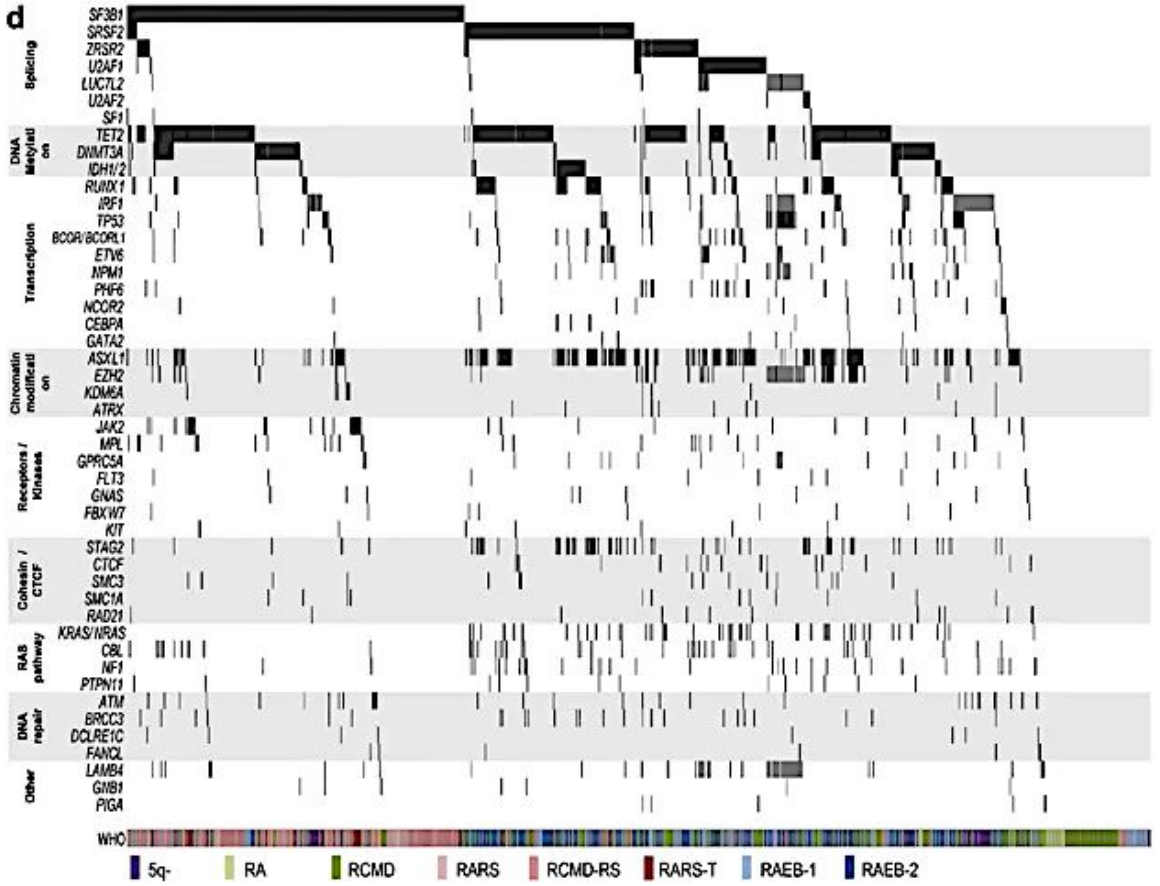
Cytogenetic abnormalities

TP53 mutations and complex karyotype are poor risk, and have no good therapies



Blood. 2012;120(12):2454

Mutations

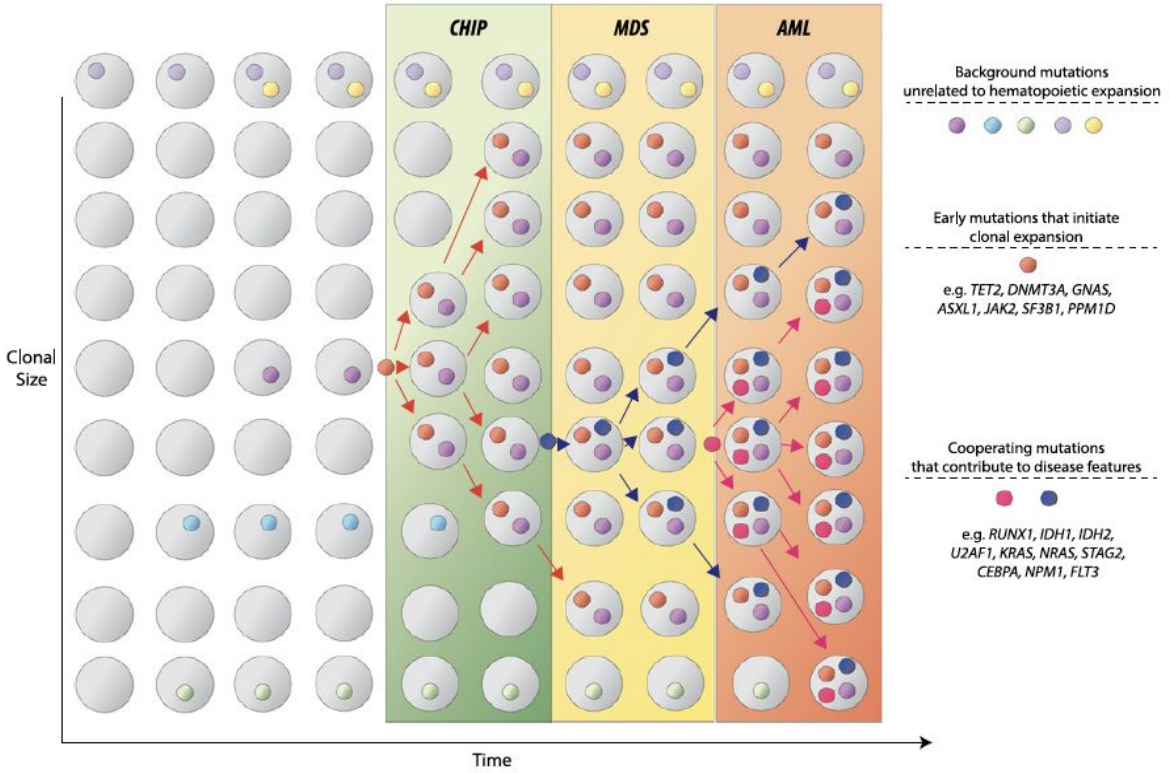


Haferlach T et al. Leukemia 2014

Spliceosome, epigenetic, transcription, chromatin mutations very common

Myeloid Malignancies – Overlapping Origins

- Overlap of mutations between AML, MDS, and myeloproliferative neoplasms (MPN)
- Some of the same mutations can be found in healthy individuals as they age
- MDS and MPN all eventually transform into AML, which is called secondary AML



Steensma DP et al. Blood. 2015;126(1):9-16.

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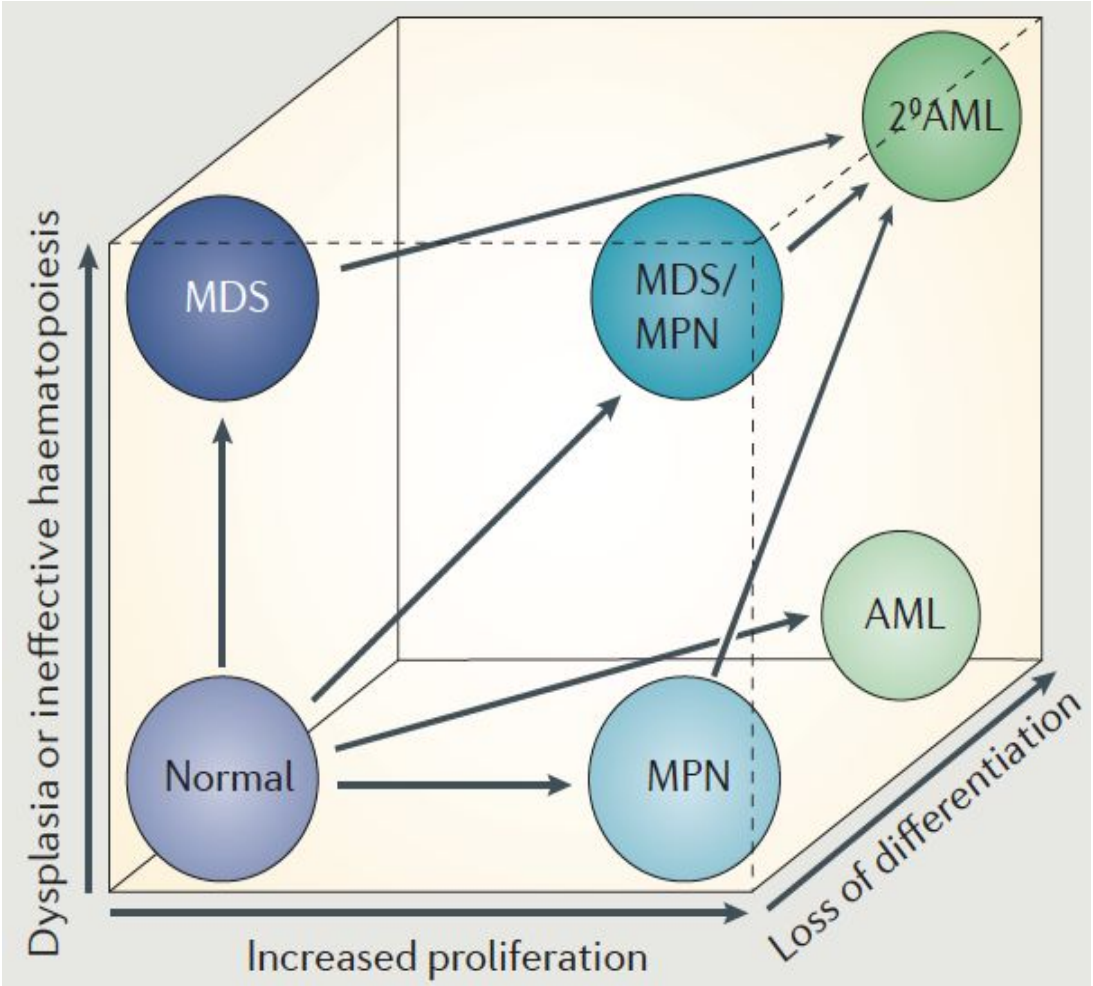
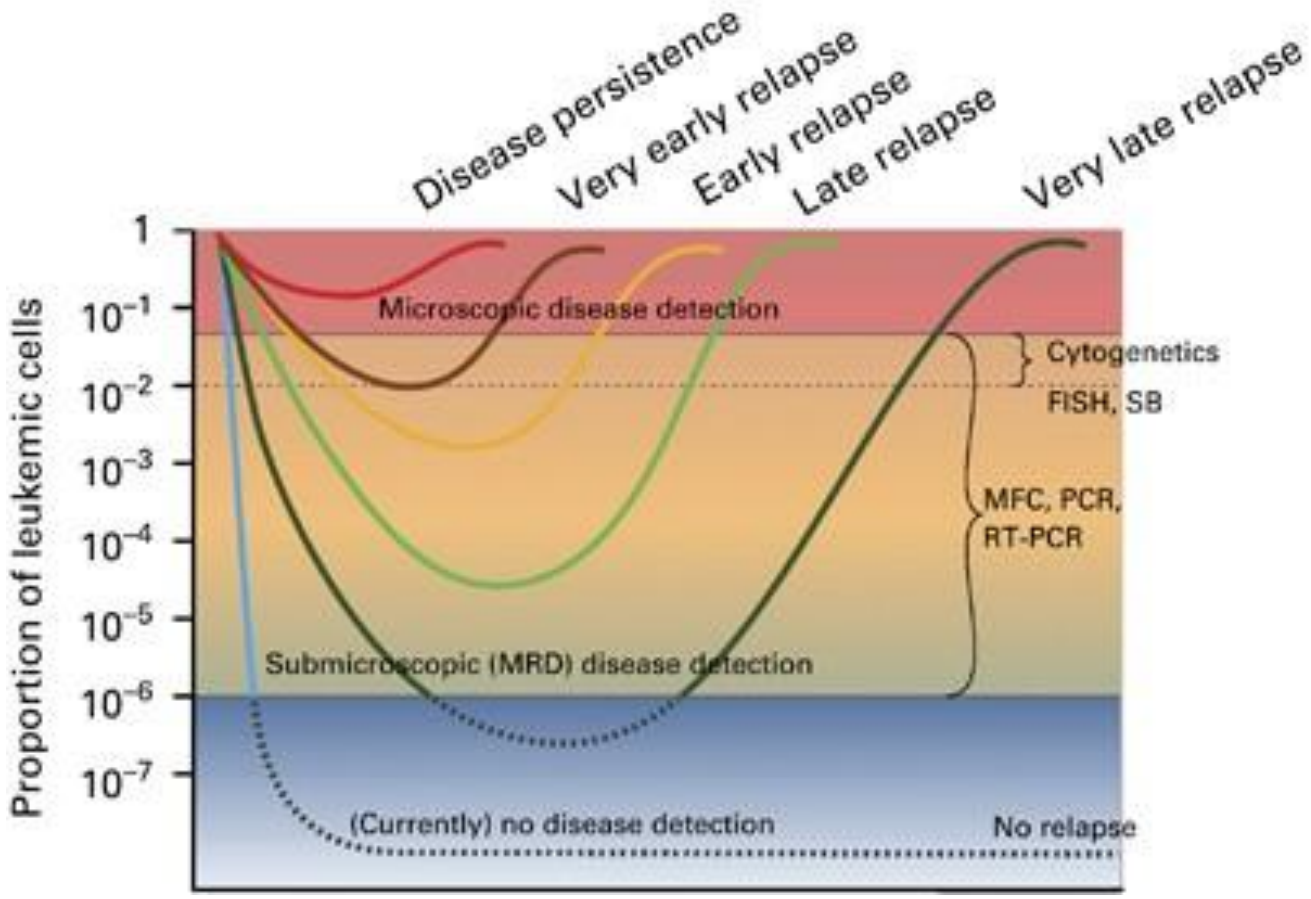


Deininger MW et al. Nat Rev Cancer. 2017;17:425-440.

Current AML therapy – and limitations

- <u>Younger patients (<65)</u>
- Intensive chemotherapy
  - 7+3
- Chance of cure for favorable risk
- Measuring residual disease is improving but still difficult

- <u>Older patients (>65)</u>
- Less intensive chemotherapy
- Residual disease leads to relapse
- Allogeneic stem cell transplant more difficult in older patients
- Median age of AML = 67



Buckley, Appelbaum, and Walter, BMT 2013

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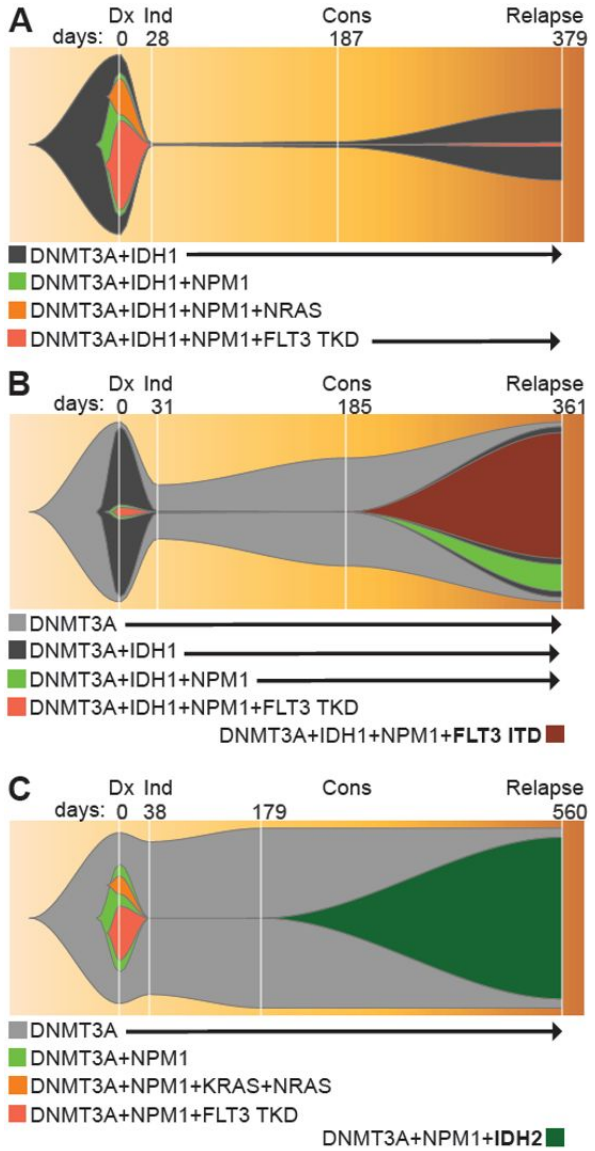
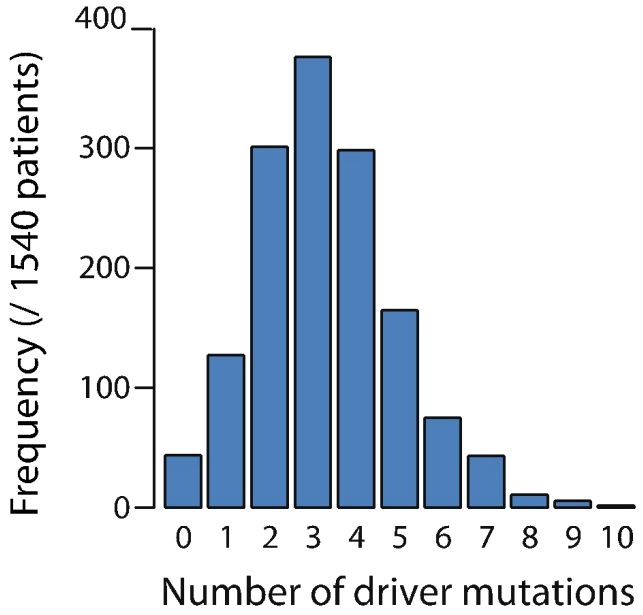
- Allogeneic stem cell transplant more difficult in older patients
- Median age of AML = 67



Dunlap *et al*. Am. J. Hemat. 2019

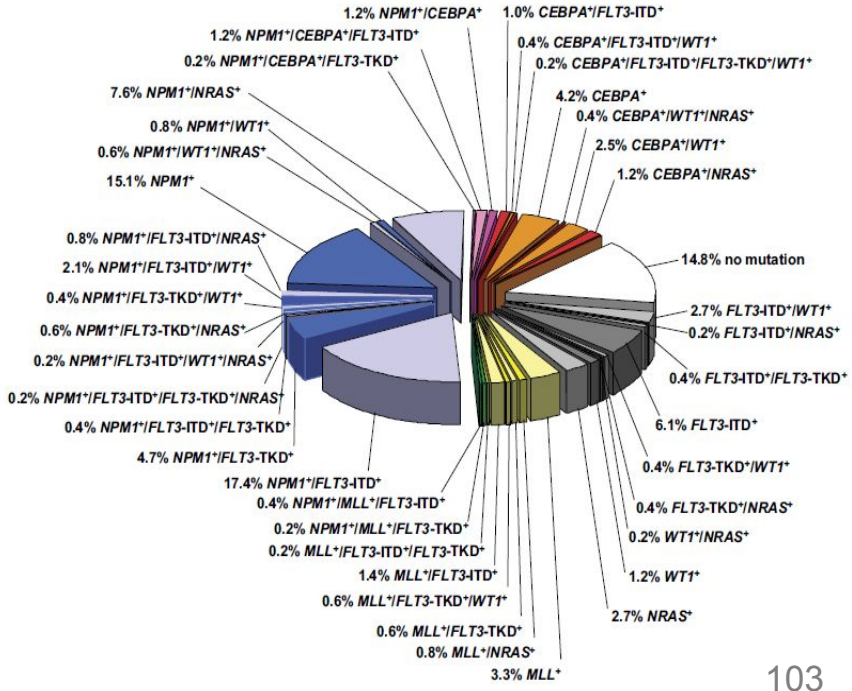
Most leukemias have multiple mutations

- This makes assessing risk a little harder
- Targeted treatment is also more challenging
- ***Need better combinations***



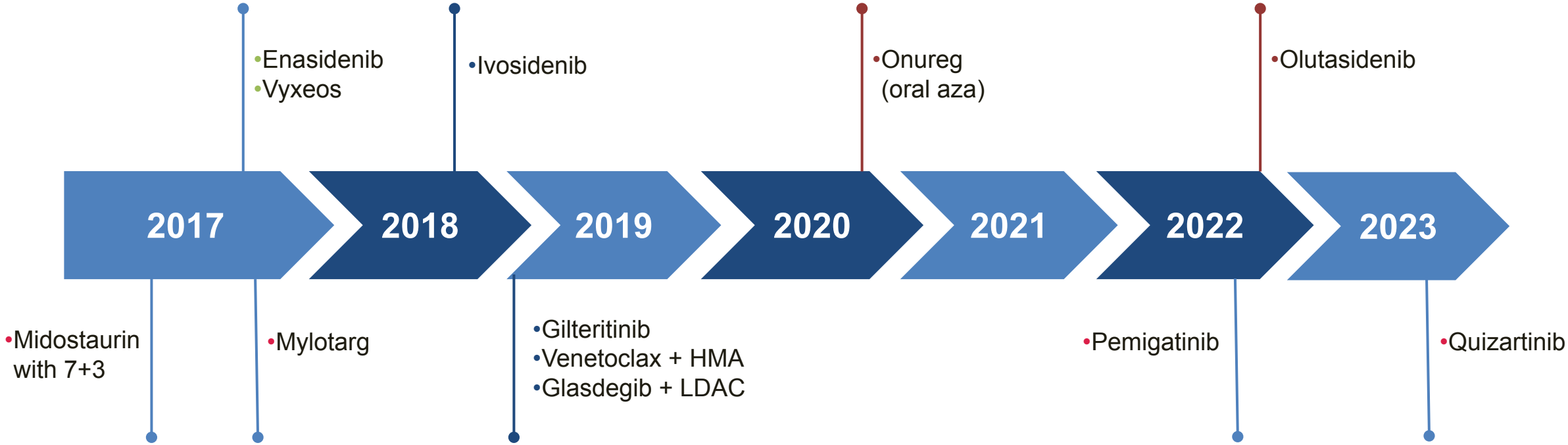
Pappaemmanuil et al. NEJM 2016

Combinatorial Complexity of 7 Mutations



Döhner, H et al. Blood. 2010; 115(3): 453-474.

We have made progress – 12 drugs approved in AML since 2017!

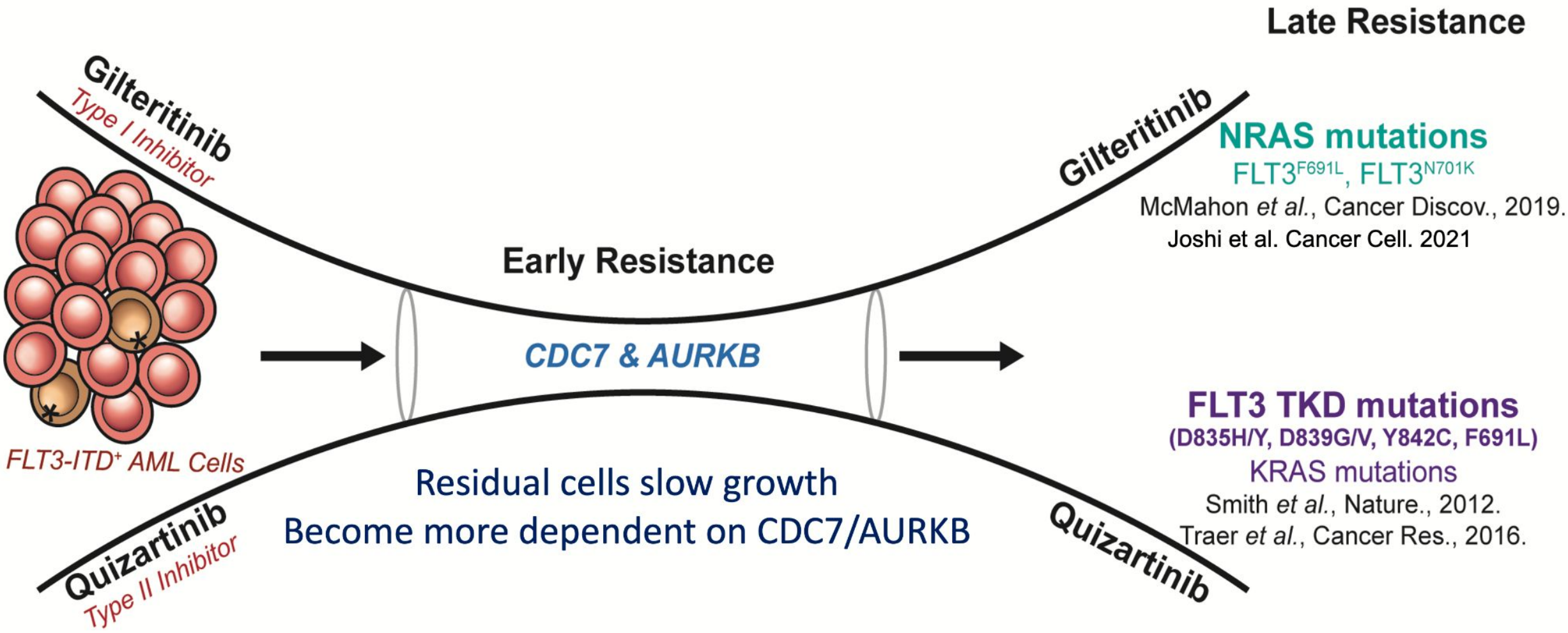


Next challenge: how best to mix and match for different types of AML patients

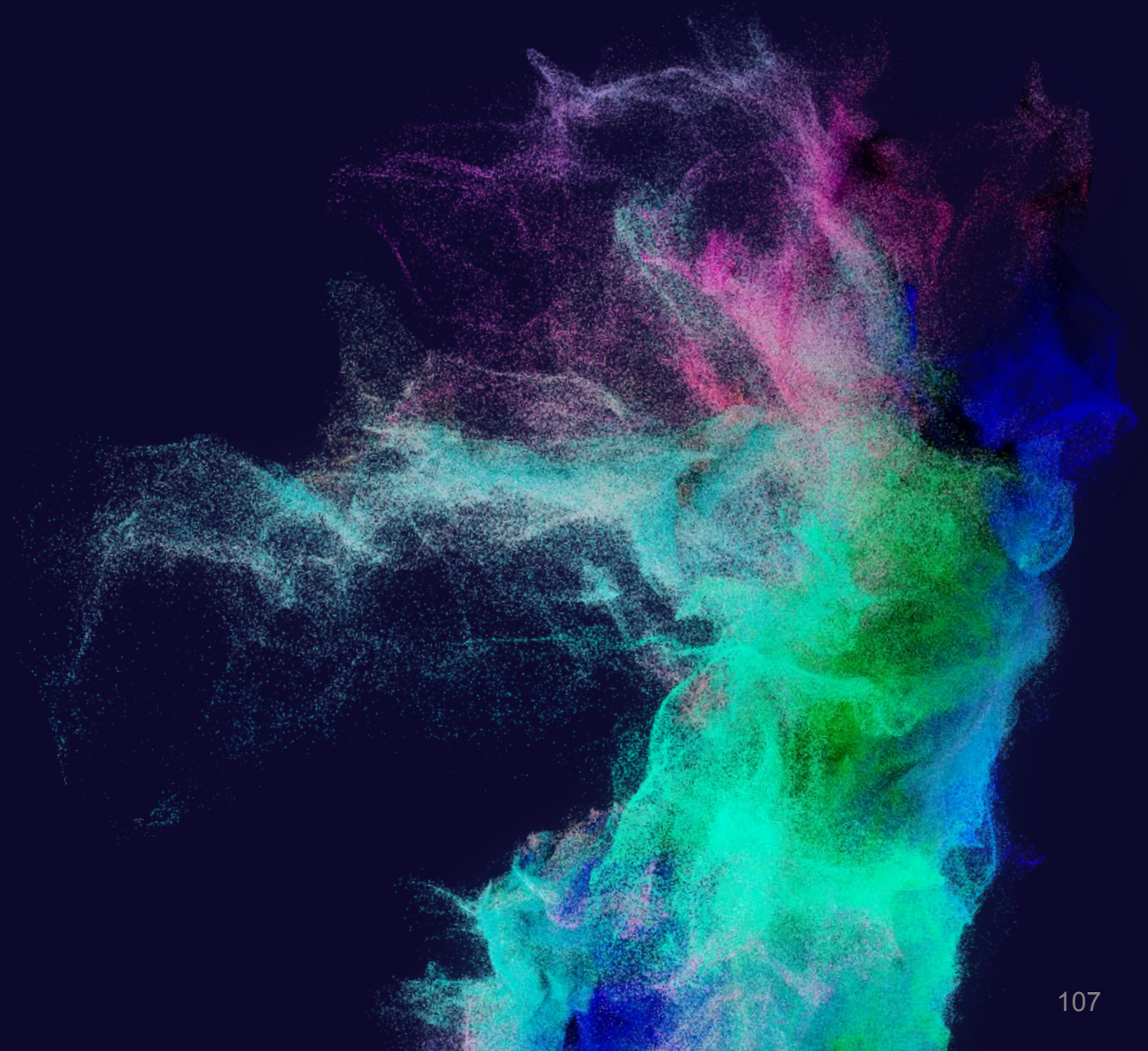
Emerging therapies and targets

- Chemotherapy (targeting replication, cell division)
- Kinase inhibitors/growth inhibition
  - Midostaurin, gilteritinib, quizartinib
- BCL2 antagonists (sensitizer)
  - venetoclax
- Differentiation agents
  - IDH inhibitors
  - Menin inhibitors
- Cell cycle inhibitors

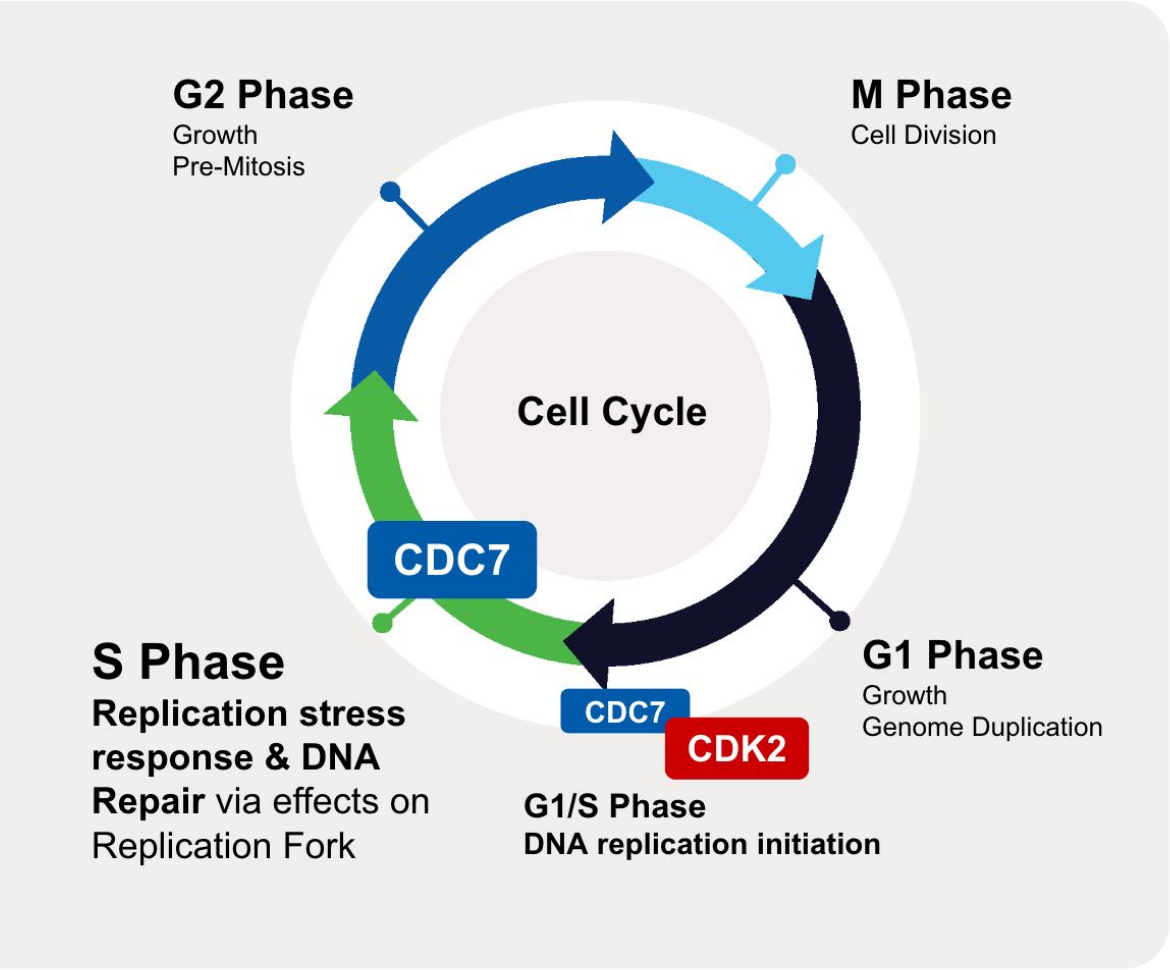
NRAS mutations enriched with gilteritinib resistance



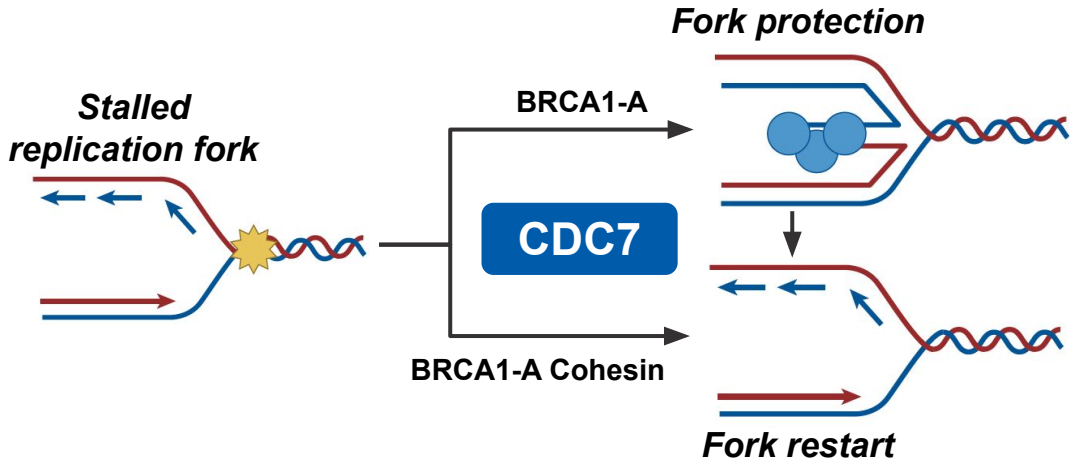
SGR-2921 (CDC7)



CDC7 Is an S-phase Kinase That Regulates DNA Replication and the Replication Stress Response



Replication stress response



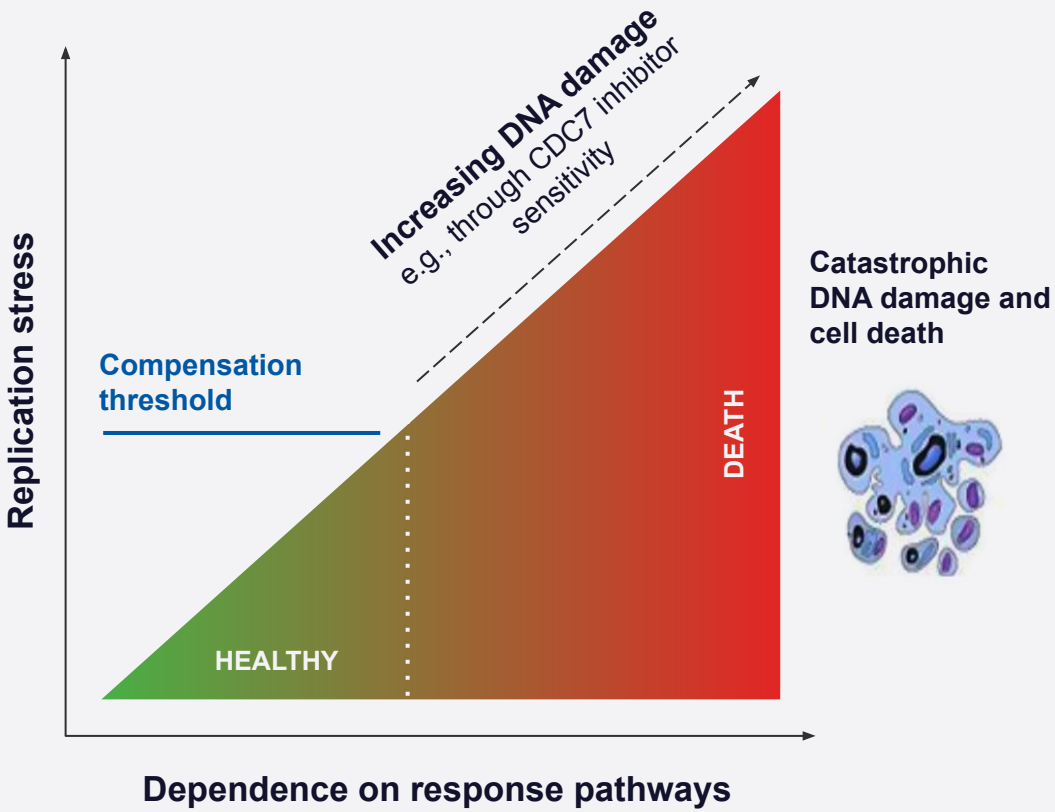
CDC7

- Maintains DNA replication fork progression by activating fork protection and restart mechanisms[1,2]
- Activates the BRCA1-A and Cohesin complexes in response to replication stress[1]
- Required for protection and restart of stalled replication forks and homologous recombination repair[1,3,4]

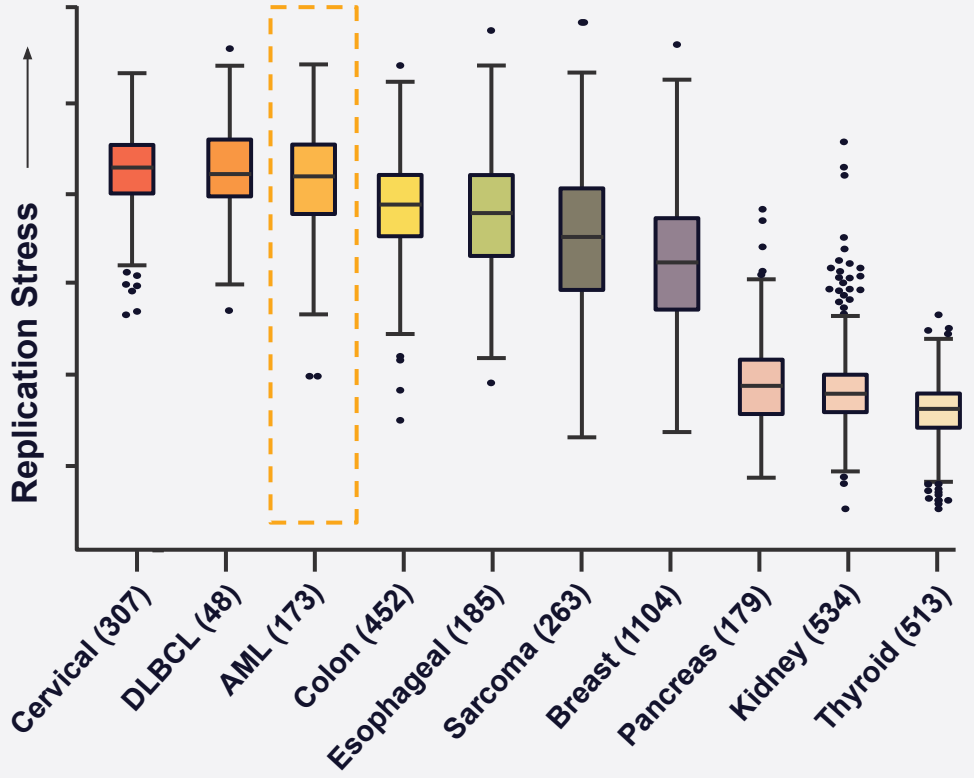
[1]*Mol Cell* 2021 Feb 4;81(3):426-441. [2]*Oncogene* 2008 May 29;27(24):3475-82.
[3]*Genes Dev* 2015 Sep 15;29(18):1955: 2506. [4]*J Biol Chem* 2020 Jan 3;295(1):146-157.

Replication Stress Is a Cancer Vulnerability and Is High in AML

Cancers with high replication stress are addicted to mechanisms that prevent catastrophic DNA damage

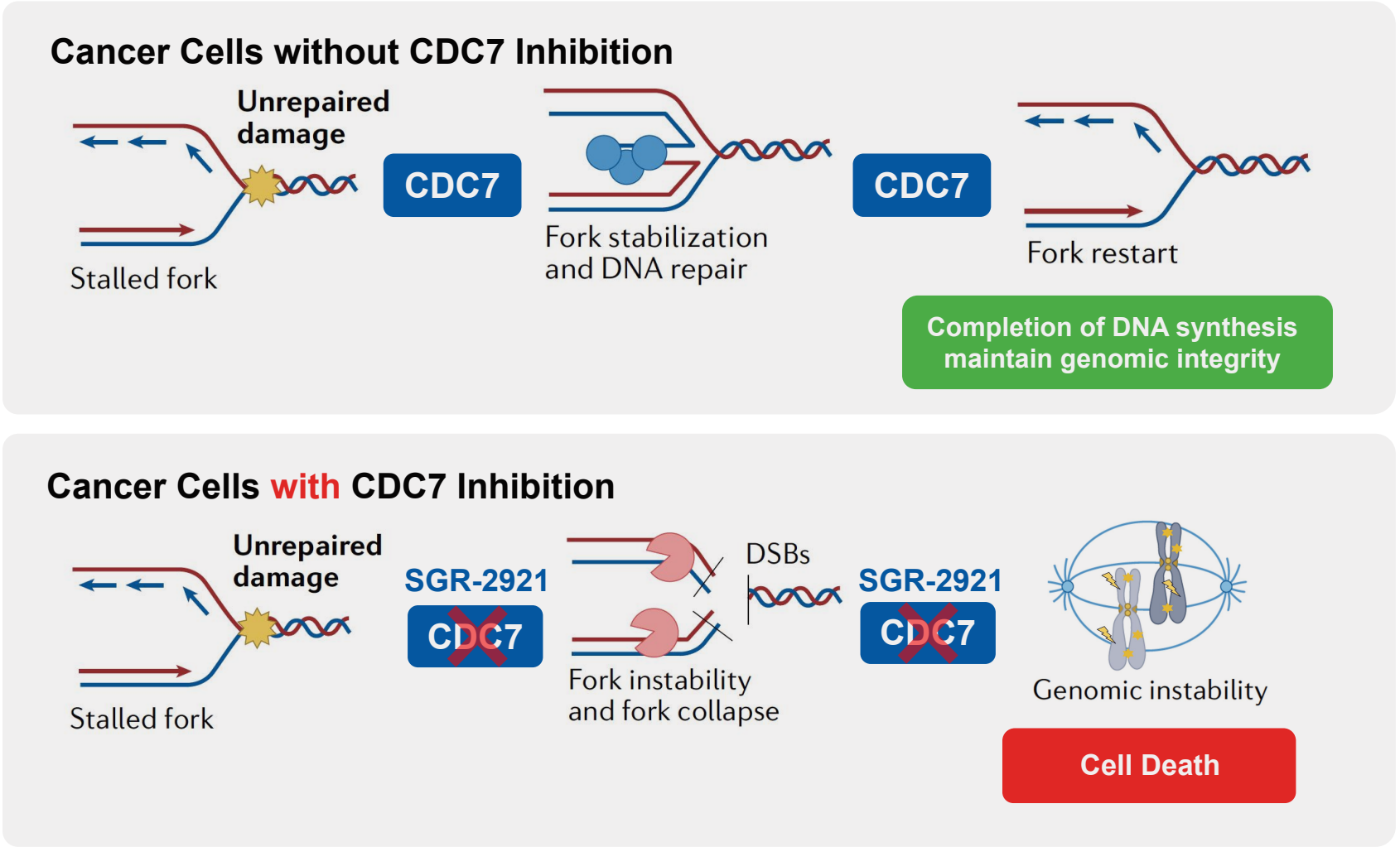


AML is characterized by high replication stress and DNA damage relative to other cancers



Adapted from Cancer Research Communications (2022) 2(6): 503-517.

CDC7 Inhibition Exploits Replication Stress Vulnerability to Trigger Cancer Cell Death



Adapted from *Nucleic Acids Res* 2021 May 7;49 (8):4239-4257.

SGR-2921 Is a Selective and Potent CDC7 Inhibitor in Phase 1

- SGR-2921 – better biochemical activity and target engagement relative to other CDC7 inhibitors
- Translates to amplified cell killing

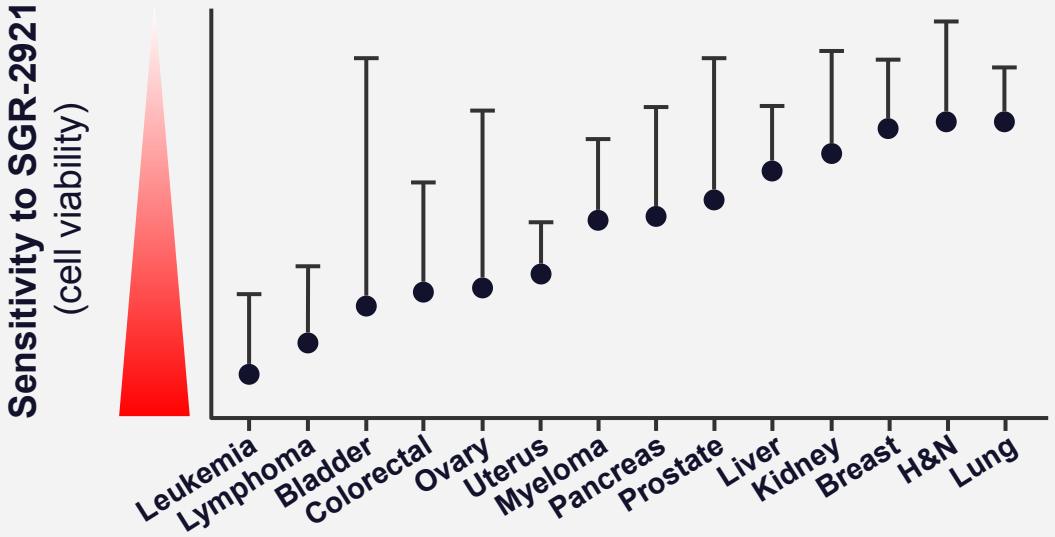
Compound	Biochemical Assay	Target Engagement		Cell Killing	
	Recombinant CDC7	MOLM-16	MV-4-11	MOLM-16	MV-4-11
SGR-2921	**0.012**	**1.2**	**1.0**	**8.5**	**57**
TAK-931	0.034	4.7	5	77	998
LY3143921	0.40	137	132	4557	12136
AS-0141	1.0	57	34	109	405

All values in nM.

Schrödinger

All competitor data is internally generated by contract research organizations using publicly available structure information.
Izadi et al., ASH 2023.

SGR-2921 Demonstrates Robust Potency Against Leukemias and Anti-proliferative Activity in AML Cell Lines



- 300 cancer cell lines screened for sensitivity to SGR-2921
- Leukemia cell lines most sensitive relative to other cancer types
- Most AML cell lines highly sensitive to SGR-2921

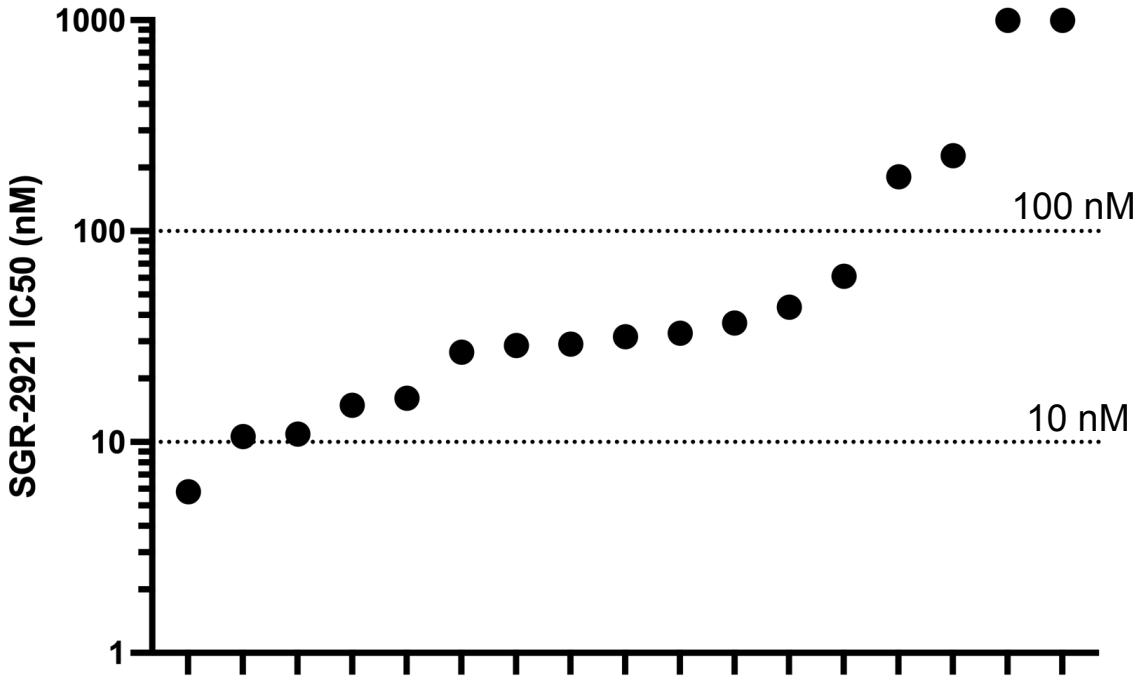
	Molm-16	NB-4I	CMK	TF-1	HL60	OCI-AML3	Kasumi-1	OCI-AML2	MV-4-11	THP-1	KG-1
pMCM2 target engagement IC_{50} (nM)	1.6	nd	nd	1.4	2.4	1.4	1.8	1.4	1.2	1.3	1.2
Cell viability IC_{50} (nM)	19.9	22.0	22.2	23.3	28.4	29.8	65	95	102	129	351

nd = not determined

Schrödinger Tsvetkov et al., ASH 2022.

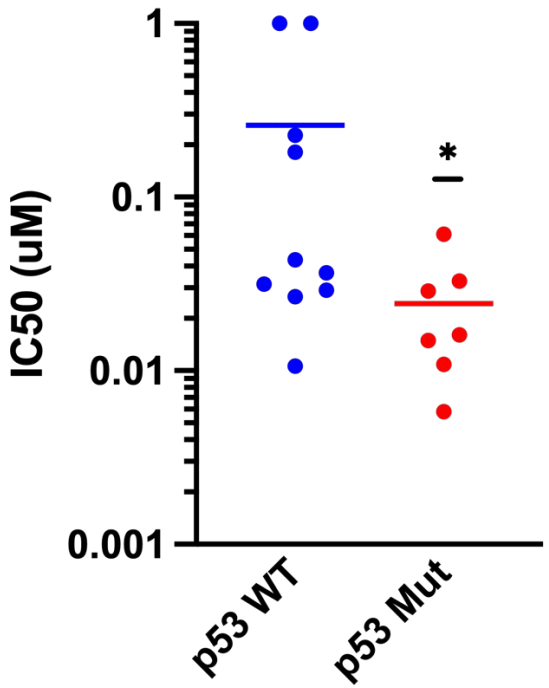
SGR-2921 Shows Potent Anti-proliferative Activity in AML Patient-derived Samples Independently of Driver Mutations, Including in p53 mut AML

Each dot represents a Patient-derived AML model (N=17)



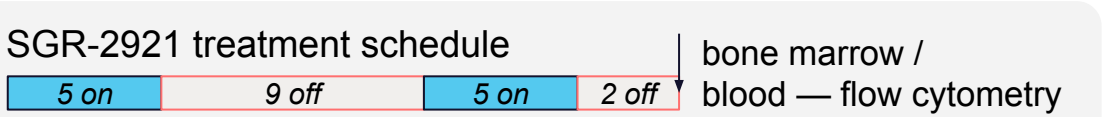
TP53 mut	X		X	X	X	X	X						X				
FLT3 mut		X		X			X	X	X			X				X	X
IDH mut		X		X									X				
NPM mut	X	X					X									X	X
Relapsed & Refractory		X	X	X			X			X	X		X	X	X		

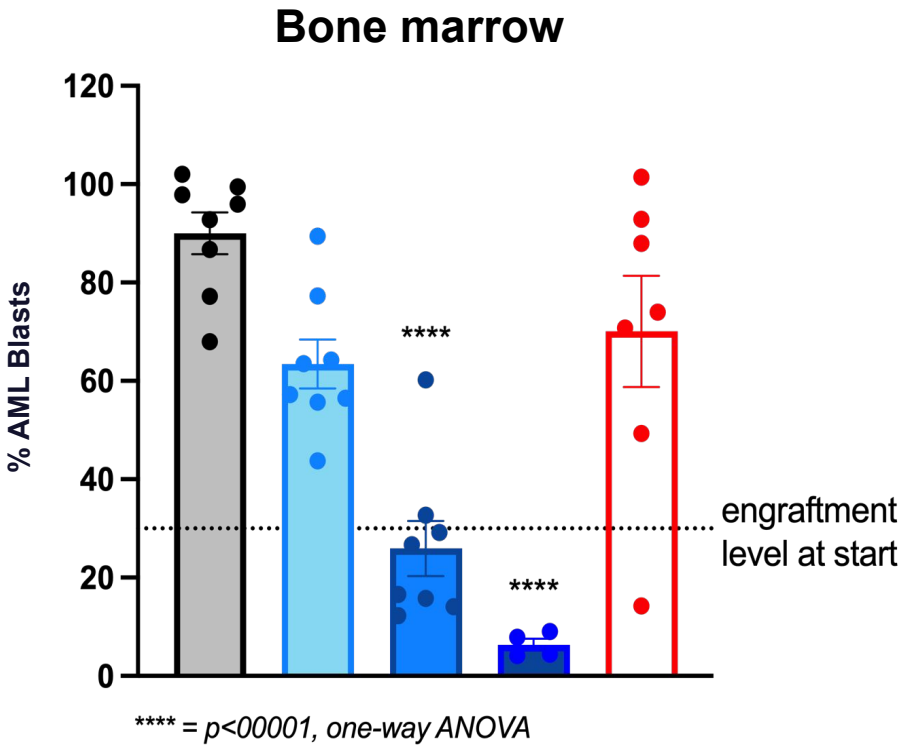
Patient-derived, p53 mutated AML models are highly sensitive to SGR-2921

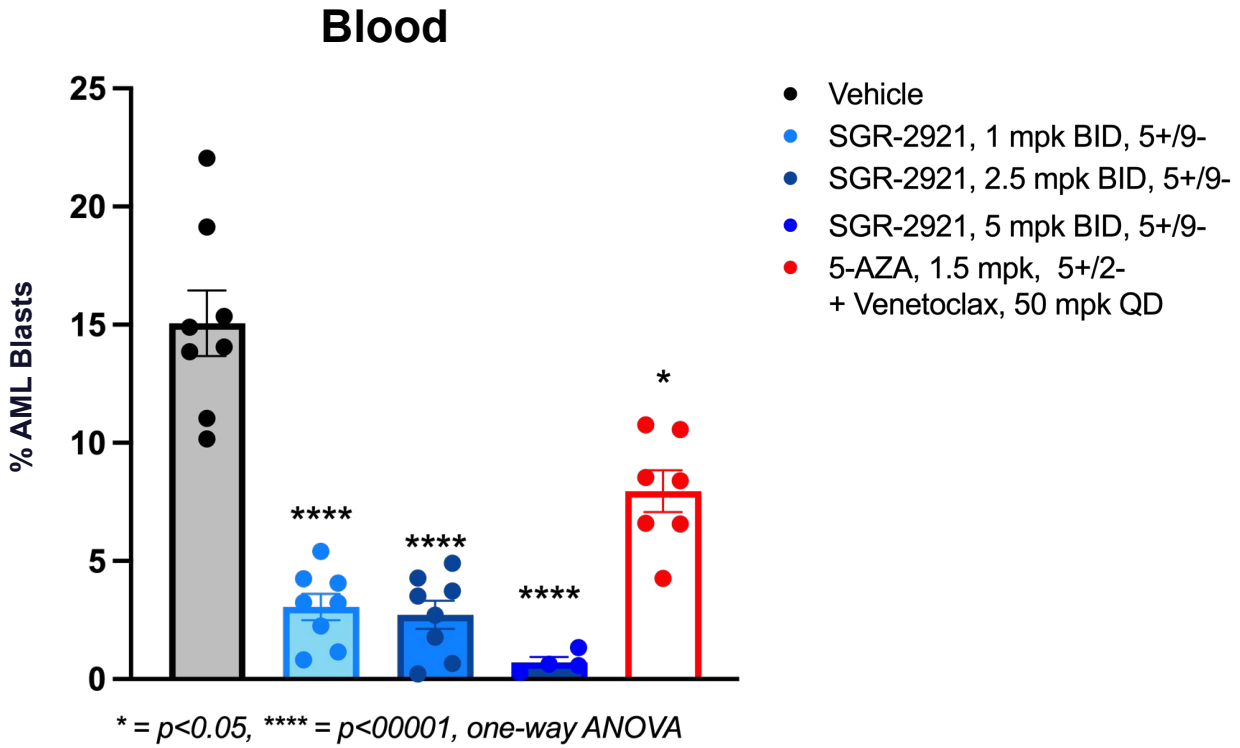


Izadi et al., ASH 2023.

SGR-2921 Shows Dose-dependent AML Blast Reduction in a TP53 Loss of Function Patient Sample *In Vivo*



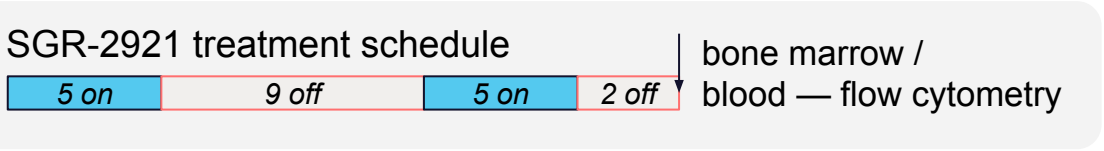


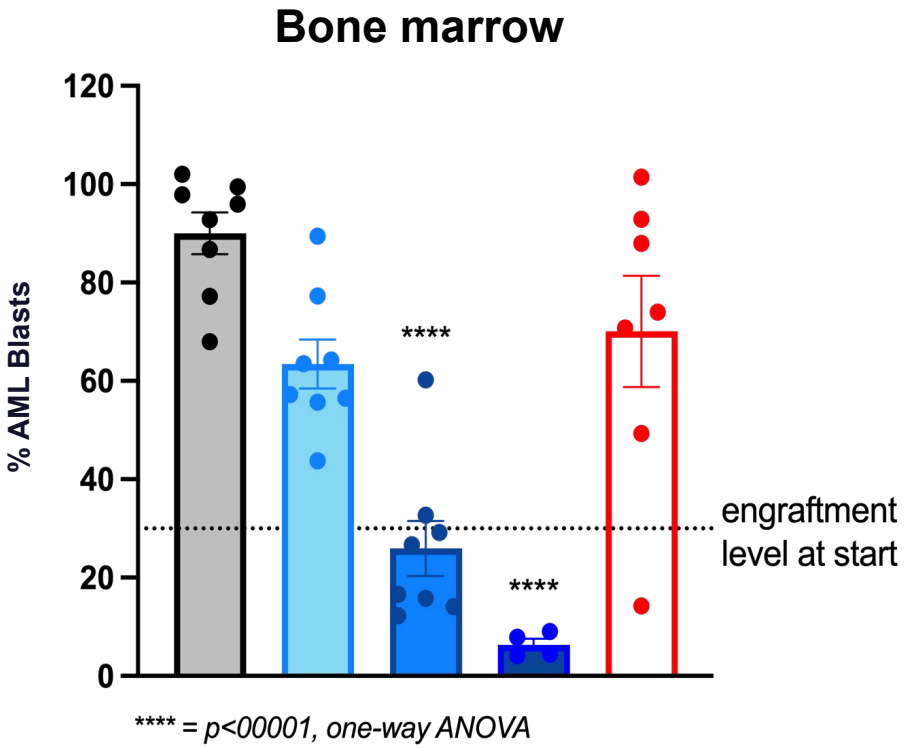


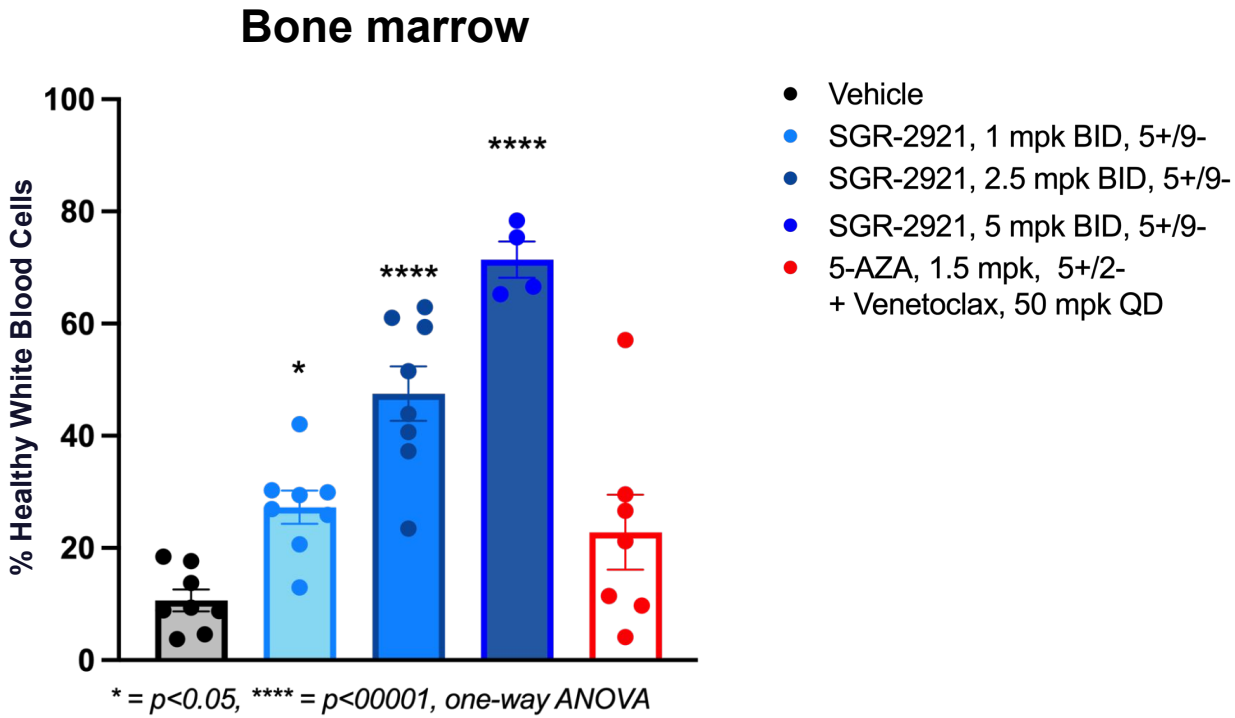
All treatments were well tolerated with <10% body weight loss

Izadi et al., ASH 2023.

SGR-2921 Shows Dose-dependent AML Blast Reduction in a TP53 Loss of Function Patient Sample *In Vivo*







All treatments were well tolerated with <10% body weight loss

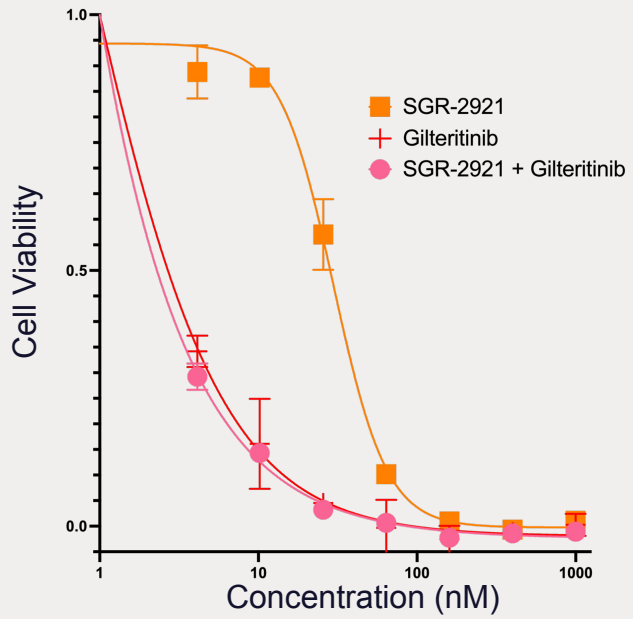
Izadi et al., ASH 2023.

SGR-2921 Is Active in AML Cell Lines Resistant and Sensitive to SoC Agents

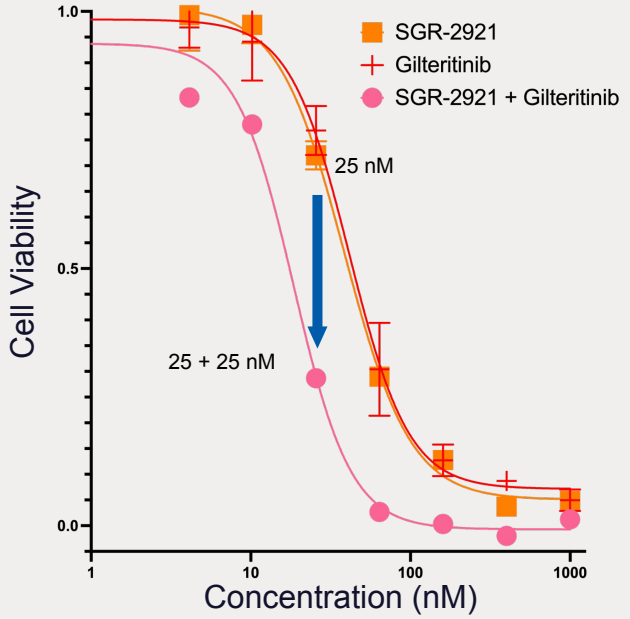
Cell Line	Post Treatment Cell Viability IC_{50} (nM)			
	SGR-2921	Decitabine	Venetoclax	Gilteritinib
Molm-16				
NB-4				
CMK				
TF-1				
HL60				
OCI-AML3				
Kasumi-1				
OCI-AML2				
MV-4-11				
THP-1				
KG-1				

poor potency — *good potency*

MV-4-11
Parental



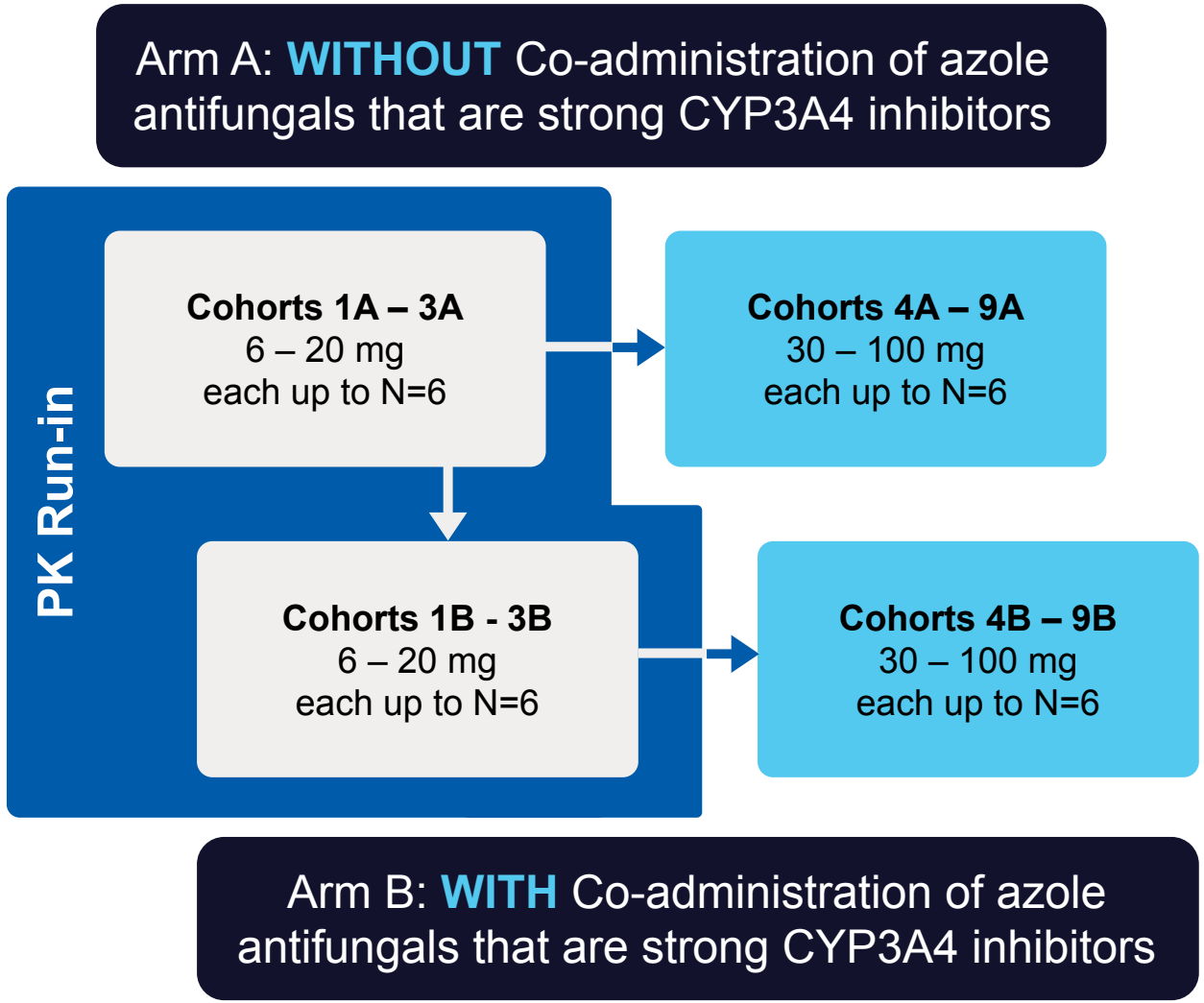
MV-4-11
Gilteritinib resistant clone



Data generated in collaboration with Dr. Elie Traer Lab at KCI, OHSU

- SGR-2921 retains activity in clones resistant to standard-of care agents: decitabine, venetoclax and gilteritinib (GILT)
- SGR-2921 resensitizes GILT-resistant clones

SGR-2921 Phase 1 Study Design and Next Steps



Study Design

- Relapsed/refractory AML and high-risk MDS
- Oral, once daily, 5 days on / 9 days off; continuous 28 day cycles

Objectives

- Primary: Evaluate safety, tolerability and RP2D
- Secondary: Evaluate PK, preliminary anti-tumor activity
- Exploratory: PK/PD, biomarkers

Status

- U.S. enrollment ongoing with planned EU expansion
- Initial Phase 1 data expected late 2024 or 2025

Today’s Agenda

Introduction — Ramy Farid

Pipeline Overview and Portfolio Strategy — Karen Akinsanya

SGR-1505 (MALT1) — Karen Akinsanya, Margaret Dugan

SGR-3515 (Wee1/Myt1) — Timothy Yap, Karen Akinsanya

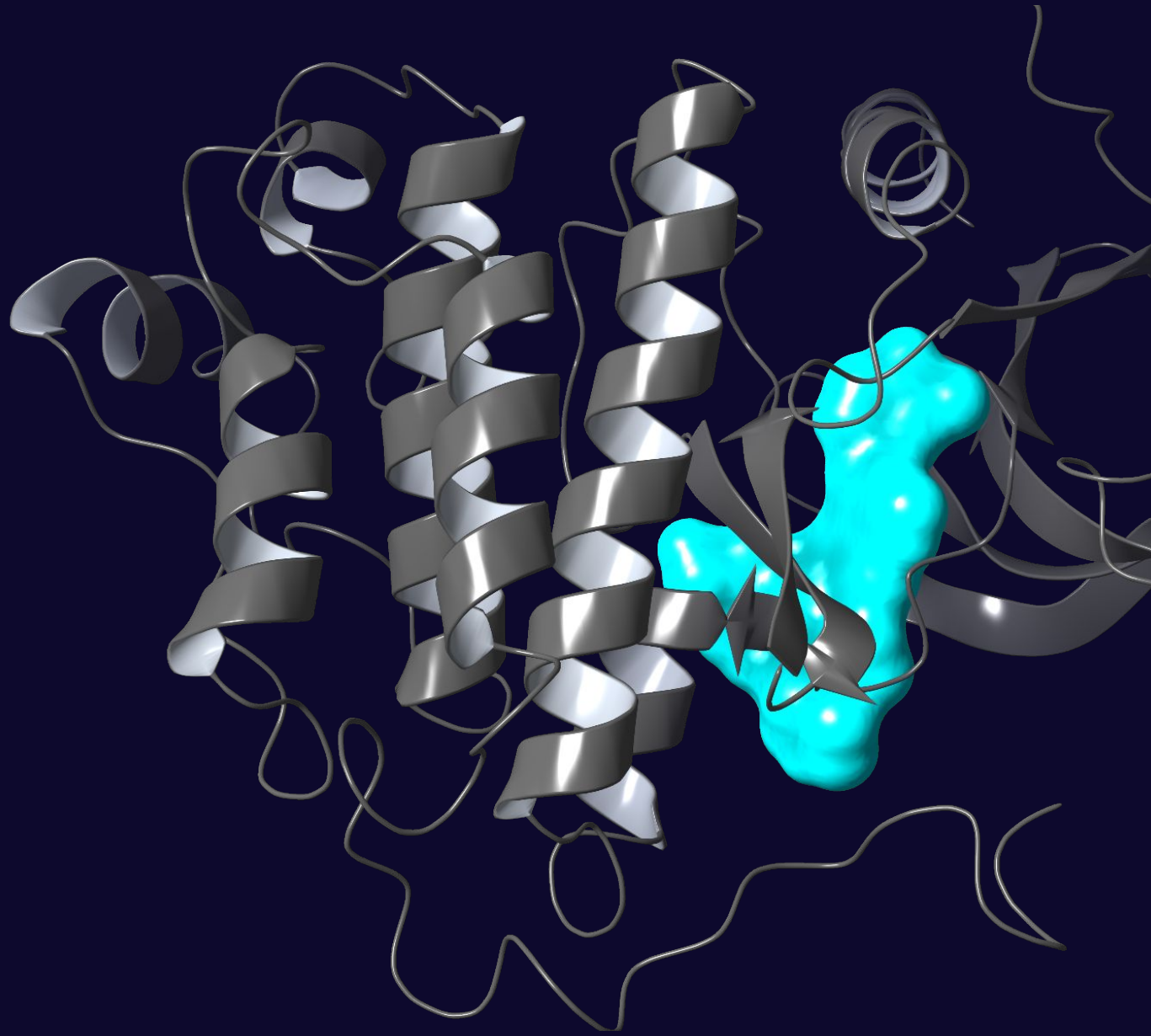
SGR-2921 (CDC7) — Elie Traer, Hamish Wright

New Discovery Programs — Jean Lachowicz

Capital Allocation and Value Creation — Geoff Porges

Q&A

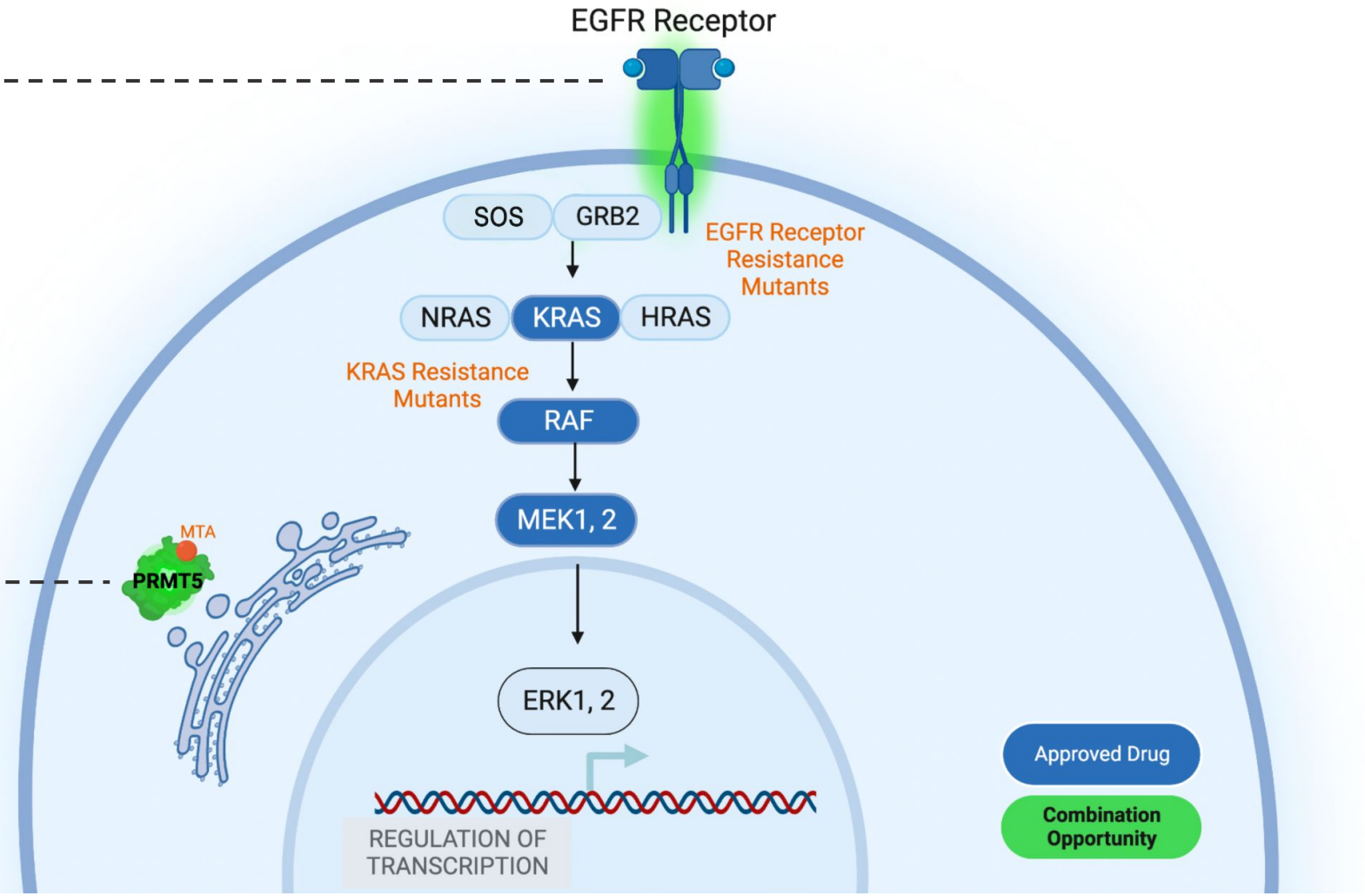
$EGFR^{C797S}$ Inhibitor Program



Next Generation Small Molecule Opportunities in Lung Cancer

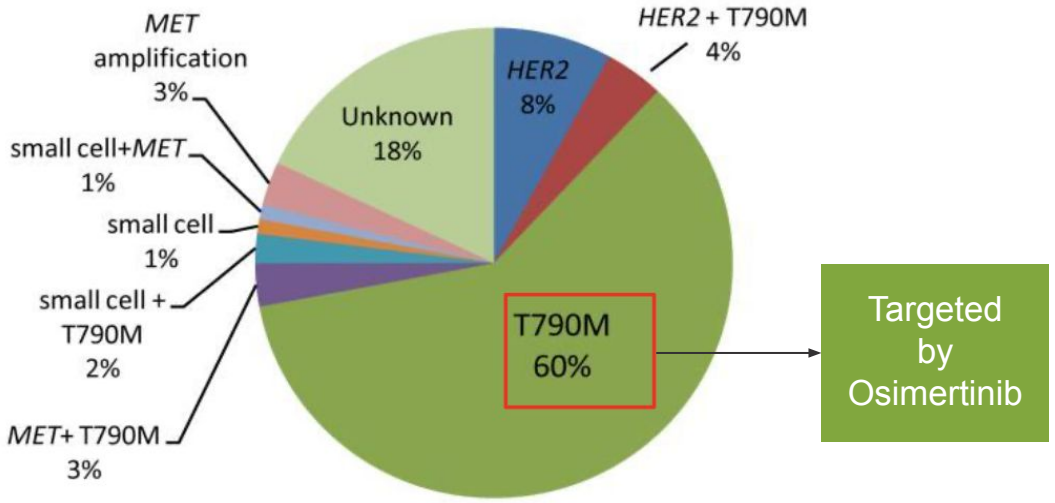
Limiting and treating brain metastasis — unmet need in advanced NSCLC

Inhibition of PRMT5-MTA complexes — emerging option in MTAP-deleted NSCLC (13%)[1]



[1] *J Clin Oncol* 39, no. 15_suppl (May 2021) 9116-9116.

Inhibition of C797S Mutant EGFR Combats Resistance to First-line Osimertinib

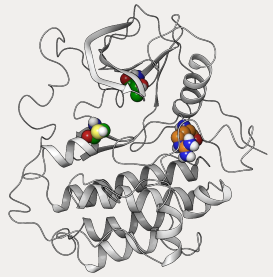


1L Osi Resistance Mechanisms	Frequency
EGFR C797S	**8%**
CCNE1 Amplifications	7.9%
MET Amplifications	6.4%
Others (non-EGFR)	77.7%

EGFRm +/- C797S Program

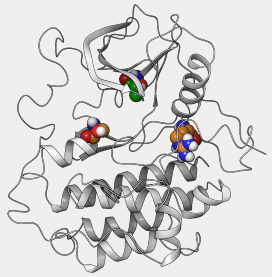
EGFR Driver Mutations (EGFRm)

L858R/Exon19Del



Resistance to 3rd-generation covalent inhibitors (osimertinib, etc)

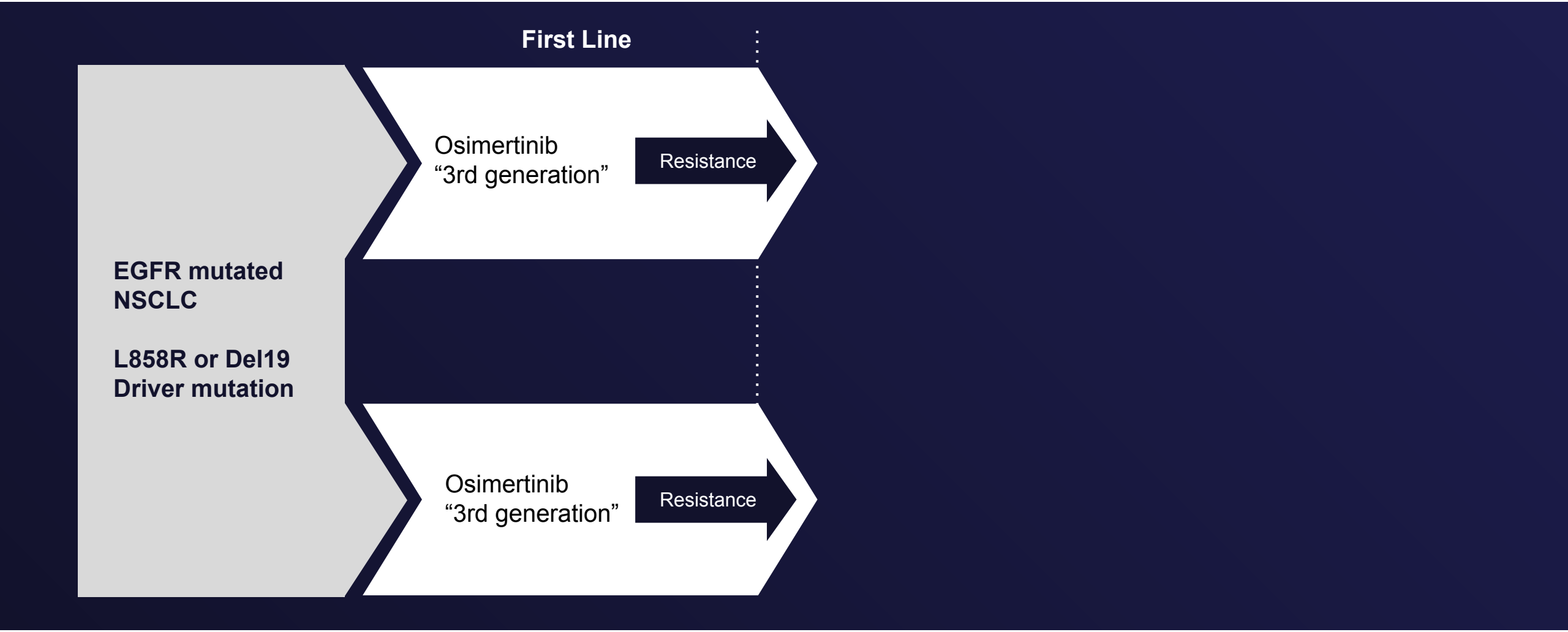
L858R/Exon19Del+C797S



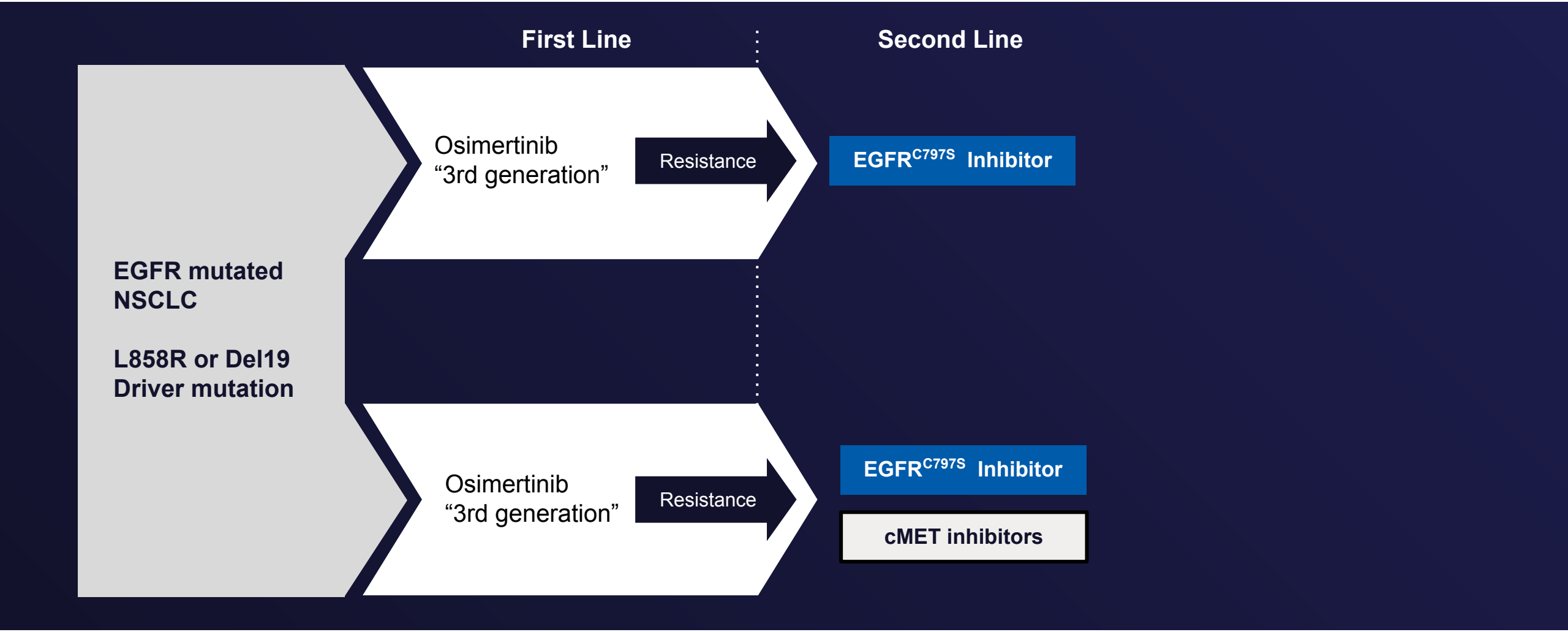
Best-in-Class Next Generation Inhibitor TPP

- CNS penetrant to address brain metastases
- Improved EGFR WT selectivity
- Kinome Selective
- Low potential for DDI risk

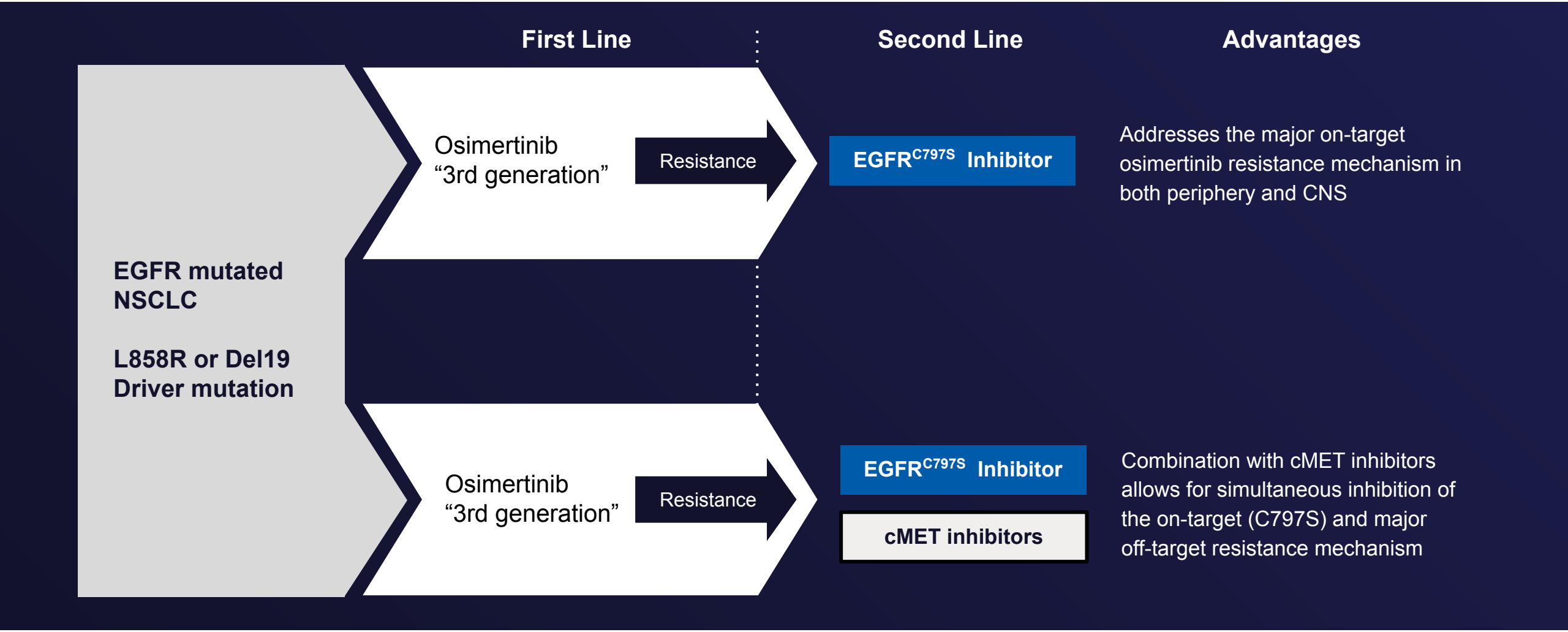
EGFR^{C797S} Program: Opportunities in Multiple Lines of Therapy



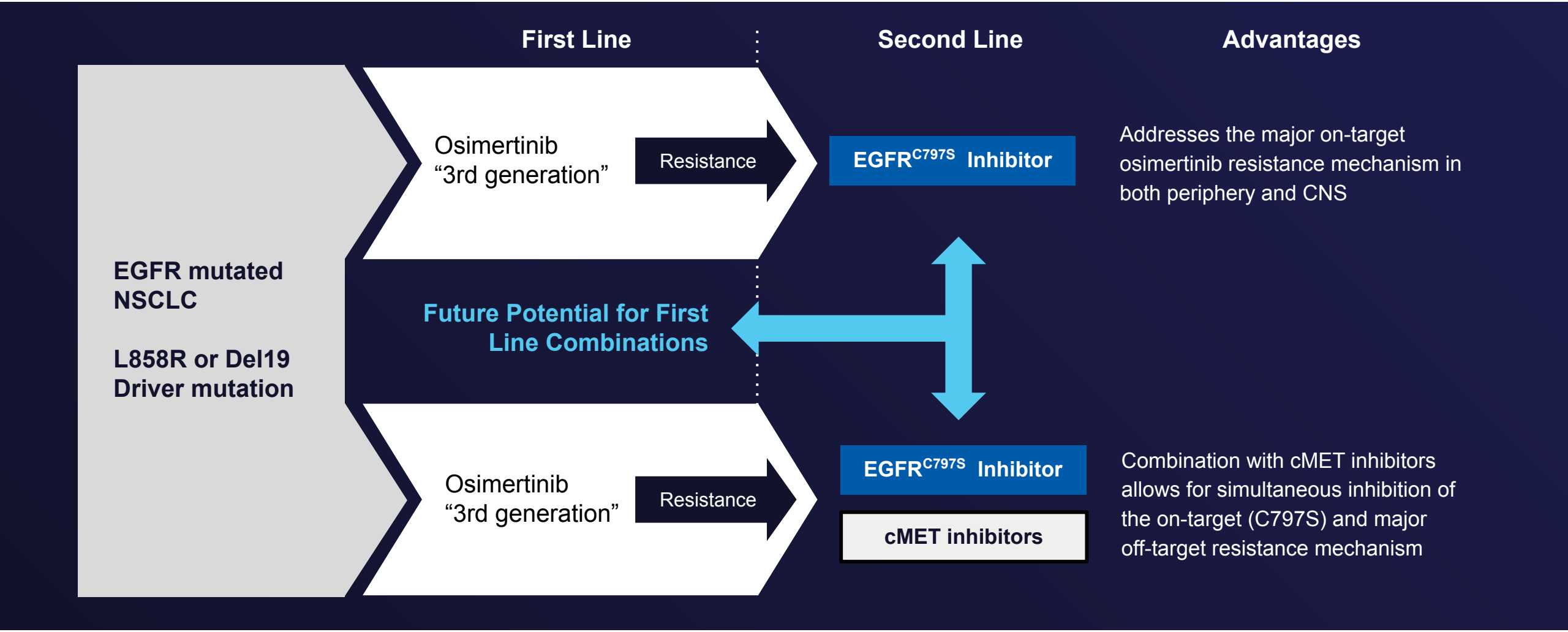
EGFR^{C797S} Program: Opportunities in Multiple Lines of Therapy



EGFR^{C797S} Program: Opportunities in Multiple Lines of Therapy



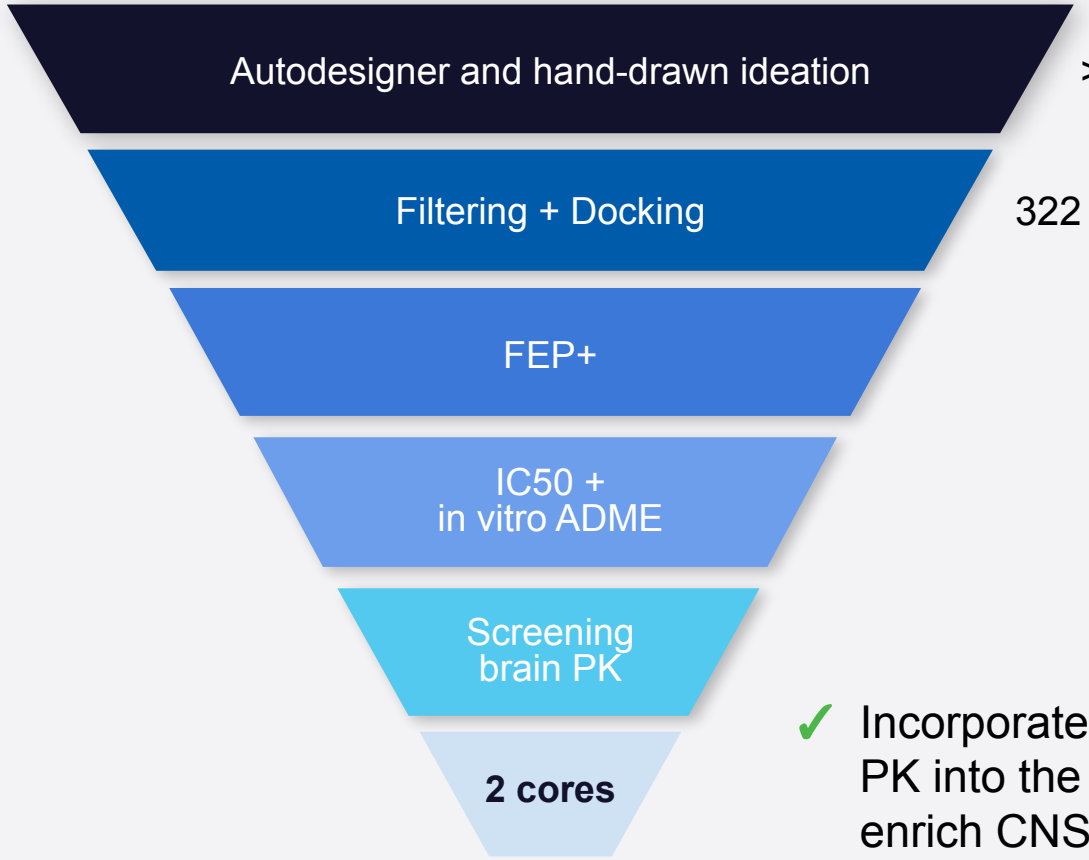
EGFR^{C797S} Program: Opportunities in Multiple Lines of Therapy



Rapid Identification and Optimization of EGFR^{C797S} Inhibitors

- Identified structurally unique, highly potent hits with strong IP position
- Efficient multi-parameter optimization via FEP+, physicochemical property predictors
- Blood brain barrier permeability predictions further enriches CNS penetrant hits

Large-scale enumeration for novel CNS cores



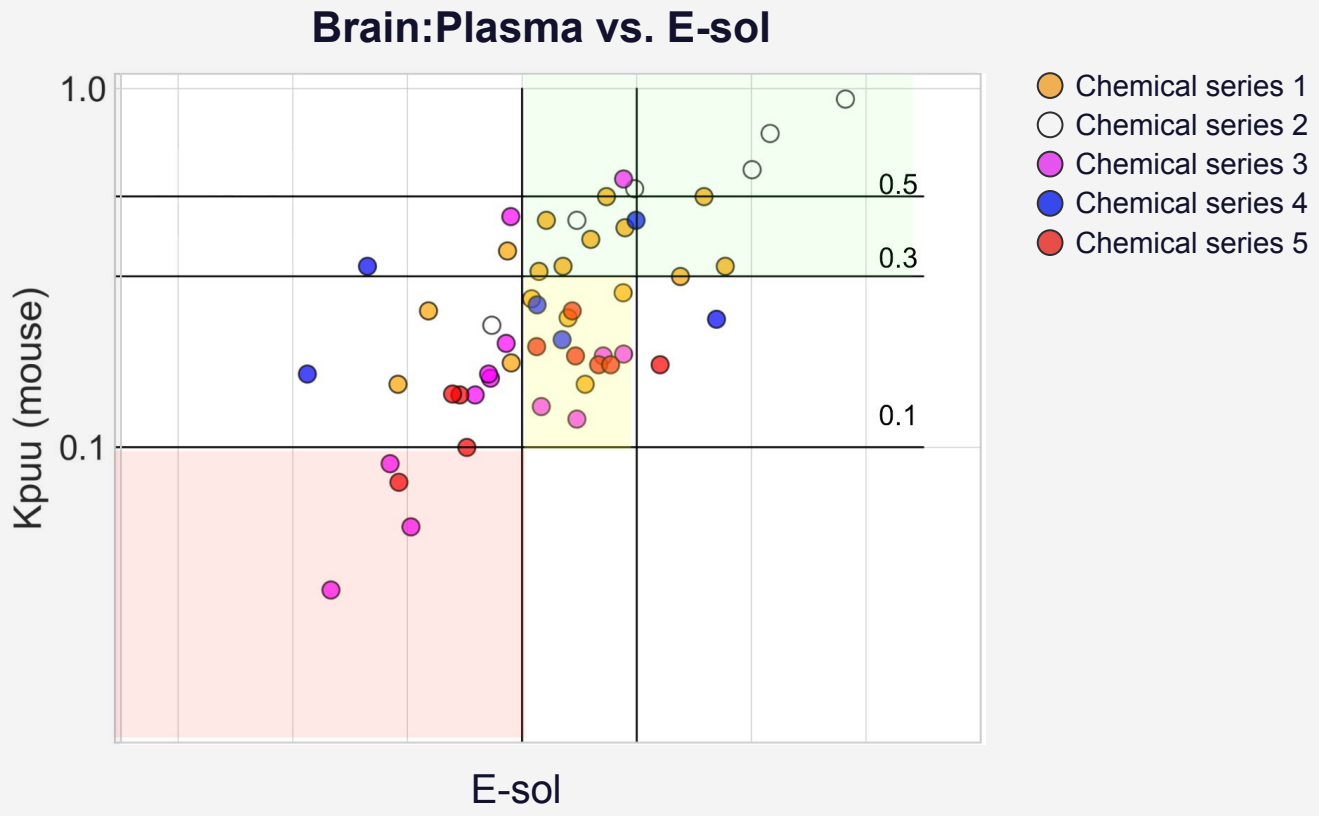
✓ Incorporated screening brain PK into the cascade to enrich CNS penetrant hits

E-sol Predictions Show Good Correlation with Brain:Plasma Exposure Across Programs

Energy of solvation (E-sol)

Quantum mechanics-based calculation:

- 3D molecular conformation
- Size effects
- Gas-water partition
- Polarity
- Energy of neutralization (pKa)



Lawrenz et al. *J Chem Inf Model* 2023, 63(12), 3786-3798.

Durable, Tumor-selective Reduction of Phospho- EGFR^{C797S} Achieved in a Mouse CDX Model

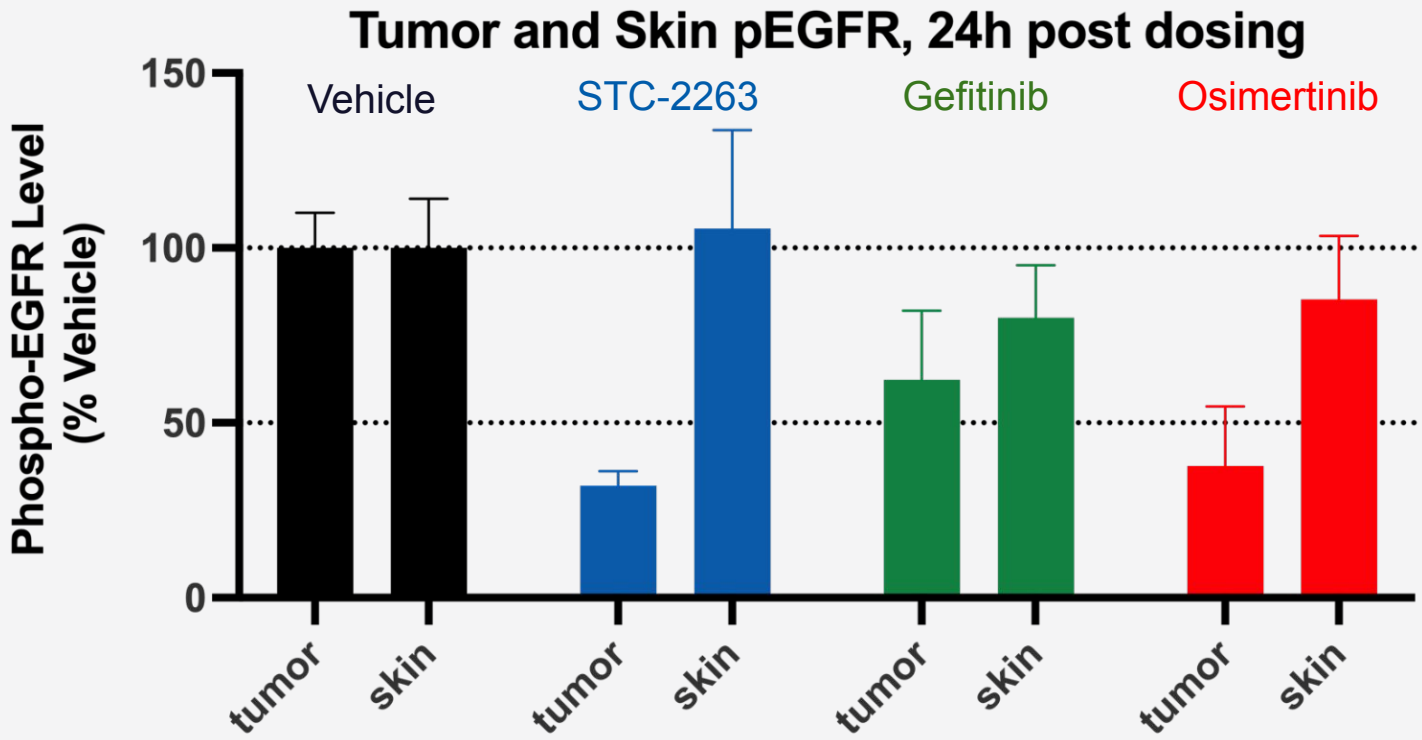
Acute Pharmacodynamic Model:



Day 1 — **Tumor cells**

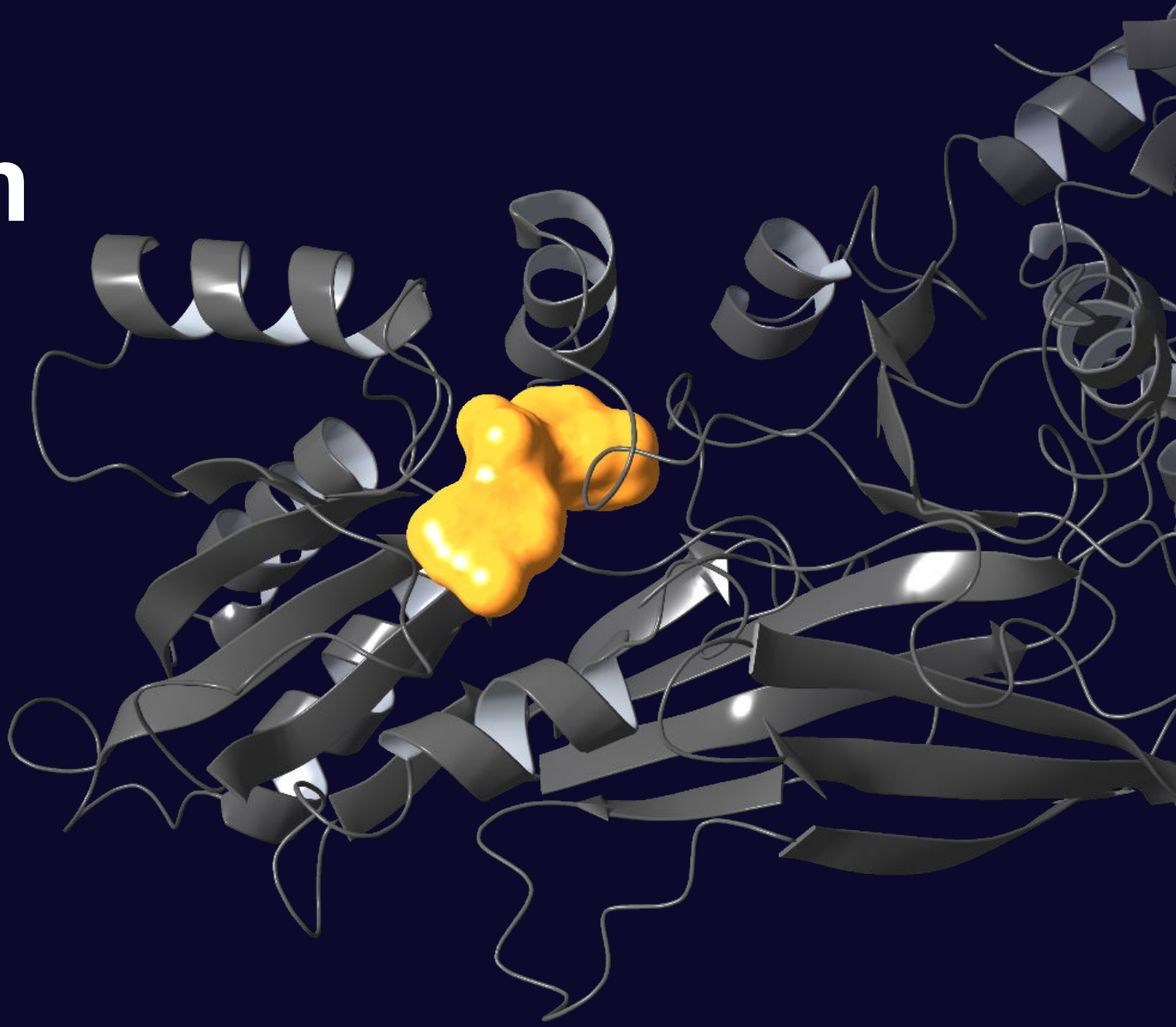
Day 15 — **Inhibitor Compound**

Day 16 — **Skin & Tumor Collection Phospho-EGRR measurement**



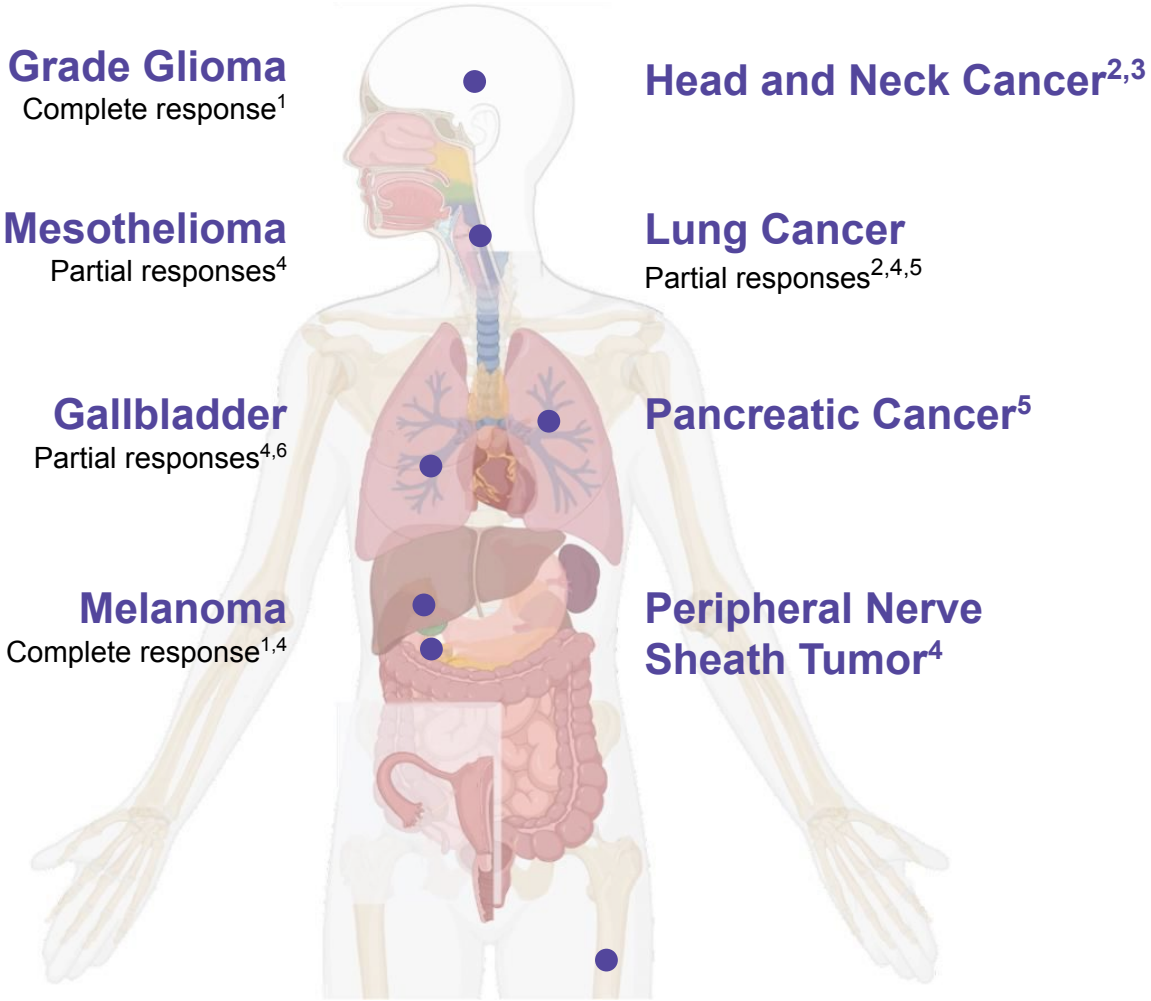
Optimizing a wild-type-sparing, CNS-penetrant molecule with the potential to address brain metastases in patients who lose response to existing agents, and to deepen responses through new combination regimens

PRMT5-MTA Inhibitor Program



Schrödinger

PRMT5 and PRMT5-MTA Inhibitors Demonstrate Clinical Signals in 3rd Party Studies



High Grade Glioma
Complete response[1]

Mesothelioma
Partial responses[4]

Gallbladder
Partial responses[4,6]

Melanoma
Complete response[1,4]

Head and Neck Cancer[2,3]

Lung Cancer
Partial responses[2,4,5]

Pancreatic Cancer[5]

Peripheral Nerve Sheath Tumor[4]

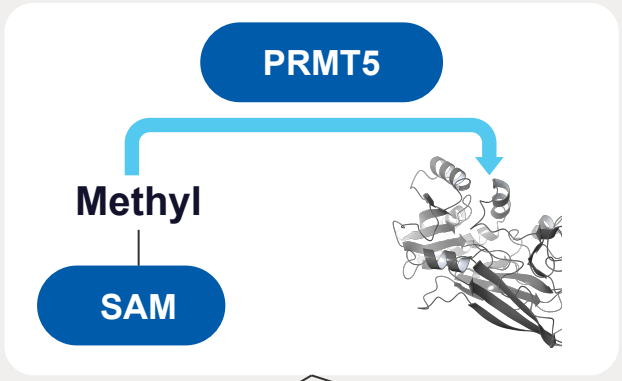
PRMT5-MTA Inhibitor Opportunity

- Address dose limiting hematological toxicity seen with 1st generation PRMT5 inhibitors that lack tumor cell specificity
- Spare WT cells to increase therapeutic index – PRMT5-MTA inhibition is limited to cells with MTAP-deletion
- Lower DDI potential and optimize brain permeability – opportunity to target multiple sensitive tumors and enable combinations

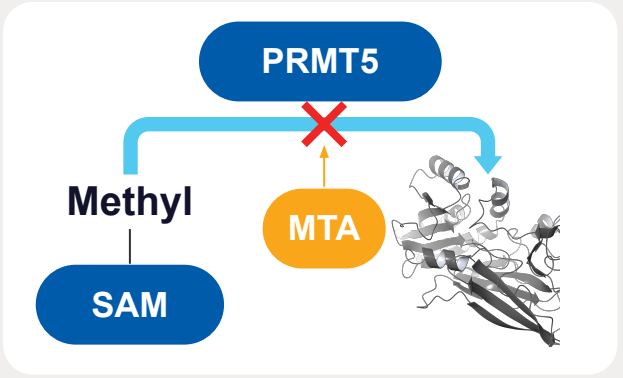
[1]Monga et al., *J Clin Oncol* (2023) 41(16 Suppl):3008. [2]Ahnert et al., *Clin Oncol* (2021) 39(15 Suppl):3019. [3]Sui et al., *Ann Oncol* (2019) 30(5 Suppl):v159. [4]Engstrom et al., *Cancer Discov* 2023 13 (11): 2412–2431. [5]Rodon et al., *Cancer Discov* (2023) 13(12): 2492.

PRMT5 Inhibition Disrupts Key Cellular Processes and Requires Tumor Cell Selectivity

PRMT5 is upregulated in most cancers and is associated with poor prognosis



MTA, an endogenous inhibitor of PRMT5 accumulates with MTAP deletion



ALL CELLS

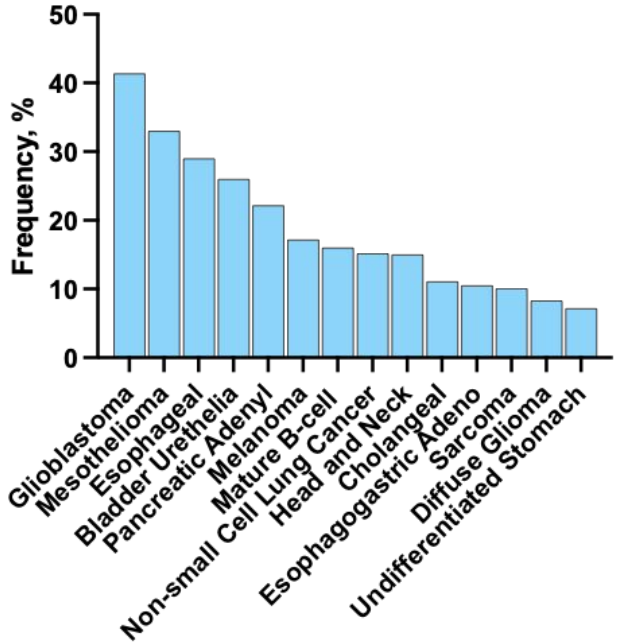
Regulation of:

- Transcription, differentiation, genome organization
- Protection from DNA damage stress

TUMOR CELLS

- Tumor microenvironment signalling
- Stem cell renewal

Frequency of MTAP deletion in cancers[1]



MTAP deletion, a feature of many tumors, is synthetically lethal with PRMT5 inhibition

Cooperativity with MTA increases PRMT5 inhibition selectively in MTAP-deleted cells

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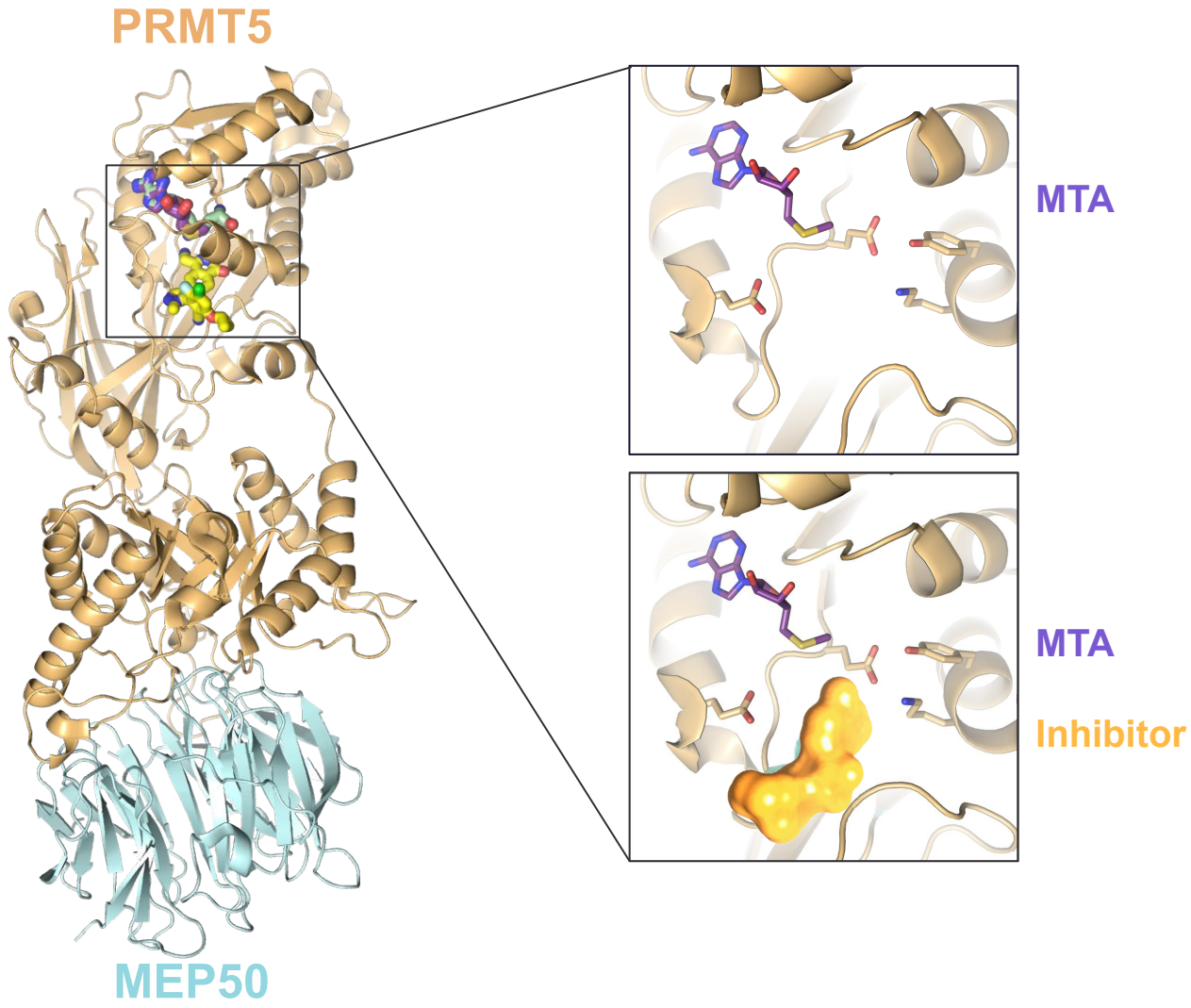
[1]Hu et al., *Cancer Res* (2021) 81(19):4964– 4980. Adapted from Fig. 1 TCGA dataset
SAM: S-adenosyl methionine (methyl donor), MTA: 5'-methylthioadenosine, MTAP: S-methyl-5'-thioadenosine phosphorylase.

High Quality Structures Inform MTAP^{WT} Selectivity Design Strategy

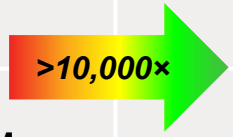
- Many CNS penetrant inhibitors display inferior MTAP-WT selectivity
- Goal is to selectively inhibit PRMT5-MTA complexes prevalent in MTAP-deleted cells
- Proprietary high-resolution crystal structures generated internally
- MTA amino acid interactions exploited to improve selectivity between WT and MTAP deleted cells



Rapid Potency Gains and Progression of Novel Series

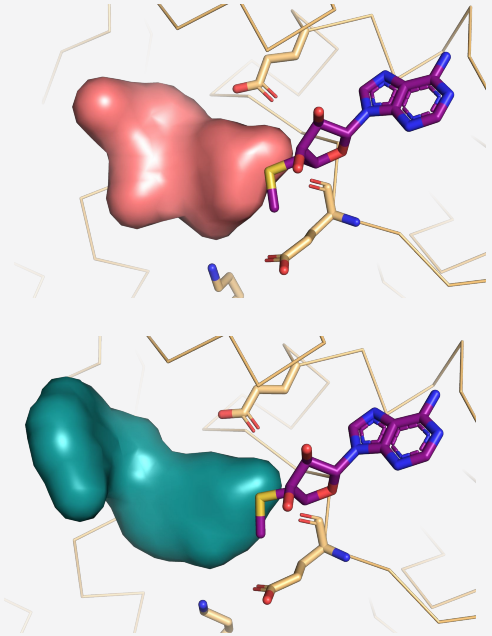
Advancing best-in-class novel compounds that combine CNS permeability with highly potent $MTAP^{KO}$ affinity, MTAP-WT selectivity and limited CYP inhibition liability

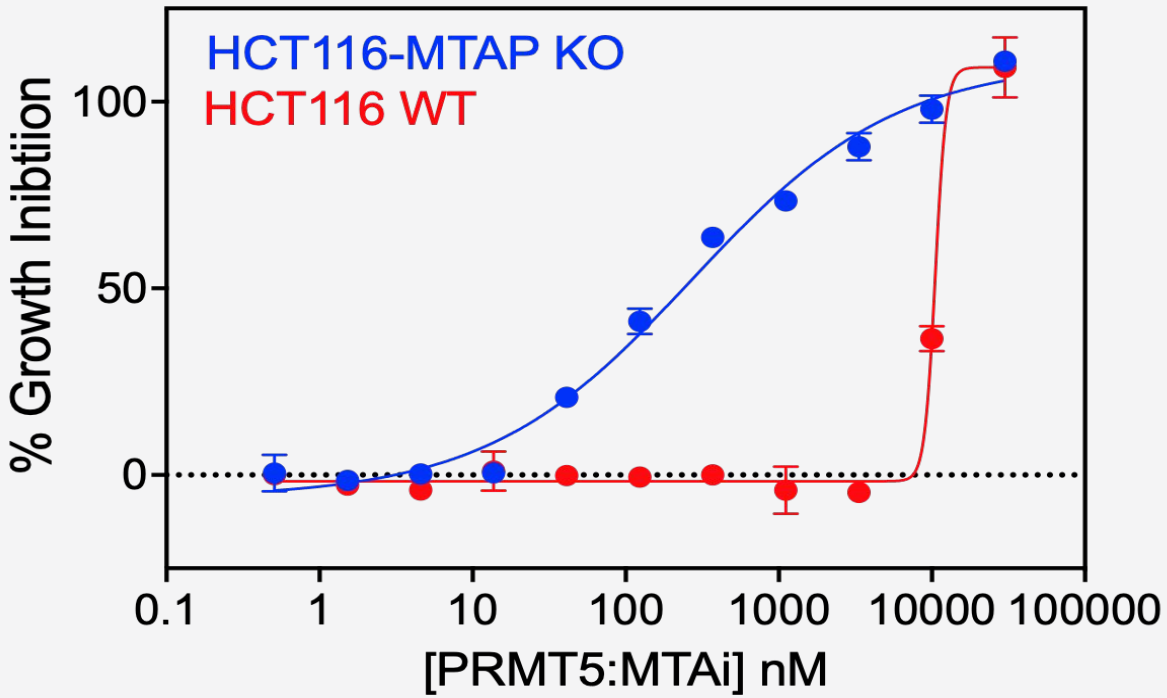
	Series A Hit Compound	Series A Lead Compounds
$LogD_{7.4}$ / TPSA	-0.4 / 65	2.1 / 64
PRMT5-MTA SPR K_d	43 µM	<0.1 nM
PRMT5-MTA FRET IC_{50}	>100 µM	<10 nM



Novel Selective Compounds Advancing Through Multiple Models

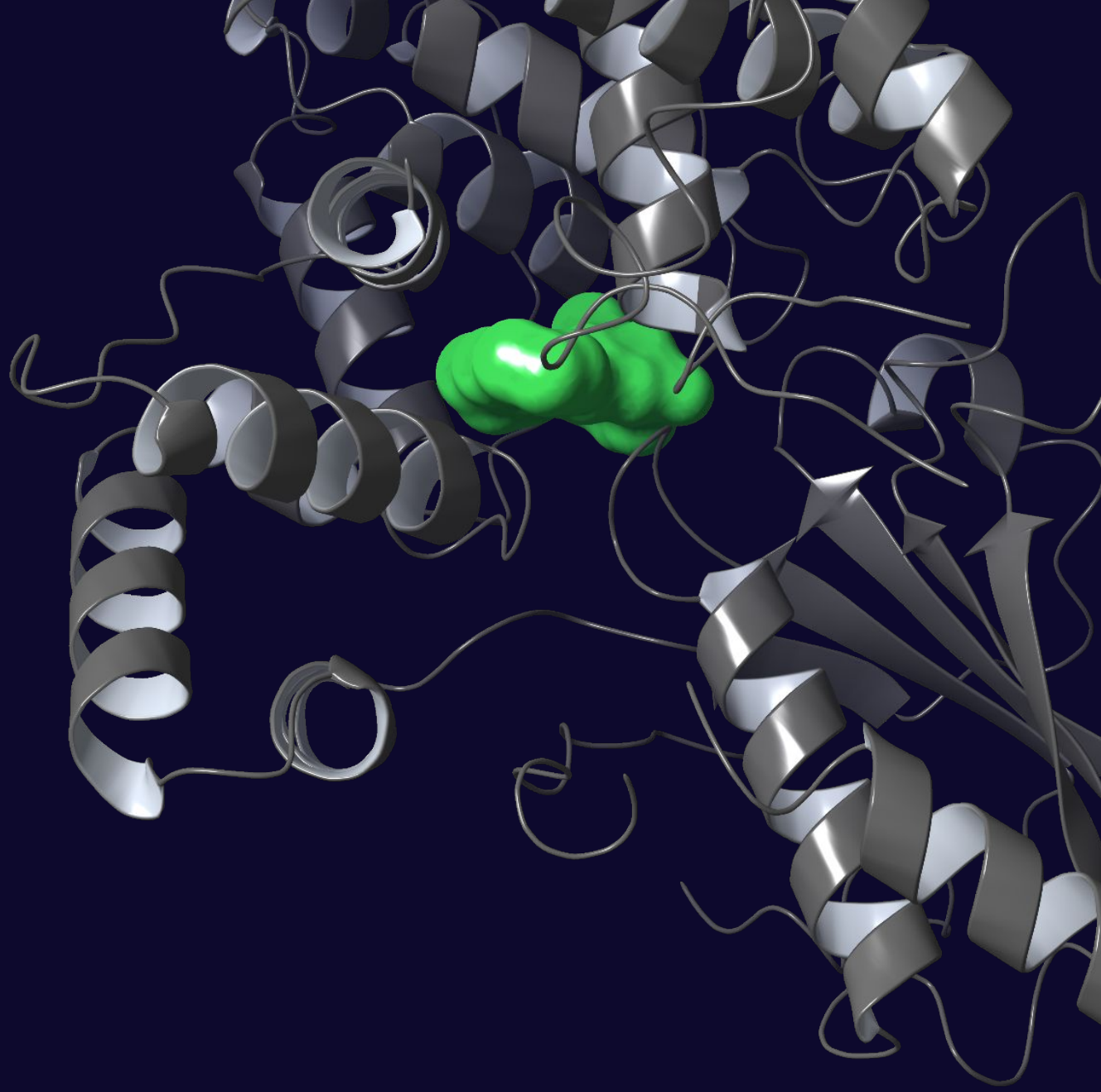
Co-crystal structures solved for two series confirm **MTA-cooperative binding**





Leads display MTAP^{KO} selective anti-proliferative effects, and favorable solubility and ADME profiles. Rapidly advancing novel, selective, potent PRMT5-MTA molecules with optimized brain-penetration.

NLRP3 Inhibitor Program



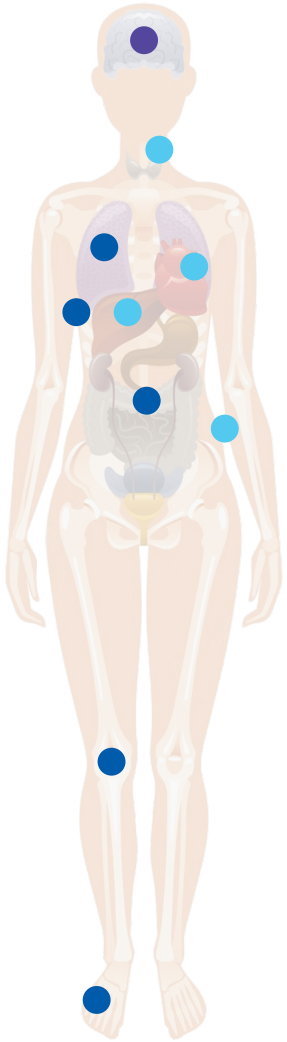
NLRP3 Inhibitors Have Potential Across Multiple Indications

Neurodegenerative and CNS Diseases

Parkinson's disease (PD)
Stroke
Traumatic brain injury (TBI)
Multiple Sclerosis (MS)
Alzheimer's disease (AD)

Inflammatory and Autoimmune Diseases

Severe asthma
Hidradenitis suppurativa (HS)
Crohn's disease (CD)
Ulcerative colitis (UC)
Osteoarthritis (OA)
Rheumatic arthritic diseases
Gouty arthritis



Chronic Diseases

Atherosclerosis
Heart failure after MI
NASH and other fibrotic diseases
Metabolic diseases (T2D)

NLRP3 Monogenic Rare Diseases

Cryopyrin associated periodic syndromes (CAPS)*

* genetic validation for gain-of-function mutations in NLRP3

NLRP3 Inhibitor Opportunity

- NLRP3 small molecule inhibitors needed as alternatives to IL1β-targeting biologics
- Most clinical-stage compounds are **sulfonylureas** – often associated with liver toxicity and poor PK
- Brain penetrant NLRP3 inhibitors may address neuro-immune indications

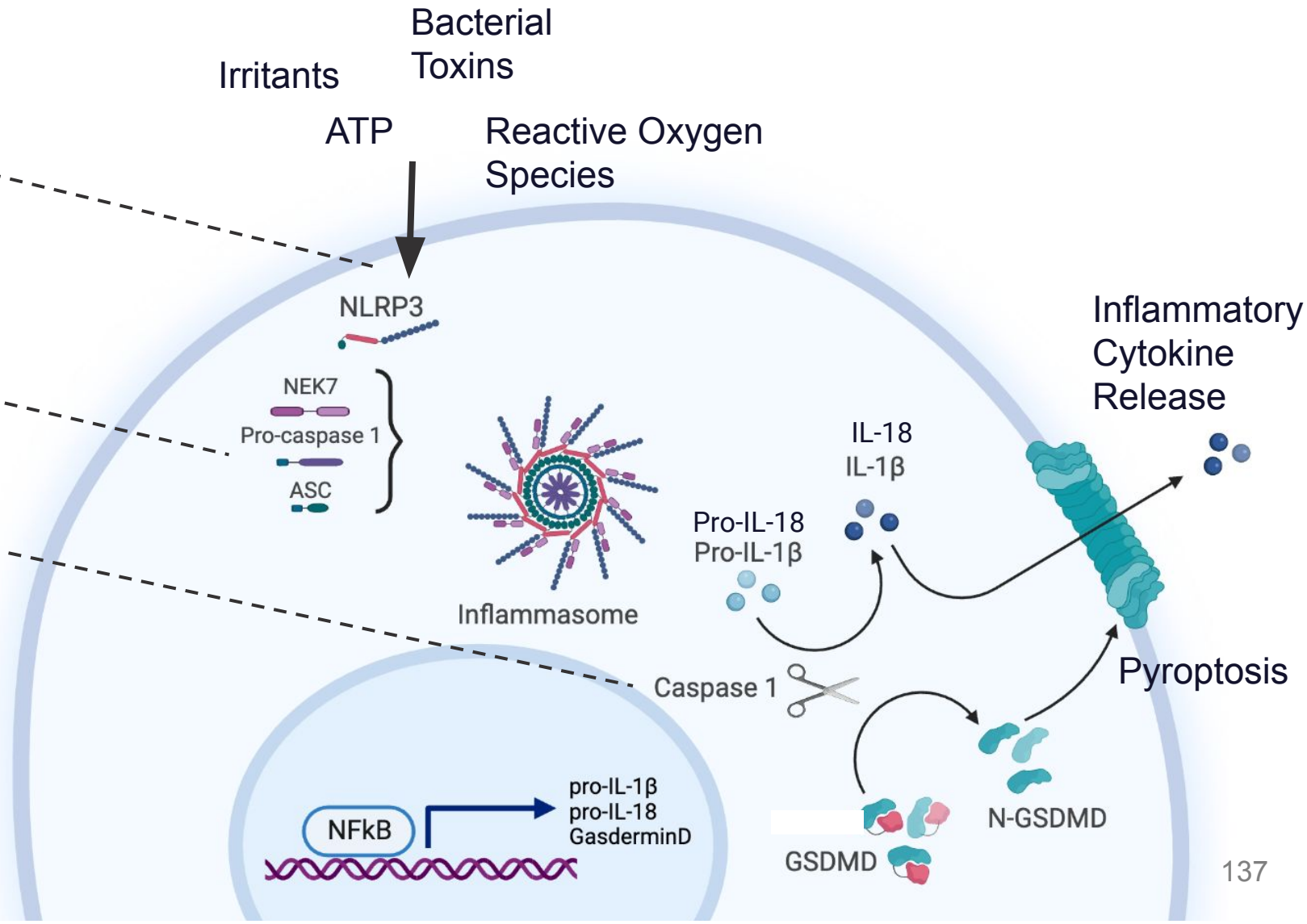
NLRP3 Is a Validated Target That Controls IL-1β, IL-18 Release and Pyroptosis

NLRP3 senses immune triggers, initiating first line of host defense

NLRP3 complexes with cofactor NEK7, adaptor protein ASC, and Caspase-1, forming the inflammasome*

Caspase-1 cleaves pro-IL1β, pro-IL-18, and GasderminD to active forms, resulting in inflammation and pyroptosis

*NEK7: Never In Mitosis gene A-related Kinase 7; ASC: Apoptosis-associated Speck-like protein containing a Caspase Recruitment Domain



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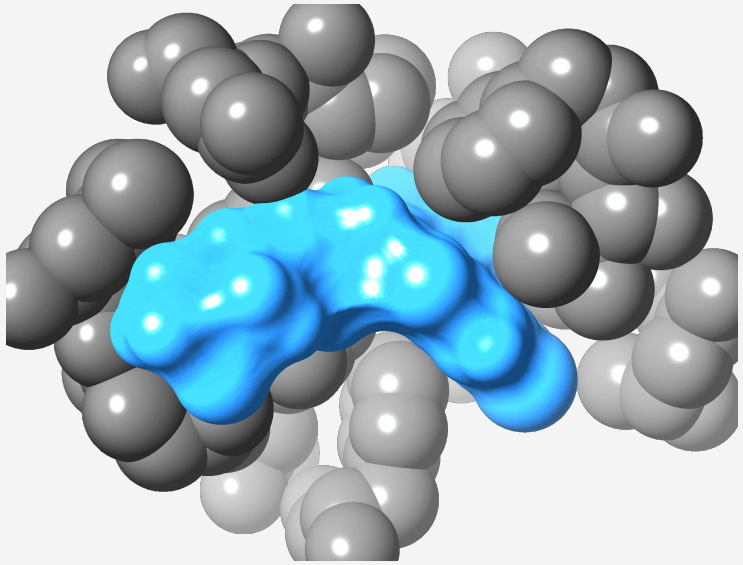
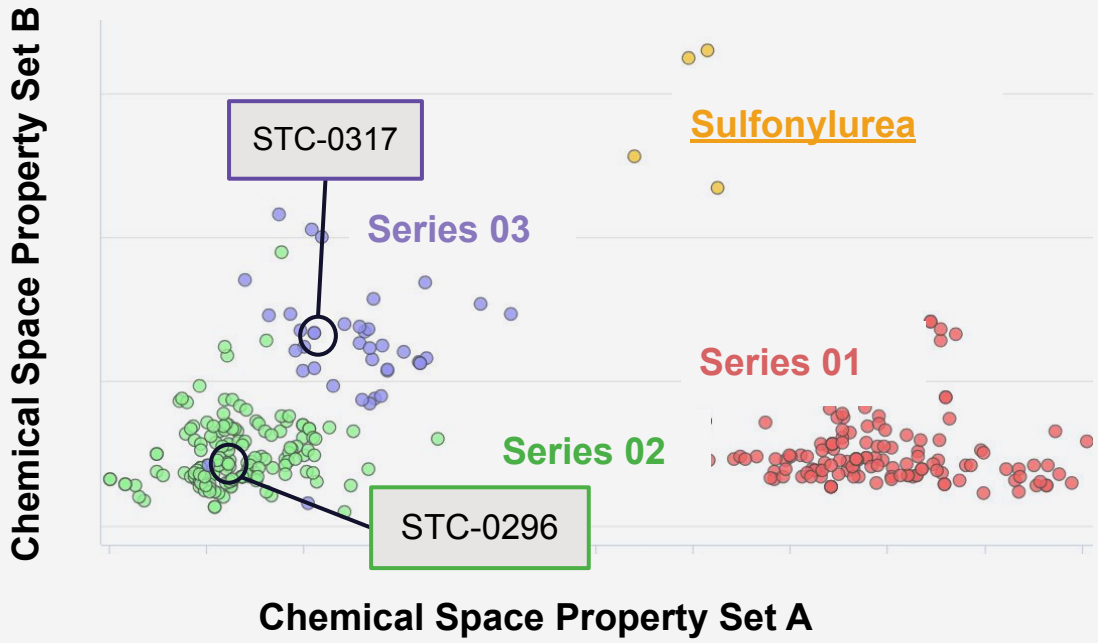
Refined Proprietary Cryo-EM NLRP3 Structure Enabled Discovery of Novel, Chemically-distinct Compounds

Refined Proprietary NLRP3 Structure



Refined cryo-EM structure led to compounds with unique binding modes

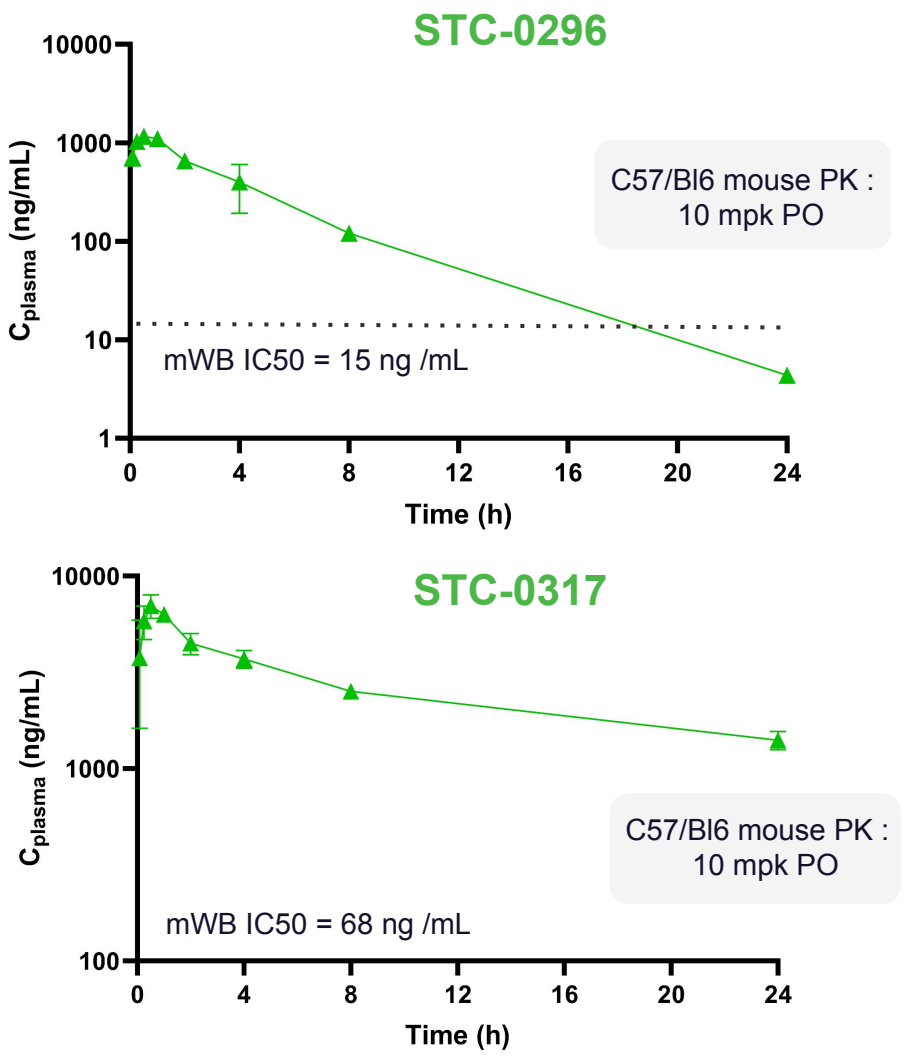
Analysis of Chemical Similarity



Molecules from Two Novel Series Demonstrate Excellent *in vitro* Potency, Selectivity, and ADME Properties

	Assay	STC-0296	STC-0317
***In vitro* potency**	Human whole blood (hWB) potency (IC_{50})	28 nM	14 nM
	THP-1 cell line potency (IC_{50})	60 nM	15 nM
Off-target potency	NLRC4, AIM2, NLRP1 (IC_{50})	>10 µM	>10 µM
	TNFa (IC_{50})	>10 µM	>10 µM
	hERG (IC_{50})	**>30 µM**	**>30 µM**
Druggability	Kinetic Solubility pH 7.4 (µM)	305	274
	Bioavailability @ 10 mg/kg, rat	36	78
	hERG (IC_{50})	**>30 µM**	**>30 µM**

Series 02 and Series 03 include peripheral and CNS permeable examples (brain/plasma: 0.3-0.6)

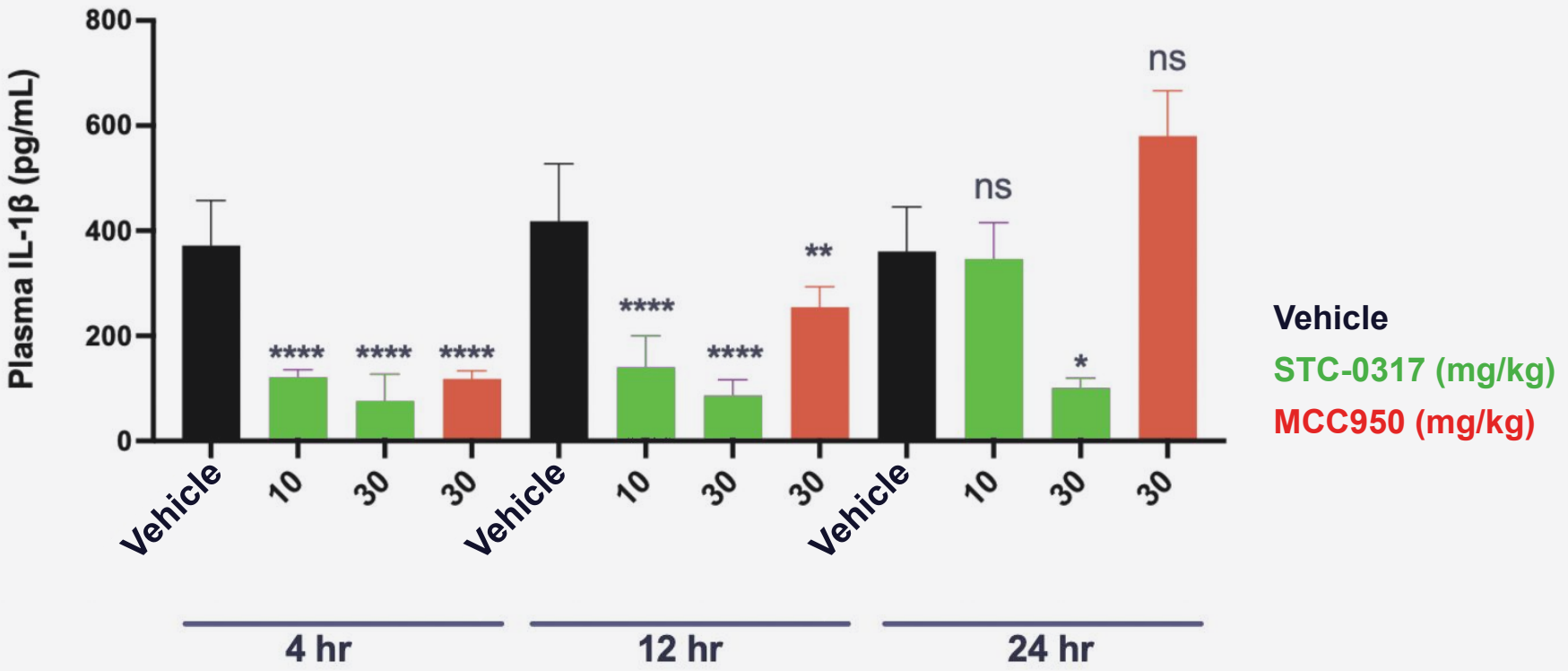


Potent, Durable Reduction of LPS/ATP-induced IL-1β Release

Acute Pharmacodynamic Model:



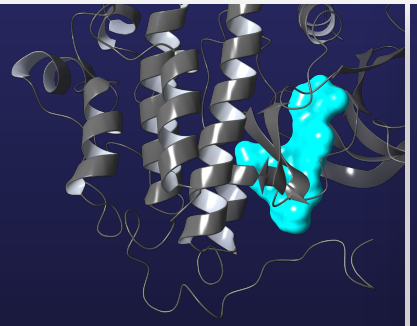
- NLRP3 inhibitor
- LPS
- ATP
- Plasma IL-1β measurement



- Advancing leads in two series with excellent *in vivo* potency and ADME profiles
- Both peripheral and CNS penetrant leads are being optimized

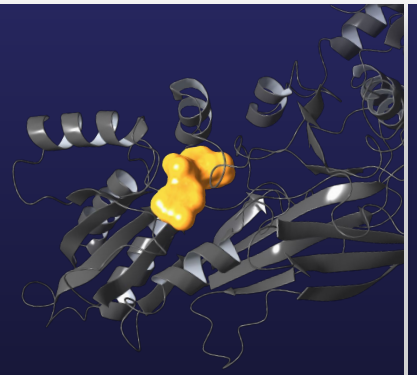
LPS = Lipopolysaccharide; ATP = Adenosine triphosphate One-way ANOVA with **** = p-value <0.0001; *** = p-value <0.001; ** = p-value <0.01; * = p-value <0.01; n = 8-10 mice/group
MCC950: *Nat Med* 2015 21(3):248-255.

Next Steps for Advancing Discovery Programs



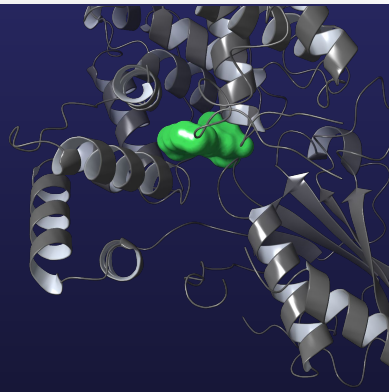
EGFR

- Optimizing a wild-type-sparing, CNS-penetrant molecule
- Potential to address brain metastases and deepen responses through new combination regimens



PRMT5

- Leads display $MTAP^{KO}$ selective anti-proliferative effects, and favorable solubility and ADME profiles
- Rapidly advancing novel, selective, potent molecules with optimized brain-penetration

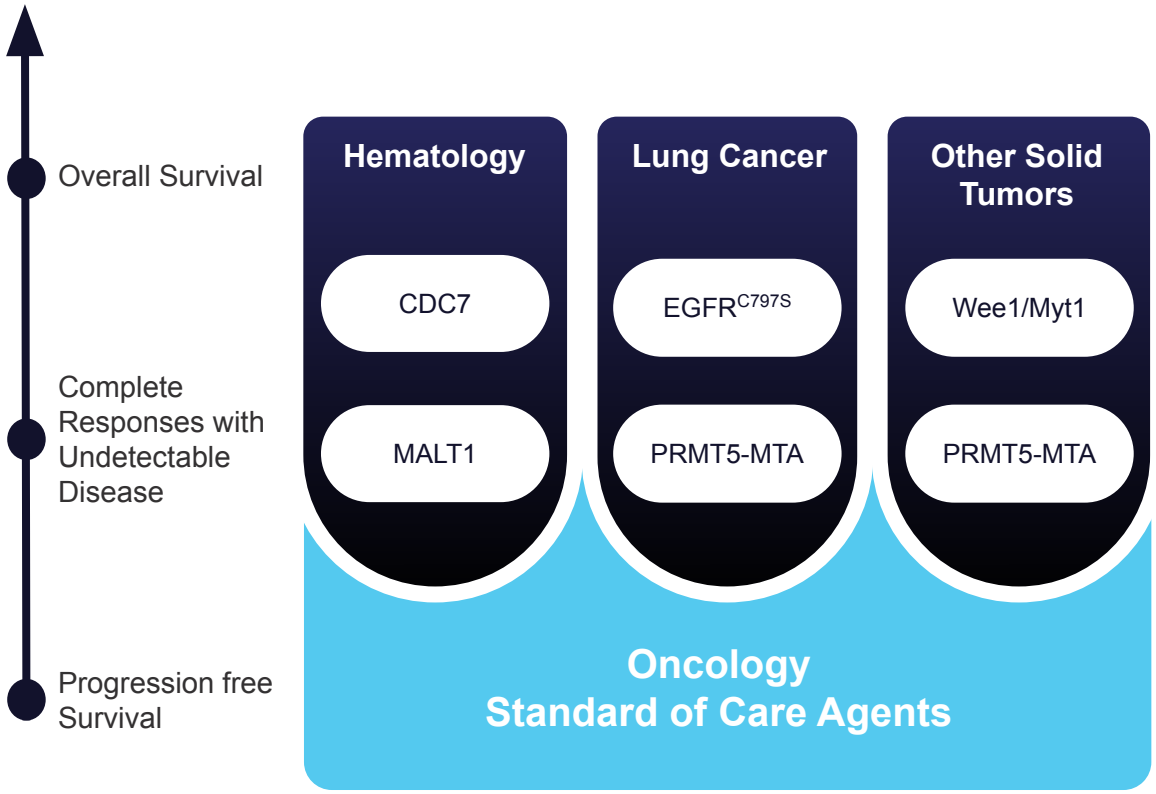


NLRP3

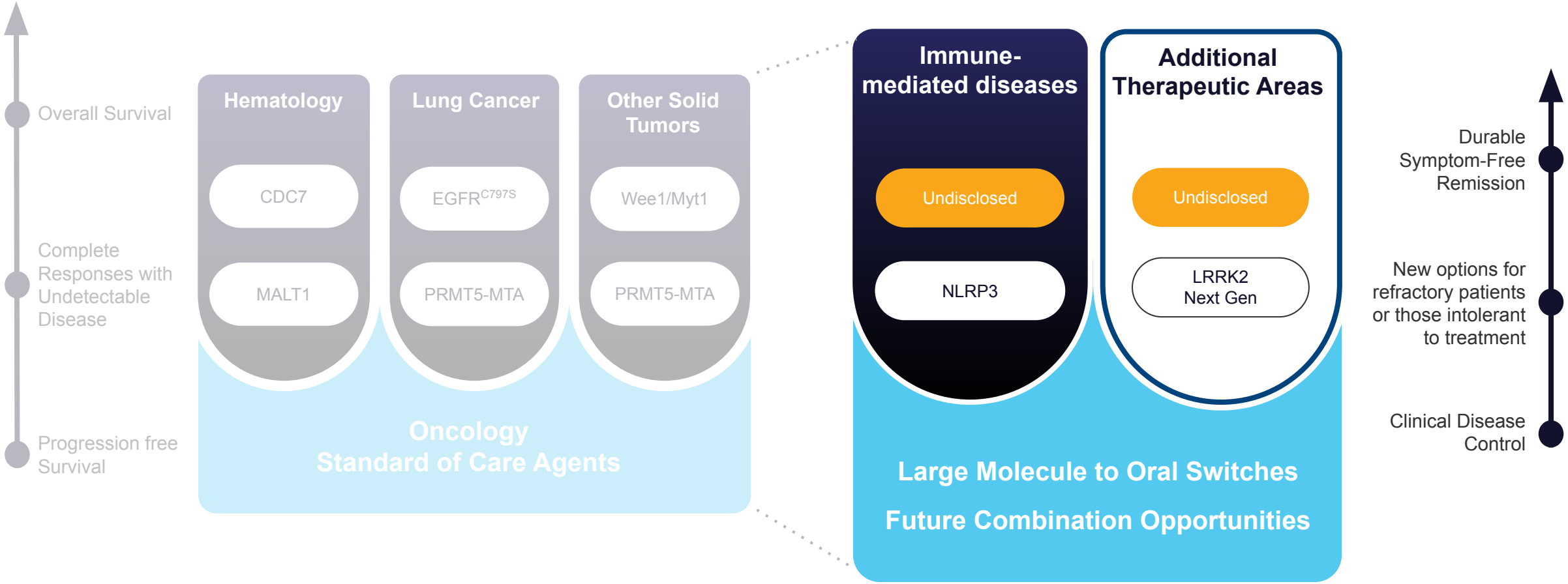
- Advancing leads in two series with excellent *in vivo* potency and ADME profiles
- Both peripheral and CNS penetrant leads being optimized

We continuously evaluate progress against the target profile and opportunity for differentiated drug candidates

Pursuing Targets in Validated Pathways with Opportunities to Improve Outcomes for Patients in Oncology



New Programs in Validated Pathways to Improve Oral Treatment Options Across Disease Areas



Expanding Proprietary Portfolio with Future IND Opportunities



- Multiple programs advanced into development since 2018
- Advanced programs with POC potential in 2024-2025
- Submit at least one IND from discovery portfolio in 2025

EGFR^{C797S}

PRMT5-MTA

NLRP3

LRRK2 Next-Gen

Undisclosed Programs

Today’s Agenda

Introduction — Ramy Farid

Pipeline Overview and Portfolio Strategy — Karen Akinsanya

SGR-1505 (MALT1) — Karen Akinsanya, Margaret Dugan

SGR-3515 (Wee1/Myt1) — Timothy Yap, Karen Akinsanya

SGR-2921 (CDC7) — Elie Traer, Hamish Wright

New Discovery Programs — Jean Lachowicz

Capital Allocation and Value Creation — Geoff Porges

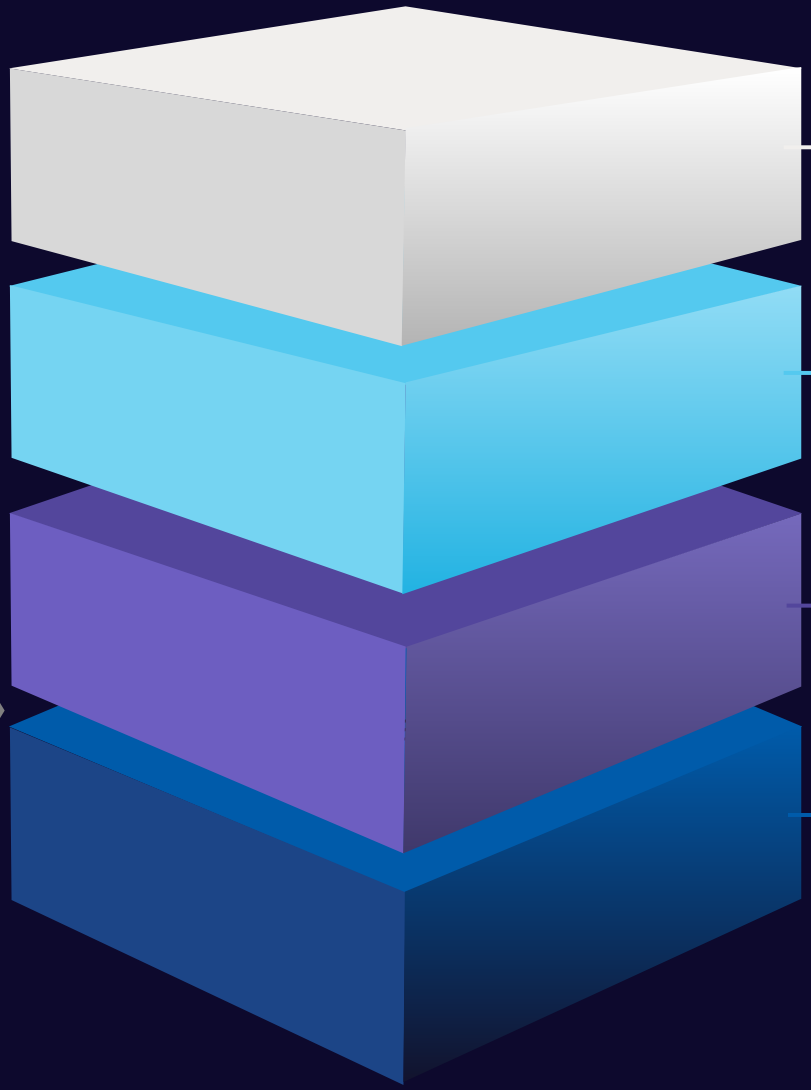
Q&A

What Distinguishes Our Therapeutics Investment Model?

- Substantial and growing Schrödinger therapeutics investment since 2018
- Cash generation from collaborations offsetting much of therapeutics investment
- Multiple approaches to creating and harvesting value (collaborations, partnering, equity, proprietary programs)
- Robust portfolio of partnered and proprietary programs with leading programs advancing into clinical development
- Diversified across TAs, indications, programs and stages
- Positive returns from capital-efficient investment model

R&D Has Created Substantial Value and a Growing Portfolio

2018-2023
Total R&D Expense
$486mm*



Proprietary Portfolio
2 Phase 1s, 1 Pre-IND, Pre-DC's

2018-2023 (through Q3 2023)
Partnered Collaboration Programs
$163mm Drug Discovery Rev.

2018-2023
Equity Sales and Equity Positions in Partner Companies
$91mm

2018-2023
Cash Distributions from Partners
$165mm

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* Reflects the company's total research and development ("R&D") expenses from the beginning of FY 2018 through the end of Q3 2023. R&D expenses consists of drug discovery and development program costs and **costs incurred for the continuous development of the company's computational platform.**

Capital Allocation Strategy Built on Proprietary Insights and Competitive Advantages in Computational Chemistry

Aiming to Generate Positive Returns from Deployment of Technology, Expertise and Capital

Validated Target or Development Goal

- Academia
- Entrepreneurs
- Investors
- Industry

Opportunities that leverage:



Computation at Scale



Schrödinger Proprietary Technology



Schrödinger Scientific Team

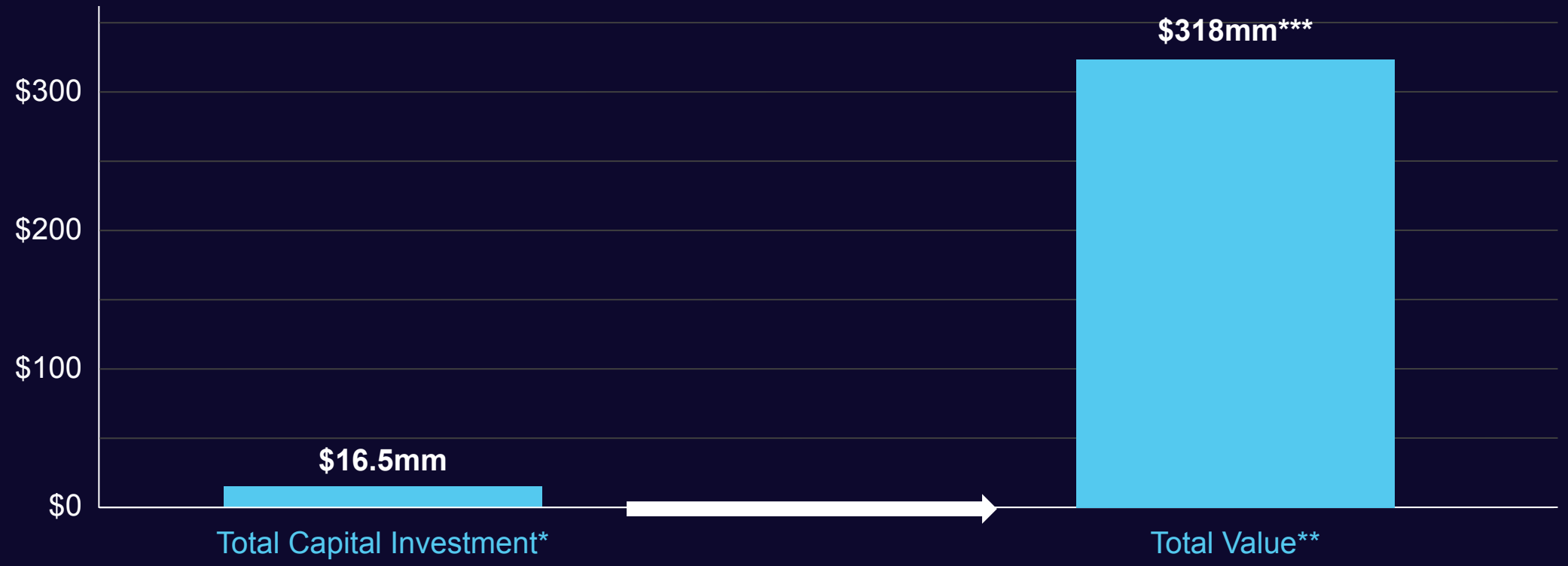


Unique Scientific Insight or Observation

Commercially Useful Innovation

- Proprietary Asset
- Venture / NewCo.
- License IP / Program

SDGR Venture Activity Has Created Substantial Value



* Total capital investment only includes the cumulative amount of capital invested by Schrödinger in seed or financing rounds for Nimbus, Petra, Relay, Morphic, Structure, Ajax and other entities in which the company holds or held equity. Total capital investment does not include any other amounts or expenses related to these investments, including, but not limited to FTE costs, technology and CRO expenses, which the company does not allocate on a per investment basis.

**Total value consists of cumulative cash distributions to Schrödinger from companies in which it holds or held equity, sales proceeds from any equity and/or other consideration received from mergers and acquisitions, and the value of remaining equity stakes that Schrödinger holds as of September 30, 2023.

Capital Allocation and Value Creation

- Cumulative total R&D expense for 2018-2023 of $486mm
- Value accruing from collaborations, proprietary programs, distributions and equity
- Tangible value created in 2018-2023 period consists of $163mm in drug discovery revenue, $165mm in cash from equity distribution, $91mm in current equity owned and prior equity realizations
- Investment has generated a growing portfolio of proprietary, partnered and collaboration programs
- Remaining disciplined and diversified in capital allocation strategy
- Continued prioritization of most promising proprietary programs and equity opportunities



Q&A