2025 Update on GIST Drug Development

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Professor of Cell, Developmental, and Cancer Biology

Summary of Key Points – making progress, more work needed!!

- Currently, there are more open clinical studies for advanced GIST than at any time in history
- More selective TKIs with broad spectrum KIT inhibition are being studied in advanced GIST
- In addition to novel TKIs, novel agents/treatment approaches are entering into clinical studies
- Significant interest and clinical trial activity in earlier lines of therapy as opposed to the historic focus on later- or last-line of therapy
- Novel approaches in SDH-deficient GIST are promising (Dr Sicklick to present on this later today)

New Treatments for KIT-mutant GIST

- Second-line therapy
  - Bezuclastinib in combination with sunitinib (PEAK phase 3)
  - IDRX 42
  - Ripretinib (Insight)

- Later line therapy
  - NB003
  - NN-3201 (anti-KIT antibody drug conjugate)
  - Imatinib + menin inhibitor (ziftomenib)
  - PMRT5 inhibitors
  - Ripretinib + DCC-3116

footnotes

New therapies for second-line treatment

What happens when we treat KIT-mutant GIST with a KIT inhibitor like imatinib?

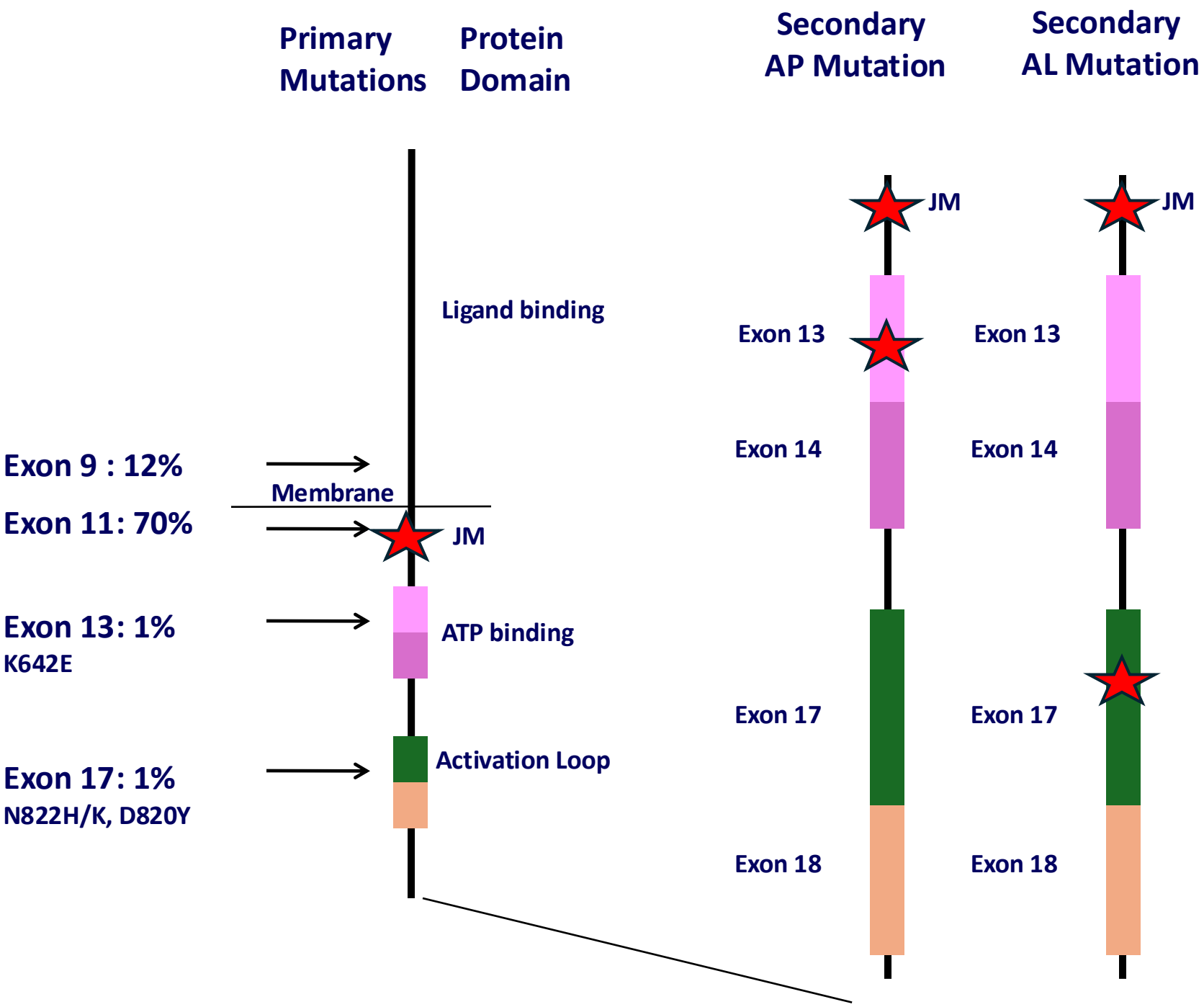

KIT


KIT
mutation


☑ KIT exon 11 deletion
KIT
mutation
NOVARTIS
Gleevec™
imatinib mesylate
Tablets
400 mg
Each tablet contains 400 mg of imatinib free base.
30 Tablets
SL
7S

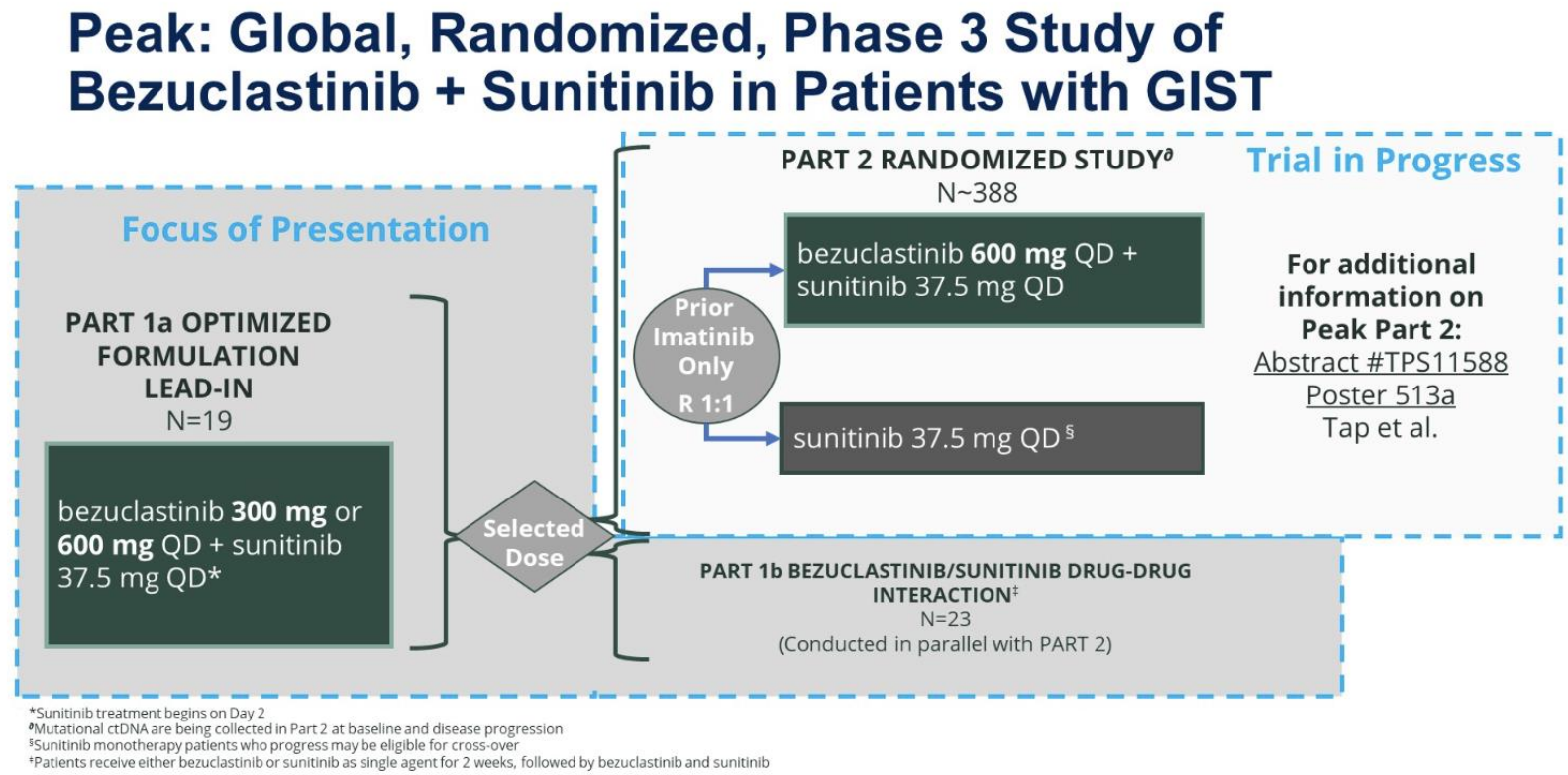

KIT
SL
7S


Gleevec
(imatinib mesylate)
Tablets
400 mg
30 Tablets
SUTENT 12.5 mg
hard capsules Sunitinib
NDC 50419-171-01
Stivarga
(regorafenib) tablets
40 mg
Rx Only
Once a bottle is opened, product must be used within 7 weeks.
Bottle Opened:
28 tablets
SL 7S
BAYER
KIT



- The activity of existing drugs is limited by the inability to inhibit both AP and AL mutations
- Examples:
  - sunitinib-active against AP but not AL
  - ripretinib-active against AL not AP
  - bezuclastinib-active against AL not AP
- Goal: develop new drugs or combination therapy that inhibits both AP and AL mutations

Bezuclastinib in combination with sunitinib



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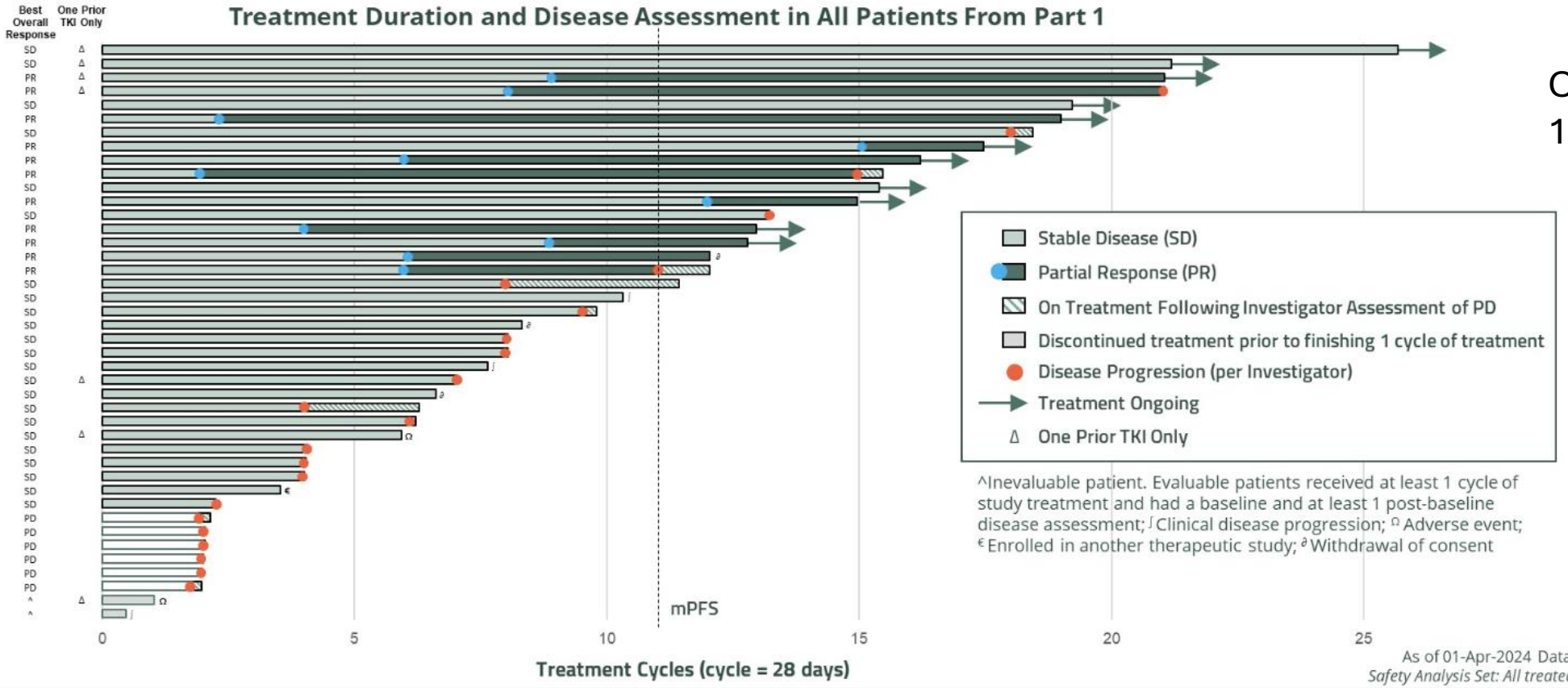
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

footnotes

Bezuclastinib in combination with sunitinib

Peak Part 1: Median progression-free survival (PFS) Was 10.2 Months in All Patients



As of 01-Apr-2024 Data-cut
Safety Analysis Set: All treated pts

ORR
11 of 40 pts (27.5%) PR

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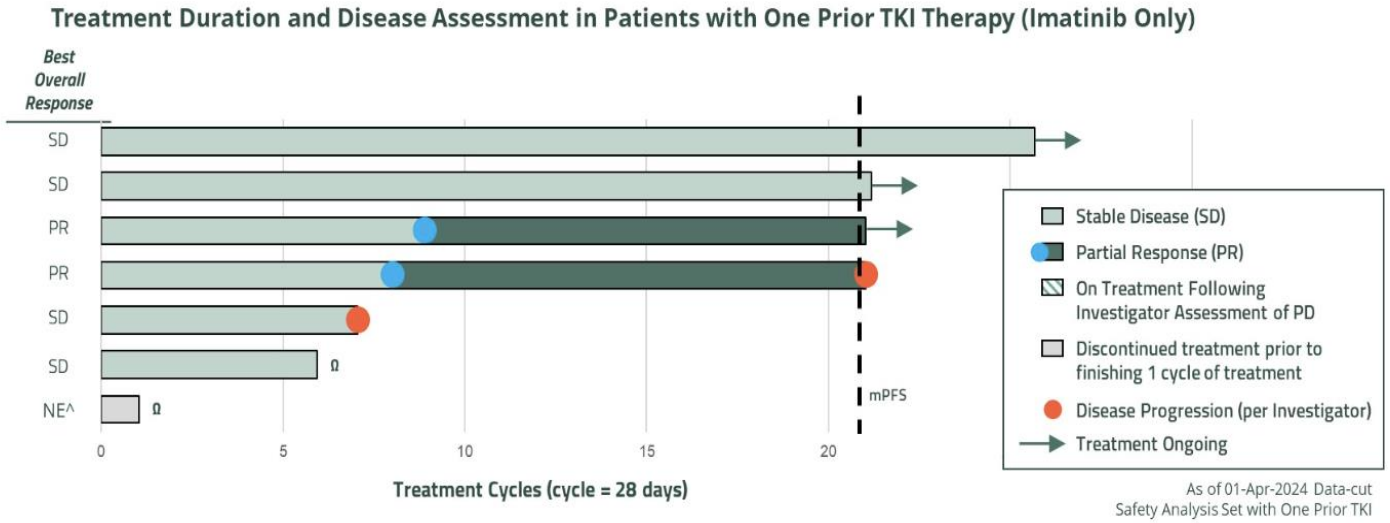
Bezuclastinib in combination with sunitinib

Peak Part 1: Median PFS Was 19.4 Months in Patients Receiving Bezuclastinib + Sunitinib Second Line



^Inevaluable patient. Evaluable patients received at least 1 cycle of study treatment and had a baseline and at least 1 post-baseline disease assessment; Ω Adverse event;

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ORR
2 of 6 pts (33%) PR

PEAK study status

- Enrollment completed 2024
- Results will be unblinded, analyzed, and reported once enough progression events have occurred
- I predict that the results for this study will be reported before the end of this summer, likely earlier
- It is predicted that the combination will be superior to sunitinib alone

- Implications: If sunitinib + bezuclastinib has superior progression-free survival compared with sunitinib, the combination would the new standard second-line therapy (after FDA-approval)

IDRX-42: a KIT TKI designed to address unmet need in GIST

- *KIT* mutations drive most GIST, with resistance to TKIs due to diverse secondary mutations in the ATP-binding pocket and activation loop
- No approved TKI inhibits the full spectrum of these mutations[1]
  - Response rates with 2nd line sunitinib, 3rd line regorafenib, and 4th line ripretinib are approximately 18%, 5%, and 9%, respectively [2,3,4]
- IDRX-42 is an investigational KIT TKI which has shown:
  - Superior *in vivo* activity vs standard TKIs in xenograft mouse models with exon 9, 11, 13 and 17 mutations[5,6]
  - Selectivity over off-target kinases, sparing VEGFR-2 and FLT3[5]

FLT3, fms-like tyrosine kinase 3; TKI, tyrosine kinase inhibitor; VEGFR-2, vascular endothelial growth factor receptor 2; Sources: 1. Kelly CM et al. J Hematol Oncol. 2021;14(1):2; 2. Bauer et al. J Clin Oncol. 2022;40(34):3918-3928; 3. Demetri et al. Lancet. 2013;381(9863):295-302; 4. Blay et al. Lancet Oncol. 2020 (7):923-934.; 5. Blum A et al. J Med Chem. 2023;66:(4):2386-2395; 6. De Sutter L et al. Clin Cancer Res. 2023;29(15):2859-2868

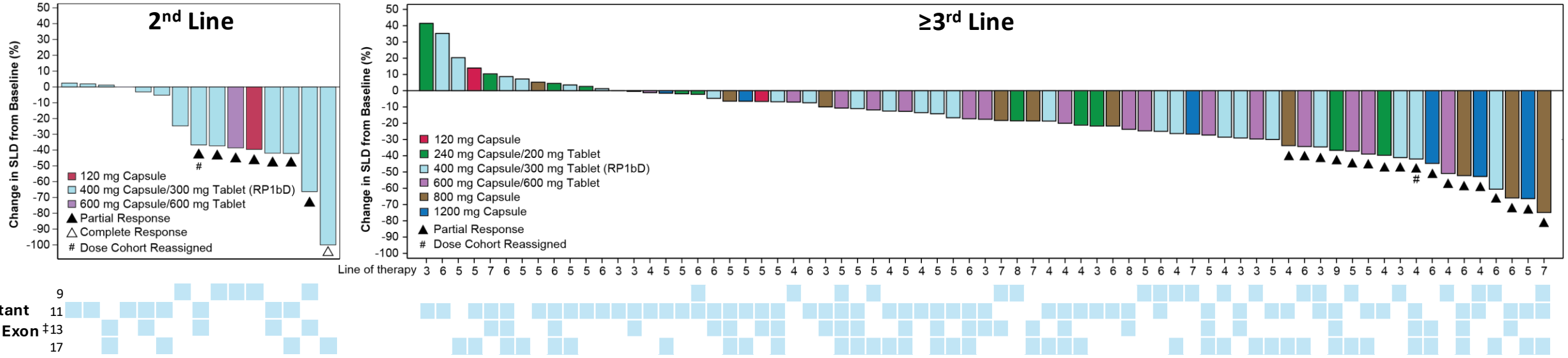
Presented by:

Suzanne George, MD

STRATEGIST 1: Promising anti-tumor activity in 2nd and later-line GIST

Objective Response Rate (ORR)†, n/N (%)	2nd Line	3rd Line	≥4th Line No Prior Ripretinib	All Patients
All Doses	8/15 (53)	2/10 (20)	9/25 (36)	25/87 (29) ††
400 mg capsule/300 mg tablet (RP1bD)#	6/13 (46)	2/4 (50)	2/10 (20)	10/38 (26)

Best Change in Tumor Target Lesions per mRECIST



† In the efficacy evaluable population, defined as all patients with at least one postbaseline disease assessment or prior clinical progression or death. Disease assessments according to mRECIST (modified RECIST v1.1; Demetri et al. Lancet. 2013;381(9863):295-302) performed at baseline, 4 weeks, 8 weeks and every 8 weeks thereafter; †† Responses (n=25) includes 1 confirmed CR, 22 confirmed PR, and 2 PRs awaiting confirmation; # One patient each in the 600 and 800 mg cohorts had dose reduction to 400 mg early in Cycle 1 (Day 2 and 14, respectively) and are analyzed as effectively treated at 400 mg; ‡ As detected by local assessment or central baseline ctDNA analysis; Based on similar steady-state plasma exposures, data from the following dose/formulation pairs are analyzed together in this presentation: 200 mg tablet/240 mg capsule, 300 mg tablet/400 mg capsule, and 600 mg tablet/600 mg capsule; QD, once daily; RP1bD, Recommended Phase 1b Dose;; SLD, Sum Lesion Diameter; Data cutoff date: 30 September 2024

Presented by:

Suzanne George, MD

IDRX-42 drug development status

- Phase 1/1b dose escalation/expansion completed
- A phase 3 second-line study of IDRX-42 vs. sunitinib will begin this year (Strategist 3)
- IDRX-42 recently acquired by GSK-should provide additional financial resources for future drug development but may slow down the start of the planned phase 3 study

- Implications: If IDRX-42 has superior progression-free survival compared with sunitinib, then IDRX-42 combination would be a standard second-line therapy (after FDA-approval)
- If PEAK is also positive study, then second-line choices would be IDRX-42 vs. bezuclastinib + sunitinib vs. sunitinib

INTRIGUE trial design

INCLUSION CRITERIA

Patients ≥18 years old with a confirmed diagnosis of GIST who progressed on or had documented intolerance to imatinib

Patients were enrolled from 122 sites across North America, South America, Europe, Australia, and Asia

Stratified by

- Mutational status:
  - *KIT* exon 11
  - *KIT* exon 9
  - *KIT*/*PDGFRA* wild type
  - Other *KIT*/*PDGFRA*
- Intolerance to imatinib

INTRIGUE PHASE 3 CLINICAL STUDY

1:1 Randomization
Open-label study

Ripretinib 150 mg QD
(continuous)

No crossover option

Sunitinib 50 mg QD
(4 weeks on, 2 weeks off)

Primary endpoint:
- PFS by IRR (using mRECIST v1.1)

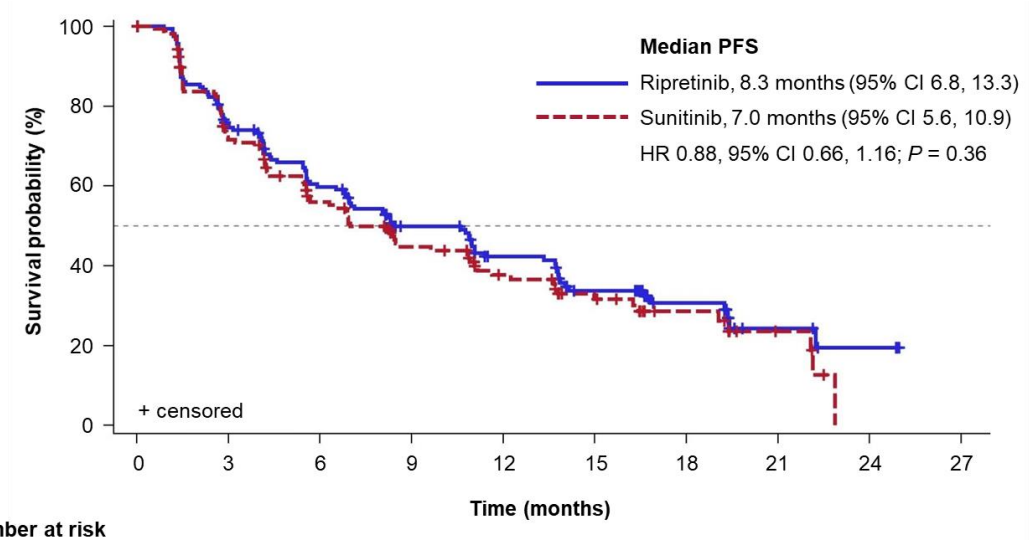
Baseline

Guardant360® ctDNA analysis

Data cutoff (except OS): September 1, 2021; OS data cutoff: September 1, 2022.
ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; OS, overall survival; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; QD, once daily.

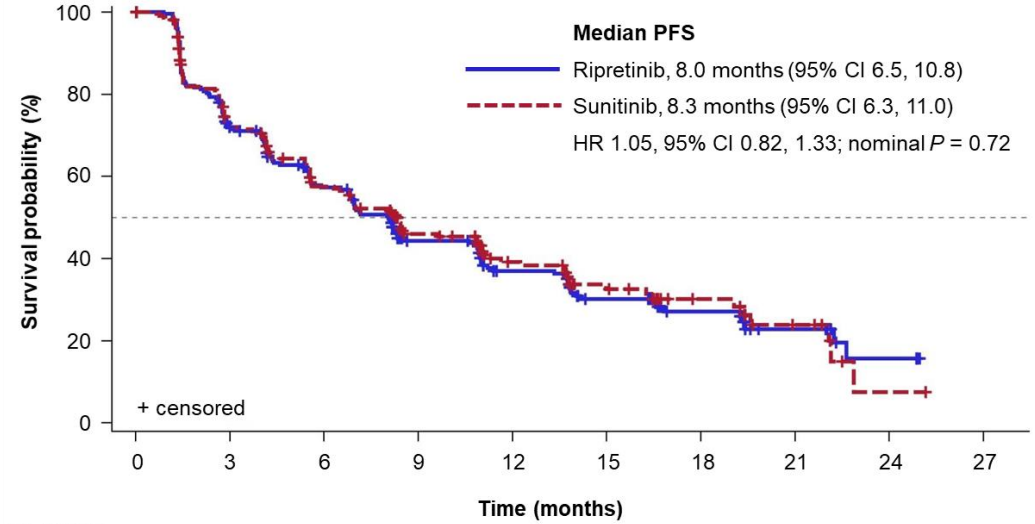
Kaplan-Meier analysis of PFS by IRR

KIT exon 11 ITT



Number at risk										
Ripretinib	163	115	88	61	46	31	18	6	3	0
Sunitinib	164	104	75	50	33	23	12	5	0	0

AP ITT



Number at risk										
Ripretinib	226	152	115	75	56	39	23	10	4	0
Sunitinib	227	143	108	68	45	29	16	8	1	0

INTRIGUE trial design

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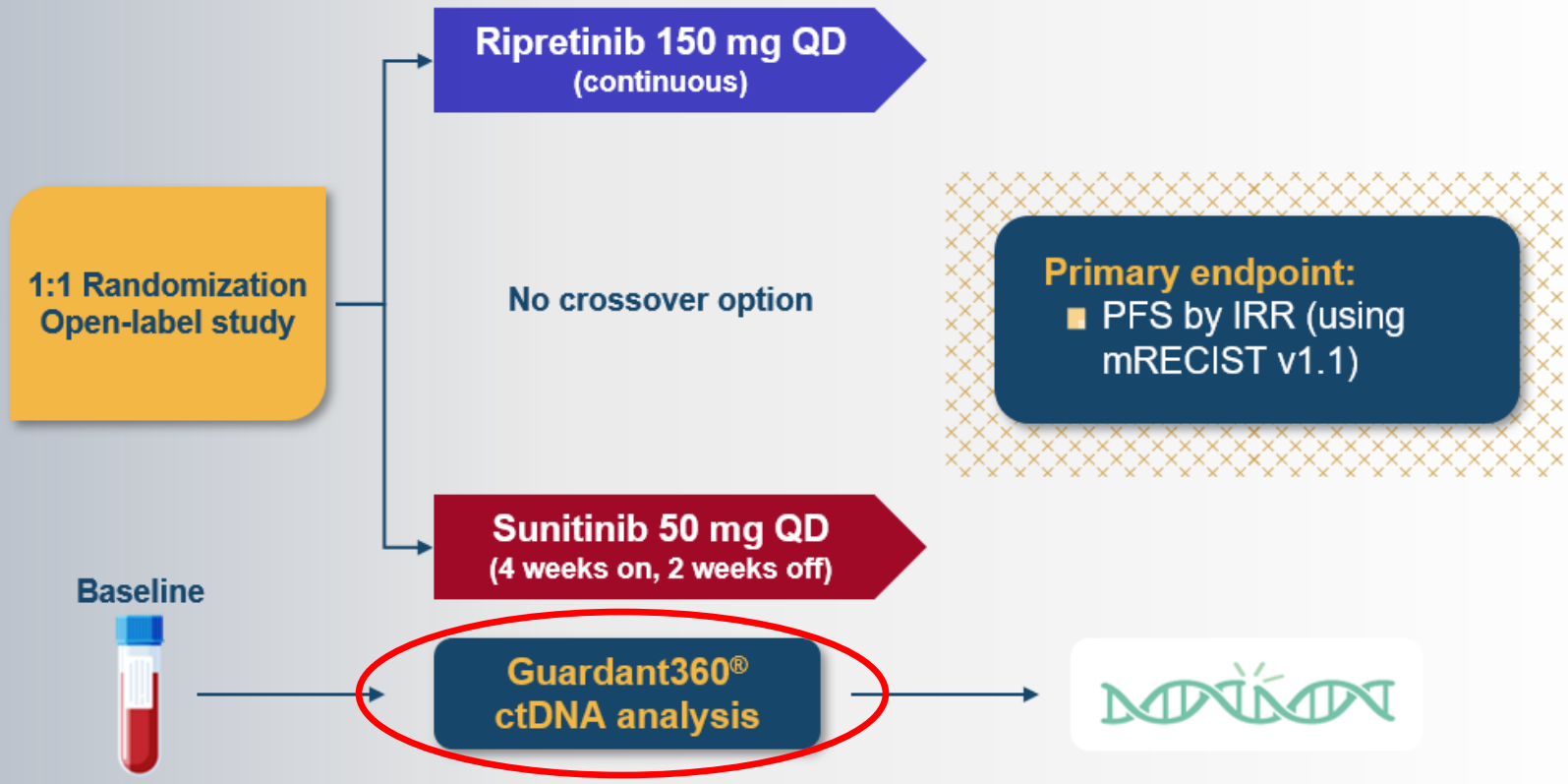
- Intolerance to imatinib

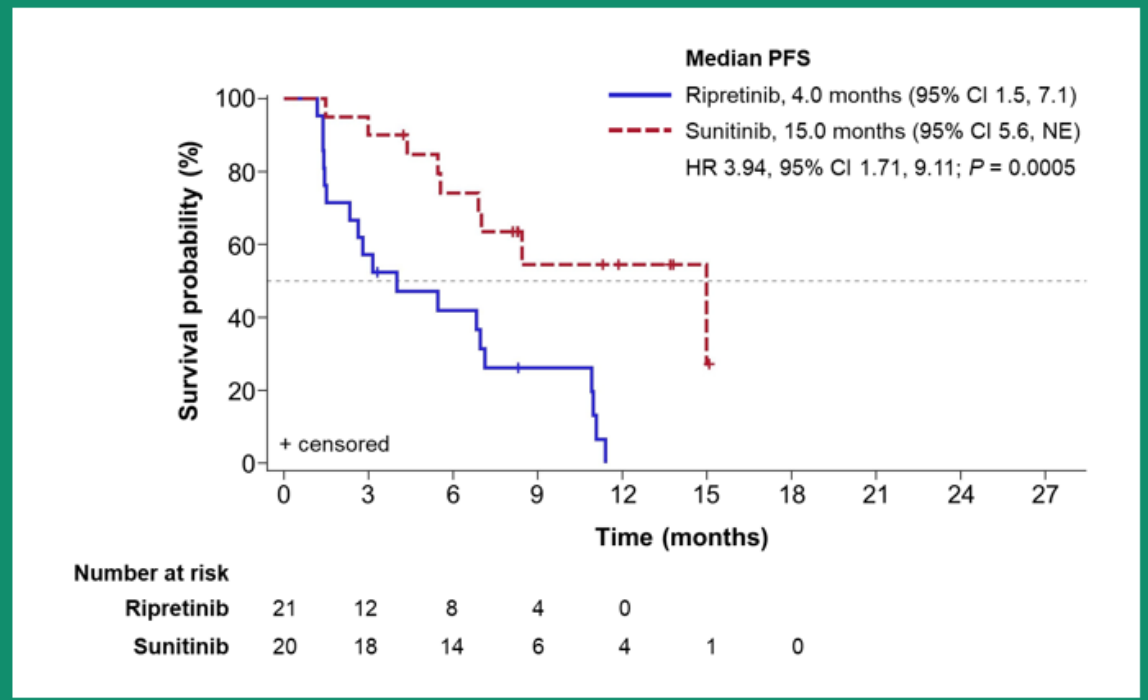
INTRIGUE PHASE 3 CLINICAL STUDY

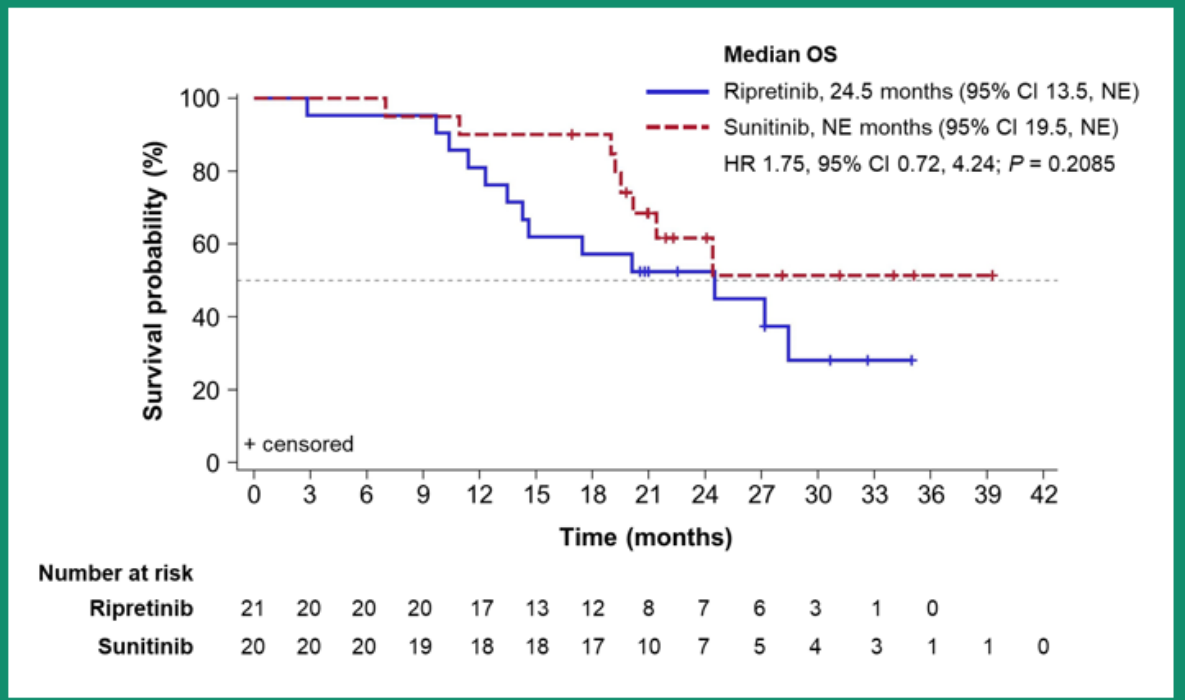


Data cutoff (except OS): September 1, 2021; OS data cutoff: September 1, 2022.
ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; OS, overall survival; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; QD, once daily.

Efficacy in *KIT* exon 11 + 13/14 population

ATP-binding pocket

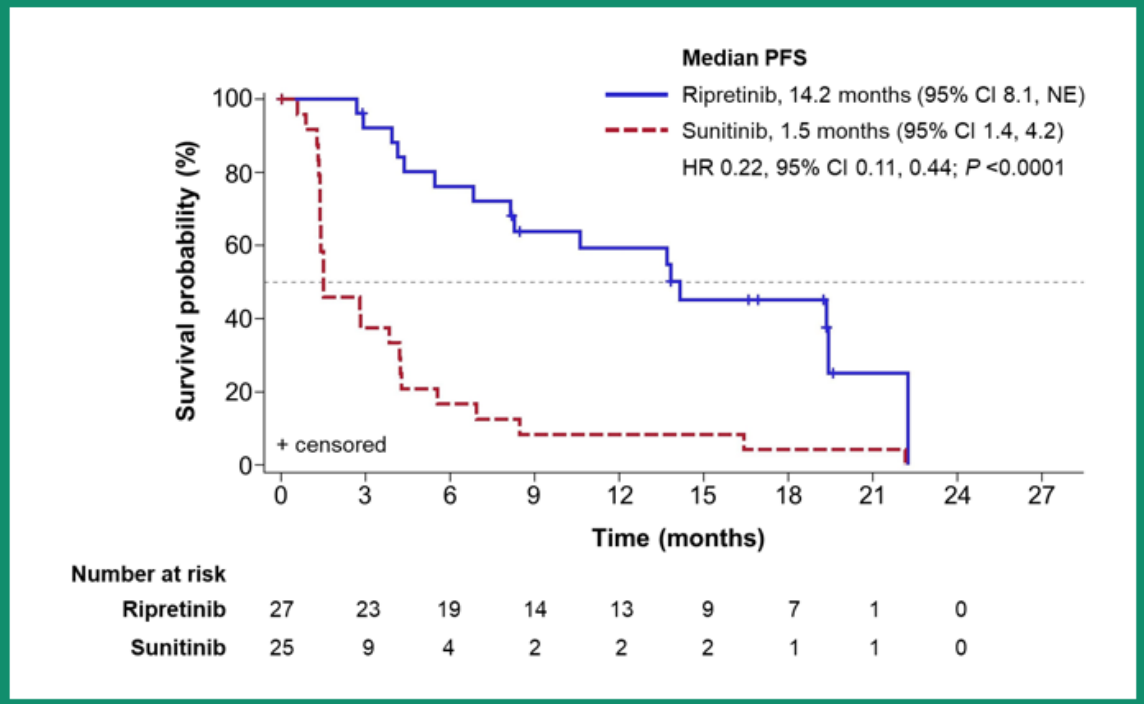


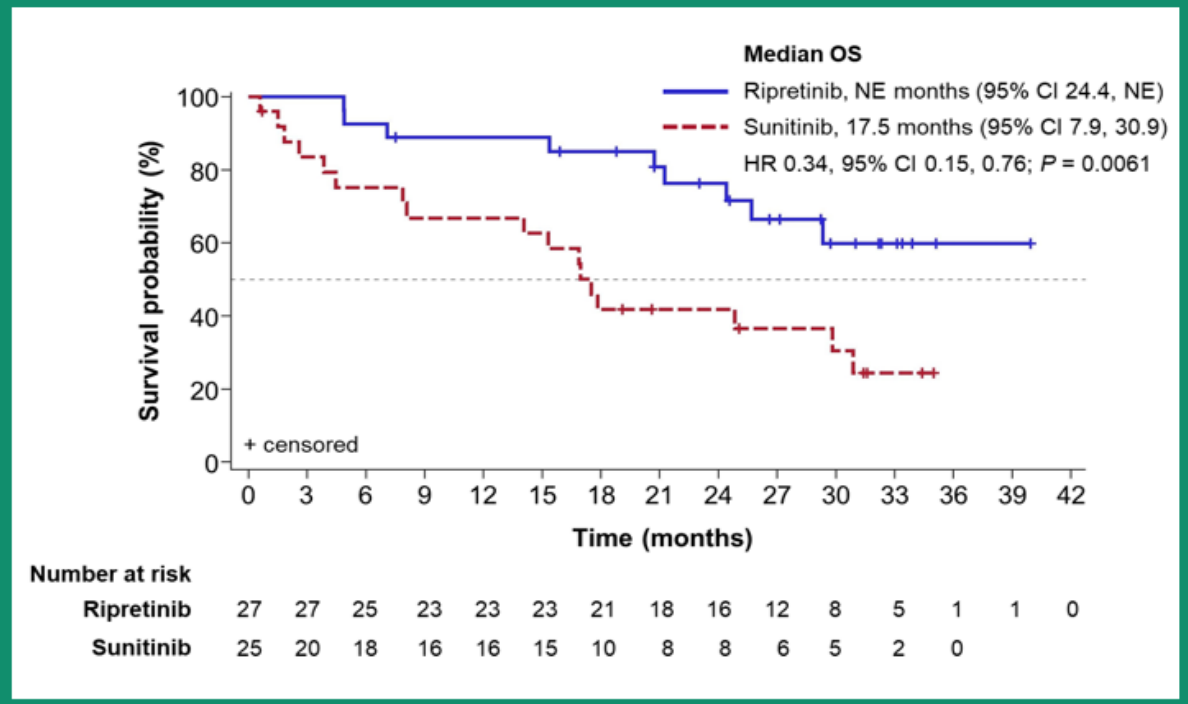


PFS data cutoff: September 1, 2021; OS data cutoff: September 1, 2022. Excludes *KIT* exons 9/17/18. *P*-values are nominal.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Efficacy in *KIT* exon 11 + 17/18 population

Activation loop





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CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Outcomes by ctDNA analysis in *KIT* exon 11 + secondary resistance mutation subpopulations

	Activation loop (*KIT* exon 11 + 17/18)[a]		ATP-binding pocket (*KIT* exon 11 + 13/14)[b]		Activation loop/ATP-binding pocket co-mutants (*KIT* exon 11 + 13/14 + 17/18)[c]	
	Ripretinib n = 27	**Sunitinib n = 25**	**Ripretinib n = 21**	**Sunitinib n = 20**	**Ripretinib n = 11**	**Sunitinib n = 11**
mPFS, months	14.2	1.5	4.0	15.0	8.1	10.9
HR (95% CI)	0.22 (0.11, 0.44)		3.94 (1.71, 9.11)		1.07 (0.41, 2.84)	
ORR, %	44.4	0	9.5	15.0	27.3	9.1
mOS, months	Not estimable	17.5	24.5	Not estimable	14.7	20.3
HR (95% CI)	0.34 (0.15, 0.76)		1.75 (0.72, 4.24)		2.61 (0.95, 7.19)	

PFS and ORR data cutoff: September 1, 2021; OS data cutoff: September 1, 2022.
[a]Excludes *KIT* exons 9/13/14; [b]Excludes *KIT* exons 9/17/18; [c]Excludes *KIT* exon 9.
ATP, adenosine triphosphate; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

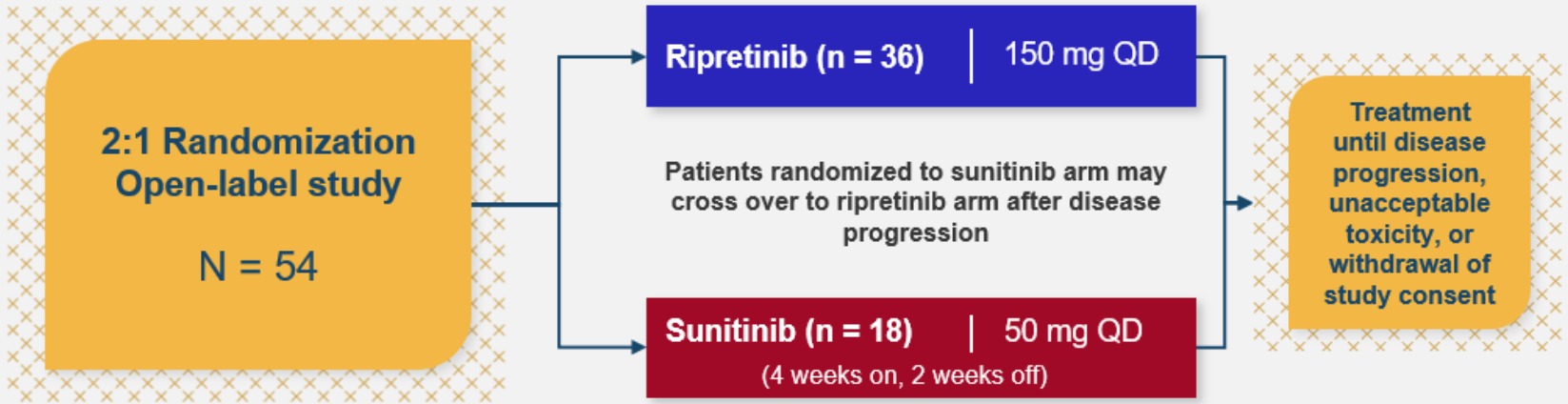
INSIGHT trial design

INCLUSION CRITERIA

Patients with GIST previously treated with imatinib

- 1 prior line of imatinib
- *KIT* exon 11 + 17 and/or 18 via ctDNA during screening
  - *KIT* exon 9, 13, and/or 14 excluded
  - Other co-mutations are allowed
- Measurable disease per mRECIST
- ECOG performance status ≤2

PLANNED PHASE 3, RANDOMIZED, MULTICENTER, OPEN-LABEL STUDY



Primary endpoint
- PFS by IRR using mRECIST

Key secondary endpoints
- ORR by IRR using mRECIST
- OS

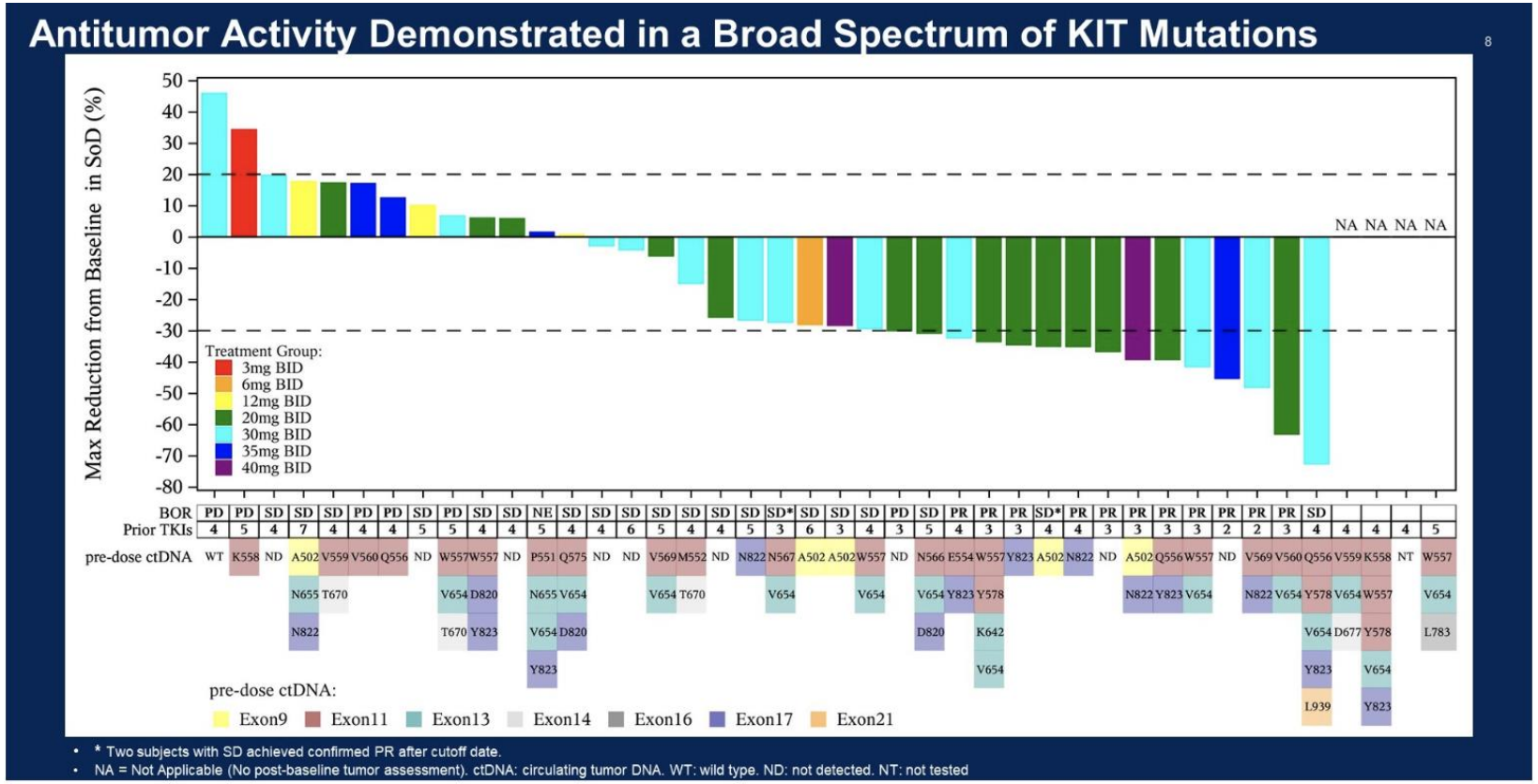
ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

INSIGHT status

- Study in progress, ? Results in 2026
- Implications: if this is a positive study along with the other discussed studies (PEAK, STRATEGIST 3), then there will be four options for second-line therapy:
  - Sunitinib (the original)
  - Sunitinib + bezuclastinib (PEAK)
  - IDRX-42 (STRATEGIST-3)
  - Ripretinib for selected patients with specific cDNA results

New therapies for third-line and later treatment

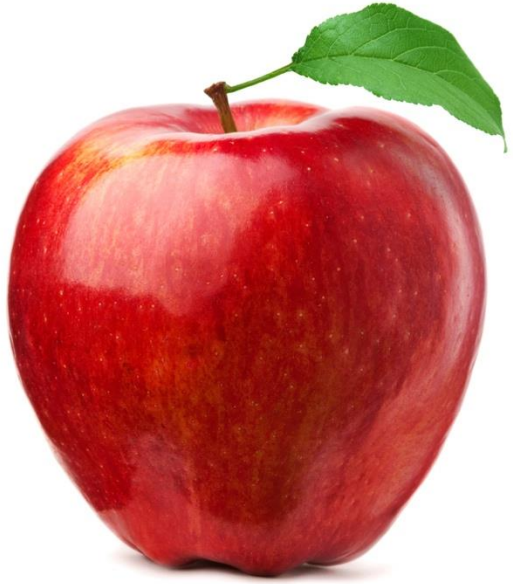
NB003 (a novel KIT inhibitor) demonstrates broad spectrum activity in advanced GIST across various KIT mutations



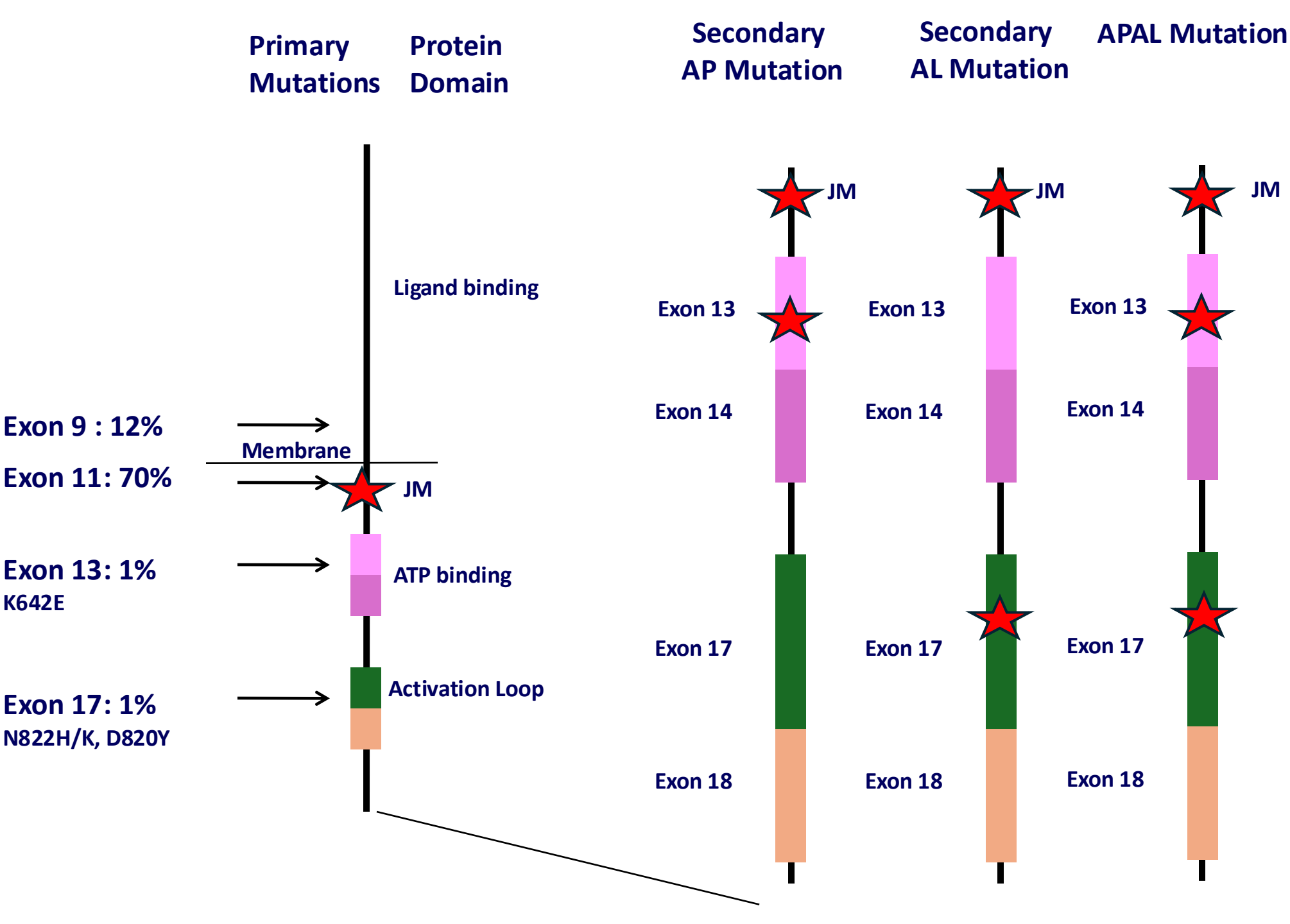
PRESENTED BY: Dr. Jian Li

NB003 drug development status

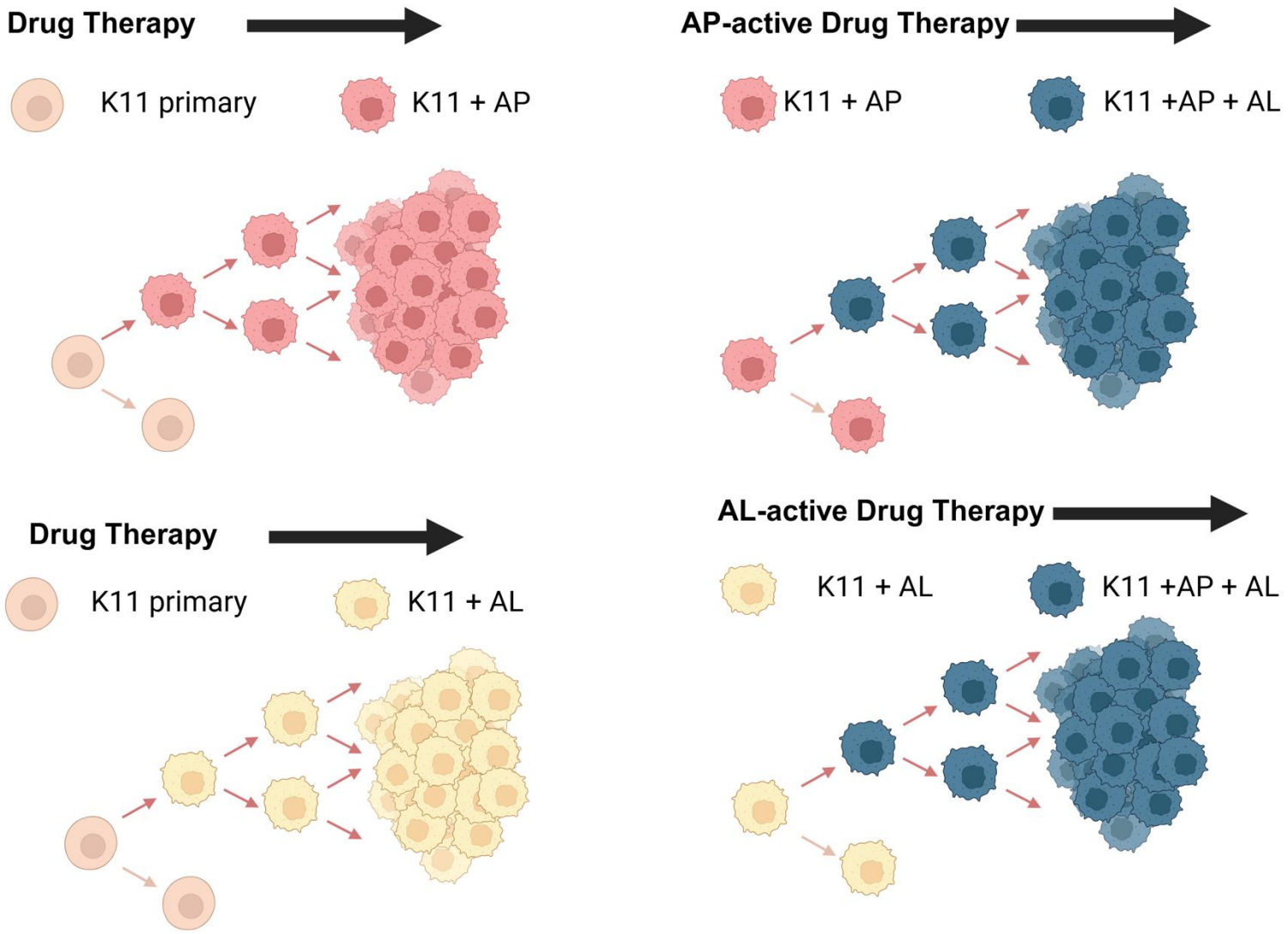
- Phase 1/1b dose escalation/expansion completed
- Future development plans not announced yet, but seems likely they will seek approval (? 2L, 3L, 4L, 4L +)
- Dose still to be determined (not yet disclosed)
- Approvals for 2L, 3L, 4L would require a phase 3 study
- Approval for post-ripretinib indication could be a phase 3 or single arm phase
- New Bay will likely announce future plans sometime in the next few months



The emerging issue of APAL mutations in advanced GIST


Primary Mutations
Protein Domain
Secondary AP Mutation
Secondary AL Mutation
APAL Mutation
Ligand binding
Exon 9 : 12%
Membrane
Exon 11: 70%
JM
Exon 13: 1%
K642E
ATP binding
Activation Loop
Exon 17: 1%
N822H/K, D820Y
JM
Exon 13
Exon 14
Exon 17
Exon 18
JM
Exon 13
Exon 14
Exon 17
Exon 18
JM
Exon 13
Exon 14
Exon 17
Exon 18

Model for Emergence of APAL mutations



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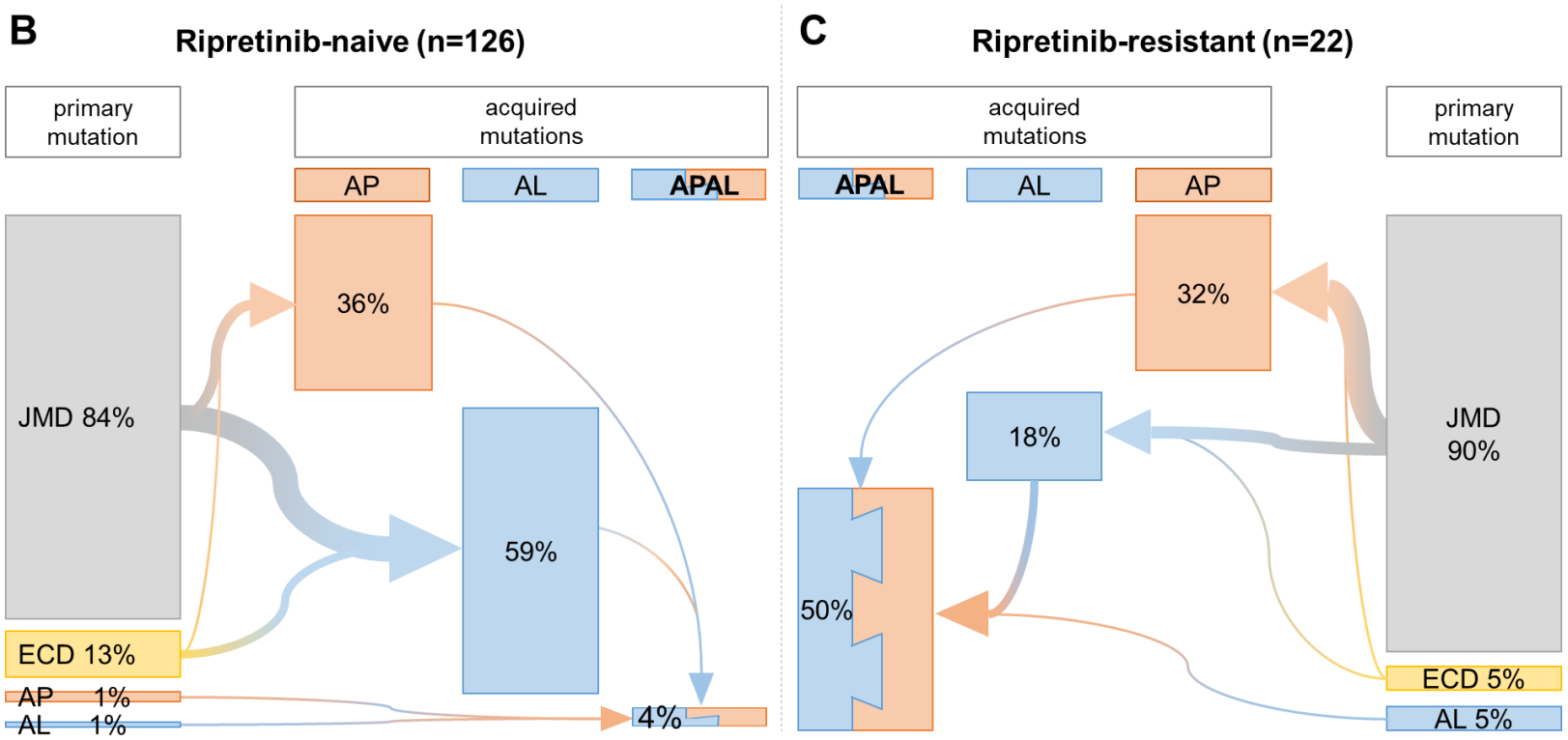
Clinical Evidence for Emergence of APAL mutations



Muhlenberg et al.. https://doi.org/10.1200/jco.23.01197

footnotes

Emerging issues with APAL mutations

Summary

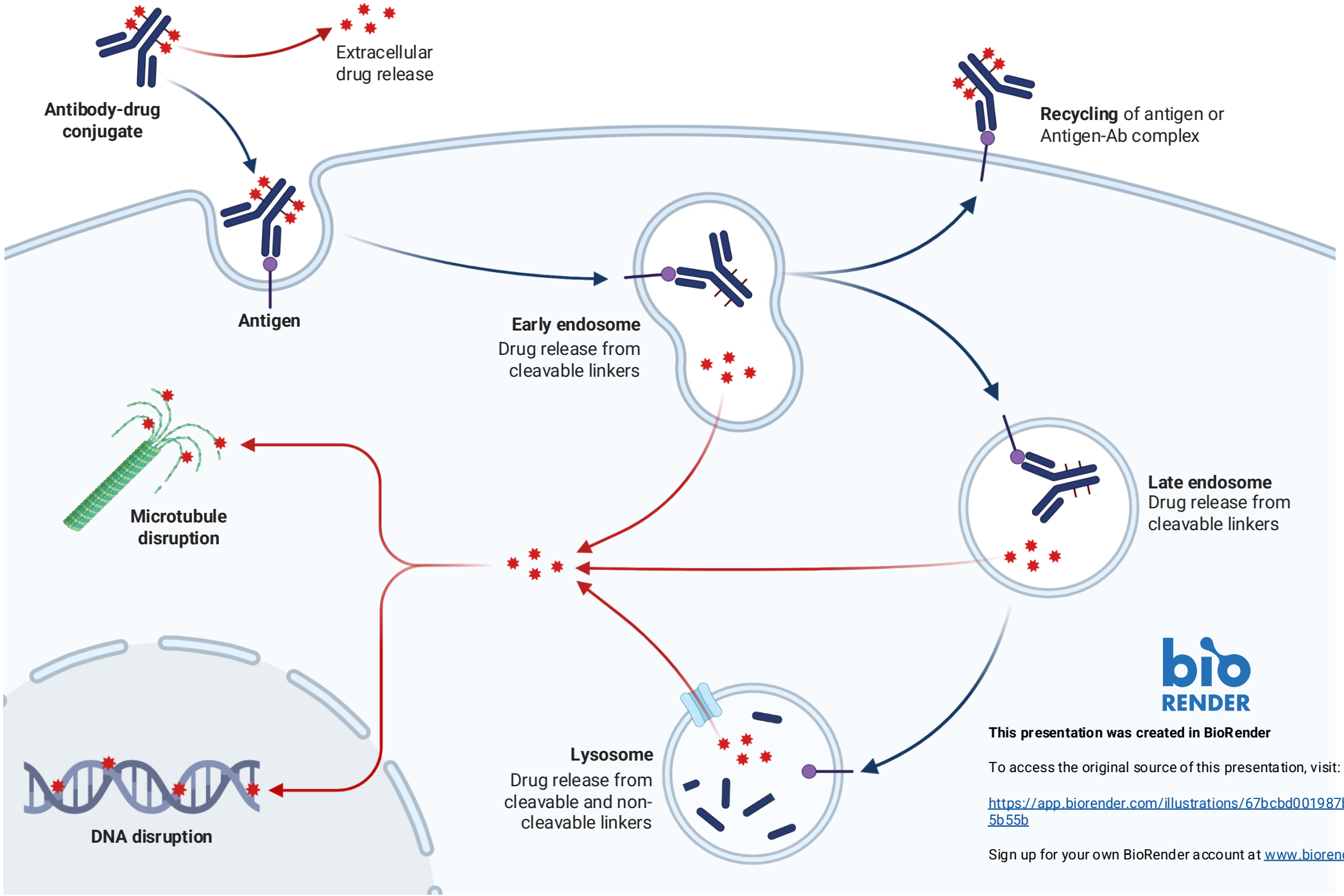
- APAL mutations are arising as more potent AL inhibitors are entering into clinical practice
- To date, there are no known TKIs that inhibit GIST clones with APAL mutations

Future Directions/Challenges

- Optimal use of potent AL inhibitors should be earlier in the treatment sequence, before the emergence of APAL mutations
- We need new drugs/strategies to treat GIST with APAL mutations
- There is a need for the continued analysis of tumor and ctDNA specimens in later line patients to determine the frequency of APAL mutations at each line of therapy
- Development of new diagnostic techniques to identify APAL mutations versus co-existing AP and AL in different clones

NN3201: Anti-KIT antibody drug conjugate (ADC)

- Antibody to KIT conjugated to MMAE (microtubule inhibitor chemotherapy agent)
- NCT06805825 (clinicaltrials.gov)
- For initial phase of study, patient only need to have received prior imatinib
- Opening this year, possibly open at some sites
- Theory: all GIST, even TKI-resistant GIST express KIT which can be targeted
- To be determined:
  - toxicity for bone marrow cells that normally express KIT
  - Sensitivity of GIST cells to MMAE (chemotherapy)


Extracellular drug release
Antibody-drug conjugate
Antigen
Recycling of antigen or Antigen-Ab complex
Early endosome
Drug release from cleavable linkers
Late endosome
Drug release from cleavable linkers
Microtubule disruption
DNA disruption
Lysosome
Drug release from cleavable and non-cleavable linkers
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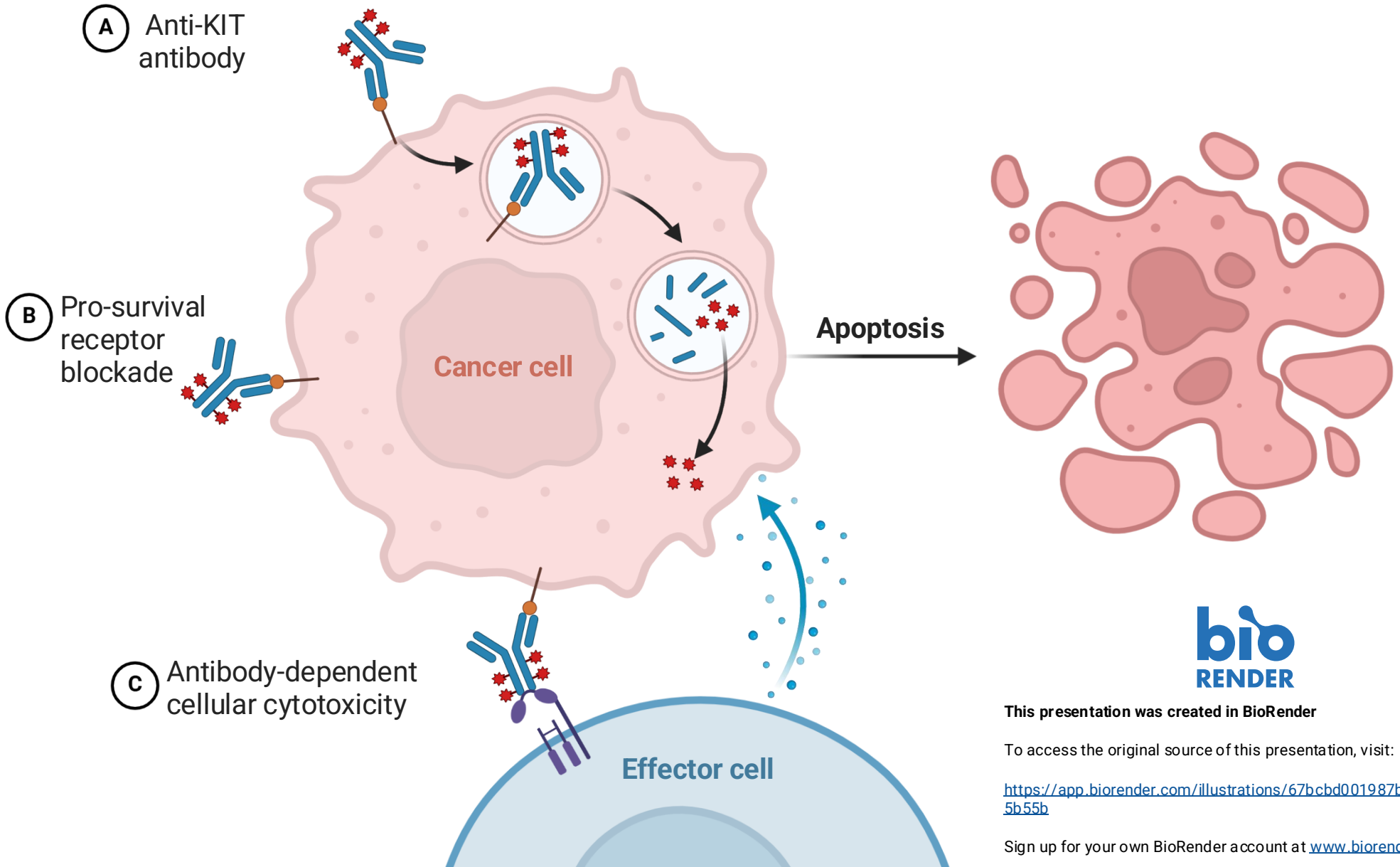
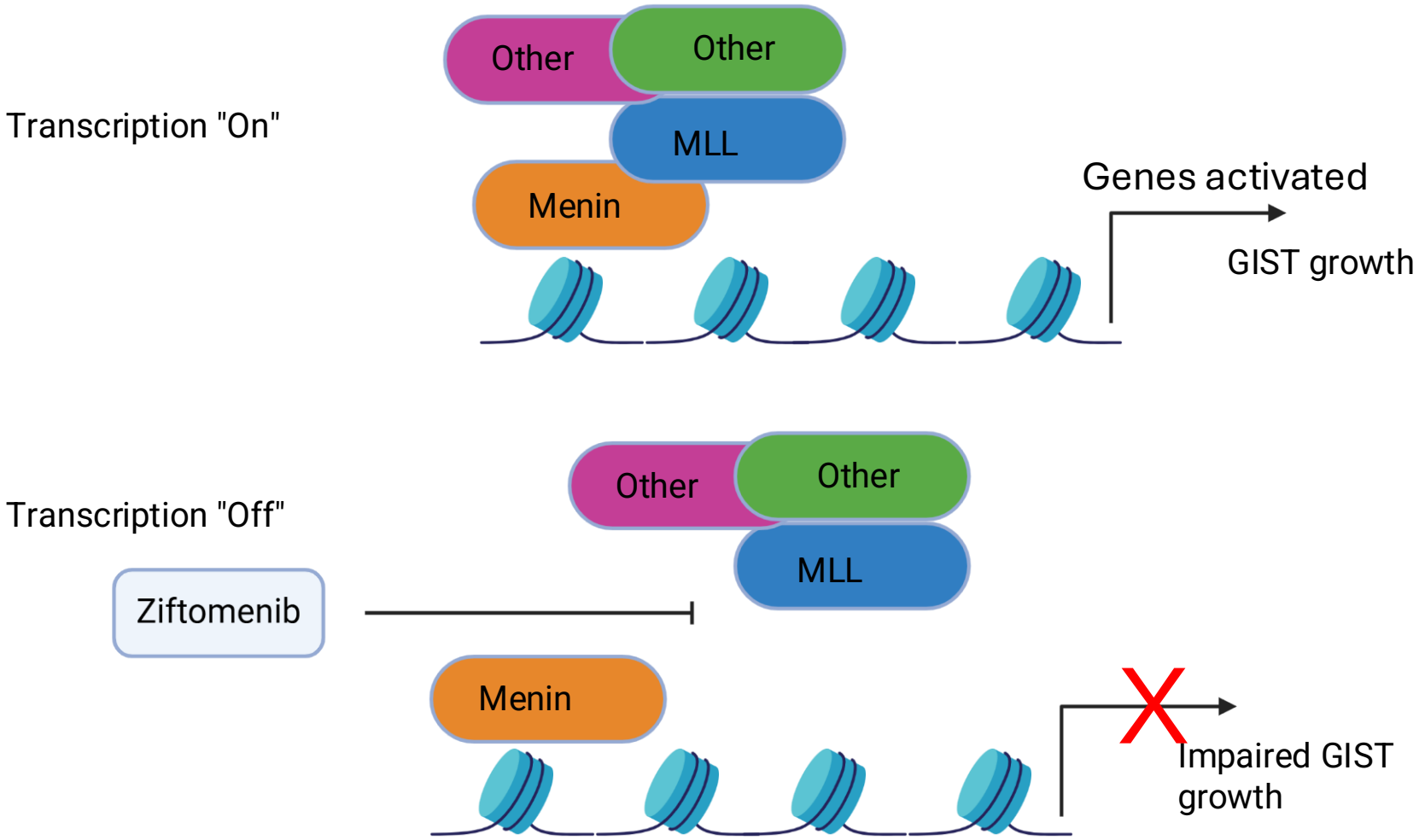
Antibody-Drug Conjugate

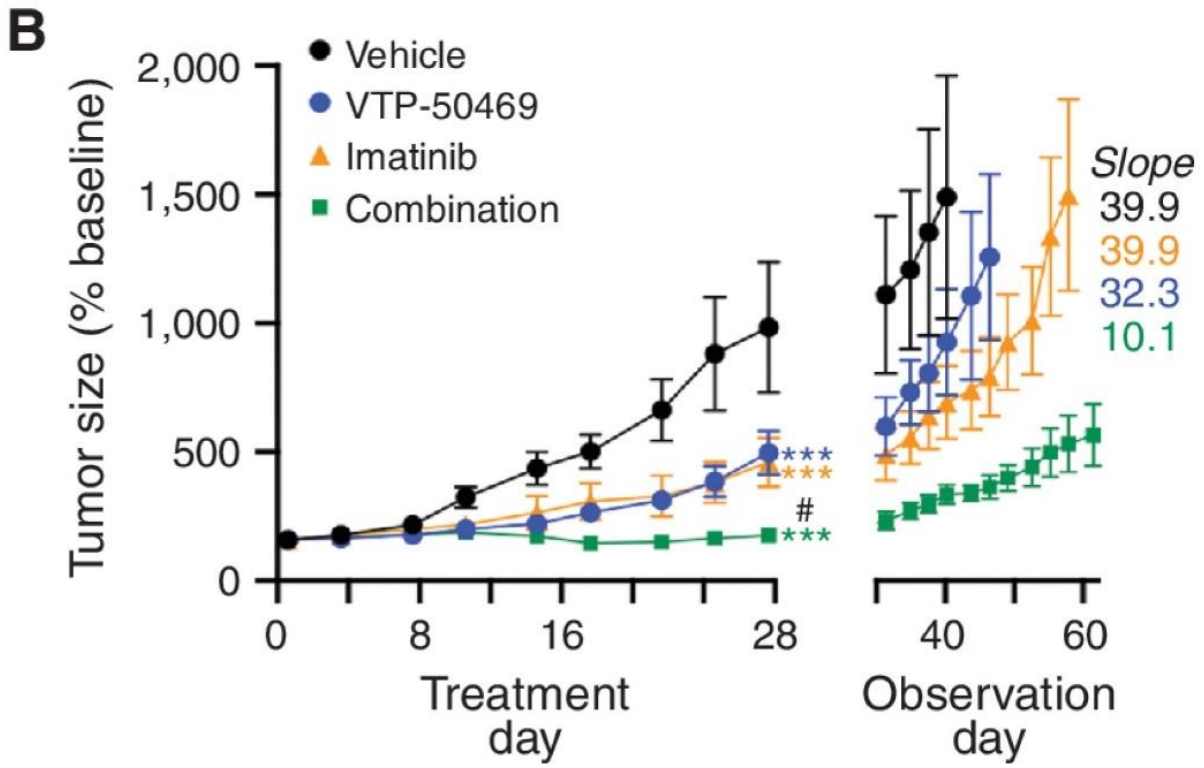
Mechanism of Action



Ziftomenib (menin inhibitor): mechanism of action



Menin inhibitors synergize with KIT inhibitor in GIST T1 (KIT exon 11-mutant GIST) PDX model

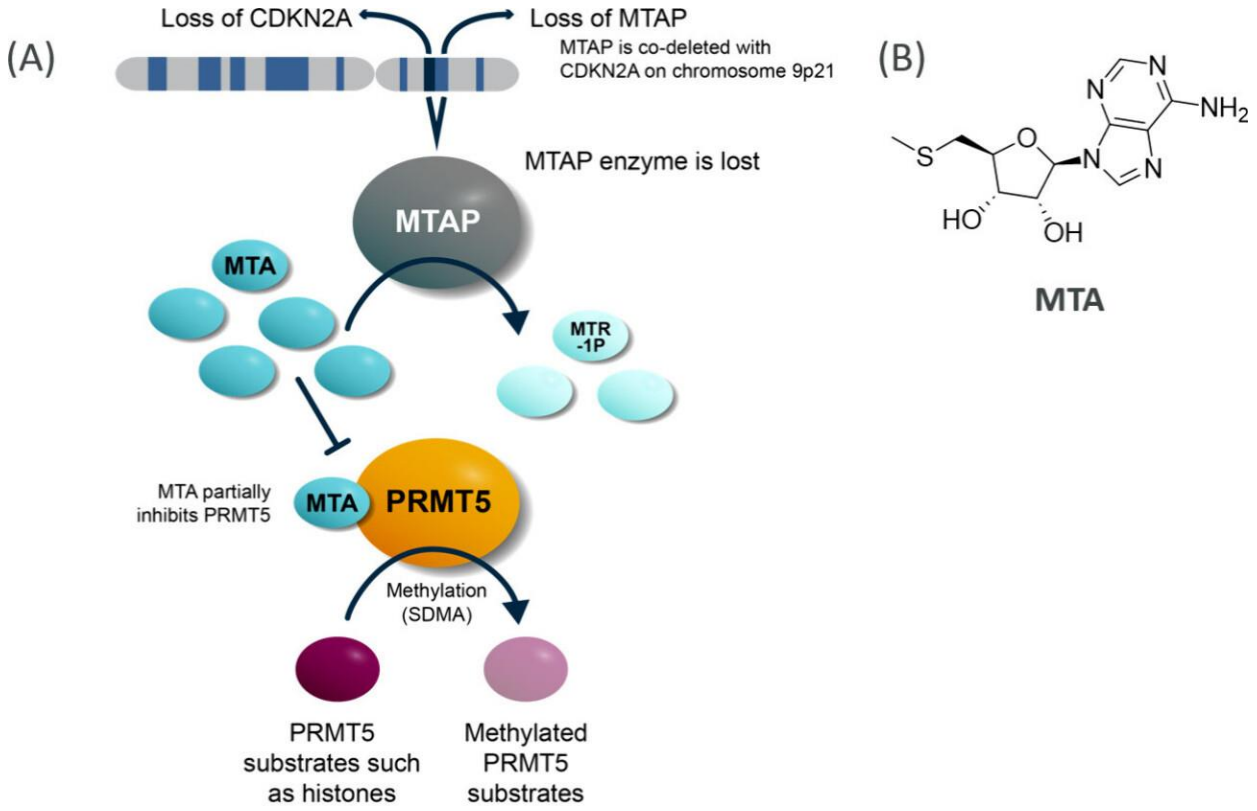


Hemming e al. Cancer Discovery 2022
https://doi.org/10.1158/2159-8290.CD-21-0646

GIST: imatinib and ziftomenib phase 1 study (NCT0665246)

- Theory: inhibiting KIT (even partially) with imatinib will synergize with ziftomenib
- Phase 1a/1b study for KIT-mutant GIST
- Patients only need to have received prior imatinib, patients with secondary KIT T670I mutation are excluded
- Opening this year, possibly already open at some sites

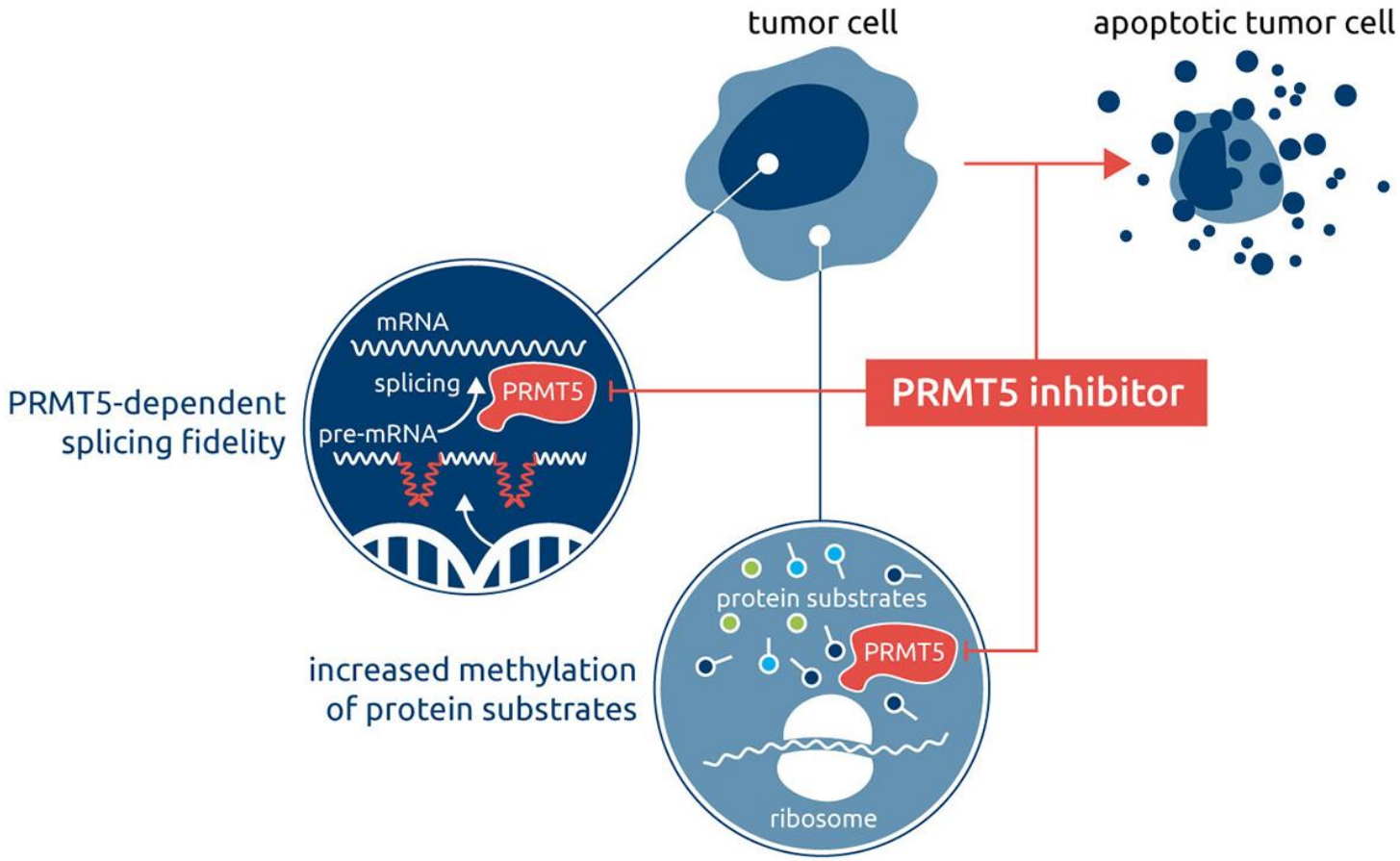
PRMT5 Inhibitors: Mechanism of Action



(A) MTAP loss leads to MTA accumulation and unique vulnerability to PRMT5 inhibition (MTAP = methylthioadenosine phosphorylase; (B) MTA = methylthioadenosine; MTR-1P = 5′-methylthio ribose-1-phosphate). (B) Structure of MTA.

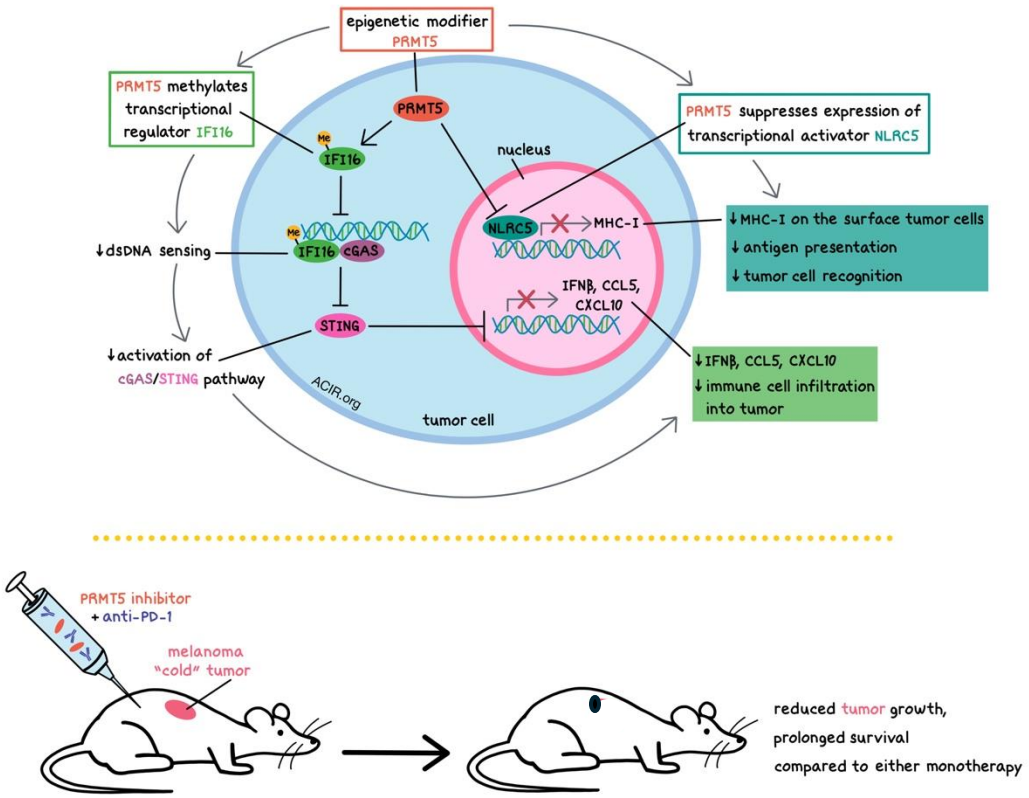
DOI: (10.1021/acs.jmedchem.4c00097)

PRMT5 Inhibitors: Mechanism of Action

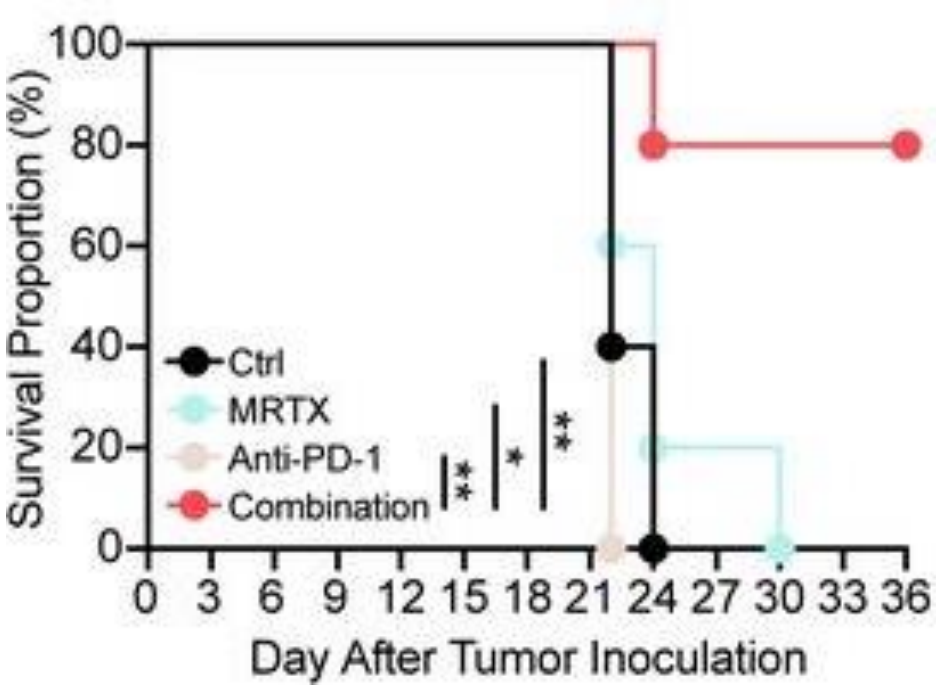


https://leadpharma.com/our-pipeline/prmt5/

PRMT5 inhibitors: increasing the response to immunotherapy agents

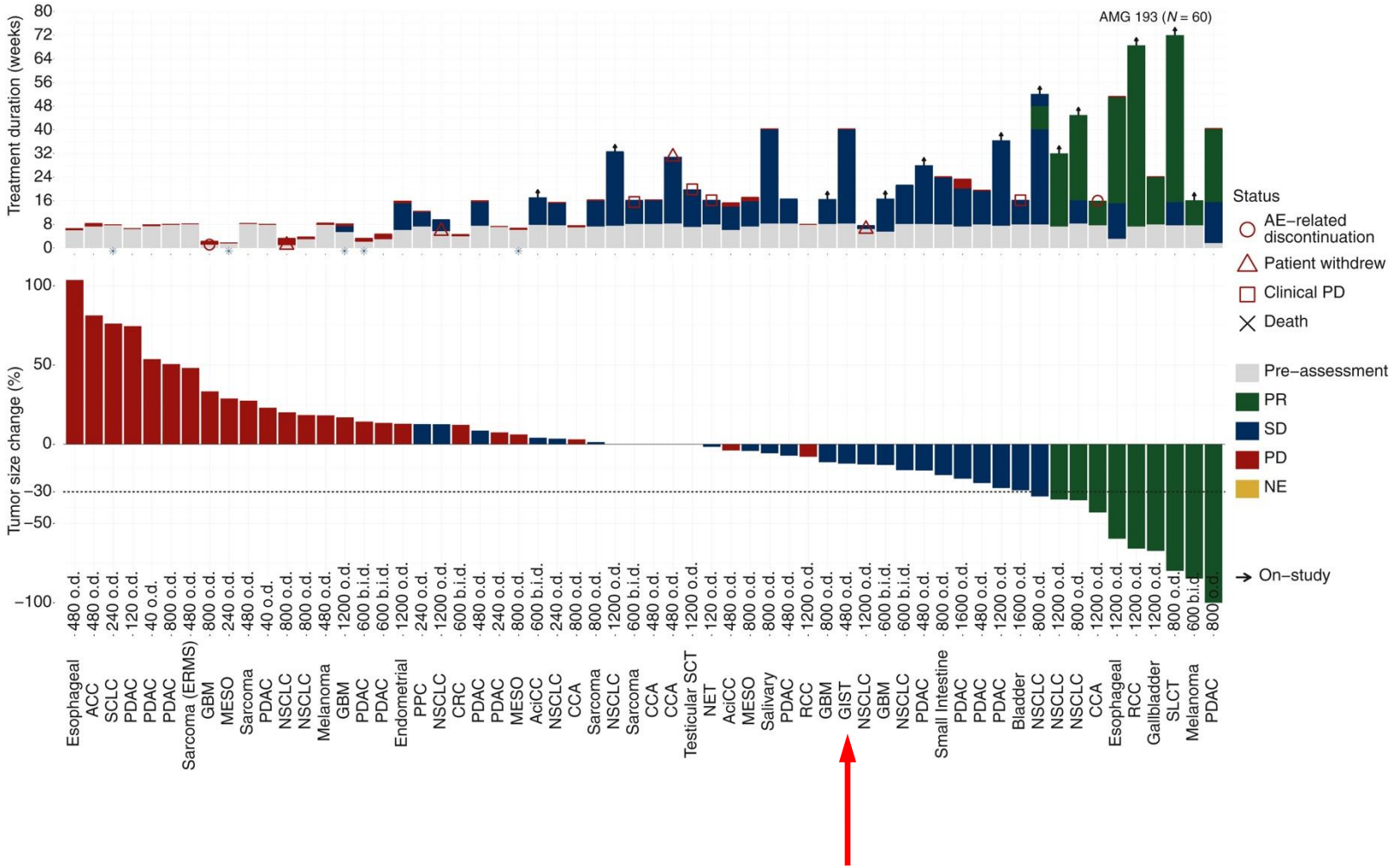


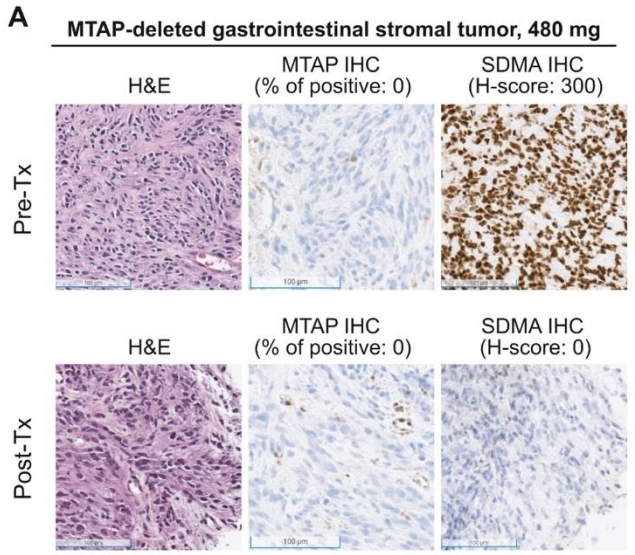
Note: this is a mouse model of melanoma, not GIST



Chen et al.
https://doi.org/10.1136/jitc-2024-009600

Phase 1 Study of AMG193



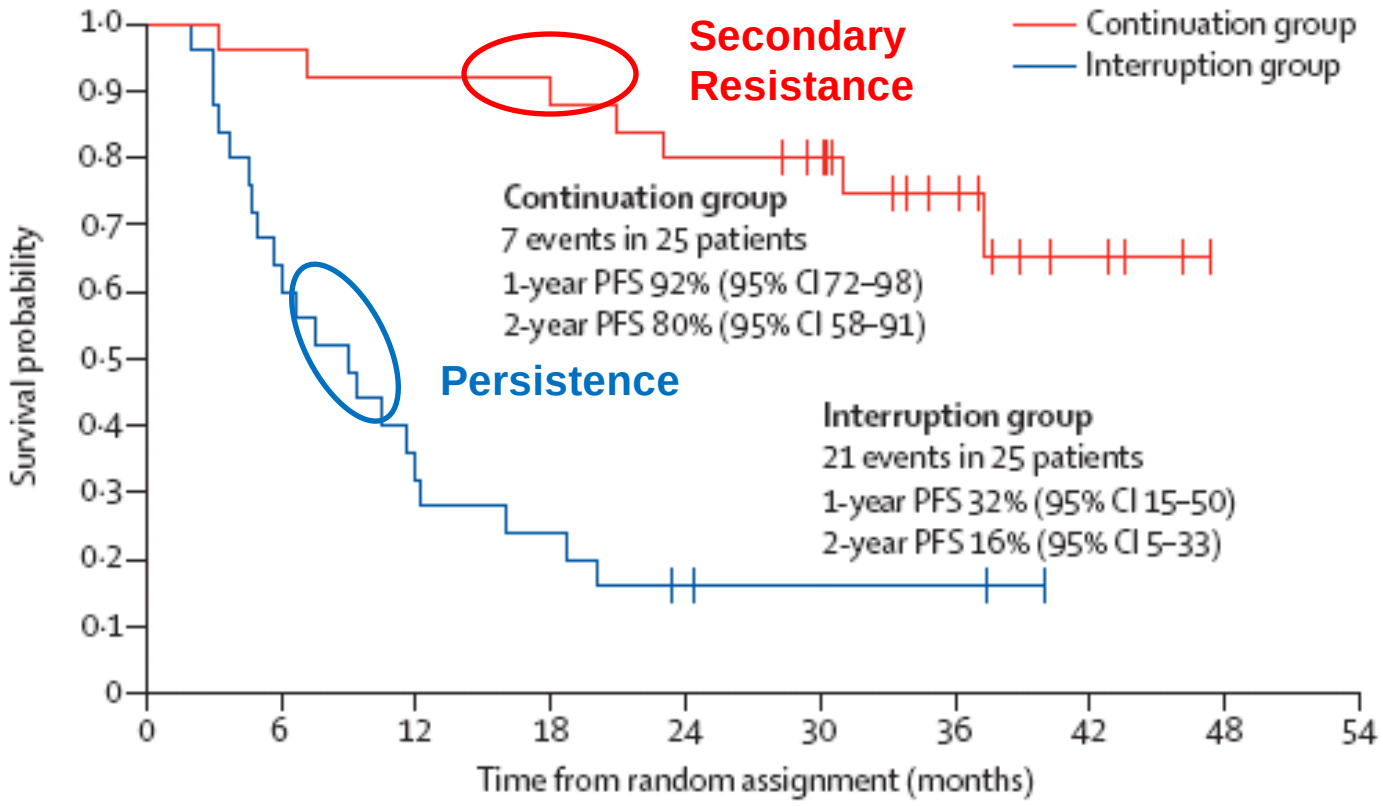


Rodon et al., Annals of Oncology 2024

PMRT5 inhibitor drug development status

- Multiple phase 1 studies underway or completed (cancer type agnostic)
- Requires specialized diagnostic testing to confirm MTAP gene inactivation
- Academic investigators planning study of a KIT TKI (e.g. imatinib) + PRMT5 inhibitor
- Stay tuned for future updates (? CTOS November 2025)

Limitations of TKI Therapy: Persistence vs. Resistance (BFR14)

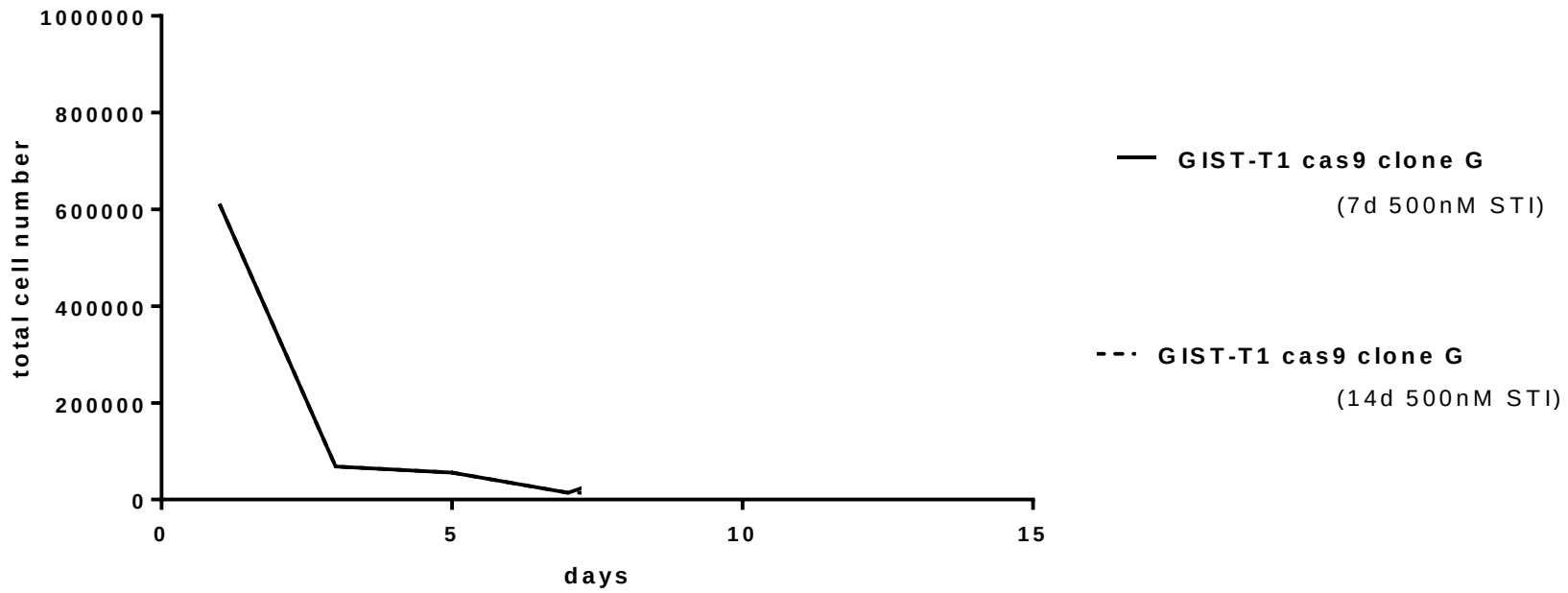


Reproduced with permission from LeCesne. *Lancet Oncol*. 2010;11:942.

Persistent vs. Resistant GIST

- Disease persistence: cells that remain viable during drug treatment and which can resume growing when drug treatment is interrupted
  - These cells are the nidus for the development of future drug resistance (when they develop secondary mutations)
  - This biology applies not only to the metastatic setting, but also to patients receiving adjuvant therapy
- Disease resistance: tumor growth despite continued drug treatment

In vitro modeling of persistence during TKI therapy



Hypothesis: GIST persistence due to a biological process known as autophagy

- Autophagy can protect cells during metabolic stress, including TKI therapy
- ULK1 and ULK2 are kinases that regulated autophagy
- DCC-3116 is a novel kinase inhibitor that inhibits ULK1 and ULK2
- Treatment of mice with GIST tumors with a combination of ripretinib and DCC-3116 results in complete tumor regression (unlike ripretinib alone)
- The combination of DCC-3116 and ripretinib is currently being evaluated in a clinical phase 1-2 study (NCT05957367 clinicaltrials.gov)
- Status:
  - Open at multiple sites, dose escalation in progress, no results
  - Once dose has been determined, the study will expand to include only second-line patients (only first line imatinib)

Summary of Key Points – making progress

- More selective TKIs with broad spectrum KIT inhibition are promising in advanced GIST
- Novel treatments that target new pathways beside KIT are being developed
- Significant interest and clinical trial activity for earlier lines of therapy


#SLAYGIST