The Role of the Experimental Therapeutics and Rare Tumor Committee (ETRTC) in Drug Development

Gary K. Schwartz, MD
Chief, Hematology and Oncology
Deputy Director
Herbert Irving Comprehensive Cancer Center
Columbia University School of Medicine
New York, NY
Conflicts

- None
Rare Cancer Definitions

- Nearly 20% (1 in 8) of all cancers diagnosed in adults ages 20 and older are rare (approximately 208,000 new cases in 2017).
- No set definition
- FDA “rare disease” called “Orphan” disease defined as “A disease or condition with a prevalence less than 200,000 persons in the United States”
- The NCI definition for “rare cancers” fewer than 15 cases per 100,000 people per year.
- European Union (RARECARE)2 defined rare cancers as those with fewer than 6 cases per 100,000 people per year.
The Problem with Rare Cancers

- Small populations
- Heterogeneity between and within diseases
- Complex biology making them poorly understood
- Many are life threatening illnesses with unmet medical need
- Lack of effective treatments and treatment guidelines
- Often delay in diagnosis
- The 5-year survival rate inferior for patients with rare cancers is inferior compared to those with common cancers (Europe: 47% vs 67%*)
- Affects children and adolescents

ETRTC Goals

- Establish new treatment paradigms for patients with rare cancers
- Identity and evaluate new agents based on compelling preclinical data
- Utilize the cooperative group network (i.e. the Alliance) to provide drug access to patients with rare cancers throughout the United States
Soft Tissue Sarcoma Heterogeneity
(50+ Soft Tissue Sarcoma Subtypes each with a unique biology, half with specific genetic alterations)

- Liposarcoma: 19%, 1309 cases
- Leiomyosarcoma: 15%, 1104 cases
- MFH: 16%, 1037 cases
- Synovial: 6%, 406 cases
- Fibrosarcoma: 3%, 2758 cases
- Other: 38%, 1309 cases
- MPNT: 3%, 184 cases

n = 7002
### Cytotoxic Chemotherapy for Sarcomas

<table>
<thead>
<tr>
<th>CHEMOTHERAPY</th>
<th>Single Agent Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>10-20% RR</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>10-20% RR</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>10-20% RR</td>
</tr>
<tr>
<td>Dacarbazine (DTIC)</td>
<td>5-10% RR</td>
</tr>
<tr>
<td>Erubilin (liposarcoma only)</td>
<td>4% RR</td>
</tr>
</tbody>
</table>

- (approved on mOS: 13.5 m vs 11.5 m with DTIC)

- Trabectedin (myxoid lipo and leiomyo only)
  - 6% RR
  - (approved on mPFS: 4.2 m vs 1.5 m with DTIC)
“Active” Second/Third Line Therapies in Sarcoma: \( mPFS \geq 40\% \) at 12 weeks (EORTC data set)
Pazopanib RTKi Approved for All Non-Adipocyte Sarcomas

in the subsequent phase III study limited to non-adipocytic sarcomas: pazopanib improved PFS vs placebo. (4.6 mos vs 1.6 mos, HR = 0.31, p < 0.0001) leading to FDA approval.


<table>
<thead>
<tr>
<th>Subtype</th>
<th>PFR_{12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipocytic</td>
<td>26%</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>44%</td>
</tr>
<tr>
<td>Synovial</td>
<td>49%</td>
</tr>
<tr>
<td>Other</td>
<td>39%</td>
</tr>
</tbody>
</table>

PFR_{12} > 40% considered promising for second line based on historical controls.
MLN8237 (Alisertib)
Inhibitor of Aurora A (B) or Both?

MLN8237 (Alisertib)
Inhibitor of Aurora A (B) or Both?

Alliance A091102: Phase II Study of MLN8237 (Alisertib) in Advanced/Metastatic Sarcoma

Study Chair: Mark A. Dickson, MD

Primary endpoint: ORR
Secondary endpoints: PFS and OS
Patients enrolled in 5 separate cohorts:

- Cohort 1: liposarcoma
- Cohort 2: leiomyosarcoma
- Cohort 3: undifferentiated sarcoma
- Cohort 4: malignant peripheral nerve sheath tumor
- Cohort 5: other sarcomas

Simon two-stage design for each cohort:
- Treat 9 patients. If ≥ 1 response, enroll additional 16.

- Treatment: Alisertib 50mg PO bid x 7 days, every 21 days
- Correlatives:
  - Pre- and on-treatment tumor biopsies
  - Pre- and on-treatment FLT-PET scans
- Study activation 8/22/2012
Alliance A091102: Phase II Study of MLN8237 (Alisertib) in Advanced/Metastatic Sarcoma

Study Chair: Mark A. Dickson, MD

Total accrual: 72 patients

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Liposarcoma</td>
<td>12</td>
</tr>
<tr>
<td>2: Leiomyosarcoma (non-uterine)</td>
<td>10</td>
</tr>
<tr>
<td>3: Undifferentiated Sarcoma</td>
<td>13</td>
</tr>
<tr>
<td>4: Malignant Peripheral Nerve Sheath Tumor</td>
<td>10</td>
</tr>
<tr>
<td>5: Other Sarcomas</td>
<td>27</td>
</tr>
</tbody>
</table>

Results: 2 confirmed PRs in angiosarcoma (cohort 5) and 1 unconfirmed PR in dediff chondrosarcoma. 3 patients (chondro, UPS, ASPS) remain on study with stable disease.

Correlates: Aurora B effect, pH3S10 (suppressed), pRb (inhibited)

Toxicity: Principally neutropenia, mucositis, hand-foot syndrome

Results reported at ASCO 2014.

Alisertib: % PF (95 CI) at 12 Weeks by Cohort
(≥ 40% considered promising)

Alliance A091401:
A multi-center phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma

Sandra P. D’Angelo¹, Michelle R. Mahoney², Brian A. Van Tine³, James Atkins⁴, Mohammed M. Milhem⁵, William D. Tap¹, Cristina R. Antonescu¹, Elise Horvath⁶, Gary K. Schwartz⁷, Howard Streicher⁸

PD-L1 Expression and TILs in Sarcoma

D'Angelo S et al Human Pathology 46: 357-365, 2015
Ipilimumab & Nivolumab

Presented by: Sandra P. D’Angelo
Eligible patients with advanced sarcoma

R 1:1

Nivo 3 mg/kg + Ipi 1 mg/kg

Q3W x 4

Cross over

Nivo 3 mg/kg

Q2W

Nivo 3 mg/kg

Q2W

Treatment until:
- PD*
- Toxicity
- Up to 2 years

* Treatment beyond PD allowed in 1st 12 wks; 4 wk confirmation required to continue.

Presented by: Sandra P. D’Angelo
### Patient Characteristics (n=85)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nivolumab n= 43 (%)</th>
<th>Nivolumab + Ipilimumab n= 42 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Mean, Range)</strong></td>
<td>53 (21-76)</td>
<td>54 (27-81)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>22 (51)</td>
<td>19 (45)</td>
</tr>
<tr>
<td><strong>ECOG PS 0</strong></td>
<td>28 (65)</td>
<td>24 (57)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>0</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Bone</td>
<td>5 (12)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>LMS</td>
<td>15 (35)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>LPS (Well/Dediff)</td>
<td>3 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Sarcoma, NOS</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Spindle cell sarcoma</td>
<td>5 (12)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>5 (12)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>UPS/MFH</td>
<td>6 (14)</td>
<td>4 (10)</td>
</tr>
<tr>
<td><strong>At least 3 Prior Therapies</strong></td>
<td>26 (60)</td>
<td>26 (62)</td>
</tr>
</tbody>
</table>

Accrual completed in 6 weeks !!!!

**Bone:**
- Chondrosarcoma,
- Osteosarcoma,
- Ewing's sarcoma

**Other:**
- ASPS, Epithelioid sarcoma, mSFT, MPNST, PECOMA, Myxofibrosarcoma

Presented by:
Sandra P. D'Angelo
## Safety Overview (Treated Patients)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab n=42 (%)</th>
<th>Nivolumab +Ipilimumab n=42 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Adverse Events (AEs)</td>
<td>42 (100)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Treatment Related AEs</td>
<td>28 (67)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Serious Adverse Events (SAEs)</td>
<td>19 (45)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Treatment Related SAEs</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* There were 11 deaths (5 Single Agent, 6 Dual Agent) unrelated to study treatment.

Presented by: Sandra P. D'Angelo
# Summary of Response

<table>
<thead>
<tr>
<th>Best Objective Status (n, %)</th>
<th>Nivolumab (n=38)</th>
<th>Nivolumab + Ipilimumab (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (8)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>SD</td>
<td>15 (39)</td>
<td>19 (50)</td>
</tr>
<tr>
<td>PD</td>
<td>20 (53)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Death/No Assessment</td>
<td>0</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

**ORR (Confirmed, CR + PR)**
- Nivolumab: 2, 5% (90% CI 1-15%)
- Nivolumab + Ipilimumab: 6, 16% (90% CI 7-29%)

**Clinical Benefit Rate (CR + PR + SD)**
- Nivolumab: 18% (90% CI 1 - 32%)
- Nivolumab + Ipilimumab: 29% (90% CI 17-43%)

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Waterfall Plots with Nivo and Nivo/IPI

Nivo 3

ORR 3%
PR
- ASPS
- LMS
- Sarcoma, NOS

Nivo 3 + Ipi 1

ORR 16%
CR
- Myxofibrosarcoma (1)
- Uterine LMS (1)

PR
- UPS/MFH (3)
- LMS (1)
- Angiosarcoma (1)

Presented by: Sandra P. D’Angelo
55 yo man with metastatic myxofibrosarcoma

- 10/20/15 Initiated nivo 3 ipi 1
- 12/1/15 sp 3 cycles CT w PR
- 2/1/16 CT w CR
- 4/5/17 sustained CR

Presented by: Sandra P. D’Angelo
Overall Survival (months)

Nivo 3

- Total (Events): 38 (26)
- Median (95% CI): 10.7 (5.5-15.4)
- Median (95% CI) Total (Events): 38 (20)

Nivo 3 + Ipi 1

- Total (Events): 38 (20)
- Median (95% CI): 14.3 (9.6-NE)

40% alive at 12m
54% alive at 12m
Conclusions

Nivolumab 3mg/kg with Ipilimumab 1mg/kg was safe and well tolerated despite higher Grade 3/4 TRAE compared to monotherapy (14% vs 7%)

Combination cohort met its primary endpoint; thereby justifying further study

- ORR 16% in heavily treated, unselected metastatic sarcoma patients
- Responses seen in LMS, Myxofibrosarcoma, UPS/MFH and Angiosarcoma

Survival at 1 year for combination cohort exceeds expectations for this patient population as 54% of patients are alive at 12 months

Expansions in LPS, UPS/MFH (and GIST) have been approved the expansions are now open

Correlative analyses on-going including PD-L1 analysis, TIL characterization, whole exome sequencing

Presented by: Sandra P. D’Angelo
A091105
A Phase III, Double Blind, Randomized, Placebo-Controlled Trial of Sorafenib in Desmoid Tumors or Aggressive Fibromatosis (DT/DF)

Study Chair: Mrinal Gounder
Statistician(s): Michele Mahoney, Lindsay Renfro and Marylou Dueck
Protocol Chair: Elise Horvath
ECT Chair: Gary Schwartz
Pathology Chair: Narasimhan Agaram
Imaging Chair: Robert Lefkowitz
QOL Chair: Ethan Basch
Sorafenib in Desmoid Tumors

Gounder MM et al CCR17:4082-4090, 2011
Study schema/design

Progressing or Symptomatic Desmoid tumor

R 2:1

Sorafenib 400 mg daily
Placebo

CT or MRI scans every 2 months

Decrease in size or stable
Stay on sorafenib or placebo

Increase in size
If progression
If on placebo, then switch to sorafenib.
If on sorafenib, then off study

Voluntary Biopsies

Primary objective: Sorafenib (PFS 15 months) vs. placebo (6 months): HR of 0.4
Study Status/Update

- First patient enrolled in July 2015
- Last patient enrolled in December 2015
- 140+ Alliance sites and Canadian sites activated.
- 88 patients enrolled in 17 months: 5 pts/month
- Study on HOLD. Data analysis ongoing.
- FDA R01 awarded to Mrinal Gounder to support tissue correlates
A Randomized Phase II Study of MLN-0128 vs. Pazopanib in Patients with Locally Advanced (Unresectable) and/or Metastatic Sarcoma (AO91302)

Study Chair: William Tap
Statistician(s): Michele Mahoney, Lindsay Renfro and Marylou Dueck
ECT Chair: Gary Schwartz
Pathology Chair: Fabrizzio Remotti
Targeting Downstream Effector Molecules
Torc1 and Torc2

Cell 2007; 129: 434
MLN0128 (Torc1/Torc2) Inhibitor Inhibits Sarcoma Induces Apoptosis in vivo

Primary end-point, median Progression Free Survival:
Median PFS of 7 months MLN-0128 will be considered promising, relative to 4.6 months for pazopanib (HR 0.66; one-sided statistical test overall alpha of 0.15.)
Planned accrual 98 patients; Futility interim analysis
- 3 pts enrolled, Dose level 0
- 3 pts enrolled, Dose level 2
- 3 pts enrolled, Dose level 3

- No DLT

- Phase 2 study: opened, on hold for pazopanib toxicity, amendment forthcoming to reduce the pazopanib dose to 400 mg/day
Randomized Phase II study in RAI-refractory Hurthle Cell Thyroid Cancer: Sorafenib vs Sorafenib/Everolimus (A091302)

Eric Sherman - PI
Nathan Foster - Statistician
Study rationale

- Hurthle Cell Thyroid Cancer is a Rare Tumor
  - Prevalence 4.2/100,000 or 13,500 cases in US total
- More aggressive than other differentiated thyroid CA
  - 5-year mortality 65% if distant mets present
- Genomic data suggest Hurthle Cell different than Follicular/Papillary thyroid cancers
  - Common mutations seen in Papillary and Follicular cancers not seen in Hurthle Cell
  - Gene amplification for activation of PI3K-Akt-mTOR pathway
Study schema/design
First prospective study in only Hurthle Cell

Hurthle Cell
Thyroid Cancer
1:1 Randomization
No Prior Sorafenib or mTOR inhibitor

Sorafenib

Sorafenib + Everolimus

Cross over to Everolimus at POD (exploratory)

Accrual to date: 18 patients

Primary Objective: Increase in median PFS 4.5 to 9 months with addition of Everolimus to Sorafenib compared to Sorafenib alone
Previous target 56 patients (28 in each arm)
Now target is 30 patients (15 in each arm)
A Phase II Study of Enzalutamide (NSC#766085) for Patients with Androgen Receptor Positive Salivary Cancer (A091404)

PI: Dr. Alan L. Ho
ECOG-ACRIN, SWOG co-chair: Dr. Barbara Burtness
NRG Co-chair: Dr. Eric Sherman
Community Oncology Co-chair: Dr. Roscoe Morton
Pathologist: Dr. Nora Katabi
Biostatistician: Nathan Foster, MS
Study rationale

Significant AR expression is high in salivary duct carcinomas (SDC) and adenocarcinoma NOS subtypes (not in normal salivary tissue)

- 43-100% positivity in SDC
- 21-29% in adenocarcinoma NOS

(Also carcinoma ex pleomorphic adenoma, basal cell adenocarcinomas)


Locati et. al., Cancer Biol Ther, 2014.
Study rationale

- 7 AR-positive salivary cancer patients treated with combined androgen blockade (GnRH agonist + antiandrogen (bicalutamide or cyproterone))
  - 3 adenoca; 3 SDC; 1 mucoepidermoid (?)
  - 1 CR, 4 PRs, 1 SD, 1 PD
  - Unpublished update of the data with now 16 patients with 3 CRs/4 PRs (RR of 44%) and median TTP of 12 months (range 2-43 mos)
- 10 SDCs treated with ADT (bicalutamide +/- GnRH agonist)
  - 2 PRs, 3 SD, 5 PD
  - Median PFS of 12 months
  - 1 response was seen in a female patient
- Two case reports of response to abiraterone in AR + salivary adenocarcinoma NOS (one responder tumor was Her2 amplified).

Locati et. al., Cancer Biol Ther, 2014.
Study objectives/stats plan

**Patients with AR-pos SGCs**
- AR IHC will be done locally
- RECIST v1.1 measureable disease
- Pervious chemotherapy
- CAB/ADT allowed

**Enzalutamide 160 mg PO daily** (28 day cycles)
- w/ RECIST evaluation q2-3 cycles

**Primary Endpoint:** Rate of best overall response (BOR)

Optimal 2-stage design: $H_0 = 5\%, H_1 = 20\%$ ; Type 1= 5% and Power= 90%

Need at least 2 response in the first 21 patients to enroll an additional 20 patients ($n=41$)

Goal: At least 5 responses out of the total 41

**Secondary Endpoint:** PFS, OS, safety/tolerability
Lab correlative/biomarkers

- Patients must be offered the opportunity to consent to the substudy, which does not require participation in all aspects of the substudy.

- Genomic/transcriptomic profiling in:
  - Archival tissues
  - Research blood draw
  - Research biopsies (Pre-therapy and at time of progression)

- Funding has been provided by Astellas for the research biopsies ($5000 per patient).
A Phase 2 Study of Efatutazone, an Oral PPAR-gamma Agonist, in Combination with Paclitaxel in Patients with Advanced Anaplastic Thyroid Cancer (A091305)

Robert C. Smallridge, MD (Study Co-Chair)
Michael Menefee, MD (Study Co-Chair)
Balkrishna Jahagirdar, MD (Community Oncology Co-Chair)
John A. Copland, PhD (Correlative Study Co-Chair)
Nate Foster (Study Statistician)

Mayo Clinic
Synergistic antitumor activity of PPARγ agonist and taxane

PPARγ agonist

↑ PPARγ:RXR regulated transcription

↑ rhoB mRNA & protein

↑ p21^{WAF1/CIP1} protein

↑ Inhibit Cell cycle progression

Taxane

↑ microtubule stabilization

↑ cytochrome c release

↑ caspase activation

↑ Apoptosis

Combinatorial Therapy

Synergistic Apoptotic & Antitumor Activity

Copland JA, et al. Oncogene 2006; 2304-17
Efatutazole, an Oral PPAR-γ Agonist, in Combination With Paclitaxel in Anaplastic Thyroid Cancer: Results of a Multicenter Phase 1 Trial


Mayo Clinic (R.C.S., J.A.C., M.E.M., L.A.M., M.G.H.), Jacksonville, Florida 32224; Abramson Cancer Center (M.S.B.), University of Pennsylvania, Philadelphia, Pennsylvania 19104; Emory University Hospital (J.T.W.), Atlanta, Georgia 30322; Weill Cornell Medical College (Y.H.), New York, New York 10021; Mayo Clinic (K.C.B.), Rochester, Minnesota 55905; The Ohio State University (M.H.S.), Columbus, Ohio 43210; National Cancer Institute (A.W.G.), Bethesda, Maryland 20892; University of Colorado School of Medicine (J.P.K.), Aurora, Colorado 80045; and Daiichi Sankyo Pharma Development (R.V.R), Edison, New Jersey 08837

(J Clin Endocrinol Metab 98: 2392–2400, 2013)
A Phase II Study of the Peroxisome Proliferator-Activated Receptor Gamma Agonist, CS-7017 (Efatutazone) in Patients with Previously Treated, Unresectable Myxoid Liposarcoma (A091202)

Study Chair: Michael Pishvaian, MD, PhD
Lombardi Comprehensive Cancer Center, Georgetown University

Study Co-Chairs: Dennis Priebat, MD, PhD – community oncology co-chair
Medstar Washington Hospital Center
Priscilla Furth, MD – correlative science co-chair
Lombardi Comprehensive Cancer Center, Georgetown University
Christopher D.M. Fletcher MD FRCPPath – study pathologist
Brigham & Women’s Hospital

Study Statistician: Nathan Foster, MS
Mayo Clinic
Upcoming Trials...
Neoadjuvant Ipilimumab plus Nivolumab and Surgical Resection of High-Risk Localized, Loco-regionally Advanced, or Recurrent Mucosal Melanoma (Alliance A091603)

Study PIs: Alexander N. Shoushtari, MD
Richard D. Carvajal, MD
Statistician: Jacob Allred
Stereotactic Body Radiotherapy + anti-PD1 antibody (pembrolizumab) in advanced Merkel Cell Carcinoma (A091605)

PI: Jason Luke, M.D. (Alliance ET Committee)
Co-PI: Steve Chmura, M.D. PhD (NRG/Alliance Radiation Committees)
The University of Chicago Medicine & Biological Sciences
A Randomized Phase II Study of CDX-1401 (fully human anti-DEC205 fused to NY-ESO-1 antigen) in Combination with Atezolizumab in NY-ESO-1 Positive Synovial Sarcoma (A091607)

Alliance Study Chair: Steven Robinson, MBBS
COG: Rajkumar Venkatramani, MD
Statistician: Michelle Mahoney, MS
Phase II Study of Atezolizumab in Combination with Obinutuzumab (ant-CD20) for Metastatic HPV+ head and neck cancer (A091704).

Maria Matsangou, MD
Assistant Professor,
Developmental Therapeutics Program, Division of Hematology and Oncology
Department of Medicine, Northwestern University Feinberg School of Medicine
and
Robert H. Lurie Comprehensive Cancer Center
Phase II randomized study of Avelumab plus Cetuximab vs. Cetuximab alone in Advanced Cutaneous Squamous Cell Carcinoma (cSCC) (A091701)

Dan P Zandberg MD*
Assistant Professor of Medicine
University of Maryland Greenebaum Cancer Center

Jacob Allred MS Mayo Clinic
Lindsay Renfro Ph.D Mayo Clinic

*Alliance Scholar Award, 2017
Conclusion

- ETRTC is a home for rare cancer clinical trial initiatives in the United States
- Provides investigators opportunities to test new hypotheses in rare cancers where few therapeutic options exist
- It provides patients with rare cancers access to the latest advances in cancer therapy and the opportunity to participate in national clinical trials
- The ETCRC encourages participation of young investigators as a step in career development
- It encourages the testing of new scientific principles and encourages the translation of preclinical discoveries into cancer medicine