Immunotherapy & GIST

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Disclosures

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  – Kartos, Exicure

• Employment – relative:
  – Daiichi-Sankyo
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
  Depends on its ability to block KIT signaling
  Synergy between imatinib and ctla4 blockade

Overview IO strategies in GIST

Arshad J et al, Cancers, 2021
Cytokine based therapy
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. Oyediji · Tom Martins · Harry R. Hill · Jonathan Schumacher · Carlynn Willmore · Courtney L. Scaife · John H. Ward · Kathryn Morton · R. Lor Randall · Alexander J. Lazar · Shreyas Kumar 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

A. Pt #4 biopsy before treatment and 3 control residual tumors post IM monotherapy
- a. Biopsy (GIST) with IFN-γ staining
- b. Biopsy (GIST) with KIT (CD117) staining
- c. Biopsy with IFN-γ staining
- d. Control #1 with IFN-γ staining
- e. Control #2 with IFN-γ staining
- f. Control #3 with IFN-γ staining
- g. Control #1 with FasL staining
- h. Control #2 with FasL staining
- i. Control #3 with FasL staining
- j. Control #1 with Granzyme B staining
- k. Control #2 with Granzyme B staining
- l. Control #3 with Granzyme B staining
- m. Control #1 with TILs Phenotype H&E staining
- n. Control #2 with CD8 staining
- o. Control #3 with CD56 staining
- p. Control #1 with CD4 staining
- q. Control #2 with CD45RO staining
- r. Control #3 with Isotype control (mouse IgG) staining
- s. Control #1 with TILs IFN-γ staining
- t. Control #2 with Isotype control (rabbit IgG) staining
- u. Control #3 with IFN-γ staining
- v. Isotype control (rabbit IgG) with Granzyme B staining
- w. Isotype control (rabbit IgG) with FasL staining

B. Pt #4 residual mass post combination treatment with IM plus PegIFNa2b
- m. TILs Phenotype H&E staining
- n. CD8 staining
- o. CD56 staining
- p. CD4 staining
- q. CD45RO staining
- r. Isotype control (mouse IgG) staining
- s. IFN-γ staining
- t. Isotype control (rabbit IgG) staining
- u. adjacent normal lymph node staining
- v. Granzyme B staining
- w. FasL staining

Memorial Sloan Kettering Cancer Center
Immune Checkpoint Blockade
Phase II study of Nivolumab +/- Ipilimumumab 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


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<thead>
<tr>
<th>Arm</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>CBR</th>
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<tr>
<td>Nivolumab (n=19)</td>
<td>0/19</td>
<td>0/19</td>
<td>10/19</td>
<td>9/19</td>
<td>52.6%</td>
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<tr>
<td>Nivolumab + Ipilimumab (n=16)*</td>
<td>1/16</td>
<td>0/16</td>
<td>4/16</td>
<td>9/16</td>
<td>31.3%</td>
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Median PFS: N=8.3wks; N&I=11.7wks
Alliance A091401: Nivo +/- Ipilimumab, 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
Durable tumor regression in highly refractory metastatic KIT/PDGFRα 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

Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Department of Medicine, Virginia Mason Medical Center, Seattle, WA, USA; Department of Radiology, University of Washington, Seattle, WA, USA; Sarcoma Unit, Royal Marsden Hospital and Institute of Cancer Research, London, UK; Department of Medicine, University of Washington, Seattle, WA, USA.

Segment VI: 19 x 13 mm
Segment VI: 15 x 14 mm
Segment VI: 12 x 10 mm

12/16/15
12/20/17
3/14/18

Segment II: 13 x 9 mm
Completely resolved
Completely resolved
Immune Checkpoint Blockade Combination Therapies
ICB & Chemotherapy
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 Bompaes, 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

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
Pembrolizumab & IDO1 inhibition in GIST

ClinicalTrials.gov Identifier: NCT03201054

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.

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

(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.
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose escalation (n = 8/12 evaluable)</th>
<th>Dose expansion (n = 6/6 evaluable)</th>
<th>''B'' dose escalation (n = 6/6 evaluable)</th>
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<tbody>
<tr>
<td>Best ORR by RECIST</td>
<td>CR/PR</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6</td>
<td>2</td>
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<tr>
<td></td>
<td>PD</td>
<td>2</td>
<td>3</td>
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<tr>
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<td>SD</td>
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<tr>
<td></td>
<td>PD</td>
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</table>

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

*Missing for 1 patient.
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 al, Cancers, 2021
Preclinical Antitumor Activity of a Novel Anti-c-KIT Antibody-Drug Conjugate against Mutant and Wild-type c-KIT-Positive Solid Tumors

Mechanistic Insights of an Immunological Adverse Event Induced by an Anti-KIT Antibody Drug Conjugate and Mitigation Strategies
Overview IO strategies in GIST: Novel Approaches

Arshad J et al, Cancers, 2021

Diagram showing various immune cell interactions and targeting strategies for GIST (Gastrointestinal Stump Tumor).

Key points:
- (A) Peginterferon α-2b
- (B) Pembrolizumab, Nivolumab, Spartializumab
- (C) Iplilimumab
- (D) Epacadostat
- (E) Axitinib
- (F) LOP628, SR1

Immune cells and molecular targets: CD4, CD8, NK, TH1, APC, IFN-γ, IL-12, SSTR2, T-cell, CAR T-cell, KIT, PD1, PDL1, CTLA-4, B7, CD28, TLR, MHC I, IDO, VEGF.
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
Anti-KIT designer T cells for the treatment of gastrointestinal stromal tumor

http://www.translational-medicine.com/content/11/1/46

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

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