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Latest from the GIST Stage

GIST Drug Development: New Targets, New Approaches

Dr. Michael Heinrich

GIST Drug Development:
new targets, new approaches

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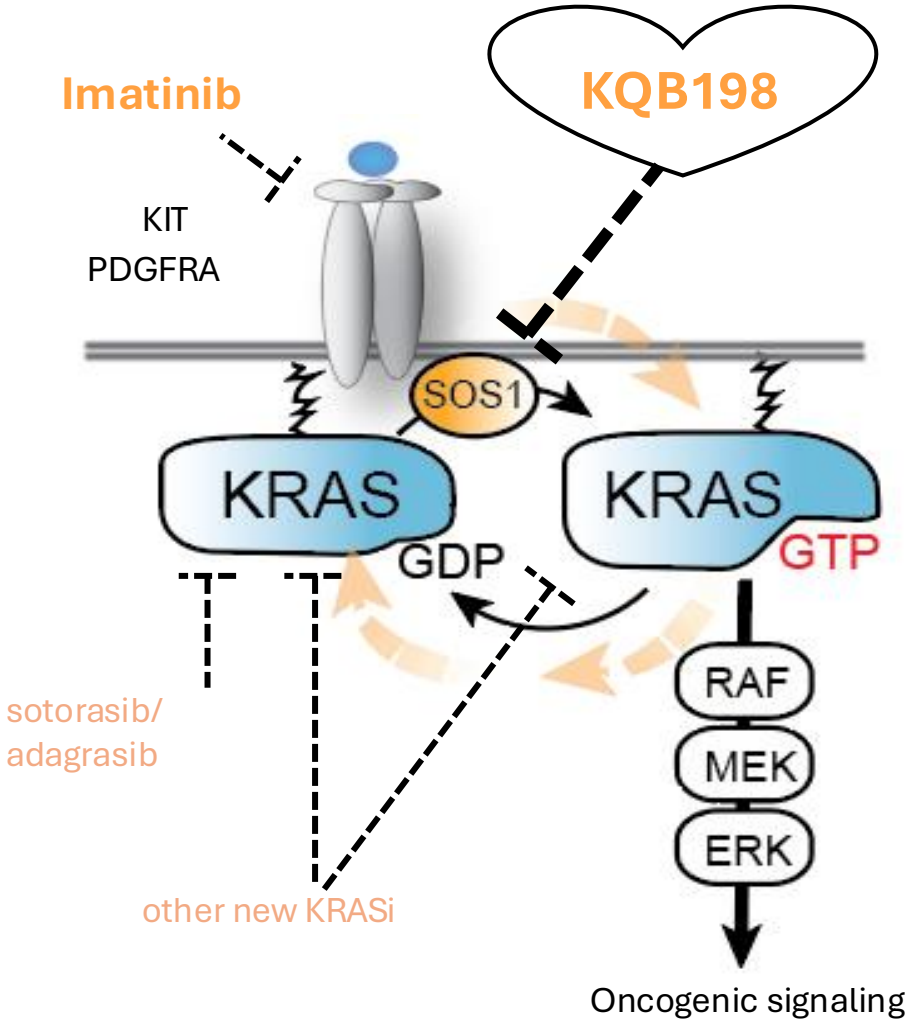
KNIGHT CANCER INSTITUTE
Oregon Health & Science University

Overview

- Inhibiting SOS is a novel target in GIST
- There are emerging strategies to use antibody therapy in GIST
- Menin is a newly identified target in GIST
- PRTM5 is a newly identified target in GIST

Beyond KIT tyrosine kinase inhibitors

Discovery of KQB198, a SOS1 Inhibitor



Lack of Efficacy **Resistance in GIST:**

- Off-Target resistance occurs due to downstream pathway activation → allows continued cell signaling even in the face of tyrosine kinase inhibition

Downstream Signaling **SOS-1 Molecule:**

- SOS1 is guanine nucleotide exchange factor (GEF) that catalyzes RAS from inactive to active state.
  - •SOS1 inhibitor reduces active RAS-GTP = inhibit RAS signaling
  - •KQB198 selectively inhibits SOS1 & blocks downstream signaling
  - •Blockade of downstream KIT signaling inhibits cell growth, leads to apoptosis, and causes normal cell differentiation

KQB198 & Imatinib **SOS-1 and Tyrosine Kinase Inhibition**

- Overcome the cell's natural resistance mechanisms, stopping the cancer from adapting, surviving, and multiplying
- Synergy in animal models of GIST

KQB198 in Combination With Imatinib in Participants With Advanced/Metastatic GIST in 1st Line Setting (SynerGIST-1st Line) NCT07406633

Study Overview

Brief Summary

This study will test an experimental drug called KQB198 in combination with imatinib. The goal is to determine if this combination is safe and tolerable and assess how effective the combination is at treating GIST. Imatinib has been approved by the FDA for the treatment of different types of cancer including GIST.

Official Title

A Phase 2, Multicenter, Study Evaluating the Efficacy, Safety, Tolerability, Pharmacokinetics of KQB198 in Combination With Imatinib in Participants With Advanced/Metastatic GI Stromal Tumor in 1st Line Setting

Conditions

GIST - Gastrointestinal Stromal Tumor | GIST | GIST Metastatic Cancer | Gastro Intestinal Stromal Tumour | Gastrointestinal Tumors

Intervention/Treatment

- Drug: KQB198
- Drug: Imatinib (Gleevec)

Other Study ID Numbers

- KQB198-103

Study Start (Estimated)

2026-06

Primary Completion (Estimated)

2027-10

Study Completion (Estimated)

2028-10

Enrollment (Estimated)

46

Study Type

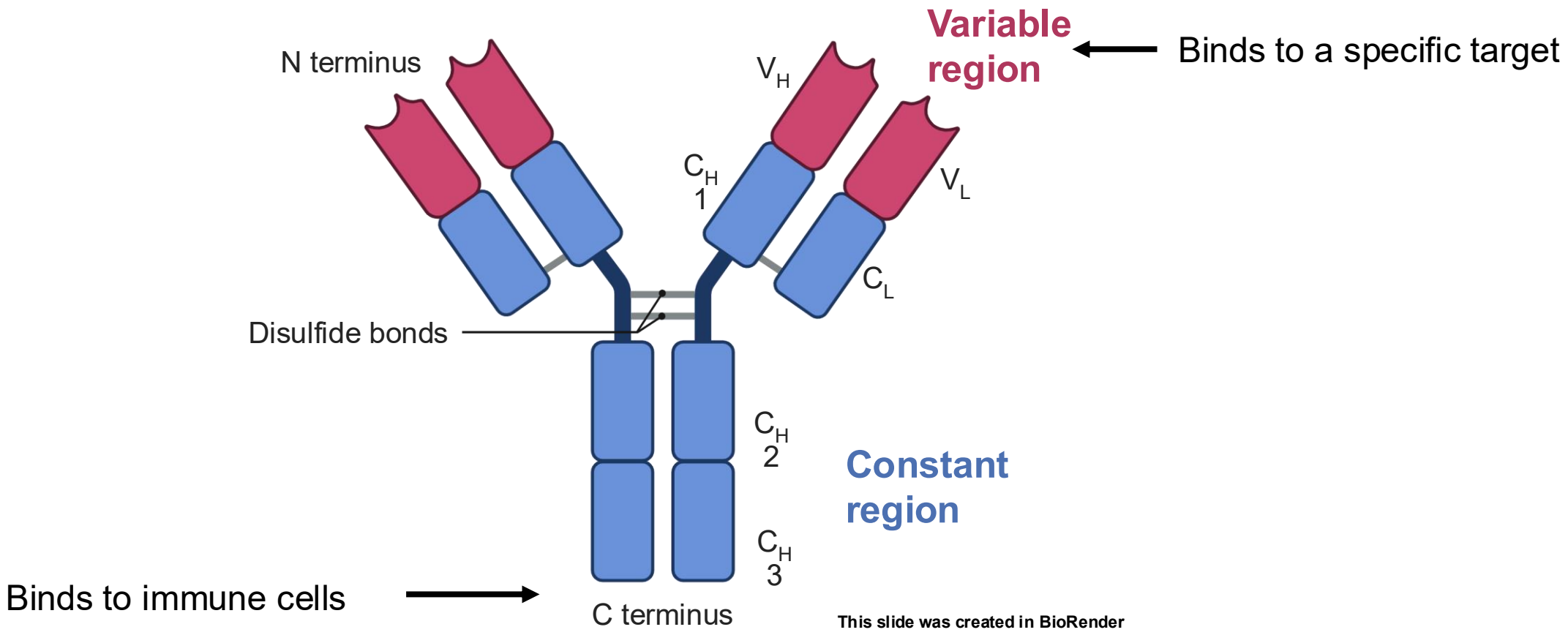
Interventional

Phase

Phase 2

Monoclonal Antibodies and Cancer Therapy

What is an antibody?



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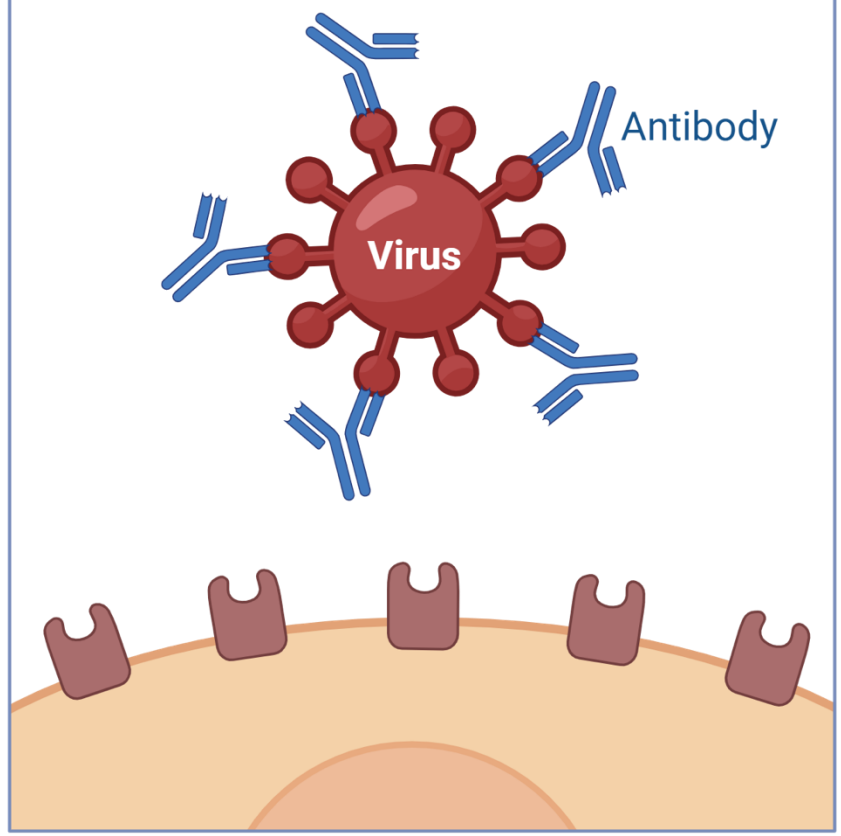
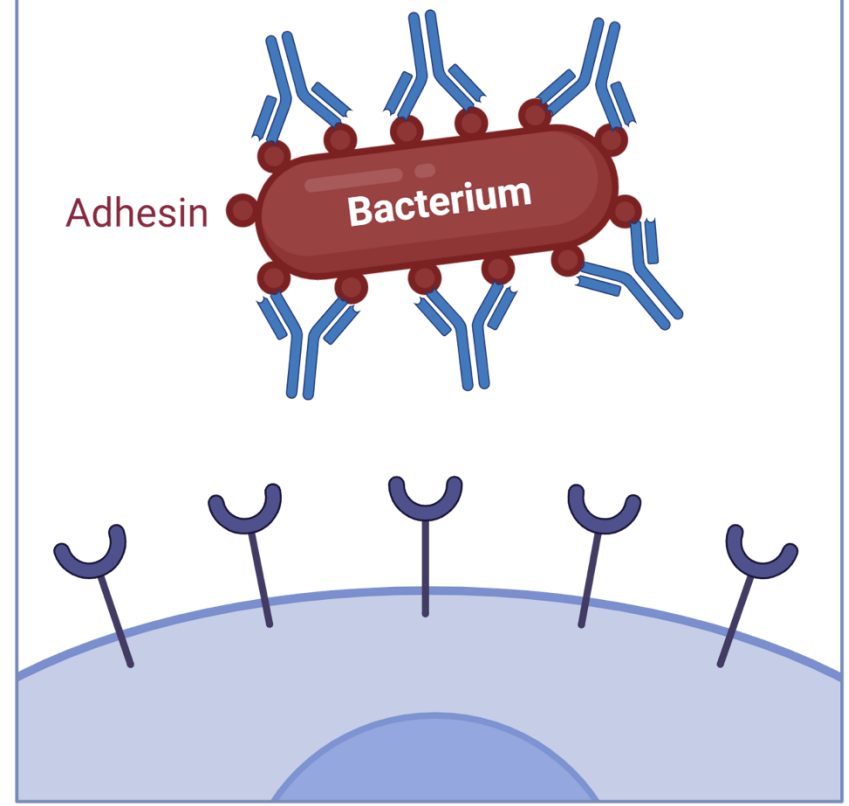
Specific Antibodies Neutralize Viruses and Bacteria

Antibody blocks binding to virus receptor and also blocks fusion event



Antibodies against adhesins block colonization and uptake

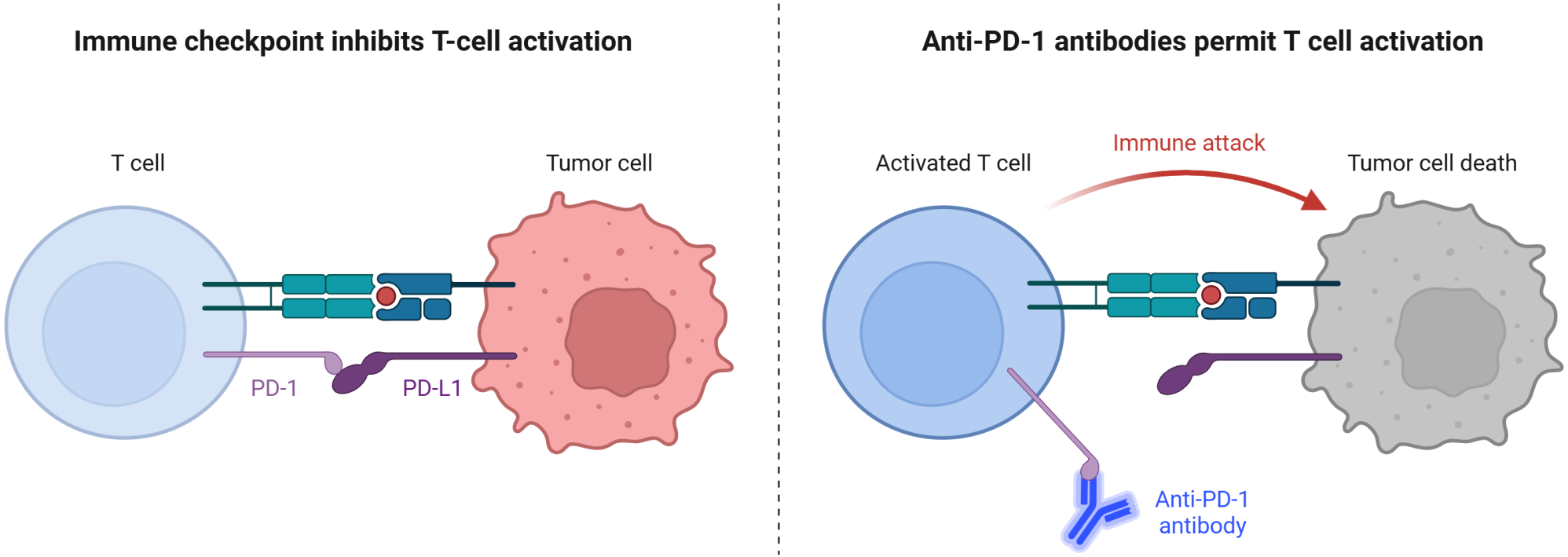


Monoclonal antibodies

- Normal immune responses are polyclonal—many different antibodies recognizing a different part of the same target antigen
- It is possible to generate a unique monoclonal antibody that only recognizes a distinct part of a target antigen
- Using manufacturing techniques, large quantities of pharmaceutical grade monoclonal antibody can be made

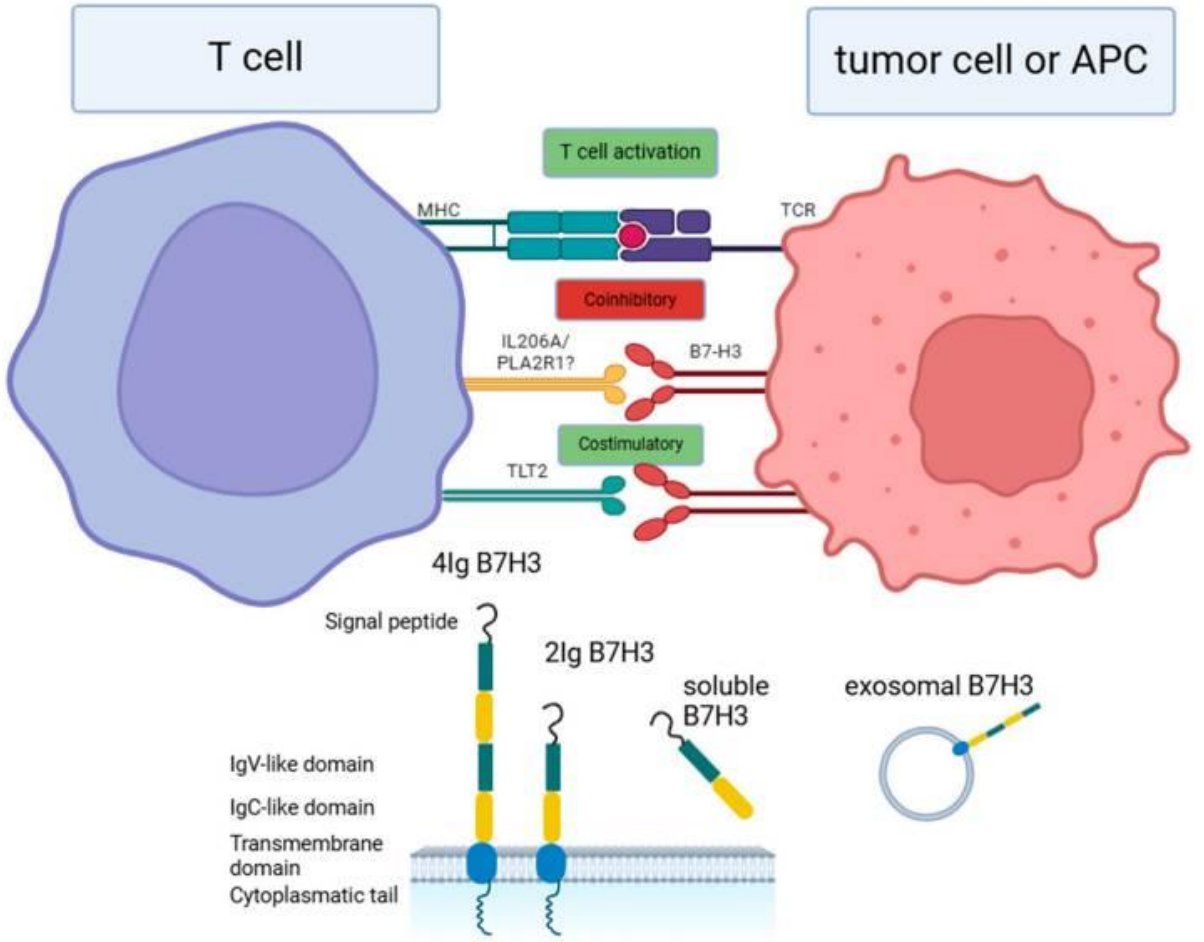
Using antibodies to block cell surface receptors

Cancer Immunotherapy



Conventional PD-1 or PD-L1 antibodies are rarely effective in the treatment of GIST

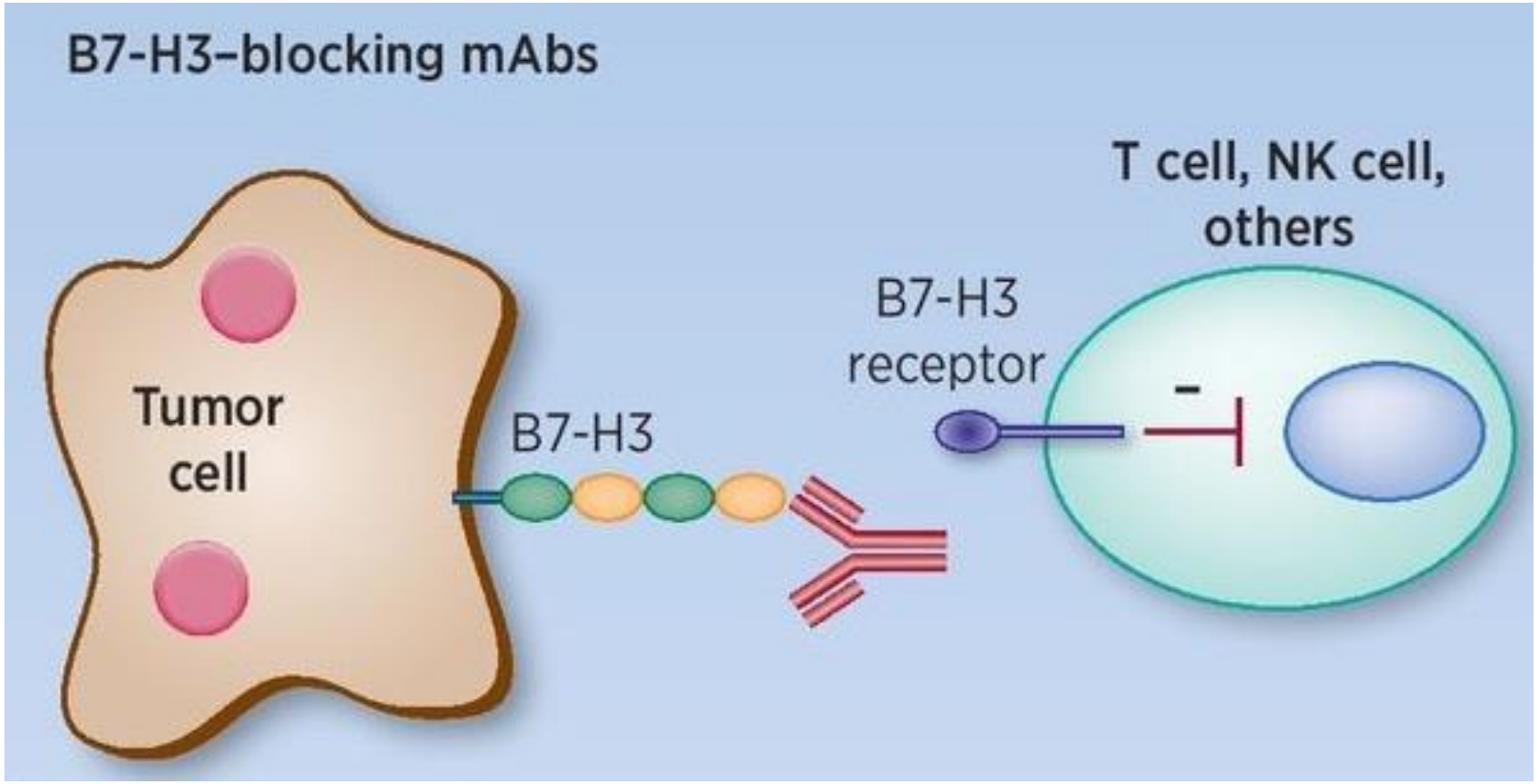
Tumor expression of B7-H3 inhibits the immune system



B7-H3 expressed by > 90% of GIST

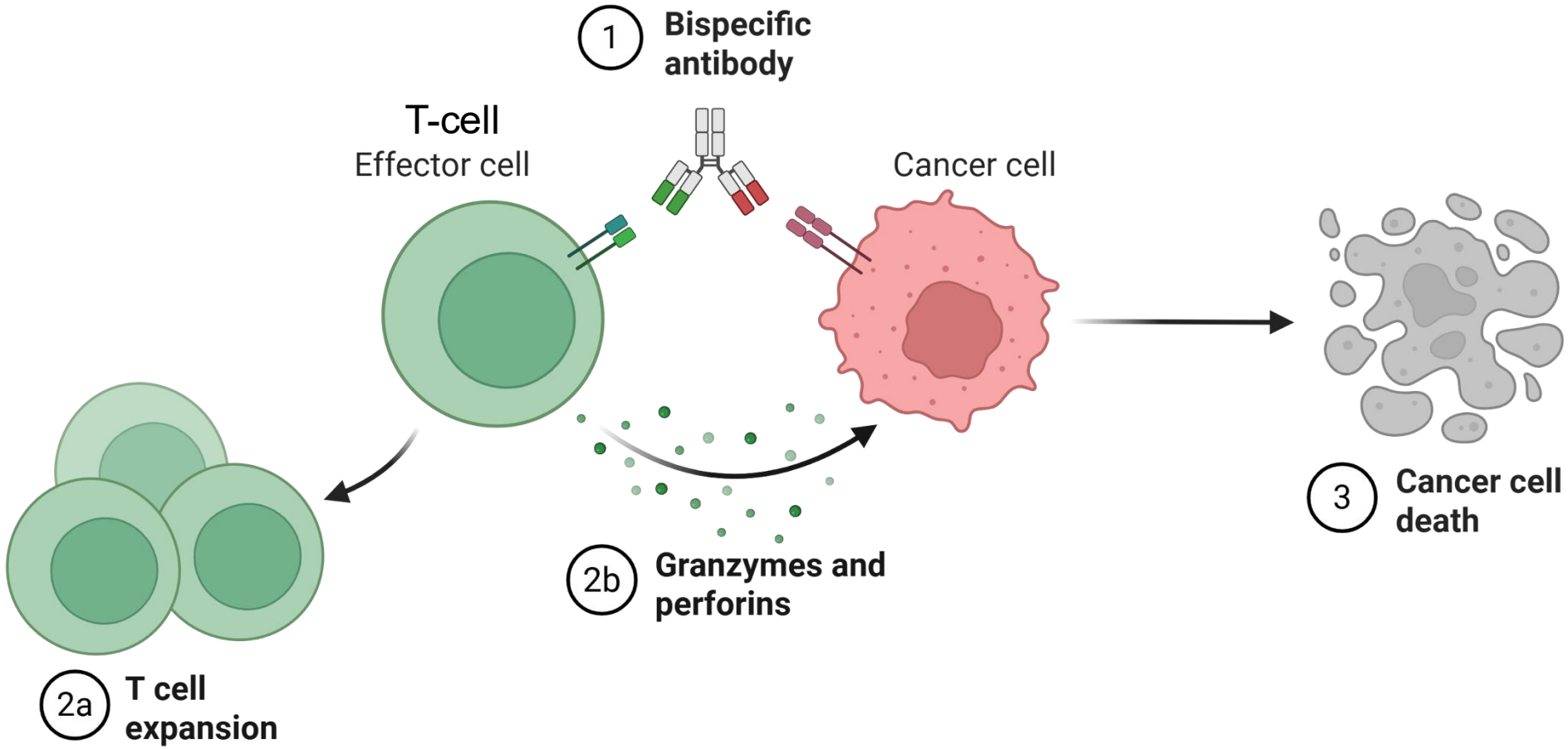
Mielcarska et al.,https://doi.org/10.3390/cells14070530

Alternative immunotherapy approaches in GIST



Clin Cancer Res. 2016;22(14):3425-3431. doi:10.1158/1078-0432.CCR-15-2428

Bispecific Antibody Mechanism of Action



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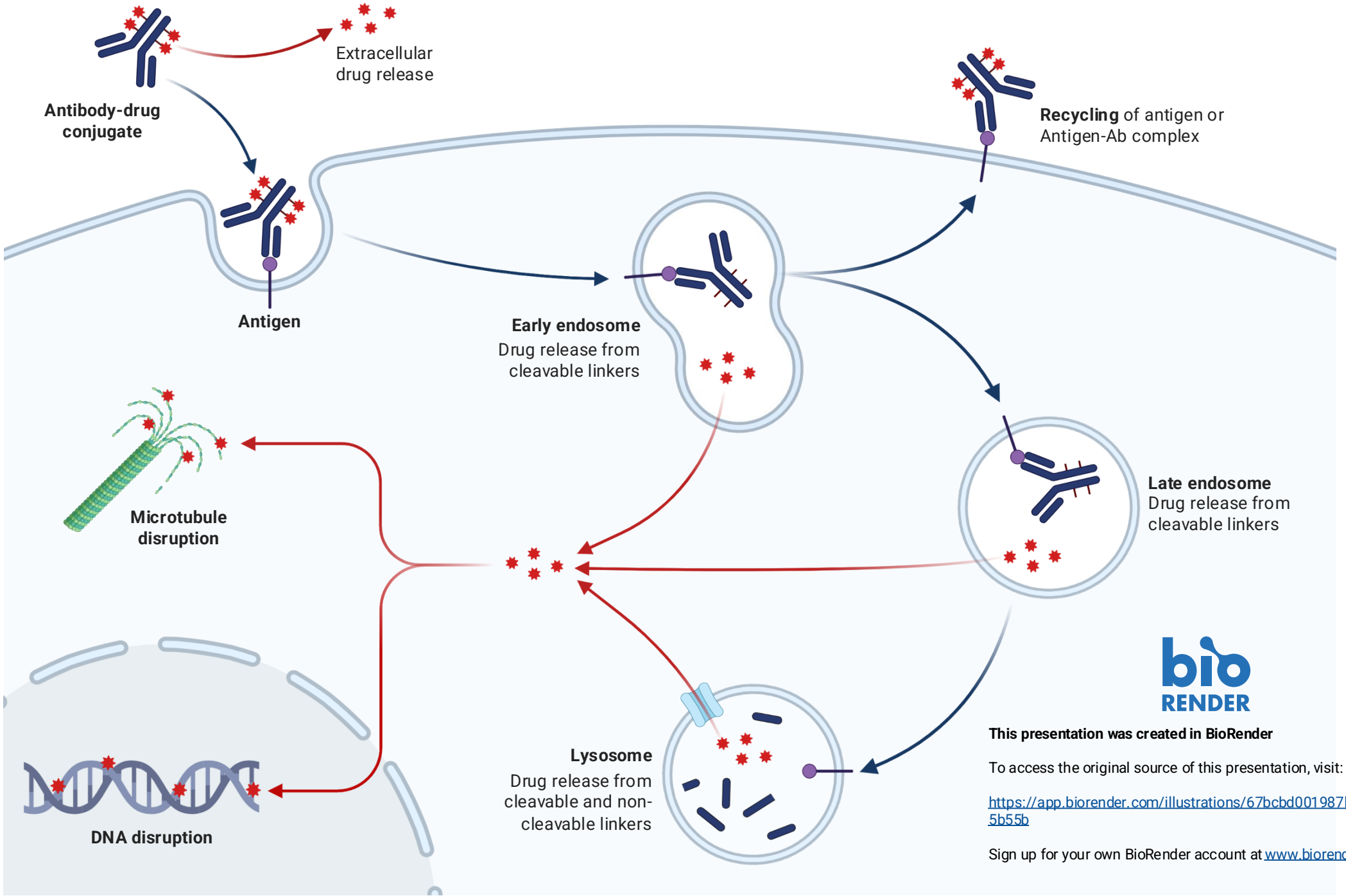
Antibody Drug Conjugates (ADC): Using antibodies to deliver chemotherapy

- ADC are composed of antibody, a linker, and a chemotherapy agent
- The antibody allows specific targeting to a protein expressed on the outside of a tumor cell
- The linker keeps the chemotherapy attached to the antibody but can be cleaved when the complex become internalized into a part of the cell known as the lysosome
- The cleaved chemotherapy agent can then cause cell death, usually by producing DNA damage
- Currently there are many approved ADC drugs for cancer treatment (e.g. breast cancer)


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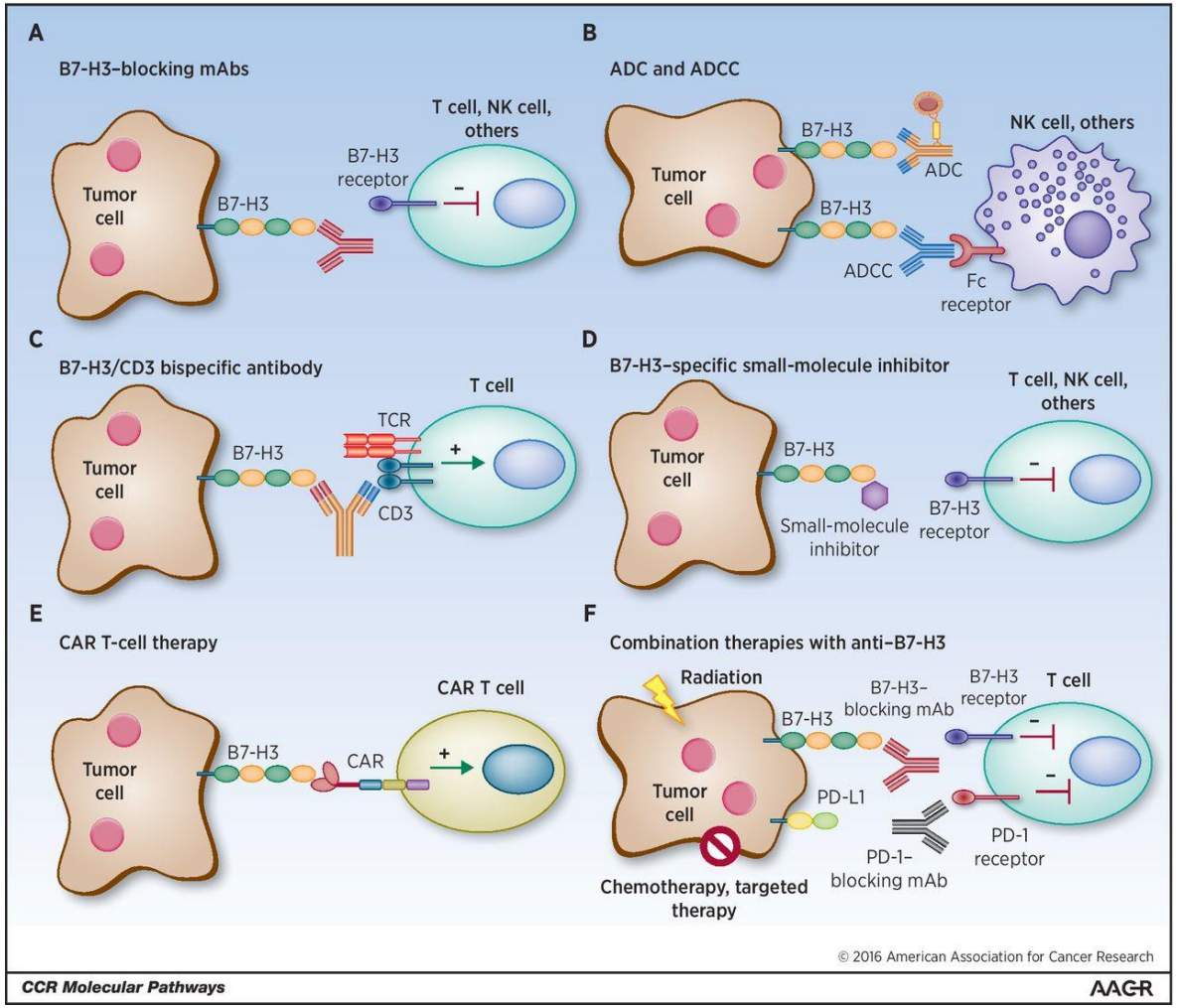
Antibody Drug Conjugates (ADC)

- To develop an ADC for GIST, an appropriate target must be identified
  - targets identified to date: KIT, B7-H3
- The chemotherapy agent must have activity against the cancer cell
  - Historically, GIST are resistant to conventional chemotherapy given intravenously
  - ? Can targeted delivery of very high doses of a chemotherapy agent kill GIST cells
  - Can we identify ADC linked chemotherapy agents that are optimal to use to treat GIST?
- Potential dual mechanism of action as ADC can also function as blocking antibodies
  - B7-H3 ADC will both stimulate immune the system by blocking inhibitory B7-H3 and by delivering chemotherapy into tumor cells expressing B7-H3

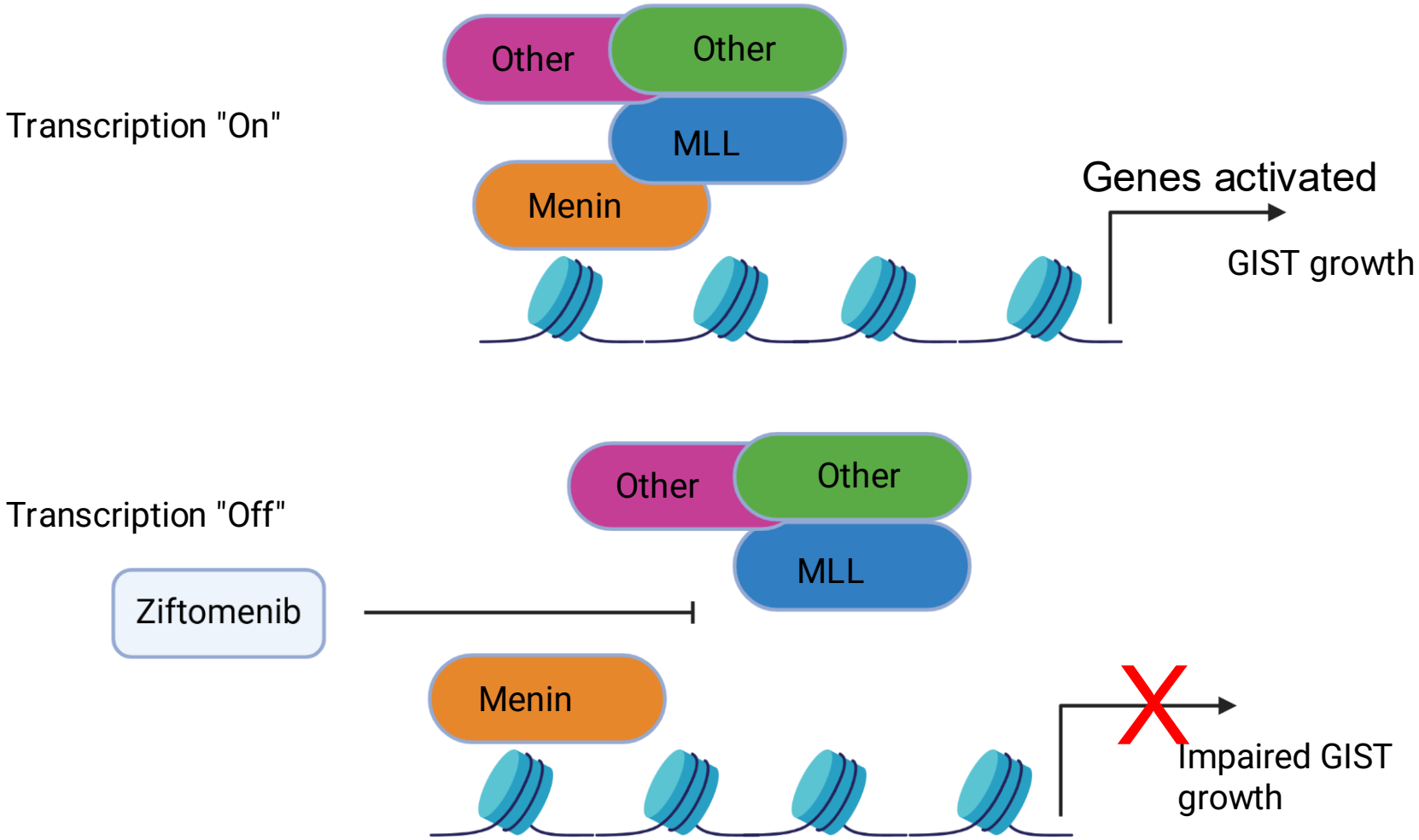
Harnessing monoclonal antibodies: one target, many therapy strategies



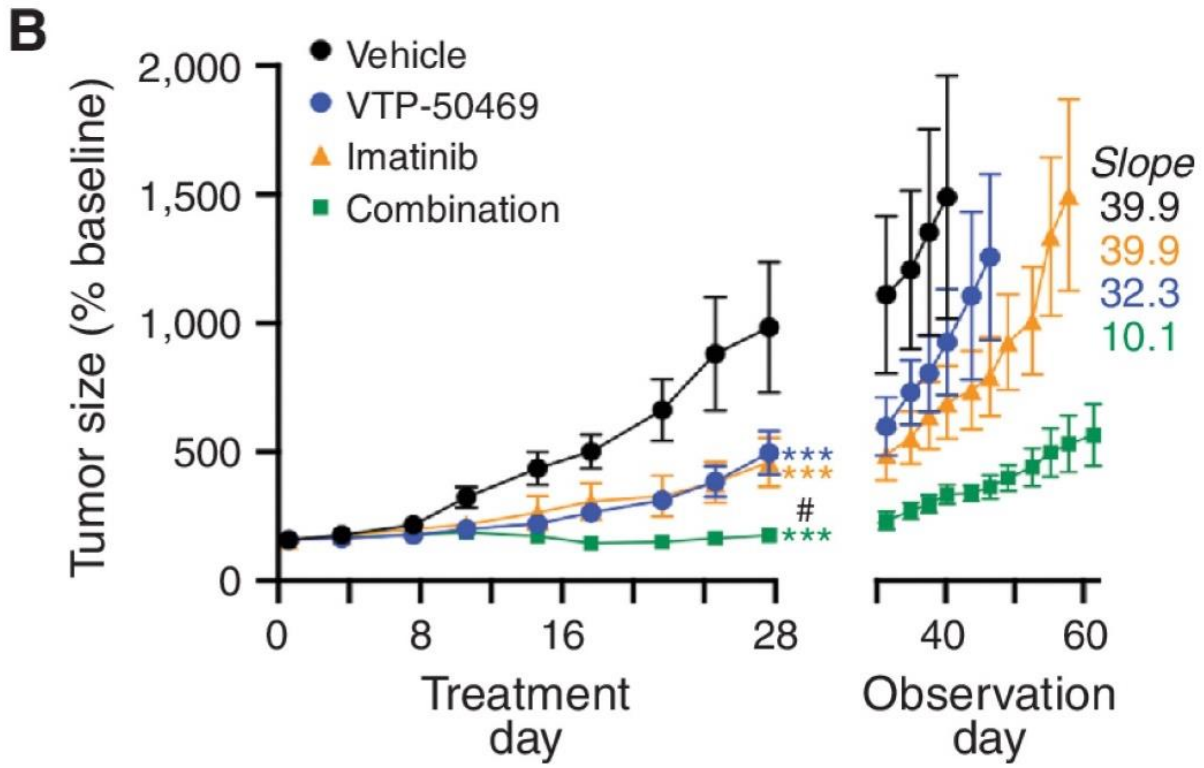
Clin Cancer Res. 2016;22(14):3425-3431. doi:10.1158/1078-0432.CCR-15-2428

Menin as a target in GIST

Ziftomenib (Menin inhibitor): mechanism of action



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



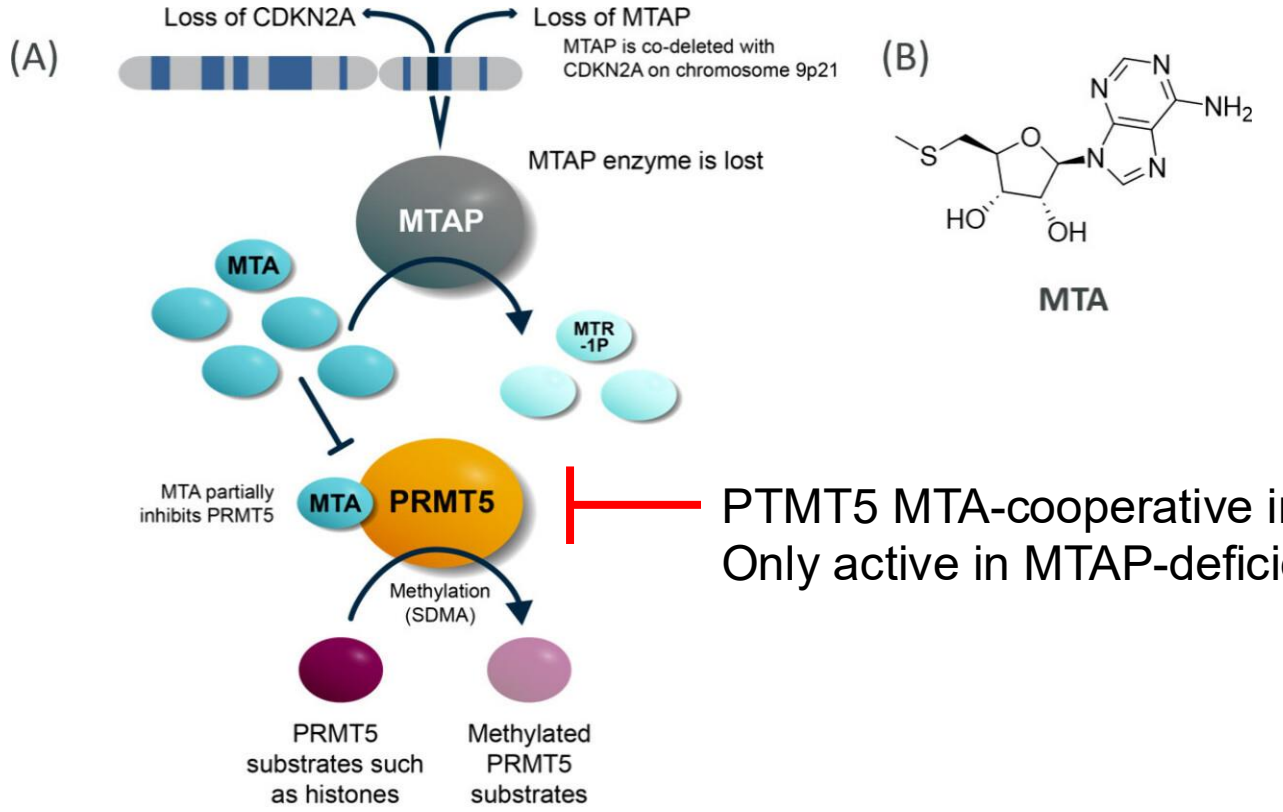
Hemming e al. Cancer Discovery 2022
https://doi.org/10.1158/2159-8290.CD-21-0646

GIST: imatinib and ziftomenib phase 1 study (NCT0665246)

- Theory: inhibiting KIT (even partially) with imatinib will synergize with ziftomenib

PRMT5 as a target in GIST

PRMT5 Inhibitors: Mechanism of Action



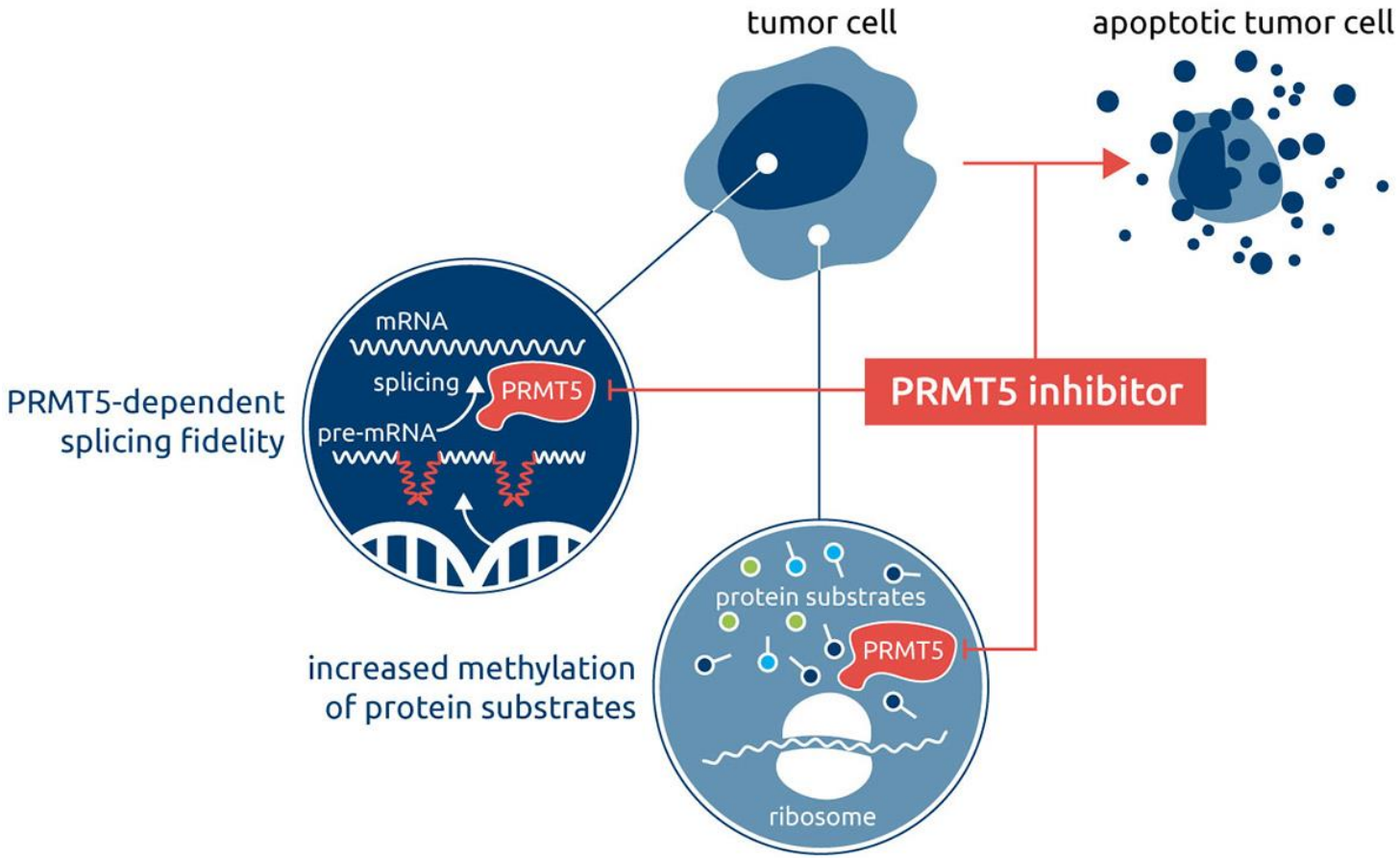
PTMT5 MTA-cooperative inhibitor
Only active in MTAP-deficient cancer cells

15-25% of GIST are MTAP deficient

(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.

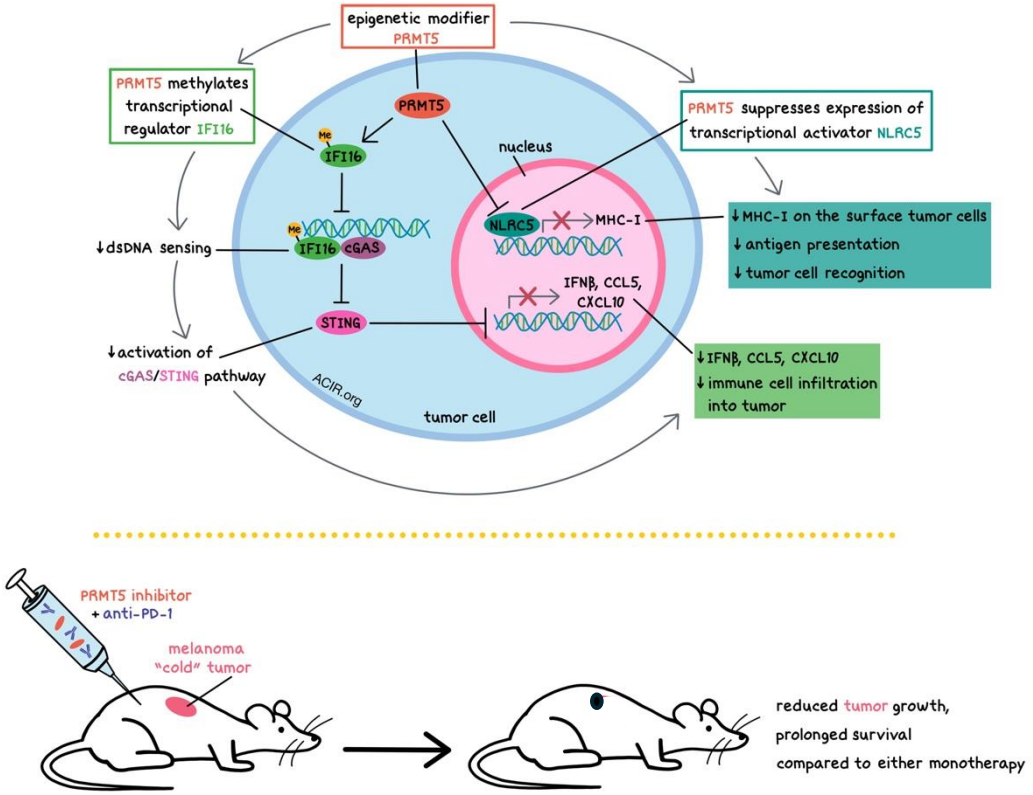
DOI: (10.1021/acs.jmedchem.4c00097)

PRMT5 Inhibitors: Mechanism of Action

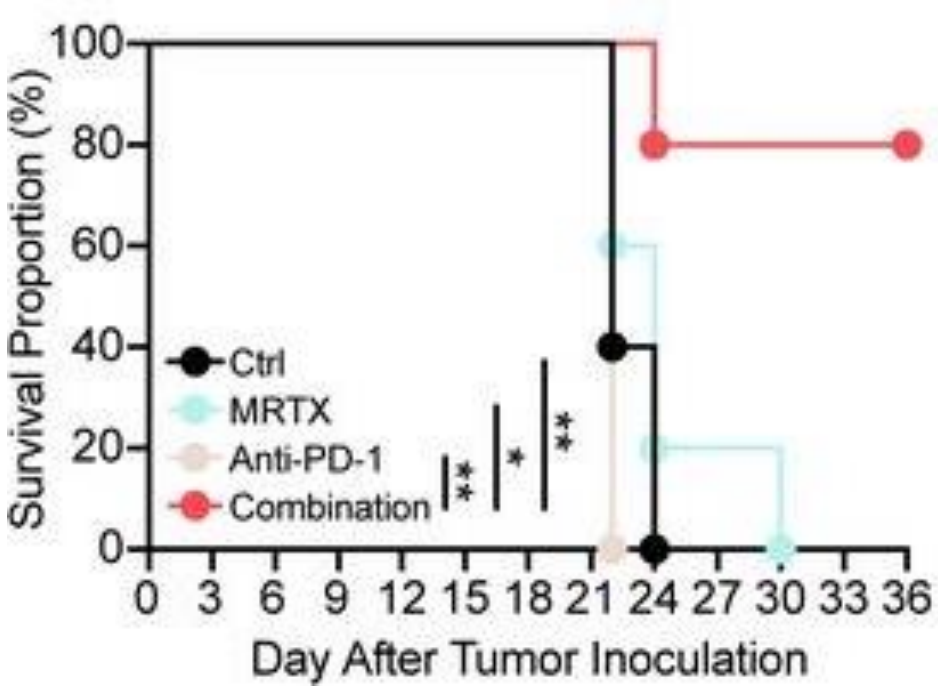


https://leadpharma.com/our-pipeline/prmt5/

PRMT5 inhibitors: increasing the response to immunotherapy agents

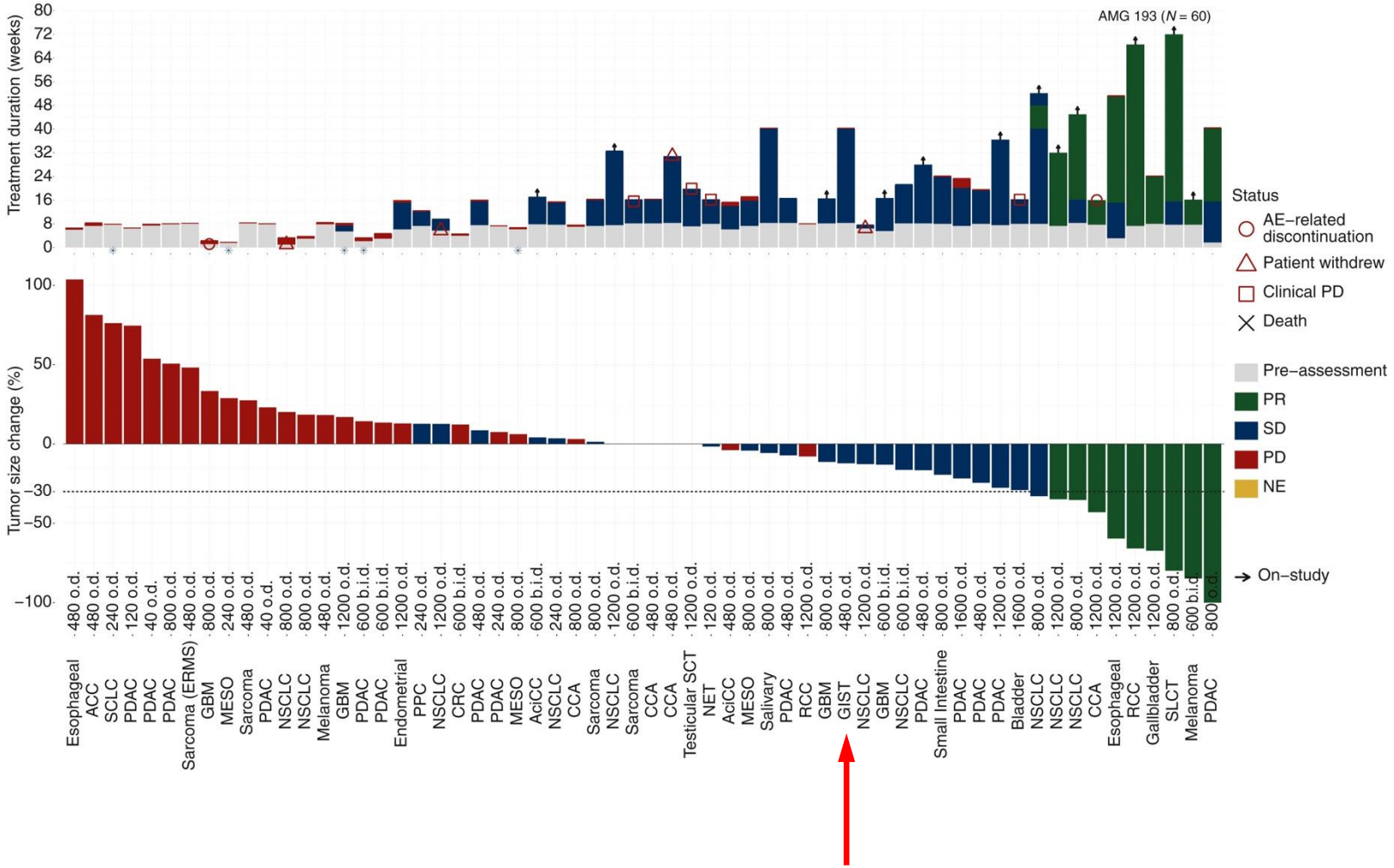


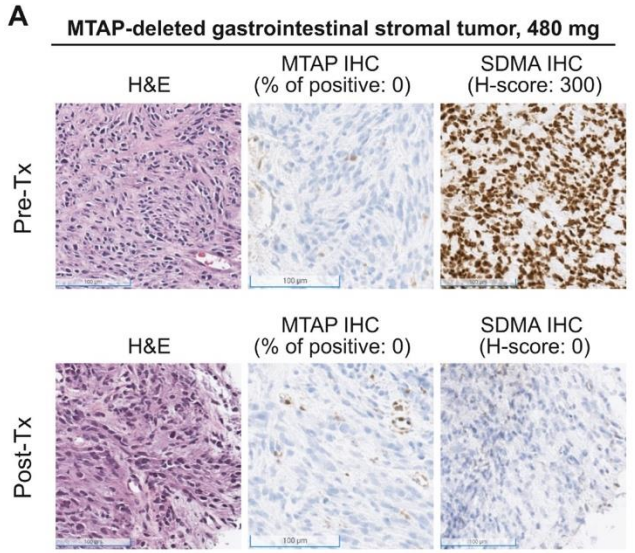
Note: this is a mouse model of melanoma, not GIST



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 deletion
- Academic investigators planning study of a KIT TKI (to be determined) + PRMT5 inhibitor for GIST
- GIST specific study may open in summer of 2026

Summary of Key Points

- Novel treatments that target new pathways beside KIT are being developed
  - SOS inhibitor + imatinib study currently enrolling
  - Menin inhibitor currently enrolling
  - PRMT5 inhibitor study coming soon
- There is an upcoming revolution in antibody therapy for GIST
  - Anti-KIT ADC(NN3201) study currently enrolling
- All of these studies are, or will be, open at major GIST centers, including OHSU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