Building New Paradigms: Trends in Combination Therapy and Pivotal Ongoing Trials

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Talk Outline

- Background
- Tyrosine kinase inhibitors: beyond Imatinib, Sunitinib and Regorafenib
- Mechanisms of resistance
- Combination therapy: Promise and pitfalls
- Novel therapies in trial for rare subtypes:
  - PDGFR mutations (D842V)
  - BRAF mutations
  - SDH mutations
  - NTRK fusions
First described by Mazur and Clark.

CD34 relatively specific marker.
(Miettinen et al. Am J Surg Path)
Similarities between GIST cells and Interstitial Cells of Cajal.

2 major discoveries.
(Hirota et al Science)
- KIT staining 94% of GIST
- Activating mutations in KIT gene (5 out of 6)

FDA Approval IMATINIB

FDA Approval SUNITINIB

FDA Approval REGORAFENIB

Accelerated FDA approval IMATINIB
**KIT and PDGFRA Mutations**

**KIT**
- Exon 9 (18.1%)
- Exon 11 (66.9%)
- Exon 13 (1.6%)
- Exon 17 (1.6%)

**PDGFRA**
- Exon 12 (0.8%)
- Exon 18 (3.9%)

Overall mutation frequency: 85-90%

Normal KIT Signaling

- The KIT kinase domain activates a substrate protein.
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the KIT kinase domain.
- This prevents substrate phosphorylation and signaling.
- A lack of signaling inhibits proliferation and survival.

Non-KIT/ PDGFR GIST (Wild Type) (10-15%)

- BRAF mutation (V600E exon 15)
  

- IGF-1R
  
  Godwin AK et al. JCO 2008, Janeway et al In J Cancer 2010

- Succinate Dehydrogenase

- Alternate mutations (AKT/PTEN/TRK)...
  
  Janeway et al. JCO 2010,
Majority are Sporadic

Associated Syndromes

- Familial GIST syndrome  
  Nishida et al. Nat Genet 1998

- Neurofibromatosis-1  
  Fuller CE et al. Histopathology 1991

- Carney Triad  
  Carney et al. NEJM 1977

- Carney Stratakis Syndrome  
The advent of targeted therapy has dramatically altered the prognosis

Pre- Imatinib
- Localized disease: 5-year survival rate < 50%.
- Metastatic GIST: median survival was 5-12 months

Era of targeted therapy (post 2001)
- Localized disease: 5-year survival rate > 80 %
- Metastatic GIST: median survival ≥ 58 months

DeMatteo et al. JCO 2005; Joensuu et al. ASCO 2011
## Overall Survival Estimates for Advanced GIST patients on S0033 treated with imatinib

<table>
<thead>
<tr>
<th>Survival (years)</th>
<th>OS Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>46%</td>
<td>43% - 50%</td>
</tr>
<tr>
<td>6</td>
<td>39%</td>
<td>36% - 43%</td>
</tr>
<tr>
<td>7</td>
<td>35%</td>
<td>31% - 38%</td>
</tr>
<tr>
<td>8</td>
<td>31%</td>
<td>28% - 35%</td>
</tr>
<tr>
<td>9</td>
<td>26%</td>
<td>23% - 30%</td>
</tr>
<tr>
<td>10</td>
<td>22%</td>
<td>19% - 26%</td>
</tr>
</tbody>
</table>

Presented By George Demetri at 2014 ASCO Annual Meeting
S0033 Overall Survival by GIST Genotype – 2014 data

Presented By George Demetri at 2014 ASCO Annual Meeting

Significantly worse OS for KIT exon 9 mutant vs. KIT exon 11 mutant

- KIT exon 11
  - N = 262
  - Deaths = 201
  - Median OS (months) = 66

- NO MUTATION
  - N = 67
  - Deaths = 47
  - Median OS (months) = 40

- KIT exon 9
  - N = 32
  - Deaths = 30
  - Median OS (months) = 38

\[ P = 0.001 \]
\[ P = 0.047 \]
## Analysis of Post-Progression Therapies (i.e. after progression on imatinib)

### Table: Therapies and Genotypes

<table>
<thead>
<tr>
<th></th>
<th>All Long-Term Survivors (n=137)</th>
<th>With Known GIST Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EXON 11 (n=70)</td>
</tr>
<tr>
<td>Any Additional Therapy</td>
<td>70 (51%)</td>
<td>36 (51%)</td>
</tr>
<tr>
<td>Systemic Therapy</td>
<td>54 (39%)</td>
<td>28 (40%)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>41 (30%)</td>
<td>22 (31%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>16 (12%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Other Agents</td>
<td>42 (31%)</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>41 (30%)</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>Metastasectomy</td>
<td>29 (21%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Other Surgery</td>
<td>18 (13%)</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Radiofrequency Ablation</td>
<td>10 (7%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>6 (4%)</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>
Sunitinib Malate (SU11248)

- Small-molecule receptor tyrosine kinase inhibitor
- Inhibits all VEGFRs, PDGFR-A, PDGFR-B, c-KIT, and FLT-3
- Oral administration
- Both antitumor and antiangiogenic activity
- FDA approved January 26, 2006 for treatment of advanced GIST
Sunitinib Improves PFS and OS Compared to Placebo

Potential for Disease Control with TKI Therapy based on Site of Mutation

<table>
<thead>
<tr>
<th>TKI</th>
<th>Primary mutations</th>
<th>Secondary mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KIT exon9</td>
<td>KIT exon11</td>
</tr>
<tr>
<td>Imatinib</td>
<td>↓</td>
<td>*</td>
</tr>
<tr>
<td>Sunitinib following Imatinib</td>
<td>↑</td>
<td>ND</td>
</tr>
</tbody>
</table>

↓: Low potential. ↑: High potential. ND: No data.
* Less likely to respond to low dose therapy

Somaiah, von Mehren. Hem Onc Clinics 2009
Randomized Phase III Trial of Regorafenib in Patients with Metastatic and/or Unresectable GIST Progressing Despite Prior Treatment with at Least Imatinib and Sunitinib: GRID Trial

Demetri GD et al. *Proc ASCO* 2012; LBA 10008.
<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>199</td>
<td>0.27 (0.19-0.39)</td>
</tr>
<tr>
<td>Anticancer line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>113</td>
<td>0.23 (0.14-0.37)</td>
</tr>
<tr>
<td>Fourth or more</td>
<td>86</td>
<td>0.31 (0.18-0.54)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>47</td>
<td>0.30 (0.15-0.62)</td>
</tr>
<tr>
<td>Rest of world</td>
<td>152</td>
<td>0.24 (0.16-0.37)</td>
</tr>
<tr>
<td>North America</td>
<td>36</td>
<td>0.42 (0.19-0.92)</td>
</tr>
<tr>
<td>Not North America</td>
<td>163</td>
<td>0.22 (0.15-0.34)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>127</td>
<td>0.31 (0.20-0.48)</td>
</tr>
<tr>
<td>Women</td>
<td>72</td>
<td>0.18 (0.09-0.34)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>136</td>
<td>0.30 (0.19-0.46)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>63</td>
<td>0.15 (0.08-0.30)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>112</td>
<td>0.29 (0.18-0.46)</td>
</tr>
<tr>
<td>25 to &lt;30 kg/m²</td>
<td>56</td>
<td>0.24 (0.12-0.48)</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>22</td>
<td>0.19 (0.06-0.61)</td>
</tr>
<tr>
<td>ECOG score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>110</td>
<td>0.22 (0.14-0.37)</td>
</tr>
<tr>
<td>1</td>
<td>89</td>
<td>0.30 (0.18-0.51)</td>
</tr>
<tr>
<td>Duration of imatinib treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>22</td>
<td>0.50 (0.17-1.73)</td>
</tr>
<tr>
<td>≥6 to &lt;18 months</td>
<td>33</td>
<td>0.19 (0.07-0.55)</td>
</tr>
<tr>
<td>≥18 months</td>
<td>144</td>
<td>0.24 (0.15-0.36)</td>
</tr>
<tr>
<td>Mutation biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT exon 11 mutation</td>
<td>51</td>
<td>0.21 (0.10-0.46)</td>
</tr>
<tr>
<td>KIT exon 9 mutation</td>
<td>15</td>
<td>0.24 (0.07-0.88)</td>
</tr>
</tbody>
</table>
## Resection Of Progressive Or Residual GIST After Imatinib

<table>
<thead>
<tr>
<th></th>
<th>Surgical CR</th>
<th>12-mo. PFS</th>
<th>12-mo. OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stable Disease</strong></td>
<td>78%</td>
<td>80%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Limited Progression</strong></td>
<td>25%</td>
<td>33%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Generalized Progression</strong></td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*P* > 0.001

Raut et al. JCO, 2006
Mechanisms of resistance
Progression on Imatinib

Primary Resistance (within 6 months 10-15%):
- KIT exon 17, PDGFR exon 18 mutations, BRAF, KRAS
- Diffuse progression

Secondary Resistance:
- Acquired secondary mutations – usually in tumors with exon 11 primary mutation
- Activation of alternate drivers/pathways: PI3K/ AKT/ mTOR, IGFR1
- Focal progression or diffuse progression
Intracellular Signaling Pathways

Resistance:
Recognition of Clonal Evolution

Courtesy of Dr. G.D. Demetri.
Novel TyROsine kinase inhibitors
Long list....

KIT+PDGFR+VEGFR+
- Sorafenib
- Cediranib
- Cabozantinib
- Pazopanib
- Vandetinib
- Motesanib
- Dovitinib
- Famitinib

KIT+PDGFR+
- Nilotinib
- Dasatinib
- Ponatinib
- Masitinib
- XL820
- DCC2618
Sorafenib
- Targets Raf, KIT, PDGFR, VEGFR 2, 3
- Has shown benefit in phase II setting
- Although not approved often used in the third line

Nilotinib
- Phase II studies showed some clinical benefit. RR<10%
- Phase III study compared to best supportive care in patients who progressed on imatinib & sunitinib showed a trend toward longer progression-free and survival but was not significant

Wiebe et al. JCO 2008
Kindler HL et al. JCO 2011

Cauchi, Somaiah, von Mehren JCO 2010
Phase I study with Cabozantinib
Yamamato et al.

- Cabozantinib is an oral, potent inhibitor of MET and VEGFR2
  - MET and its ligand HGF drive tumor cell invasion and metastasis\(^1,2\)
  - MET and VEGFR2 promote angiogenesis\(^3\)
Antitumor Activity

- A patient with GIST had stable disease with reductions in the sum of 5 target lesions of 16% (Figure 4), and continues treatment with cabozantinib.

Figure 4. CT images of a patient with a primary diagnosis of GIST tumor positive for KIT over-expression (pretreated with 2 prior regimens including imatinib and sunitinib) who achieved reductions in the sum of target lesions of 16% during treatment with cabozantinib 60 mg (lesions indicated by red arrows). Grade 2 AEs included PPE, leukopenia and diarrhea. No grade 3 or greater AEs were reported.
Ph2 Trial of Ponatinib in GIST
Study Design

**Key Inclusion/Exclusion Criteria**
- ≥18 yrs with metastatic and/or unresectable GIST *after failed ≥1 prior TKI*

**Primary Endpoint**
- Clinical benefit rate (CBR): CR+PR+SD at 16 weeks KIT e11+ve pts

**Secondary Endpoints**
- CBR at 16 weeks KIT e11-ve pts and total
- PFS, ORR (CR+PR), OS by cohort and total
- Safety and tolerability
- PK

**Exploratory Objectives**
- Optional FDG-PET and tumor biopsy
- ctDNA studies

Data as of 07 April 2014: median follow-up 6 months all pts

*Protocol amended (22 Apr 2014) to include only patients with failure of all 3 TKIs approved for GIST: imatinib, sunitinib, and regorafenib
### Ph2 Trial of Ponatinib in GIST

Demographics & Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>KIT e11+ve</th>
<th>KIT e11-ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>24</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td><strong>Median age, yrs [range]</strong></td>
<td>61 [40 - 81]</td>
<td>53 [24 - 73]</td>
<td>58 [24 - 81]</td>
</tr>
<tr>
<td><strong>Gender, male (%)</strong></td>
<td>15 (63)</td>
<td>5 (45)</td>
<td>20 (57)</td>
</tr>
<tr>
<td><strong>2 prior GIST-approved TKIs, n (%)</strong></td>
<td>10 (42)</td>
<td>6 (55)</td>
<td>16 (46)</td>
</tr>
<tr>
<td><strong>3 prior GIST-approved TKIs, n (%)</strong></td>
<td>12 (50)</td>
<td>4 (36)</td>
<td>16 (46)</td>
</tr>
<tr>
<td><strong>Median number of prior cancer regimens [range]</strong></td>
<td>4 [1 - 10]</td>
<td>5 [2 - 7]</td>
<td>4 [1 - 10]</td>
</tr>
</tbody>
</table>

*Includes investigational TKIs

Presented By Michael Heinrich at 2014 ASCO Annual Meeting
Ph2 Trial of Ponatinib in GIST
Target Tumor Lesion Best Change from Baseline

% Change from Baseline

Best Response:  PR  SD  PD

All Patients

Presented By Michael Heinrich at 2014 ASCO Annual Meeting
Ph2 Trial of Ponatinib in GIST
FDG-PET, Biopsy, Plasma Molecular Analysis

KIT mutations in biopsy (NGS, Foundation Med)

<table>
<thead>
<tr>
<th>Mutations</th>
<th>% reads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>ΔEx11</td>
</tr>
<tr>
<td>Secondary</td>
<td>Y823D</td>
</tr>
</tbody>
</table>

KIT mutations in plasma (BEAMing)

![Graph showing percent mutant over time](image)

**FDG PET**

Baseline

Cycle 1 Day 17

Presented By Michael Heinrich at 2014 ASCO Annual Meeting
Ph2 Trial of Ponatinib in GIST
CT Scan

Baseline

Cycle 3 Day 1
Ph2 Trial of Ponatinib in GIST Survival

OS at 6 months (95%CI) [median]:
- KIT e11+ve: 80% (54, 92) [not reached]
- KIT e11-ve: 71% (26, 92) [not reached]

PFS at 6 months (95%CI) [median]:
- KIT e11+ve: 60% (33, 79) [7 months]
- KIT e11-ve: 39% (9, 69) [4 months]
Novel pathways / Combination therapy options
<table>
<thead>
<tr>
<th>PI3K/AKT/mTOR inhibitors</th>
<th>HSP90 inhibitors</th>
<th>IGFR1 inhibitors</th>
<th>Immune therapy</th>
<th>Drug repurposing</th>
</tr>
</thead>
<tbody>
<tr>
<td>BKM120&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IPI-504&lt;sup&gt;a,b,d&lt;/sup&gt;</td>
<td>R1507&lt;sup&gt;a,e&lt;/sup&gt;</td>
<td>Pegylated interferon alpha-2b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Mithramycin A&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>GDC-0941&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IPI-493&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Linsitinib</td>
<td></td>
<td>Mitoxantrone&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SF1126&lt;sup&gt;b&lt;/sup&gt;</td>
<td>STA-9090&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Auranofin&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BEZ235&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BIIB021&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDC-0980&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AT13387&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Perifosine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AUY922&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Everolimus&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sirolimus&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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</tbody>
</table>
### Table 2. Active GIST clinical trials with therapeutic targets beyond tyrosine kinase inhibition

<table>
<thead>
<tr>
<th>PI3K/AKT/mTOR inhibitors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase Ib study with BKM120 and Imatinib in 3rd-line setting (NCT01468688)(^a)</td>
<td></td>
</tr>
<tr>
<td>Phase Ib study with BYL719 and Imatinib in 3rd-line setting (NCT01735968)(^a)</td>
<td></td>
</tr>
<tr>
<td>Phase I/II study with Perifosine and Sunitinib in advanced disease (NCT00399152)(^b)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>HSP90 inhibitors</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Phase II study with AUY922 in 3rd-line setting (NCT01389583, NCT01404650)(^a)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IGFR1 inhibitors</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Phase II study with Linsitinib in adult and pediatric wild-type GIST (NCT01560260)(^b)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I study with Ipilimumab and Dasatinib in advanced/unresectable disease (NCT01643278)(^a)</td>
<td></td>
</tr>
<tr>
<td>Phase I study with Ipilimumab and Imatinib in advanced disease (NCT01738139)(^a)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\), recruiting; \(^b\), completed and awaiting results.
FGFR- alternate pathway of activation
BGJ398 enhances the antiproliferation activity of imatinib in GIST cells in the absence of exogenous FGF ligands.

DRUG Repurposing- Identifies Fludarabine as a candidate

Ziyan Y. Pessetto et al. Mol Cancer Ther 2014;13:2276-2287
Synergistic antitumor effects of imatinib mesylate (IM) in combination of F-AMP against GIST in a xenograft nude mouse model.

Ziyan Y. Pessetto et al. Mol Cancer Ther 2014;13:2276-2287
The cancer immunotherapy premise

**Immunization**

1. Dendritic Cells capture tumor antigens (Ag)

**T-cell response**

2. Activated DC present tumor Ag to CD8 T cells which become anti-tumor CTLs

**Immunosuppression**

3. Tumor expresses molecules (e.g. PDL1) that fend off CTLs

---

*Mellman, Ira et al, Nature 2011*
Imatinib plus Pegylated Interferon α-2b

Abbreviations: IM, imatinib; PR, partial response; CR, complete response; Pt, patient; III, stage III unresectable; IV, stage IV metastatic; PFS, progression-free-survival.
A  Pt #4 biopsy before treatment and 3 control residual tumors post IM monotherapy

IFN-γ

H&E

KIT (CD117)

IFN-γ

IFN-γ

IFN-γ

FasL

Control #1

Control #2

Control #3

Granyme B

Control #1

Control #2

Control #3

B  Pt #4 residual mass post combination treatment with IM plus PegIFNa2b

TILs Phenotype

H&E

CD8

CD56

CD4

CD45RO

Isotype control (mouse IgG)

TILs

IFN-γ

Isotype control (rabbit IgG)

IFN-γ

Granyme B

FasL
Exploring the role of novel immunotherapy agents: check point inhibitors

Figure 6: CTLA-4 blockade is synergistic with imatinib. GIST mice were treated with chronic CTLA-4 blockade and either imatinib or vehicle for 7 d. A third group was treated with imatinib for 7 d and chronic isotype control antibody. (a) Tumor volume, monitored using serial magnetic resonance imaging. (b-d) Frequency and absolute number of CD4$^+$ and CD8$^+$ T cells in DLN (b), frequency of intratumoral CD4$^+$ and CD8$^+$ T cells (c), and ratio of intratumoral CD8$^+$ T cells to T_{reg} cells (d) of GIST mice analyzed on days 16–18. (e) IFN-γ production in intratumoral CD8$^+$ T cells stimulated for 4 h with phorbol 12-myristate 13-acetate and ionomycin. Contour plots show representative gating of IFN-γ expression on intratumoral CD8$^+$ T cells. Bar graphs represent the intratumoral frequency of CD8$^+$ IFN-γ$^+$ cells; $P = 0.09$, two-tailed Student’s t test. Data in a represent means ± s.e.m. of a composite of two independent experiments, each with 3–5 mice per group. Data in b–e represent means ± s.e.m. with $n = 6–8$ per group. *$P < 0.05$. 
# PD-L1 expression

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>% PD-L1+</th>
<th>% L PD-L1+</th>
<th>% M PD-L1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiosarcoma</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>GIST</td>
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<td>27</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Leiomyosarcoma</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>25</td>
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<tr>
<td>Liposarcoma</td>
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<td>0</td>
<td>20</td>
<td>60</td>
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<tr>
<td>Synovial Sarcoma</td>
<td>3</td>
<td>0</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Radiation associated pleomorphic sarcoma</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>5</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>Overall</td>
<td>50</td>
<td>12</td>
<td>30</td>
<td>58</td>
</tr>
</tbody>
</table>

Sandra P. D'Angelo et al ASCO 2014
Advanced/metastatic STS

1. Adipocytic tumors
2. Vascular tumors
3. Undifferentiated pleomorphic sarcoma
4. Synovial sarcoma
5. Osteosarcoma
6. Others

Blood draw and tumor biopsy
Pre-treatment

Follow-up with restaging every 8 weeks. Confirmatory scan at 12 weeks

Blood draw and tumor biopsy at relapse

Treatment schema:

Q4W MEDI4736 20 mg/kg and Q4W tremelimumab 1 mg/kg

Treatment period 50 weeks

Follow-up

Primary endpoint: Progression-free survival at 12 weeks
Secondary endpoints:
- irRC and RECIST response rate
- PFS at 24 weeks, and overall survival
- PD-1/PD-L1 expression analysis (pre & post tx samples)
- Tumor infiltrating lymphocytes (pre & post tx samples)
- Immunoscore (identification of molecular response/resistance patterns)
PDGFR mutations (D842V)
• **PDGFRA D842V Mutation**
  - Identified in 2-5% of GISTs
  - Resistant to imatinib
    - Imatinib had no objective response and a median **PFS of 2.8 months and OS of 14.7 months**

First line imatinib treatment (PFS: 2.8mos)  
Second line treatment (PFS: 2.1mos)

Cassier, *Clin Cancer Res*, 2012
Crenolanib (CP-868,596) overview

- Crenolanib is an orally bioavailable, highly potent, specific and selective TKI
  - Targets PDGFRA, PDGFRB, and FLT3, both WT and its mutants

- Type I Inhibitor
  - Binds to the phosphorylated, constitutively active receptors

- Clinical activity in patients with select mutations
  - GIST
    - Significantly more potent than imatinib for inhibiting imatinib resistant PDGFRA exon 18 mutations (D842I, D842V, D842Y and DI842-843IM)
Metabolic response in poor prognosis GIST D842V mutant patient following 20 days of crenolanib therapy

ARO-002:

von Mehren et al., CTOS 2011
• **Overview of Study Design**
  • Patients will be randomly allocated to one of the 2 study arms (2:1) to receive
    • Arm 1: Crenolanib (300 mg/d : 100 mg TID, po, daily)
    • Arm 2: Placebo
  • Dosing will be daily, beginning on C1D1 through day 28 for a 28-day cycle. Treatment will be administered until disease progression, unacceptable toxicity or willingness to stop. Dose adaptations are planned in case of toxicity
  • Randomization will be stratified according to the number of prior lines received before randomization: 1\(^{st}\) versus > 1 prior line of treatment at baseline
SDH mutations
Glutaminase Inhibition Suppresses Multiple Downstream Metabolic Intermediates

- Alanine → Pyruvate → Oxaloacetate → Citrate → Glutamine
- Aspartate → α-KG → Glutamate → Malate → Fumarate → Succinate → α-Ketoglutarate

Cell line: HCC-1806 (TNBC)
Compound: CB-839 (1 μM)
Timepoint: 4 h
NTRK fusions
What is a gene fusion?

- Gene fusions can be generated by translocations, inversions & deletions.

http://54.84.12.177/PanCanFusV2/
How can we detect gene fusions?

**NGS, Next-Generation Sequencing**
- Detects known and novel fusions with arbitrary breakpoints in DNA or RNA.
- Exact capabilities depend on enrichment strategy.

**RT-PCR, Reverse Transcription Polymerase Chain Reaction**
- Detects known fusion transcripts in RNA.
- Detects 5’/3’ imbalance as a fusion signature, but cannot determine novel partner.

**FISH, Fluorescence In Situ Hybridization**
- Detects gene rearrangements in DNA that may generate a fusion transcript.

**IHC, Immunohistochemistry**
- Detects protein expression, which may be attributable to a fusion event.
Signaling of Oncogenic TRK Fusions

**Ligand-dependent**
- Expression of receptor (typically limited to nervous system)
- Availability of ligand (autocrine, paracrine)

**Ligand-Independent (TRKA-fusion)**
- Ligand binding domain replaced by 5’ fusion gene
- Highly expressed by promoter of 5’ fusion partner
- Dimerization induced by protein domains within 5’ gene
- Ligand-mediated dimerization no longer a requirement for activation

KD = kinase domain
CCD = coiled-coil domain
LOXO-101 is Highly Specific for TRK Receptors

LOXO-101 has favorable TRK inhibitor properties:

1. High potency for TRKA, TRKB, TRKC

2. Limited inhibition of other kinases

1 Upstate kinase panel shown does not include TRK C. LOXO-101 shown to be equipotent for TRK C in other assays.
55-year-old gentleman, who initially was diagnosed with GIST in 2003. At that time, he had metastasis to liver, spleen, and GE junction of the stomach and abdomen. He underwent:

1. Subtotal gastrectomy on 05/20/03, status post 4-flap. He then went on to receive,
2. Gleevec on 06/17/03 to 12/05/03 with progression.
3. Sunitinib from 02/04/07 to 01/22/08, again with progression. He had recurrence and then underwent gastric debulking surgery on 08/08/08.
4. Sorafenib 09/25/08 to 10/07/08. He went on to receive,
5. Drug called Tasigna and with progression of disease,
6. An experimental therapy unclear as to the name.
7. They went on to also receive regorafenib, unclear as to the specific date.
8. Embolization of hepatic mass x2 in 2014 and repeat laparotomy and debulking.
9. In December 2014, he underwent a trial regorafenib in combination with Sutent and his last dose was approximately yesterday. He is here for possible enrollment in clinical trial of therapy.

- Foundation Medicine analysis showed ETV6-NTREK3 Fusion, PAX5 mutation, SETD2 mutation.
- Enrolled on LOXO 101 protocol 2014-1056
LOXO-101 Phase 1 TRK Fusion Case History

Pre-Trial
First restaging end of cycle #2
I’ll come work with you in the sarcoma when I grow up mommy!