New Medical Treatment in Chemotherapy and Targeted Drugs in Sarcomas

Kumar Sankhala MD
Sarcoma Oncology Center
Sarcoma: Uniqueness and challenges

- Tissue Origin
- Rarity
- Heterogeneity
- Response Evaluation
• First Tumor type with Limb/organ sparing surgery

• First tumor with successful Targeted Therapy: Gleevec

• Role of Neoadjuvant chemotherapy
Sarcoma

- Biological significance is disproportionate to their clinical frequency
- 1% of all the tumors in adults
- Most subtypes varies in clinical Presentation, molecular and genetic characteristics
Sarcoma:

- 1% of all cancers in adults
- (similar to Multiple myeloma, Testicular cancer, Esophageal cancer – well defined treatment strategies)

<table>
<thead>
<tr>
<th></th>
<th>ACS 2001</th>
<th>NEW CASES</th>
<th>DEATHS</th>
</tr>
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<tbody>
<tr>
<td>ALL SITES</td>
<td></td>
<td>1,268,000</td>
<td>553,400</td>
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<tr>
<td>BONE &amp; JOINTS</td>
<td></td>
<td>2,900</td>
<td>1,400</td>
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<tr>
<td>SOFT TISSUES</td>
<td></td>
<td>8,700</td>
<td>4,400</td>
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<tr>
<td>PROSTATE</td>
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<td>198,100</td>
<td>31,500</td>
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<td>BREAST</td>
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<td>193,700</td>
<td>40,600</td>
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<tr>
<td>LUNG</td>
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<td>169,500</td>
<td>157,400</td>
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<tr>
<td>COLO-RECTAL</td>
<td></td>
<td>135,400</td>
<td>50,400</td>
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Soft Tissue Sarcoma

Sarcomas of Fibrous Tissue
- Malignant Fibrous Histiocytoma (MFH)
- Low-grade Fibromyxoid Sarcoma (Fibrosarcoma)
- Dermatofibrosarcoma Protruberans
- Desmoid Fibromatosis
- Nodular Fasciitis

Sarcomas of Peripheral Nervous Tissue
- Malignant Peripheral Nerve Sheath Tumor (AKA)
  - Malignant Schwannoma
  - Neurofibrosarcoma
  - Neurogenic Sarcoma

Sarcomas of Skeletal Muscle
- Leiomyosarcoma
  - GI
  - GU
  - Skin
  - Vessel
  - Other

Sarcomas of Smooth Muscle
- Liposarcoma
  - Atypical Lipomatous Tumor
  - Myxoid Liposarcoma
  - Cellular Myxoid Liposarcoma
  - Dedifferentiated Liposarcoma
  - Pleomorphic Liposarcoma

Sarcomas of Unknown Tissue
- Synovial Sarcoma
  - Monophasic
  - Biphasic
- Alveolar Soft Part Sarcoma
- Epithelioid Sarcoma
- Unclassified Sarcoma

Sarcomas of Blood and Lymph Vessels
- Angiosarcoma
  - Hemangiosarcoma
  - Lymphangiosarcoma
- Epithelioid Hemangioendothelioma
- Hemangiopericytoma
- Kaposi’s Sarcoma

Sarcomas of Skeletal Muscle
- Embryonal Rhabdomyosarcoma
- Alveolar Rhabdomyosarcoma
  - (Pleomorphic Rhabdomyosarcoma)

Extraskeletal Sarcomas
- Extraskeletal Osteosarcoma
- Extraskeletal Chondrosarcoma
- Extraskeletal Ewing’s Sarcoma (PNET)

Soft-tissue Tumors of Melanocytic Tissue
- Melanoma of Soft Parts
  - AKA - Clear Cell Sarcoma
Molecular Heterogeneity of Sarcomas

- Tumor Suppressor Gene Mutations or Deletions
  - P53 mutation/deletion, MDM2, PTEN, Rb

- Oncogene Mutations, Amplification, or Overexpression
  - C-Myc, Met, Ras, src-implicated in cell growth, proliferation, apoptosis and angiogenesis

- Receptor Tyrosine Kinase and the PI3K-AKT-mTOR Pathway
  - c-KIT, IGF-1R, EGFR, HER-2/neu, PDGFR

- Angiogenesis: VEGF, TSP-1, PEDF

- Genetic Alterations: Wilms (WT1), Myxoid liposarcoma (DDIT3), EWS t(11;22)

- Dysregulation of Apoptosis: bcl-2 overexpression, TNF related Apoptosis Inducing Ligand (TRAIL)
Molecular Heterogeneity: Specific Translocations

- Ewing’s Sarcoma/PNET
  - t(11;22)(q 24, q 12) (EWS-FLI1)
  - t(21;22)(q22, q12) (EWS-ER)
  - t(7;22)(p22;q12) (EWS-ETV1)

- Desmoplastic Small Cell Tumor
  - t(12;22)(q13;q12) (EWS ATF1)
    aka (EWS-WT1)

- Extraskeletal myxoid chondrosarcoma
  - t(9;22)(q22;12) (EWS-TEC)
    aka (EWS-CHN)

- Myxoid Liposarcoma
  - t (12:16) (q13;p11) (FUS-CHOP)
  - t (12:22:20) (EWS-CHOP)

- Synovial Sarcoma
  - t(X:18)(p11.2;q11.2) (SYT-SSX1)
    and (SYT-SSX2)

- Alveolar rhabdomyosarcoma
  - t (2:13)(q35;q14) (PAX3-FKHR)
Active Agents:

• 2000: Doxorubicin, ifosfamide, +/- DTIC

• 2015: Doxorubicin, Ifosfamide, Gemcitabine+docetaxel, paclitaxel, trabectedin, imatinib, sunitinib, DTIC, mTOR inhibitors, IGF-R1 inhibitors, Denosumab, Eribulin, Aldoxorubicine, Immune Therapies…
## Bone Sarcoma Progress

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<thead>
<tr>
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<th>Before 1973</th>
<th>2002</th>
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<tr>
<td>Amputation</td>
<td>100%</td>
<td>5%</td>
</tr>
<tr>
<td>Survival</td>
<td>5%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Before 1973</td>
<td>2002</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Amputation</td>
<td>60%</td>
<td>5%</td>
</tr>
<tr>
<td>Survival</td>
<td>30%</td>
<td>75%</td>
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</table>
A Cured Intact Patient
What is the Best Regimen?
It Depends on Which Sarcoma and Which Patient

“Personalized approach”
# Selected drugs for selected subtypes

<table>
<thead>
<tr>
<th>Histotypes</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>GIST/DFSP</td>
<td>Imatinib, sunitinib</td>
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<tr>
<td>Angiosarcoma</td>
<td>Taxanes, Vinorelbin</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>DTIC, ET-743</td>
</tr>
<tr>
<td>Uterine leiomyosarcoma</td>
<td>Gemcitabine +/- Taxanes</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>Doxorubicin</td>
</tr>
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</table>
Novel Therapies in Sarcomas

- Developmental basis:
  - Chemotherapies: Improvisation of most effective chemotherapies
  - Newer Targeted therapies: based on Molecular heterogeneity and rationale for Sarcomas: Imatinib, Pazopanib
Aldoxorubicine: Targeting Tumors Using Endogenous Albumin

Acid-sensitive linker coupled to doxorubicin binds covalently to circulating albumin in < 5 minutes

- Able to deliver several times more drug because drug is inactive until released at the tumor
Aldoxorubicin is infused into the patient.

Linker rapidly binds to cysteine-34 residue of albumin in the bloodstream.

Albumin transports drug to the tumor.

Tumor cells.

Linker releases the drug payload due to acidic environment of the tumor.
First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma: A Phase 2b Randomized Clinical Trial

Sant P. Chawla, MD; Zsuzsanna Papai, MD; Guzel Mukhametshina, MD; Kamalesh Sankhala, MD; Leonid Vasylyev, MD; Alexander Fedenko, MD; Kenneth Khamly, MD; Kristen Ganjoo, MD; Rajnish Nagarkar, MD; Scott Wieland, PhD; Daniel J. Levitt, MD

Table 2. Best Overall Tumor Responses

<table>
<thead>
<tr>
<th>Patients With Response</th>
<th>Assessment, No. (%)</th>
<th>Investigator</th>
<th>Central Laboratory</th>
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<tr>
<td></td>
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<td>Aldoxorubicin Group (n = 83)</td>
<td>Doxorubicin Group (n = 40)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>17 (20)</td>
<td>2 (5)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Overall response (CR+PR)</td>
<td>19 (23)</td>
<td>2 (5)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>SD</td>
<td>45 (54)</td>
<td>25 (62)</td>
<td>30 (38)</td>
</tr>
<tr>
<td>Disease control (CR+PR+SD)</td>
<td>64 (77)</td>
<td>27 (68)</td>
<td>50 (62)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13 (16)</td>
<td>11 (28)</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6 (7)</td>
<td>2 (5)</td>
<td>6 (8)</td>
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</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

* For 3 patients in the aldoxorubicin group and 2 patients in the doxorubicin group, the independent central laboratory did not identify a measurable lesion at screening.
Median progression-free survival was significantly improved (5.6 vs 2.7 months; \( P = .02 \)) with aldoxorubicin as compared with doxorubicin.
A Phase 1b/2 Study of Aldoxorubicin + Ifosfamide/Mesna in Untreated Sarcoma Patients

Kamalesh Kumar Sankhala MD1, Neal S. Chawla MS1, Syed Imran MD1, Fritz C. Elber MD2, Victoria Chua-Alcala1, Vivek Subbiah MD3, Kelli Sung4, Shanta Chawla MD1, Scott Wieland PhD1, Daniel J. Levitt MD, PhD4, Sant P. Chawla MD1
1Sarcoma Oncology Center, Santa Monica, CA; 2University of California, Los Angeles, CA; 3MD Anderson Cancer Center, Houston, TX; 4CytRx Corporation, Los Angeles, CA

Abstract

Background

Adoxorubicin + IFM is in the clinical development pipeline for the treatment of metastatic, advanced, and recurrent sarcomas. Adoxorubicin (INNO-100) is a hydrazine prodrug of doxorubicin (DOX) designed to target the rapidly proliferating tumor vasculature, minimally impact normal vasculature, and enable prolonged exposure of tumor cells to DOX. Adoxorubicin has shown promising activity in multiple Phase I/II trials in hematologic malignancies and sarcomas. The results of a Phase II study demonstrated that adoxorubicin has a favorable side effect profile. This combination indicates promising clinical activity in patients with liposarcoma, synovial sarcomas and unclassified pleomorphic sarcomas.

Objective:

- Demonstrate the safety, tolerability, and antitumor activity of adoxorubicin + IFM in patients with sarcoma.

Methods:

- Patients with locally advanced or metastatic sarcoma were eligible.
- Patients received 5 cycles of adoxorubicin + IFM at escalated dose levels.

Results:

- A safety analysis was performed on all patients who received at least one dose of adoxorubicin + IFM.
- An efficacy analysis was performed on all patients who received at least one cycle of adoxorubicin + IFM.

Conclusions:

- Adoxorubicin + IFM was well tolerated and demonstrated antitumor activity in patients with sarcoma.

References


Disclosures

Palifosfamide

- Tris formulation that is the functional active metabolite of Ifosfamide
- Toxic metabolites are not present with Palifosfamide as they are with Ifosfamide
- It lacks the hemorrhagic cystitis and CNS toxicity of IFOS
Palifosfamide

- Phase II study: Enrolled 67 pts (Doxorubicin alone or Doxo+Palifosfamide)
  - PFS was 4.4 months with single agent Doxo and 7.8 months with combination
- Phase III study (PICASSO): Randomized double blind, placebo controlled study in 447 patient: failed to show difference in PFS
Hypoxia Activated Prodrugs (HAPs)

- Hypoxia-activated prodrugs (HAPs) selectively target hypoxic tumor cells
- Hypoxia is a feature of solid tumors
  - Associated with a worse prognosis
  - Associated with an aggressive phenotype, invasiveness, metastasis, and relapse
  - Often underlies treatment failure
- HAPs should complement conventional cancer therapies
Chemotherapy Targets Oxygenated Tumor Compartment

Vessels: Red
Doxorubicin: Blue
Hypoxia: Green

Chemistry Strategy for Targeting Hypoxia

Hypoxia-Activated Prodrugs (HAPs)
TH-302 + Doxorubicin in Soft Tissue Sarcoma
The 403 Phase 1/2 Trial: 84% of Patients Experienced SD or Better (10/27/11)

Waterfall Plot: Change in Target Lesion Diameters

- CR - 2% (2/89)
- PR - 34% (30/89)
- SD - 48% (43/89)
- PD - 16% (14/89)
Eribulin: Phase 3 Sarcoma study

Median PFS was 2.6 months in both arms of the study (HR = 0.877; 95% CI, 0.710-1.085; P = .229)
Platelet-Derived Growth Factor Receptor (PDGFR)

- Cell surface receptor tyrosine kinase (α,β) activated by the platelet-derived growth factor (PDGF A–D) family of ligands

- In normal mesenchymal biology, PDGF/PDGFR signaling has a significant role in the following\(^1\)-\(^3\):
  - Mesenchymal stem cell differentiation
  - Growth of mesenchymal cells
  - Angiogenesis and wound healing
A Randomized Phase 1b/2 Study Evaluating the Safety and Efficacy of Olaratumab (IMC-3G3), a Human Anti–platelet-derived Growth Factor α (PDGFRα) Monoclonal Antibody, with or without Doxorubicin (Dox), in Advanced Soft Tissue Sarcoma (STS)

William D. Tap*

Robin L. Jones, Bartosz Chmielowski, Anthony D. Elias, Douglas Adkins, Brian A. Van Tine, Mark Agulnik, Matthew Cooney, Michael B. Livingston, Gregory Pennock, Amy Qin, Ashwin Shahir, Robert Ilaria Jr, Ilaria Conti, Jan Cosaert, Gary K. Schwartz

*Presenting Author
Open-label, Multicenter, Phase 1b/2 Trial

Phase 2

- Same entry criteria as Phase 1b
- Stratification:
  - PDGFRα (IHC)
  - Lines of prior treatment
  - ECOG PS
  - Histology (leiomyosarcoma, synovial sarcoma, other)

Randomize:

- Olaratumab 15 mg/kg D1,8 + Dox 75 mg/m² D1 × 8 cycles (21 days)*

- Optional olaratumab monotherapy after progression

Primary endpoint: Progression-free survival (PFS) (predefined statistical significance: 2-sided alpha = 0.2)
Secondary end points: Overall survival (OS), objective response rate, PFS at 3 months
Biomarker: PDGFRα (IHC) and related ligands

* During Cycles 5-8, patients receiving Dox could receive dexrazoxane, at the investigator’s discretion.
Progression-Free Survival (ITT) (Phase 2)

- **Olaratumab + Dox**
  - N: 66
  - Event: 55 (83.3)
  - Censored: 11 (16.7)
  - Median PFS (95% CI): 6.6 (4.1, 8.3)
  - Stratified p-value: 0.0615
  - Hazard ratio (95% CI): 0.672 (0.442, 1.021)

- **Dox**
  - N: 67
  - Event: 48 (71.6)
  - Censored: 19 (28.4)
  - Median PFS (95% CI): 4.1 (2.8, 5.4)
  - Hazard ratio (95% CI): 0.670 (0.401, 1.117)

*Tap W et al. Slides presented at ASCO 2015. Abstract 10501*
Overall Survival (ITT) (Phase 2)

- **Olaratumab + Dox**
  - N: 66
  - Event: 34 (51.5)
  - Censored: 32 (48.5)
  - Median OS (95% CI): 25.0 (20.9, 30.9)
  - Stratified p-value: 0.0004
  - Hazard ratio (95% CI): 0.441 (0.277, 0.702)

- **Dox**
  - N: 67
  - Event: 50 (74.6)
  - Censored: 17 (25.4)
  - Median OS (95% CI): 14.7 (9.2, 18.0)

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Tap W et al. Slides presented at ASCO 2015. Abstract 10501

Lilly | ONCOLOGY
Yondelis; Trabectedin (ET-743)

- ET-743 is a unique DNA-interacting agent with covalent binding to the DNA minor groove
- ET-743 blocks cell cycle progression in G2/M phase through a $p-53$–independent apoptotic process
- Inhibits the transcriptional activation of inducible genes
- Minimal or no cross-resistance to several conventional chemotherapeutic agents
Efficacy and Safety of Trabectedin in Patients With Advanced or Metastatic Liposarcoma or Leiomyosarcoma After Failure of Prior Anthracyclines and Ifosfamide: Results of a Randomized Phase II Study of Two Different Schedules

George D. Demetri, Sant P. Chawla, Margaret von Mehren, Paul Ritch, Laurence H. Baker, Jean Y. Blay, Kenneth R. Hande, Mary L. Keohan, Brian L. Samuels, Scott Schuetze, Claudia Lebedinsky, Yusri A. Elsayed, Miguel A. Izquierdo, Javier Gómez, Youn C. Park, and Axel Le Cesne

A

Cumulative Probability of Progression

Time (months)

P = .0302
Yondelis; Trabectedin (ET-743)

- EMEA approval 19th July 2007:
  - Indicated for the ASTS, after failure of anthracyclines and ifosfamide or who are not suitable to receive these agents.
  - Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.
Pazopanib

- Oral multi-tyrosine kinase inhibitor
  - VEGFR-1,2,3
  - PDGFR-a,b
  - C-kit
- Approved April 26, 2012
- Use in advanced STS in patients having received prior chemotherapy
Pazopanib Phase III (PALETTE) Results

Progression Free Survival

Median progression-free survival (months)
- Pazopanib: 4.6 (95% CI 3.7–4.8)
- Placebo: 1.6 (95% CI 0.9–1.8)

HR 0.31, 95% CI 0.24–0.40
p<0.0001

Leiomyosarcoma: HR 0.88 (0.63-1.21)
Synovial: HR 0.86 (0.51-1.32)
Denosumab:

- Fully human monoclonal antibody that binds to RANKL<sup>1</sup>
- Inhibits osteoclast-mediated bone destruction
- Initial open-label, proof-of-concept, phase 2 study of denosumab in GCTB (N = 37):<sup>2</sup>
  - Tumor response in 86% of patients with GCTB
  - Clinical benefit in 84% of patients (reduced pain or improvement in functional status per investigator)
  - No serious treatment-related adverse events

Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study

Sant Chawla, Robert Henshaw, Leanne Seeger, Edwin Choy, Jean-Yves Blay, Stefano Ferrari, Judith Kroep, Robert Grimer, Peter Reichardt, Piotr Rutkowski, Scott Schuetze, Keith Skubitz, Arthur Staddon, David Thomas, Yi Qian, Ira Jacobs
Results – Efficacy

36-year-old man with GCTB and severe pain, left lower extremity

Baseline

After 29 weeks of denosumab treatment
Histologic Response to Denosumab

Baseline

20% Giant cells

25 Weeks (8 Doses)

0% Giant cells

Tumour Giant Cell content (H&E)

RANKL expression*

PM01183 - Lurbinectedin

- PM01183 is a synthetic analog of Yondelis (ET743)
  - Blocks transactivated transcription and causes double strand breaks in wide range of cancer types
  - Shown efficacy in platinum resistant ovarian cancer

- Phase II clinical trial with sarcoma, ovarian, endometrial, head & neck, and lung cancer
AP23573 (Redeforolimus) – Potent mTOR Inhibitor

- mTOR – a master switch connecting a cell’s environment with its behavior
- Key role in angiogenesis
- Abnormal dependence on mTOR signaling renders tumors more sensitive to mTOR inhibition
- AP23573 – potent, non-prodrug mTOR inhibitor
AP23573 (Ridaforolimus)

• Phase I: 7/32 Pts were of Sarcoma (2 PR, 2MR, 2SD)
• Phase II: 212 sarcoma pts:
  • CBR (CR+PR+SD ≥ 16 weeks) : 29%
  • PPS: 15.3 weeks, RR: 2%
• Phase III (SUCCEED): AP as maintenance therapy after getting control with primary therapy
Redaforolimus Phase III (SUCCEED) study

- 702 pts were enrolled in US, South America, Europe and Asia
- Median PFS in the ridaforolimus arm was 16.1 weeks compared to 14 weeks in the placebo arm ($P = .0006$)
- Median OS was 93.3 weeks with ridaforolimus vs 83.4 weeks with placebo (HR=0.88; 95% CI) —Not statistically significant
- ? treatment alternative to surveillance alone
MDM2 Inhibitor – AMG 232

- MDM2 is an E3 ubiquitin protein ligase which acts as a negative regulator for p53 tumor suppressor
  - Prerequisites: MDM2 gene amplification, and p53 wild-type
- Suppression of MDM2 is aimed at increasing natural p53 activity
- MDM2 overexpression occurs in 20% of sarcoma, myeloma, glioblastoma and breast cancer
  - 51% MDM2 overexpression in liposarcomas
Pigmented Villonodular Synovitis (PVNS)
Tenosynovial Giant Cell Tumor (TGCT)

- **Rare synovial tumor** of joints & tendon sheaths
- Incidence ~ 600 new cases per year in US, often young adults

![Diagram showing cellular processes](image)

- **Clonal neoplastic process** resulting in over-expression of CSF1 in synovium
  - Frequently due to genetic translocation: t(1;2) CSF1:COL6A3
  - Propagation of neoplastic clone (autocrine)
  - Reactive inflammatory process with *proliferation & recruitment of CSF1R-expressing cells*: macrophages, giant cells, osteoclasts

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Presented by: William D. Tap, MD

Permission: West, et al. (2005)
PNAS, USA 103, 690-695

Presented By William Tap at 2014 ASCO Annual Meeting
<table>
<thead>
<tr>
<th>Date</th>
<th>Changes</th>
</tr>
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<tr>
<td>2/13/13</td>
<td>Narcotic Analgesia Not working, Using a cane to ambulate, Poor Appetite</td>
</tr>
<tr>
<td>6/5/13</td>
<td>Off Narcotic Analgesia (On naproxen) Back to nursing – 12 hours per day</td>
</tr>
<tr>
<td></td>
<td>Walking unassisted, Gaining Weight, Hair now white, skin lighter in complexion</td>
</tr>
<tr>
<td></td>
<td>Surgeon Offered Amputation, Surgeon now referring patients</td>
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</tbody>
</table>
Example of Objective Response: Patient #205

85% response by Tumor Volume Score

Baseline  2 months  4 months

Presented by: William D. Tap, MD

Presented By William Tap at 2014 ASCO Annual Meeting
Example of PET Response: Patient #205

2 weeks on PLX3397

SUV 21.7

SUV 6.4

Presented by: William D. Tap, MD
Duration of Treatment (DOT), April 2014 data cutoff:
Median 256 days (range 21-585 days)

Subject ID
n = 21

n= 20
ORR evaluable by RECIST
local read:
60% PR (12/20)
35% SD (7/20)
5% PD (1/20)
FPA008 is an antibody that inhibits colony stimulating factor-1 receptor (CSF1R), targets macrophages and monocytes.
Angiosarcoma: TRC105 (anti-endoglin antibody) in combination with Pazopanib

A Phase 1b Dose-Escalation Study of TRC105 (anti-Endoglin Antibody) in Combination with Pazopanib in Patients with Advanced Soft Tissue Sarcoma (STS)

INTRODUCTION

- Endoglin is a membrane receptor targeted for its expression on angiosarcoma cells, which is highly expressed in proliferating endothelial cells in solid tumors (Sear, 2011).
- Endoglin expression appears to continue in angiosarcoma following VEGF inhibition.

RESULTS

- TRC105 at its RP2D of 10 mg/kg weekly was well tolerated with pazopanib in STS patients.
- The most common adverse events were generally low grade and included epistaxis, gingival bleeding, headache, and fatigue.
- A phase 2 trial (NCT017975515) of TRC105 in combination with pazopanib is planned in STS, including angiosarcoma.

CONCLUSION

- A multicenter Phase 2 trial at 8 mg/kg of TRC105 dose level in combination with pazopanib is planned to assess further signs of activity in angiosarcoma.

REFERENCES

- Beckhorn M, Clinical Cancer Research 9:4211-4220, 2005
- Choueiri TK, ASCO Annual Meeting 2015
- Fritchie MA, Baskin DS, Gordon MS, Clinical Cancer Research 20:5918-5927, 2014
- Seon R, Clinical Cancer Research 10:1248-1255, 2004
- NCCN Technology Assessment Panel on Current Drug Delivery, 8:130-143, 2011
Novartis Phase II clinical trials: Depending on molecular profile

- All Novartis clinical trials require specific gene alterations to be present
  - BGJ398 – FGF gene alteration
  - Binimetinib (MEK162) – RAS/RAF/MEK gene alteration
  - Buparlisib (BKM120) – P13K/PTEN gene alteration
  - Ceritinib (LDK378) – ALK or ROS1 gene alteration
  - Dovitinib (TK1258)-RTK gene alteration
  - Encorafenib (LGX818)-BRAFV600 gene alteration
  - Lee011- CDK4/6, Cyclin D1/3 or p16 gene alteration
  - Sonidegib (LDE225)- PTCHI and SMO gene alteration
Taxol + Bayer – BAY1217389

- Oral BAY1217389 in combination with standard dosing of weekly intravenous Paclitaxel

- Bay1217389 selective inhibitor of protein enzyme monopolar spindle 1 (Mps1)
  - Mps1 is a core component of spindle assembly checkpoint (SAC)
  - Inhibition of Mps 1 leads to inactivation of SAC, causing rapid acceleration os through mitosis resulting in increase chromosomal segregation errors and induce cell death

- Paclitaxel halts cellular proliferation at G2 inducing cell death
  - Interferes with microtubule proliferation during cell division
PD-1/PD-L1: A Critical Immuno Checkpoint Pathway

Inhibitory Signal
Immune Therapy in Sarcomas

- Only destroys cancer tissue
- Spares normal tissue
- Minimal or no toxicity
TUMOR ASSOCIATE D PROTEINS

TUMOR CELL

NORMAL CELL

T CELL THERAPY FOR SARCOMAS
Genetically Modified T-cell Study

1. Apheresis
2. T-cell engineering
3. Expansion
4. Infusion
5. Recognition of T-cell
6. T-cell activation
7. Killing of tumor cells
Immune Design – IMDZ C131/C232

• Combination therapy using LV305 and G305 targeting NY-ESO1 tumor marker
  • Patient must be NY-ESO1 positive
  • NY-ESO1 is a fetal antigen present in a number of malignancies
  • NY-ESO1 found in 20-30% of melanoma, sarcoma, ovarian, breast and bladder cancers.
• Use CD8 and CD4 T cells to target NY-ESO1 expressing tumor tissue

• Atezolizumab:
  • Checkpoint inhibitor (anti-PD-L1 mAb)
  • Enables anti-tumor immune activity
  • Compared with Combo vaccine therapy in C232 study
LV305 & G305

- LV305 is a viral vector designed to bind and infect dendritic cells stimulating an immune response against NY-ESO1
  - LV305 is partly derived from HIV
  - Increases CD8 T cell levels targeting NY-ESO1 markers

- G305 is composed of NY-ESO1 and glucopyranosyl lipid A (GLA)
  - Increases CD4 T cell levels which maximizes the efficacy of CD8 T cells in killing tumor tissue expressing NY-ESO1 markers

- In animal studies G305 has shown to amplify the anti-tumor effect of LV305 when given sequentially
Prime Boost LV305+G305

% Ag specific CD4 or CD8 T cells (ICS)

<table>
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<th>PRIME:</th>
<th>BOOST:</th>
<th>CD4</th>
<th>CD8</th>
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GLAAS + NY-ESO1 protein = G305

ZVex- NY-ESO1 RNA = LV305

ZVex- NY-ESO1 RNA & GLAAS + NY-ESO-1 protein = CMB305
Sarcomas: Conclusion

- Rare, heterogeneous, needs specialized multidisciplinary team care
- Best Example of rationale drug development in Oncology-GIST
- Most challenging subtypes of cancers for novel drug development
Conclusions

Future therapy for Sarcomas:

- Molecular subtype will play important role along with the histological subtype.
- Important to understand the molecular biology events to define proper therapeutic targets.
- Routine use of molecular biology to guide initial and subsequent treatments.
- Coordinated translational research for targeted therapies.
Thank You

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