Memorial Sloan Kettering Cancer Center

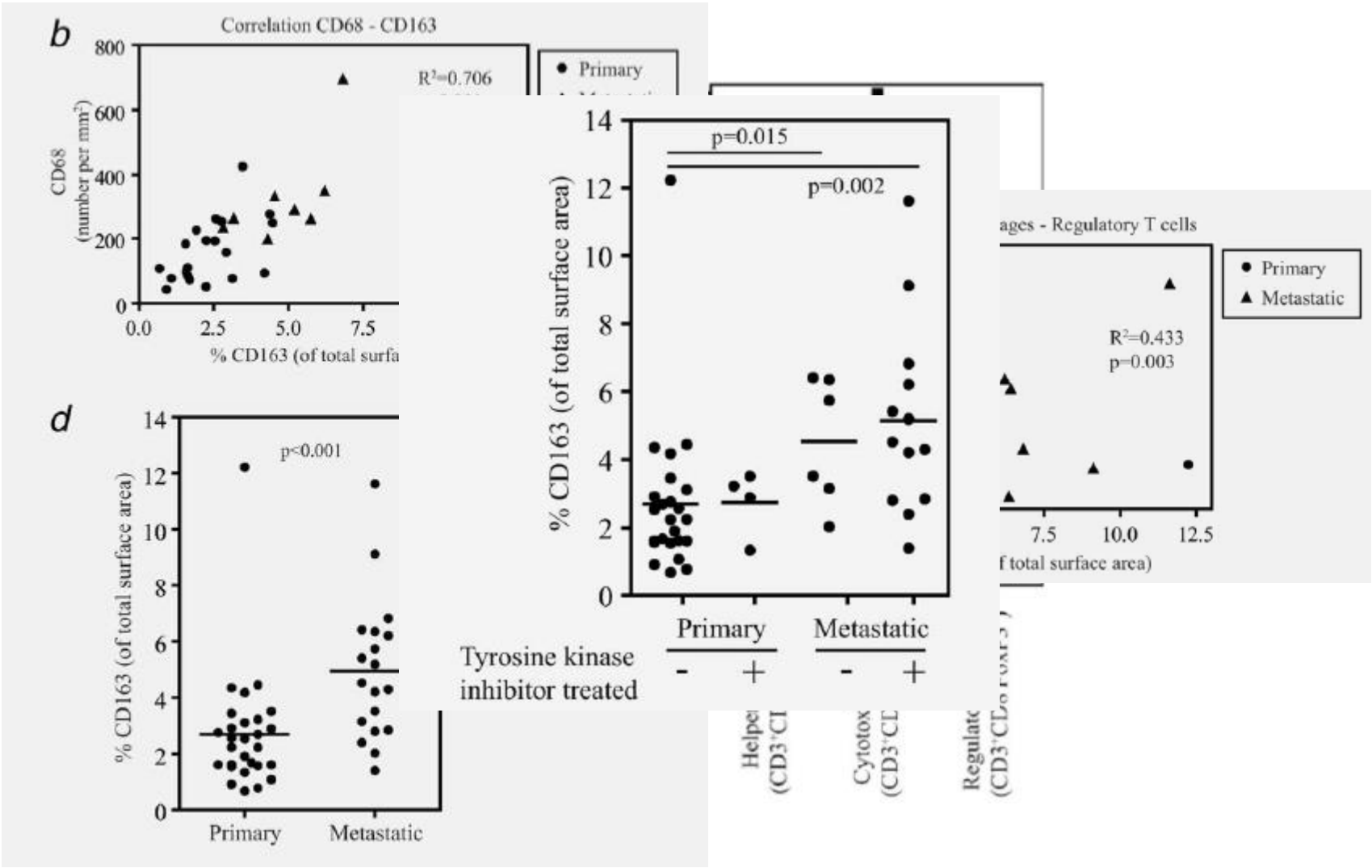
Immunotherapy & GIST

Dr. Ciara Kelly,
Assistant Attending,
Sarcoma Medical Oncology Service,
Memorial Sloan Kettering Cancer Center

Disclosures

- Research funding:
  - Amgen, Merck, Kartos, Servier, Incyte, Exicure, Xencor
- Consulting:
  - Kartos, Exicure
- Employment – relative :
  - Daiichi-Sankyo

GIST IMMUNE MICROENVIRONMENT



Dongen Mv, et al, IJC, 2009

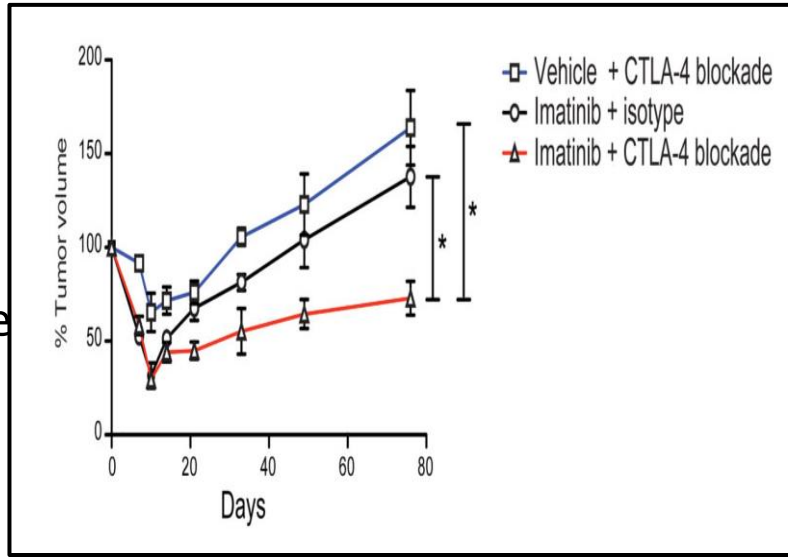
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

IMMUNOSUPPRESSIVE MICROENVIRONMENT

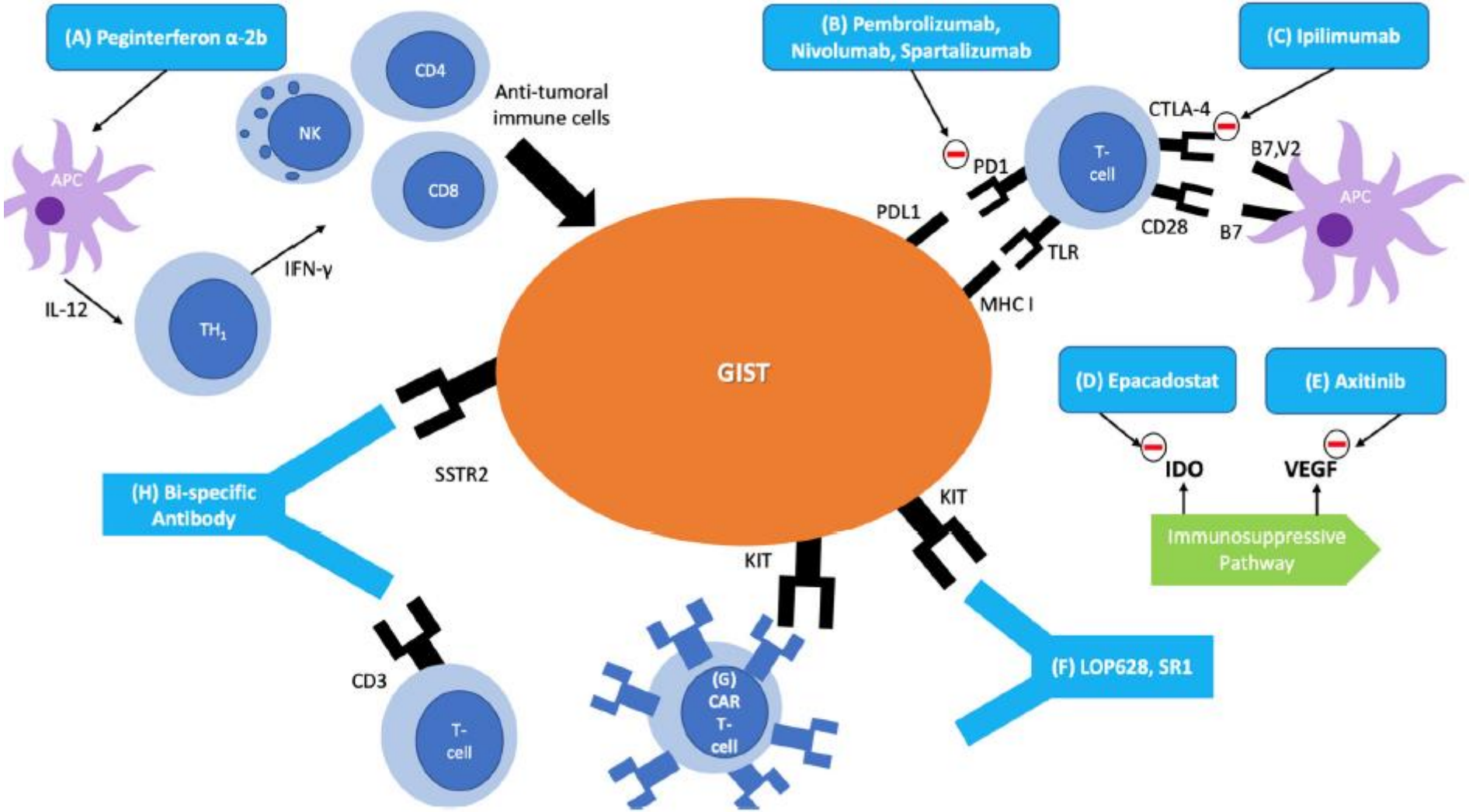
Imatinib potentiates anti-tumor T cell responses in GIST through the inhibition of IDO

- Imatinib amplifies a pre-existing immune response in mouse GIST
  - Increases CD8+ T cells in DLN and tumor
  - Decreases Treg in tumor only
  - Increases intratumoral CD8+ T cell to T reg ratio (associated with favorable immunological outcome)
- CD8+ T cells are required for its maximal effects
  - CD8+ T cell depleted tumors were larger and the imatinib anti-tumor effect was blunted
- Imatinib induces intratumoral CD8+ T cell activation and regulatory T cell apoptosis in mouse GIST through the inhibition of IDO1
  - IDO1 – intracellular enzyme – converts tryptophan to kynurenine
- Intratumoral CD8+ T cell to T reg ratio was lower in resistant tumors compared with sensitive GISTs
- Imatinib-mediated reduction of IDO
  Depended on its ability to block KIT signaling
  Synergy between imatinib and ctla4 blockade



. Balachandran VP, et al, Nature Med, 2012

Overview IO strategies in GIST



Arshad J et a, Cancers, 2021

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Cytokine based thrapy

Cancer Immunol Immunother (2012) 61:1113–1124
DOI 10.1007/s00262-011-1185-1

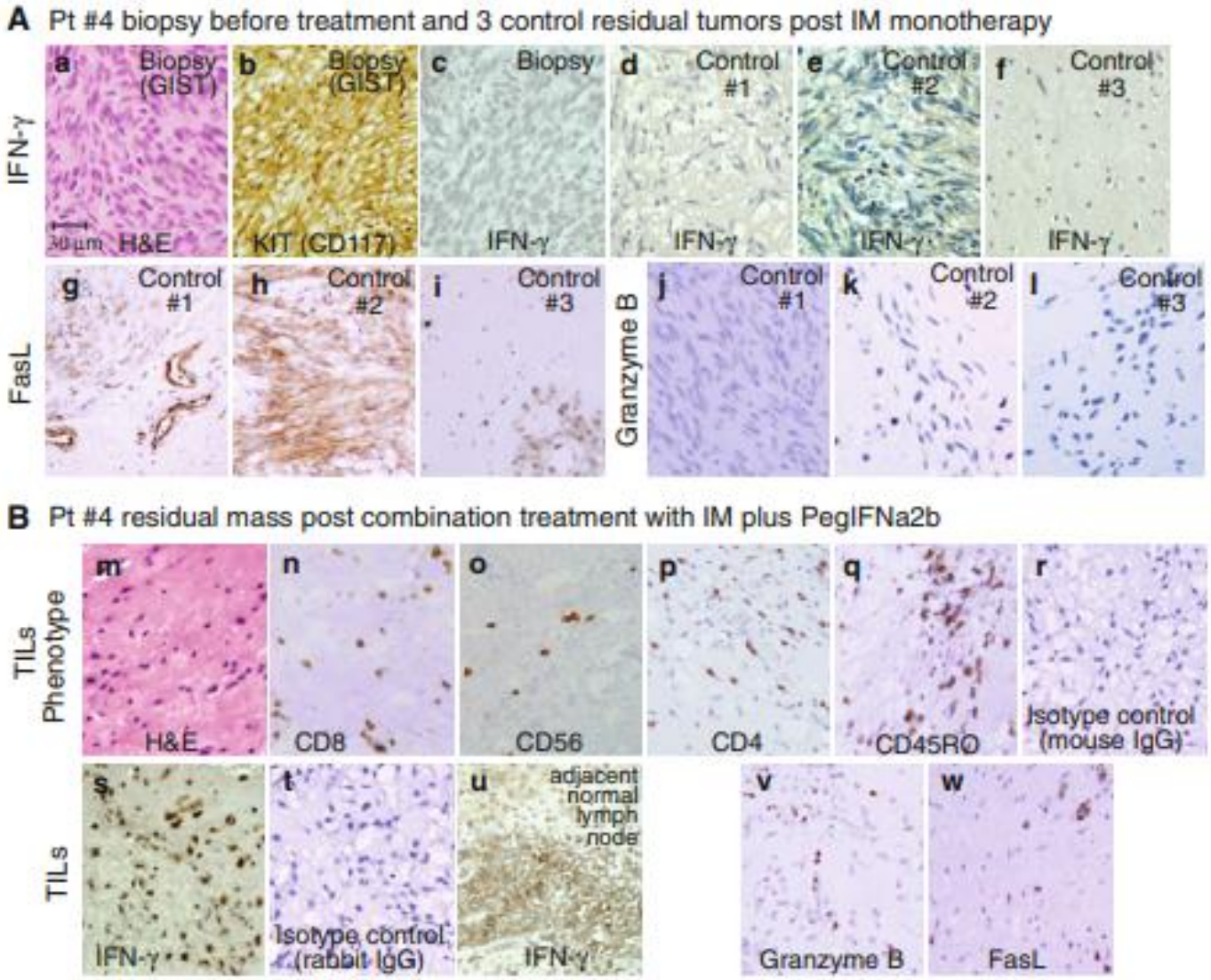
ORIGINAL ARTICLE

Exploiting antitumor immunity to overcome relapse and improve remission duration

Lei L. Chen · Xinjian Chen · Haesun Choi · Hongxun Sang · Leo C. Chen · Hongbo Zhang · Launce Gouw · Robert H. Andtbacka · Benjamin K. Chan · Christopher K. Rodesch · Arnie Jimenez · Pedro Cano · Kimberly A. Jones · Caroline O. Oyedeji · Tom Martins · Harry R. Hill · Jonathan Schumacher · Carlynn Willmore · Courtney L. Scaife · John H. Ward · Kathryn Morton · R. Lor Randall · Alexander J. Lazar · Shreyaskumar Patel · Jonathan C. Trent · Marsha L. Frazier · Patrick Lin · Peter Jensen · Robert S. Benjamin

- Th1 adaptive cell-mediated immunity (Th1 response) signified by interferon-γ (IFN- γ) secretion plays a major role in anti-tumor immunity
- Pre-clinical data:
  - Immune tolerant lymphocytes extracted in vivo from a rx- refractory, synovial sarcoma pt
  - Presenting an antigen cocktail to DCs, produced IL12 (inducer of a Th1 response in vivo), stimulating the CD8 cells – demonstrated anti-tumor activity in vitro
- Study design: Peginterferon α-2b with imatinib for treatment naïve stage III/IV gastrointestinal stromal tumor
- 8 patients enrolled, CBR = 100%, one individual experienced a pathologic CR

Correlatives



Memorial Sloan Kettering Cancer Center

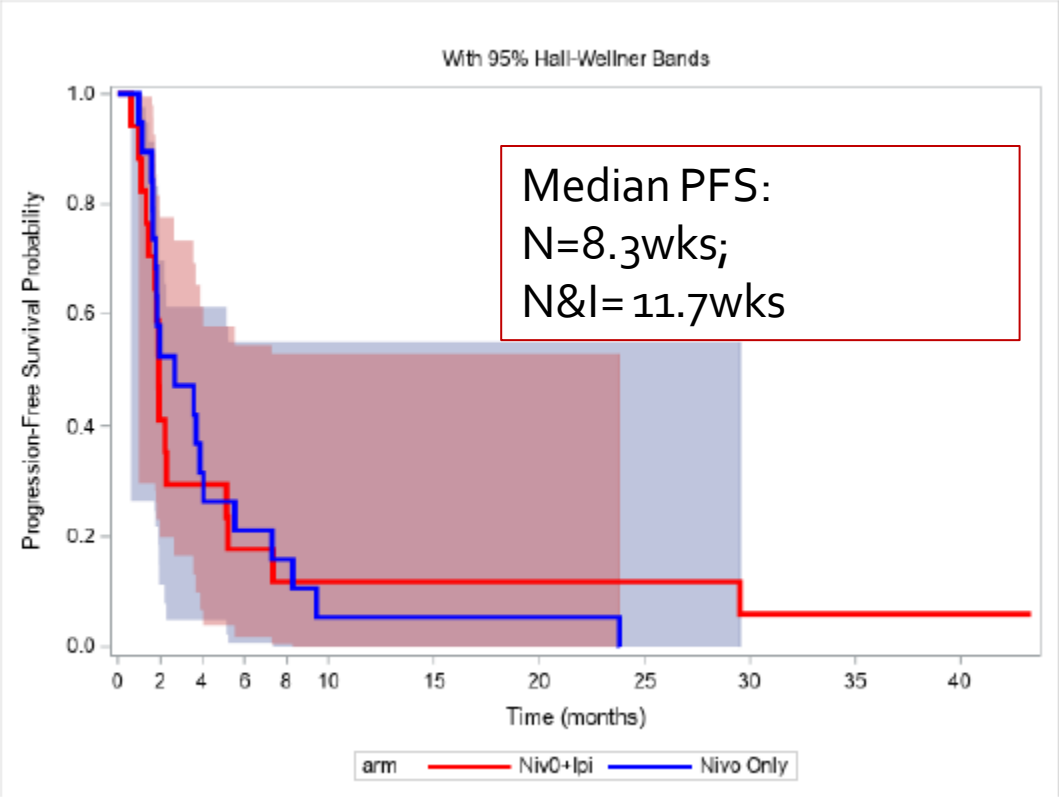
Memorial Sloan Kettering Cancer Center

Immune Checkpoint Blockade

Phase II study of Nivolumab +/- Ipilimumab in Advanced GIST

- Advanced GIST
  Imatinib refractory
- Randomized 1:1
- N (240mg Q2wks) or
  N + I (240 mg Q2wks + 1mg/kg Q6wks)
- Primary endpoint – ORR by RECIST 1.1

Arm	CR	PR	SD	PD	CBR
Nivolumab (n=19)	0/19	0/19	10/19	9/19	52.6%
Nivolumab + Ipilimumab(n=16)*	1/16	0/16	4/16	9/16	31.3%



Singh A., et al, Clin Cancer Res, 2021

Memorial Sloan Kettering Cancer Center

Alliance A091401: Nivo +/- Ipi, GIST Expansion Cohort

- 18 patients enrolled – 9 pts in each study arm
- Prior lines of therapy ≥3: Nivo (80%); Nivo/Ipi (46%)
- ORR at 6mo: 0%
- mPFS: Nivo monotherapy – 1.5mo, Nivo/Ipi – 2.9mo
- Grade 3 TRAES: Nivo (10%) vs Nivo/Ipi (46%)

Chen JL, et al, ASCO Annual Meeting, 2020

ONCOIMMUNOLOGY
2020, VOL. 9, NO. 1, e1710064 (6 pages)
https://doi.org/10.1080/2162402X.2019.1710064

Taylor & Francis
Taylor & Francis Group

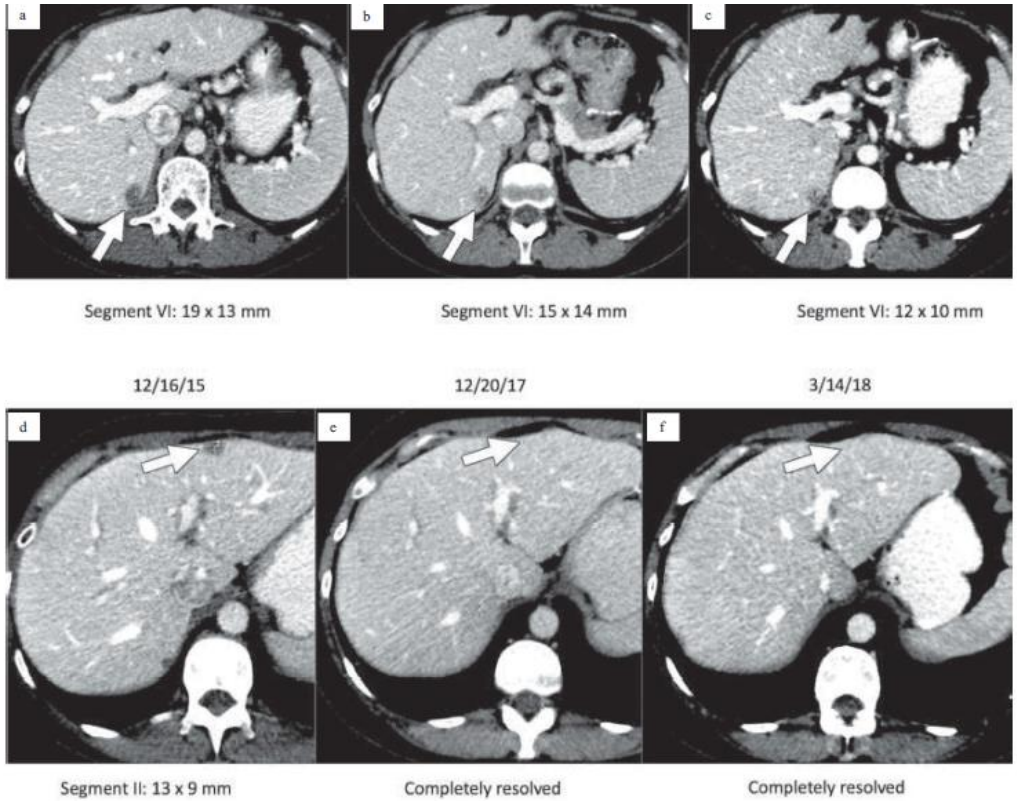
BRIEF REPORT

OPEN ACCESS Check for updates

Durable tumor regression in highly refractory metastatic *KIT/PDGFRA* wild-type GIST following treatment with nivolumab

Brett A. Schroeder [a,b], Karan Kohli[a], Ryan B. O'Malley[c], Theresa S. Kim[a], Robin L. Jones[d], Robert H. Pierce[a], and Seth M. Pollack[a,e]

[a]Clinical Research Division, Fred Hutchison Cancer Research Center, Seattle, WA, USA; [b]Department of Medicine, Virginia Mason Medical Center, Seattle, WA, USA; [c]Department of Radiology, University of Washington, Seattle, WA, USA; [d]Sarcoma Unit, Royal Marsden Hospital and Institute of Cancer Research, London, UK; [e]Department of Medicine, University of Washington, Seattle, WA, USA



Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Immune Checkpoint Blockade Combination Therapies

Memorial Sloan Kettering Cancer Center

ICB & Chemotherapy

JAMA Oncology | Brief Report

Use of PD-1 Targeting, Macrophage Infiltration, and IDO Pathway Activation in Sarcomas

A Phase 2 Clinical Trial

Maud Toulmonde, MD; Nicolas Penel, MD, PhD; Julien Adam, MD, PhD; Christine Chevreau, MD; Jean-Yves Blay, MD, PhD; Axel Le Cesne, MD; Emmanuelle Bompas, MD; Sophie Piperno-Neumann, MD; Sophie Cousin, MD; Thomas Grellety, MD; Thomas Ryckewaert, MD; Alban Bessede, PhD; François Ghiringhelli, MD, PhD; Marina Pulido, MSc; Antoine Italiano, MD, PhD

Treatment regimen:
Metronomic cyclophosphamide (50mg od) & pembro 200mg q 3 wk

Table. Characteristics of 57 Patients

Characteristic	No. (%)
Sex	
Male	33 (58)
Female	24 (42)
Age, median, (range), y	59.5 (18.5-84.0)
ECOG PS	
0	21 (37)
1	33 (58)
ND	3 (5)
Histological subtype	
Leiomyosarcoma	15 (27)
UPS	16 (28)
Others[a]	16 (28)
GIST	10 (18)
Stage	
Locally advanced	9 (16)
Metastatic	48 (84)
Prior line(s) of chemotherapy	
0	2 (3)
1	13 (23)
2	22 (39)
>2	20 (35)

Efficacy:

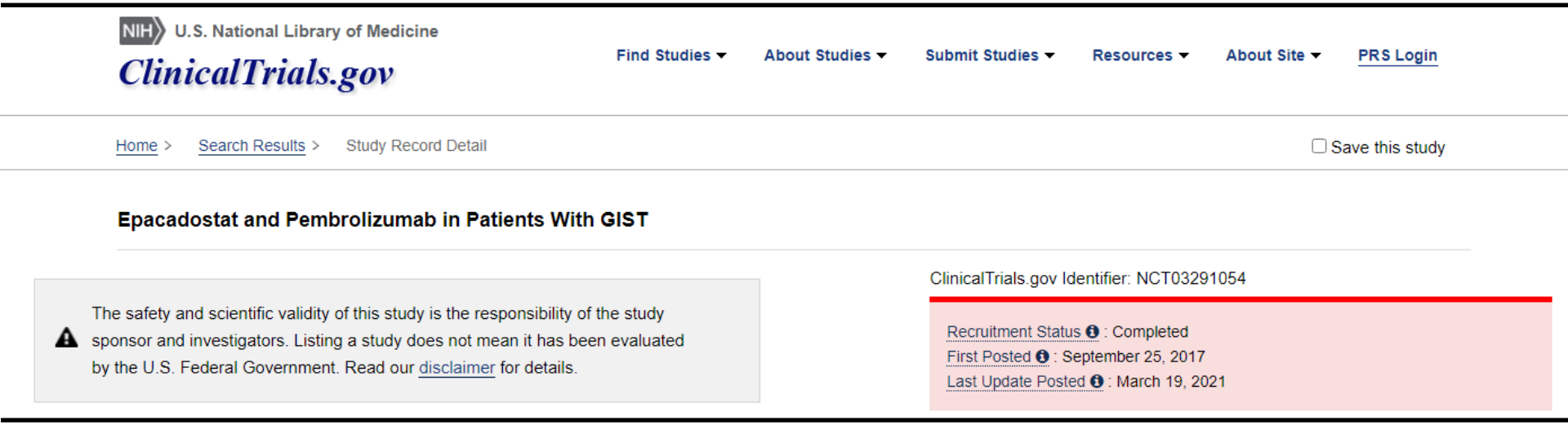
- 6mo PFS rate = 11.1%, mPFS = 1.4mo
- Best ORR= SD (30%), PD = 60%

Correlatives:

- **PDL1 +ve ≥ 1% tumor cells, n=2**
- **PDL1 +ve ≥ 1% immune cells, 43%**
- **Immune cell infiltrate: predominance of M2 macrophages** (CD163 to (CD68+CD163) cell ratio above the median = 38% in GIST)
- **IDO1 expression by immune cells 63% (macrophages)**
- **Kynurenine to tryptophan plasma ratio increased on treatment and correlated with higher density IDO1 expression**

Memorial Sloan Kettering Cancer Center

Pembrolizumab & IDO1 inhibition in GIST



NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾ PRS Login

Home > Search Results > Study Record Detail

☐ Save this study

Epacadostat and Pembrolizumab in Patients With GIST

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03291054

Recruitment Status ⓘ : Completed
First Posted ⓘ : September 25, 2017
Last Update Posted ⓘ : March 19, 2021

Memorial Sloan Kettering Cancer Center

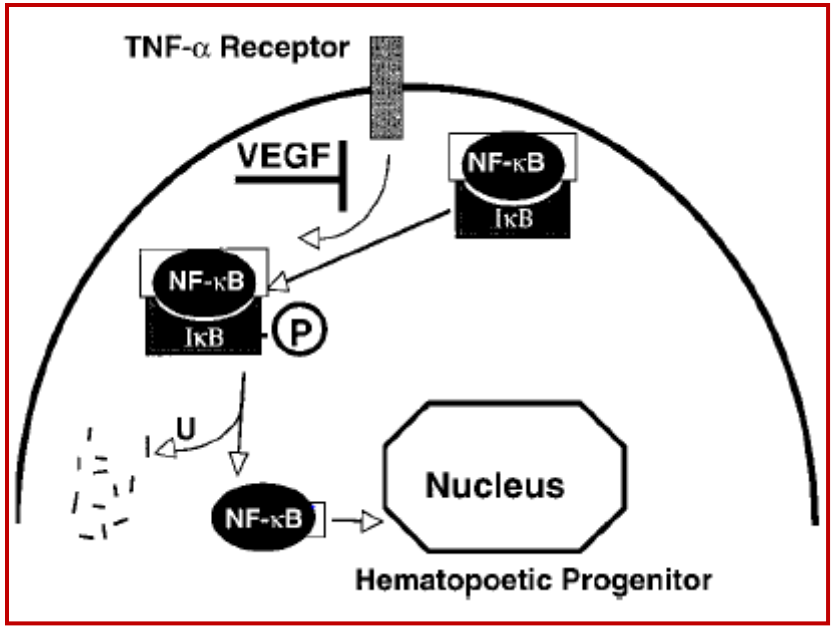
Memorial Sloan Kettering Cancer Center

ICB & TKI

VEGF as a Mediator of Tumor Immune Escape

- **VEGF causes a defect in the functional maturation of dendritic cells (DC)/antigen presenting cells (APC) from progenitors**

- **VEGF is a key factor produced by solid tumors that inhibits recognition and destruction of tumor cells by the immune system**

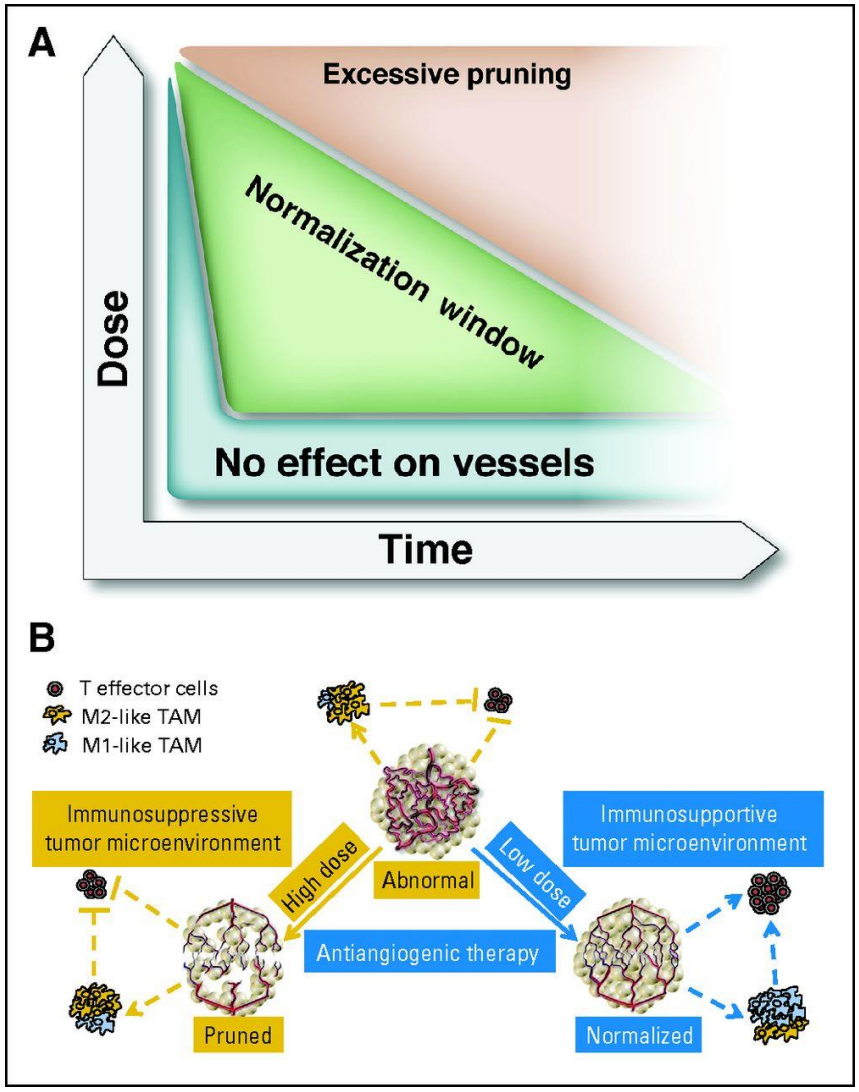


VEGF inhibits induction of NF-κB by TNF-α. The inhibitory effects of VEGF impact phosphorylation and degradation of IκB.

Ohm JE, Immunol Res 2001

Memorial Sloan Kettering Cancer Center

NORMALISATION HYPOTHESIS



(A) Normalization window is dose dependent. Higher doses can also lead to adverse effects by destroying too much vasculature. As a result no additional treatments will penetrate the tumor or other growth factors will surge to compensate for VEGF inhibition and lead to resistance of anti-angiogenic therapy and promote re-growth of abnormal vasculature

(B) Vascular normalization produced by anti-angiogenic therapy can convert the immunosuppressive microenvironment of a tumor to an immunostimulatory microenvironment and improve the outcome of various immunotherapies by increasing flow and oxygenation.

Memorial Sloan Kettering Cancer Center

©2013 by American Society of Clinical Oncology

Rakesh K. Jain JCO 2013;31:2205-2218

CLINICAL CANCER RESEARCH

Cancer Therapy: Clinical

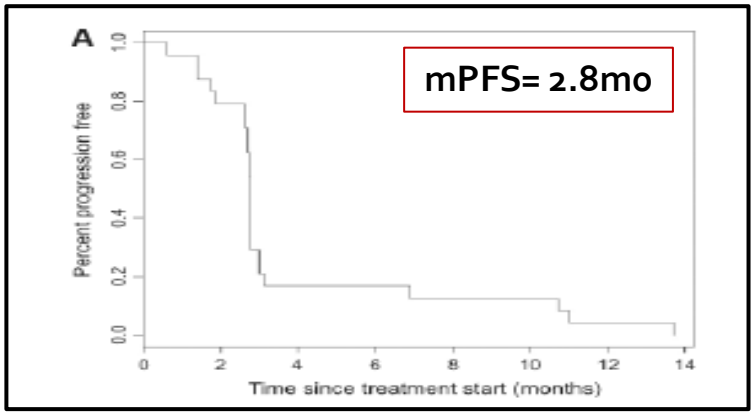
Combined KIT and CTLA-4 Blockade in Patients with Refractory GIST and Other Advanced Sarcomas: A Phase Ib Study of Dasatinib plus Ipilimumab

Sandra P. D'Angelo, Alexander N. Shoushtari, Mary Louise Keohan, Mark A. Dickson, Mrinal M. Gounder, Ping Chi, Jennifer K. Loo, Leigh Gaffney, Lee Schneider, Zarine Patel, Joseph Patrick Erinjeri, Mark J. Bluth, Ana Sjoberg, Howard Streicher, Naoko Takebe, Li-Xuan Qin, Cristina Antonescu, Ronald P. DeMatteo, Richard D. Carvajal, and

	n = 20
Gender (M:F)	13:7
Age (median, range)	54 (40–75)
ECOG (median, range)	0 (0–1)
Prior treatments (median, range)	3 (1–8)
Primary site	
Gastric	8
Small bowel	12
Mutations[a]	
KIT exon 9 (502_503 duplication)	
KIT exon 9 (S501)	
KIT exon 9 (6bp deletion) and KIT exon 17 (D820Y)	
KIT exon 9 (6bp insertion) and KIT exon 14 (N680K)	
KIT exon 11 (9bp insertion/deletion)	
KIT exon 11 (L575P) and KIT exon 9 (6bp insertion)	
KIT exon 11 (point mutation) and exon 11 (21 bp in frame deletion)	
KIT exon 11 (W557R) and KIT exon 11 (G565V)	
KIT exon 11 (6bp deletion) and KIT exon 13 (V654A)	
KIT exon 11 (L576P) and KIT exon 13 (V654A)	
KIT exon 11 (WK557) and KIT exon 13 (V654A)	
KIT exon 11 (6bp deletion) and KIT exon 17 (Y823D)	
KIT exon 11 (6bp deletion) and KIT exon 17 (D820Y)	
KIT exon 13 (V654A)	
KIT exon 13 (V654A)	
PDGFR exon 18 D842V	
PDGFR exon 18 D842V	
mTOR exon 30 and SDHB exon 2	
NF1 (deletion), TERT (amplification), and SDHA (amplification)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; F, female; M, male.

[a]Missing for 1 patient.



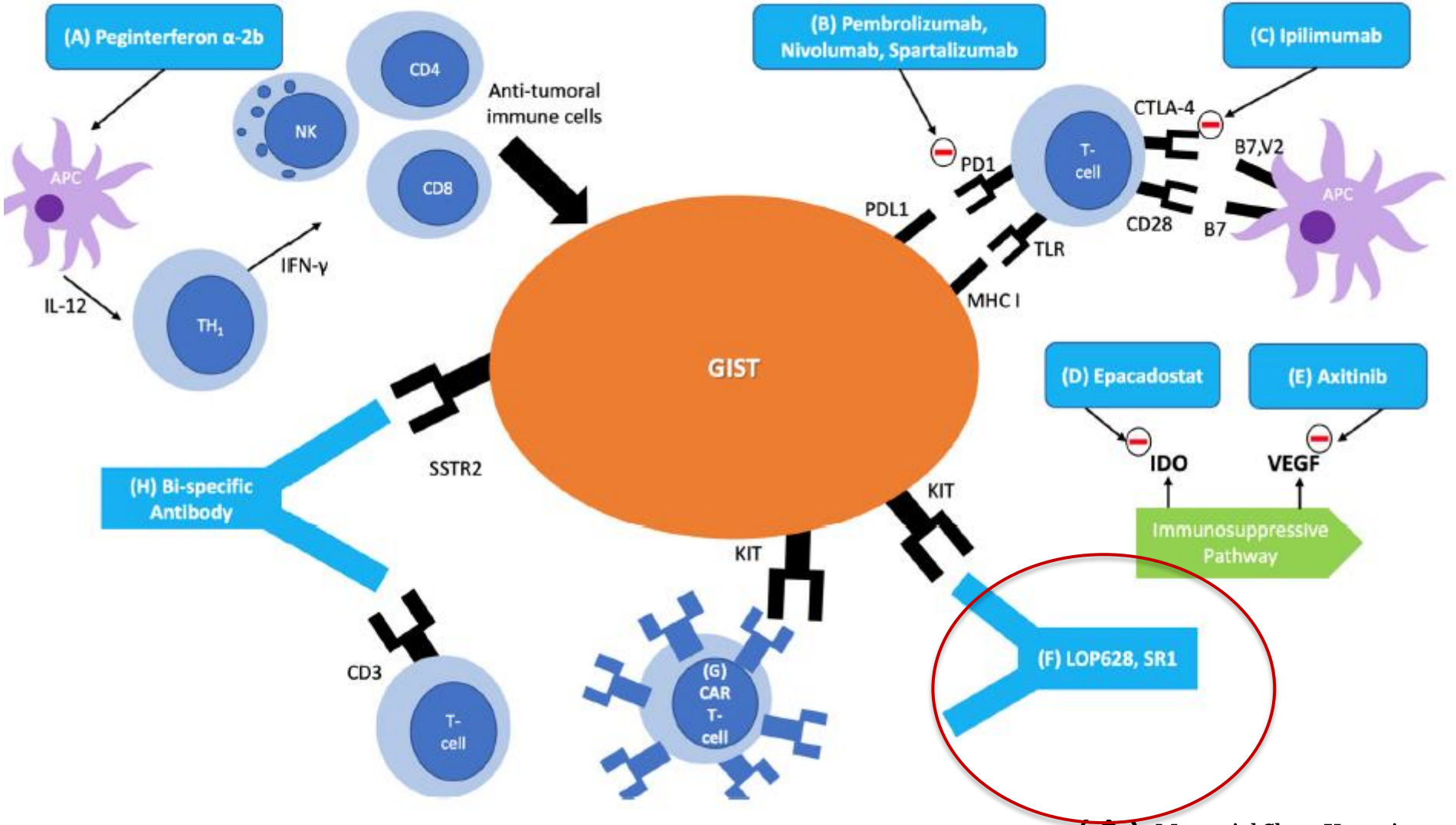
Parameter (*n* = 24)	Dose escalation (*n* = 8/12 evaluable)	Dose expansion (*n* = 4/6 evaluable)	"B" dose escalation (*n* = 6/6 evaluable)
Best ORR by RECIST			
CR/PR	0	0	0
SD	3	2	4
PD	5	2	2
Best ORR by irRC			
CR/PR	0	0	0
SD	6	2	3
PD	2	2	3
GIST patients only (*n* = 17)	*n* = 5/7 evaluable	4/6 evaluable	4/4 evaluable
Best ORR by Choi			
CR/PR	3	1	3
SD	1	2	0
PD	1	1	1

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

ICB & TKIs: Ongoing clinical trials

- NCT03609424: **PDR001 Plus Imatinib** for Metastatic or Unresectable GIST
- NCT01738139: **Ipilimumab and Imatinib Mesylate** in Advanced Cancer
- NCT04258956: A Study of **Avelumab In Combination With Axitinib** in Patients With Unresectable/Metastatic Gastrointestinal Stromal Tumor After Failure of Standard Therapy (AXAGIST)
- NCT03475953 : A Phase I/II Study of **Regorafenib Plus Avelumab** in Solid Tumors (REGOMUNE)

Overview IO strategies in GIST: Novel Approaches



Arshad J et a, Cancers, 2021

Memorial Sloan Kettering Cancer Center

ADC directed against KIT: LOP628

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Preclinical Antitumor Activity of a Novel Anti–c-KIT Antibody–Drug Conjugate against Mutant and Wild-type c-KIT–Positive Solid Tumors

Tinya Abrams[1], Anu Connor[2], Christie Fanton[1], Steven B. Cohen[3], Thomas Huber[4], Kathy Miller[1], E. Erica Hong[5], Xiaohong Niu[1], Janine Kline[1], Marjorie Ison-Dugenny[1], Sarah Harris[3], Dana Walker[2], Klaus Krauser[3], Francesco Galimi[3], Zhen Wang[1], Majid Ghoddusi[1], Keith Mansfield[2], Si Tuen Lee-Hoeflich[2], Jocelyn Holash[1], Nancy Pryer[1], William Kluwe[6], Seth A. Ettenberg[2], William R. Sellers[2], Emma Lees[1], Paul Kwon[1], Judith A. Abraham[1], and Siew C. Schleyer[1]

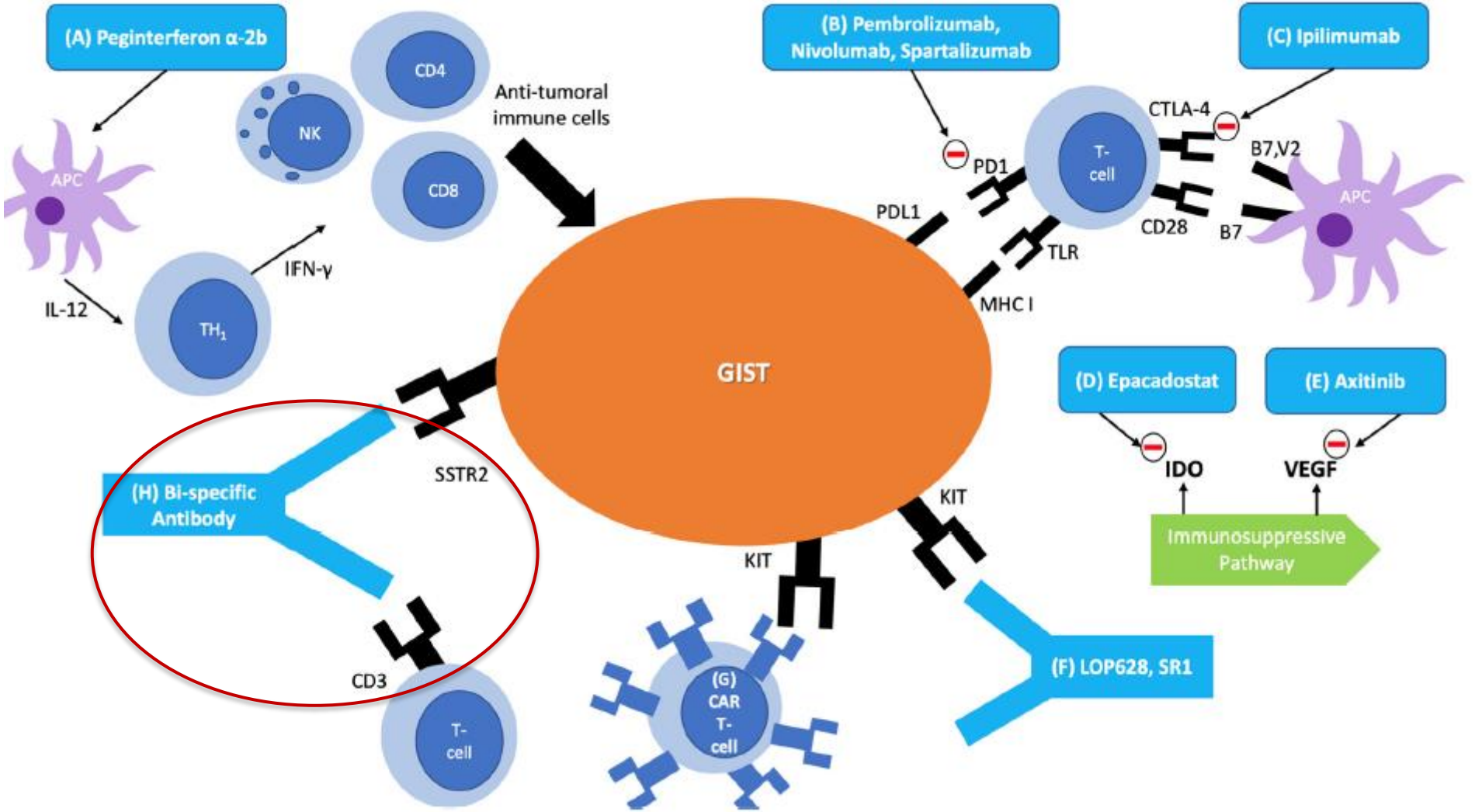
Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Mechanistic Insights of an Immunological Adverse Event Induced by an Anti-KIT Antibody Drug Conjugate and Mitigation Strategies

Lawrence L'Italien[1], Olivia Orozco[1], Tinya Abrams[1], Lisa Cantagallo[1], Anu Connor[1], Jayesh Desai[4], Hilmar Ebersbach[2], Hans Gelderblom[5], Keith Hoffmaster[1], Emma Lees[1], Heiko Maacke[2], Siew Schleyer[3], Darko Skegro[2], and Si Tuen Lee-Hoeflich[1]

Overview IO strategies in GIST: Novel Approaches



Arshad J et a, Cancers, 2021

Memorial Sloan Kettering Cancer Center

Bi-specific antibody targeting CD3 & SSTR2

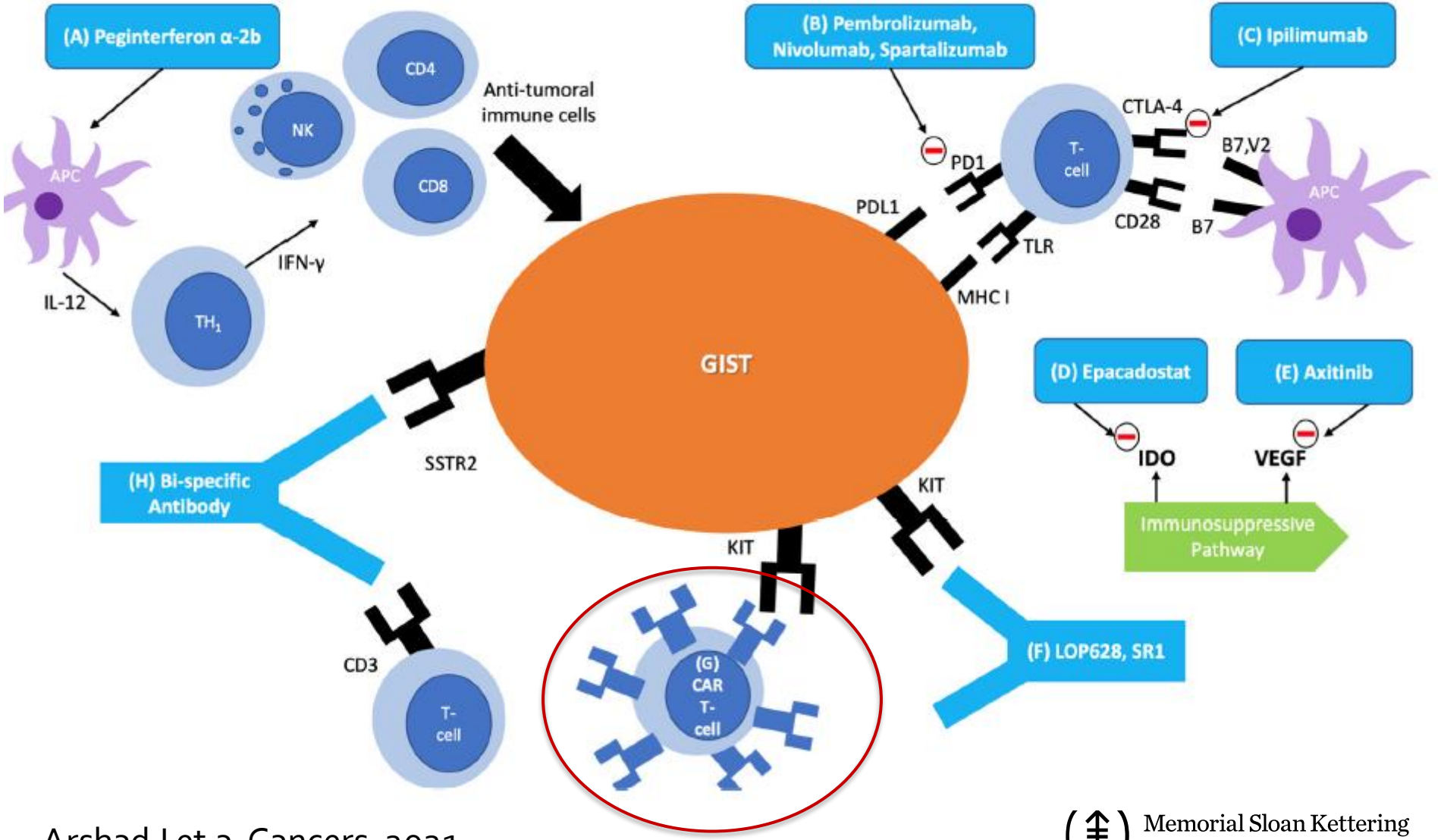
Tidutamab (SSTR2 x CD3)

Ongoing Phase 1 clinical trial for the treatment of neuroendocrine tumors (NET).

Tidutamab (previously XmAb18087) is a bispecific antibody that engages the immune system against tumors by binding to somatostatin receptor 2 (SSTR2) and CD3. Xencor's XmAb® Bispecific Fc Domain serves as the scaffold for these two antigen binding domains and confers long circulating half-life, stability and ease of manufacture on tidutamab. Engagement of CD3 by tidutamab activates T cells for highly potent and targeted killing of SSTR2-expressing tumor cells.

High SSTR2 expression in GIST – 87%

Overview IO strategies in GIST: Novel Approaches



Arshad J et a, Cancers, 2021

Memorial Sloan Kettering Cancer Center

Chimeric Antigen Receptor T Cell Therapy

Katz *et al. Journal of Translational Medicine* 2013, **11**:46
http://www.translational-medicine.com/content/11/1/46

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Anti-KIT designer T cells for the treatment of gastrointestinal stromal tumor

Steven C Katz[1*], Rachel A Burga[1], Seema Naheed[1], Lauren A Licata[1], Mitchell Thorn[1], Doreen Osgood[1], Cang T Nguyen[1], N Joseph Espat[1], Jonathan A Fletcher[3] and Richard P Junghans[2]

Leukemia (2020) 34:2688–2703
https://doi.org/10.1038/s41375-020-0818-9

ARTICLE

Immunotherapy

Anti-human CD117 CAR T-cells efficiently eliminate healthy and malignant CD117-expressing hematopoietic cells

Renier Myburgh[1] · Jonathan D. Kiefer[1,2] · Norman F. Russkamp[1] · Chiara F. Magnani[1] · Nicolás Nuñez[3] · Alexander Simonis[1] · Surema Pfister[1] · C. Matthias Wilk[1] · Donal McHugh[3] · Juliane Friemel[4] · Antonia M. Müller[1] · Burkhard Becher[3] · Christian Münz[3] · Maries van den Broek[3] · Dario Neri[2] · Markus G. Manz[1]

Memorial Sloan Kettering Cancer Center

Summary

- GIST has an immunosuppressive immune microenvironment
- Immunotherapy strategies in GIST
  - Target various aspect of the immune cascade
  - Aim to convert immunosuppressive tumor microenvironment towards an immune stimulated one
  - Combination approaches may be necessary
- Several IO studies in GIST are currently in progress
- Correlative data will be important to inform future IO trial design in GIST