WHAT WE NEED TO KNOW ABOUT TARGETED THERAPIES AND NGS IN 2021

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As Cancer Care Has Progressed, There Has Been a Trend Toward Targeted Treatment

Evolution of cancer treatment

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>1800s and earlier</th>
<th>Late 1800s-mid 1900s</th>
<th>Late 1900s and beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remove cancer</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Kill cancer cells</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Modify pathways and processes that support or block cancer</td>
<td>+</td>
<td>+</td>
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<table>
<thead>
<tr>
<th>TREATMENT TYPE</th>
<th>1800s and earlier</th>
<th>Late 1800s-mid 1900s</th>
<th>Late 1900s and beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Immunotherapy</td>
<td>-</td>
<td>+</td>
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</table>
Targeted Therapies for Cancer

- Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumor growth and progression.

- Ideally- A primary goal of targeted therapies is to fight cancer cells with more precision and potentially fewer side effects.

- Targeted cancer agents are broadly classified as:
  - **Therapeutic monoclonal antibodies** target specific antigens found on the cell surface.
  - **Small molecules** can penetrate the cell membrane to interact with targets inside a cell.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Target(s)</th>
<th>FDA-approved indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ado-trastuzumab emtansine (Kadcyla)</td>
<td>HER2 (ERBB2/neu)</td>
<td>Breast cancer (HER2+)</td>
</tr>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>EGFR (HER1/ERBB1), HER2 (ERBB2/neu)</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Aldesleukin (Proleukin)</td>
<td></td>
<td>Renal cell carcinoma, Melanoma</td>
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<tr>
<td>Alectinib (Alecensa)</td>
<td>ALK</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Avapritinib</td>
<td>KIT and PDGFR</td>
<td>GIST</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>PD-L1</td>
<td>Urothelial carcinoma, Non-small cell lung cancer</td>
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<tr>
<td>Axitinib (Inlyta)</td>
<td>KIT, PDGFRβ, VEGFR1/2/3</td>
<td>Renal cell carcinoma</td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>VEGF ligand</td>
<td>Cervical, Fallopian tube and Ovarian cancer, Colorectal cancer, Glioblastoma, Non-small cell lung cancer, Renal cell carcinoma</td>
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<tr>
<td>Cabozantinib (Cabometyx [tablet], Cometriq [capsule])</td>
<td>FLT3, KIT, MET, RET, VEGFR2</td>
<td>Medullary thyroid cancer, Renal cell carcinoma</td>
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<tr>
<td>Ceritinib (Zykadia)</td>
<td>ALK</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Cetuximab (Erbitux)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Colorectal cancer, Squamous cell cancer of the head and neck</td>
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<tr>
<td>Cobimetinib (Cotellic)</td>
<td>MEK</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>ALK, MET, ROS1</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Agent</td>
<td>Target(s)</td>
<td>FDA-approved indication(s)</td>
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<tr>
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<tr>
<td>Dabrafenib (Tafinlar)</td>
<td>BRAF</td>
<td>Melanoma</td>
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<tr>
<td>Denosumab (Xgeva)</td>
<td>RANKL</td>
<td>Giant cell tumor of the bone</td>
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<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td></td>
<td></td>
<td>Pancreatic cancer</td>
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<tr>
<td>Everolimus (Afinitor)</td>
<td>mTOR</td>
<td>neuroendocrine tumor</td>
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<tr>
<td></td>
<td></td>
<td>Renal cell carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
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<tr>
<td>Gefitinib (Iressa)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Imatinib (Gleevec)</td>
<td>KIT, PDGFR, ABL</td>
<td>GI stromal tumor</td>
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<tr>
<td></td>
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<td>Dermatofibrosarcoma protuberans</td>
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<td>Ipilimumab (Yervoy)</td>
<td>CTLA-4</td>
<td>Melanoma</td>
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<td>Lapatinib (Tykerb)</td>
<td>HER2 (ERBB2/neu), EGFR (HER1/ERBB1)</td>
<td>Breast cancer</td>
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<td>Lenvatinib (Lenvima)</td>
<td>VEGFR2</td>
<td>Renal cell carcinoma</td>
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<td></td>
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<td>Thyroid cancer</td>
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<td>Necitumumab (Portrazza)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Squamous non-small cell lung cancer</td>
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<tr>
<td>Agent</td>
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<tr>
<td>Nivolumab (Opdivo)</td>
<td>PD-1</td>
<td>Head and neck squamous cell carcinoma, Melanoma, Non-small cell lung cancer, Renal cell carcinoma, Urothelial carcinoma</td>
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<tr>
<td>Olaparib (Lynparza)</td>
<td>PARP</td>
<td>Ovarian cancer</td>
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<tr>
<td>Osimertinib (Tagrisso)</td>
<td>EGFR</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Palbociclib (Ibrance)</td>
<td>CDK4, CDK6</td>
<td>Breast cancer</td>
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<tr>
<td>Panitumumab (Vectibix)</td>
<td>EGFR (HER1/ERBB1)</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Pazopanib (Votrient)</td>
<td>VEGFR, PDGFR, KIT</td>
<td>Renal cell carcinoma, Soft tissue sarcoma</td>
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<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>PD-1</td>
<td>Melanoma, Non-small cell lung cancer (PD-L1+), Head and neck squamous cell carcinoma</td>
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<tr>
<td>Pertuzumab (Perjeta)</td>
<td>HER2 (ERBB2/neu)</td>
<td>Breast cancer</td>
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<tr>
<td>Pexidartinib</td>
<td>CSF1R</td>
<td>Tenosynovial giant cell tumor</td>
</tr>
<tr>
<td>Ramucirumab (Cyramza)</td>
<td>VEGFR2</td>
<td>Colorectal cancer, Gastric cancer or Gastroesophageal junction, Non-small cell lung cancer</td>
</tr>
<tr>
<td>Regorafenib (Stivarga)</td>
<td>KIT, PDGFRβ, RAF, RET, VEGFR1/2/3</td>
<td>Colorectal cancer, Gastrointestinal stromal tumors</td>
</tr>
<tr>
<td>Agent</td>
<td>Target(s)</td>
<td>FDA-approved indication(s)</td>
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<td>-------------------------------</td>
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</tr>
<tr>
<td>Ribociclib (Kisqali)</td>
<td>CDK4, CDK6</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Ripretinib</td>
<td>KIT and PDGFRα inhibitor</td>
<td>GIST</td>
</tr>
<tr>
<td>Sipuleucel-T (Provenge)</td>
<td></td>
<td>Prostate cancer</td>
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<tr>
<td>Sonidegib (Odomzo)</td>
<td>Smoothened</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>VEGFR, PDGFR, KIT, RAF</td>
<td>Hepatocellular carcinoma, Renal cell carcinoma, Thyroid carcinoma</td>
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<tr>
<td>Sunitinib (Sutent)</td>
<td>VEGFR, PDGFR, KIT, RET</td>
<td>Renal Cell Carcinoma, GIST, Pancreatic NET</td>
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<tr>
<td>Tazemetostat</td>
<td>EZH2</td>
<td>Epithelioid Sarcoma</td>
</tr>
<tr>
<td>Temsirolimus (Torisel)</td>
<td>mTOR</td>
<td>Renal cell carcinoma</td>
</tr>
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<td>Trametinib (Mekinist)</td>
<td>MEK</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>HER2 (ERBB2/neu)</td>
<td>Breast cancer, Gastric cancer</td>
</tr>
<tr>
<td>Vandetanib (Caprelsa)</td>
<td>EGFR (HER1/ERBB1), RET, VEGFR2</td>
<td>Medullary thyroid cancer</td>
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<td>Vemurafenib (Zelboraf)</td>
<td>BRAF</td>
<td>Melanoma</td>
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<tr>
<td>Vismodegib (Erivedge)</td>
<td>PTCH, Smoothened</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Ziv-aflibercept (Zaltrap)</td>
<td>PIGF, VEGFA/B</td>
<td>Colorectal cancer</td>
</tr>
</tbody>
</table>
Pazopanib is a small-molecule TKI of growth factor receptors associated with angiogenesis and tumor cell proliferation.

Pazopanib exhibits inhibition of:
- Vascular endothelial growth factor receptors (VEGFR-1, -2, and -3)
- Platelet-derived growth factor receptors (PDGFR-α and -β)
- Fibroblast growth factor receptors (FGFR-1 and -3)
- Stem cell factor receptor (c-Kit)
- Interleukin-2 receptor inducible T-cell kinase (Itk)
- Leukocyte-specific protein tyrosine kinase (Lck)
- Transmembrane glycoprotein receptor tyrosine kinase (c-Fms)

Sleijfer et. al., J Clin Oncol 2009; 3126
PALETTE (PAzopanib ExplorEd in SofT-Tissue Sarcoma; EORTC 62072): Phase III Trial Pazopanib vs. Placebo in STS

N=359

RANDOMIZE

Pazopanib 800 mg OD N = 246

1° Endpoint

2° Endpoint

PFS RECIST

Followed for survival

OS ORR QOL Safety

Matching placebo N=123

2:1

Stratification:
Performance Status (0 vs 1)
# of prior line of therapy

PALETTE Study
Efficacy: primary endpoint

<table>
<thead>
<tr>
<th>Median PFS</th>
<th>pazopanib (n=246)</th>
<th>Placebo (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>4.6</td>
<td>1.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.35 (0.26-0.48)</td>
<td></td>
</tr>
</tbody>
</table>

HR, Hazard ratio

P<0.001
PALETTE Study
Efficacy: primary endpoint (cont’d)

- Pazopanib demonstrated PFS benefit in prespecified subgroups based on STS histology

![Bar chart showing median PFS (months) for different subgroups]
Phase 3 Trials in Advanced STS

**2012**
- **PALETTE**
  - pazopanib vs. placebo
  - mOS: 12.5 vs. 10.7 mo
  - HR: 0.86
  - (95% CI, 0.67-1.11)
  - PFS: 4.6 vs. 1.6 mo

**2014**
- **EORTC-62012**
  - dox vs. dox + ifosfamide
  - mOS: 12.8 vs. 14.3 mo
  - HR: 0.83
  - (95% CI, 0.67-1.03)
  - PFS: 4.6 vs. 7.4 mo

**2015**
- **PICASSO-III**
  - dox vs. dox + palifosfamide
  - mOS: 16.9 vs. 15.9 mo
  - HR: 1.05
  - (95% CI, 0.79-1.39)
  - PFS: 5.2 vs. 6.0 mo

**2016**
- **ET743-SAR-3007**
  - trabectedin vs. dacarbazine
  - mOS: 13.7 vs. 13.1 mo
  - HR: 0.93
  - (95% CI, 0.75-1.15)
  - PFS: 4.2 vs. 1.5 mo

**2017**
- **SARC 216**
  - dox vs. dox + evofosfamide
  - mOS: 19.0 vs. 18.4 mo
  - HR: 1.06
  - (95% CI, 0.88-1.29)
  - PFS: 6.0 vs. 6.3 mo

**2018**
- **E7389-G000-3095**
  - eribulin vs. dacarbazine
  - mOS: 13.5 vs. 11.5 mo
  - HR: 0.77
  - (95% CI, 0.62-0.95)
  - PFS: 2.6 vs. 2.6 mo

**2019**
- **GeDDiS**
  - dox vs. doce + gemcitabine
  - mOS: 17.6 vs. 15.5 mo
  - HR: 1.14
  - (95% CI, 0.83-1.57)
  - PFS: 5.4 vs. 5.5 mo

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**Led to drug approval**
- First Line
- Second Line +
- Third Line +

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dox, doxorubicin; doce, docetaxel; EORTC, European Organisation for Research and Treatment of Cancer; GEDDIS, gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas; mOS, median overall survival; mo, month; PICASSO, palifosfamide-tris with doxorubicin for soft tissue sarcoma; SARC, Sarcoma Alliance for Research Through Collaboration; STS, soft tissue sarcoma; wks, weeks.

Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis)

- Vascular, proliferative, inflammatory synovium
  - Multinucleated giant cells, macrophages, and hemosiderin

- Localized or diffuse-type growth pattern

- Intra- or extra articular locations

- Translocations (1p13)/alterations involving CSF1 gene

- ↑ CSF1 expression → macrophage recruitment to tumor site → CSF1/CSF1R autocrine/paracrine loop of neoplastic/non-neoplastic cells
Tenosynovial Giant Cell Tumor Therapies

- Localized
  - Surgical- subtotal/ total resection, synovectomy to arthroplasty
  - Radiation/ radio-synovectomy

- Systemic → anti-CSF1R therapies
Study Design

Patients
- Histologically confirmed, advanced, symptomatic tenosynovial giant cell tumours
- Surgical resection associated with potential for worsening of functional limitation or severe morbidity
- Measurable disease ≥2 cm by RECIST 1.1

Stratification
- US versus non-US sites
- Upper versus lower extremity

Part one
Placebo-controlled and masked (24 weeks)
- Randomly assigned 1:1
- Pexidartinib
  - 1000 mg per day split twice a day (2 weeks), then
  - 800 mg per day split twice a day (22 weeks)
- Placebo (matching placebo)

Part two
Open-label extension (≥25 weeks)
- Pexidartinib Current dose

Patient-reported outcome
- Week 1: ▲
- Week 9: ▲
- Week 13: ▲
- Week 17: ▲
- Week 25: ▲
- Every 12 weeks

MRI
- Week 1: ◇
- Week 9: ◇
- Week 13: ◇
- Week 17: ◇
- Every 12 weeks

Range of motion
- Every 12 weeks
Maximum change in tumor size according to RECIST and tumor volume score
On August 2, 2019, the FDA approved pexidartinib capsules for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Pexidartinib is the first systemic therapy approved for patients with TGCT.

The approval was based on durable ORR. After 25 weeks of treatment, the ORR was 38% (95% confidence interval: 27, 50), with a 15% complete response rate and a 23% partial response rate.

No patients receiving placebo had a response (p<0.0001). 22 of 23 patients who responded and had been followed for a minimum of 6 months after the initial response maintained the response for ≥6 months.
PHASE 2, INTERNATIONAL, MULTICENTER STUDY OF TAZEMETOSTAT IN ADULT PATIENTS WITH INI1-NEGATIVE TUMORS OR RELAPSED/REFRACTORY SYNOVIAL SARCOMA (NCT02601950)

COHORT 5* – INI1-NEGATIVE EPITHELIOID SARCOMA (ES) PATIENTS

- 2-stage Green-Dahlberg design
- Enrollment in cohort 5 initiated in December 2015, closed in September 2018
- Last data cut for cohort 5: September 17, 2018
- Conducted at 32 sites across USA, Europe and Asia
- Sponsored by Epizyme

* Cohort 5 was 1 of 7 cohorts within the study. ES, epithelioid sarcoma.
# PRIMARY STUDY ENDPOINT: OBJECTIVE RESPONSE RATE (ORR) PER RECIST

<table>
<thead>
<tr>
<th>Endpoint Category (RECIST), n (%)</th>
<th>No Prior Systemic Therapy (n=24)</th>
<th>Prior Systemic Anticancer Therapy (n=38)</th>
<th>Total (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR [CR+PR]</strong></td>
<td>6 (25%) (9.8–46.7)</td>
<td>3 (8%) (1.7–21.4)</td>
<td>9 (15%) (6.9–25.8)</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
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<tr>
<td><strong>CR</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>6 (25%)</td>
<td>3 (8%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>15 (63%)</td>
<td>20 (53%)</td>
<td>35 (56%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>2 (8%)</td>
<td>11 (29%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td><strong>Not evaluable</strong></td>
<td>1 (4%)</td>
<td>4 (11%)</td>
<td>5 (8%)</td>
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</tbody>
</table>

* ORR is the percentage of subjects achieving a confirmed CR or PR from the start of tazemetostat until PD or the start of subsequent anticancer therapy, whichever is earlier. CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors.
BEST PERCENT CHANGE IN SUM OF DIAMETERS PER INVESTIGATOR ASSESSMENT

51% of patients demonstrated reduction in lesion diameter

* Post-baseline sum of diameters was not calculated for 7 subjects in the Intent-to-Treat population due to a lack of complete tumor diameter measurements at any post-baseline visit. These subjects were excluded from the figure.
TREATMENT WITH TAZEMETOSTAT, AN INVESTIGATIONAL, FIRST-IN-CLASS ORAL EZH2 INHIBITOR, ACHIEVED

- An ORR by RECIST in 15% of all patients
- A decrease in tumor size in 51% of all patients
- Durable responses. At a median follow-up of 59.9 weeks, the median DOR was not reached
- A median PFS of 23.7 weeks, with 21.3% patients progression-free at 1 year.
- A median OS of 82.4 weeks

TAZEMETOSTAT WAS GENERALLY WELL TOLERATED WITH NO TREATMENT-RELATED DEATHS AND <2% DEFINITIVE DISCONTINuations

TAZEMETOSTAT, WAS APPROVED 1/23/2020 FOR ACCELERATED APPROVAL FOR THE TREATMENT OF PATIENTS WITH METASTATIC OR LOCALLY ADVANCED EPITHELIOID SARCOMA NOT ELIGIBLE FOR CURATIVE SURGERY

DOR, duration of response; ES, epithelioid sarcoma; EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; ORR, objective response rate; PFS, progression-free survival; RECIST, response evaluation in solid tumors.
Sarcoma as a “targetable” disease

- Dermatofibrosarcoma protuberans
- Tenosynovial giant cell tumor/Pigmented villonodular synovitis
- PEComa
- Inflammatory myofibroblastic tumor
- Giant cell tumor of bone
- Angiosarcoma
- Alveolar soft part sarcoma
- Desmoid tumor/deep fibromatosis
- Liposarcomas
- Solitary fibrous tumor / HPC
- Ewing sarcoma
- Chordoma
- Clear cell sarcoma
City of Hope Sarcoma Care Team

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Future Directions

▪ As cancer care has progressed, there has been a trend toward targeted treatment

▪ The potential benefits of targeted therapies is realized only if patients can be tested and matched to appropriate treatments

▪ Many genomic alterations are rare: testing for only one (rare) alteration is not feasible; broad molecular profiling is needed

▪ Various methodologies are currently available, including several NGS platforms for comprehensive diagnostic testing
Growing Role of Precision Medicine

- With advances in medicine and genetics, over 135 drugs have been developed since 2018 that include genetic (pharmacogenomic) information in their labels.
- A 2015 survey showed that over 40% of drugs in development now include biomarkers in their research and development study design.
- An estimated 69% increase in the number of therapies developed by the year 2020.
- Cancer remains at the vanguard of precision medicine: >70% of investigational cancer therapies are dependent on biomarker data.
  - Broad range of actionable oncogenic biomarkers.
Key Drivers in Growing Role of Precision Medicine

- Growing prevalence of cancer; increased understanding of cancer biology
- Large-scale human genome databases, NGS and computational tools
- Advances in targeted therapy against specific oncogenic molecular targets
Precision Medicine Has Particular Relevance to Oncology

Precision Medicine Impacts All Aspects of Cancer Care\(^1\)

- Identify/classify tumor type\(^2,3\)
- Identify patients likely to benefit from a therapy\(^1,3,5\)
- Identify risk of relapse, progression, or median survival\(^1,3,6\)
- Monitor response to therapy or disease relapse\(^6\)

Matching Actionable Alterations with Appropriate Therapies

To realize the potential benefits of precision oncology for a specific cancer, actionable alterations must be matched with appropriate therapies\(^1\)

A genetic alteration may be actionable if it produces a protein product (or its immediate downstream effectors) that\(^2\):

- Is part of a defined molecular pathway for which there is a corresponding FDA-approved or investigational drug
- Can be differentially recognized in tumor cells versus normal cells by an established or experimental agent\(^2\)
- Predicts sensitivity or resistance to approved or standard therapies\(^3\)

Advent of Anti-cancer Treatments
Targeting Specific Actionable Alterations

- **1995**: HER2 overexpression
  - Breast cancer
  - Trastuzumab
- **1998**: HER2 overexpression
  - Breast cancer
  - Trastuzumab
- **2000**: BCR/ABL-1 fusion
  - CML Imatinib
- **2001**: PD-1/PD-L1 expression
  - Melanoma Pembrolizumab
- **2004**: EGFR mutations
  - NSCLC Erlotinib
- **2005**: ALK fusion
  - NSCLC Crizotinib
- **2008**: EGFR V600E mutation
  - Melanoma Vemurafenib
- **2010**: FLT3 mutation
  - AML Midostaurin
- **2011**: ALK fusion
  - NSCLC Crizotinib
- **2011**: IDH2 mutation
  - AML Enasidenib
- **2012**: ROS-1 fusion
  - NSCLC Crizotinib
- **2014**: PD-1/PD-L1 expression
  - Melanoma Pembrolizumab
- **2015**: MSI-H/dMMR
  - Tumor-agnostic Pembrolizumab
- **2016**: IDH1 mutation
  - AML Ivosidenib
- **2017**: IDH2 mutation
  - AML Enasidenib
- **2017**: IDH1 mutation
  - AML Ivosidenib
- **2017**: AML Midostaurin
- **2017**: MSI-H/dMMR
  - Tumor-agnostic Pembrolizumab
- **2017**: AML Enasidenib
- **2018**: IDH1 mutation
  - AML Ivosidenib
The Importance of Identifying Actionable Genomic Alterations

- The potential benefits of targeted therapies is realized only if patients can be tested and matched to appropriate treatments\(^1\)

- Many genomic alterations are rare: testing for only one (rare) alteration is not feasible- broad molecular profiling is needed
  - No single biomarker will be relevant for every patient\(^1\)

- Various methodologies are currently available, each with distinct strengths and limitations\(^2\)

- Clinicians must make informed decisions about when/whom to test and which assays to use\(^3\)

Major Types of Genomic Alterations in Cancer

Mutations
Changes in the DNA sequence that makes up a gene\(^1\)
- Includes base substitutions, insertions, deletions, and duplications\(^2\)

Structural variations/rearrangements
Changes in the orientation, location, or number of copies of larger DNA segments\(^3\)
- Includes fusions, translocations, inversions, deletions, and duplications

Copy number variations/alterations
Changes in the number of copies of a gene\(^3\)
- Includes gene amplification

Distinguishing between the various alterations is important because not all alterations are driver alterations or are actionable.
Most Actionable Genomic Alterations are Uncommon, Highlighting the Need for Comprehensive Genomic Testing³

- An NGS-based cancer genome profiling test interrogated 4,557 exons of 287 cancer-related genes
  - Detected all classes of clinically relevant genomic alterations in a single, tissue-sparing test

- The average number of actionable alterations in any individual patient’s sample was low (1.57)

- However, wide variety of alterations found across all samples:– 1579 unique alterations

- Comprehensive testing can accurately detect most genomic alterations in all therapeutically relevant cancer genes in a single assay

Detecting Actionable Genomic Alterations

▪ Next Generation Sequencing (NGS)
  o High-throughput nucleic acid sequencing that allow parallel sequencing of multiple targets and multiple samples in order to detect concomitant mutations in the same run

▪ Immunohistochemistry (IHC)
  o Detects antigen of interest (protein) using a labelled antibody (direct) or a set of monoclonal or polyclonal antibodies (indirect)

▪ Reverse Transcription Polymerase Chain Reaction (RT-PCR)
  o RNA molecules converted into complementary DNA (cDNA) sequences by reverse transcriptases, followed by amplification of newly synthesized cDNA by standard qPCR procedures

▪ Fluorescence in situ Hybridization (FISH)
  o Uses DNA or RNA probes labeled with a fluorophore or modified nucleotide to bind complementary sequences
Future Directions in Precision Oncology

- 73% of oncology compounds in development are precision medicines\(^1\)

- NCI-MATCH (NCT02465060) is a precision oncology clinical trial\(^2\)
  - Determine how treatment directed by genetic testing works in patients with solid tumors or lymphomas that have progressed after ≥ 1 line of standard treatment or for which no agreed upon treatment approach exists
  - Patients to receive treatment based on genomic alterations found in their tumors rather than tissue type

<table>
<thead>
<tr>
<th>Eligibility Criteria</th>
<th>Treatment Arms*</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥18 years</td>
<td>• 22 different treatments/interventions</td>
<td>• Primary endpoint</td>
</tr>
<tr>
<td>• Histologically documented solid tumors or confirmed diagnosis of lymphoma or multiple myeloma</td>
<td>• 50 different tumor types</td>
<td>• ORR- the percentage of patients whose tumors have a complete or partial response to treatment (up to 3 years)</td>
</tr>
<tr>
<td>• Measurable disease</td>
<td>• solid tumors</td>
<td>• Secondary endpoints</td>
</tr>
<tr>
<td>• ECOG performance status ≤ 1 and life expectancy of ≥ 3 months</td>
<td>• Lymphomas</td>
<td>• OS, evaluated specifically for each drug</td>
</tr>
<tr>
<td></td>
<td>• multiple myeloma</td>
<td>• PFA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Time to progression</td>
</tr>
</tbody>
</table>

*Currently enrolling treatment arms as of September, 2018
Impact of Next Generation Sequencing (NGS) On the Treatment of Patients with Sarcoma

Background:

▪ NGS is increasingly being used for patients with Sarcoma

▪ The role of NGS in the management of patients with Sarcoma remains undefined

▪ Basket trials, and tissue agnostic therapies are increasingly prevalent and may be compelling options for patients in later lines of treatment

Objective:

▪ To review usage of NGS testing in patients with Sarcoma

▪ To characterize the effect of NGS on management of patients with Sarcoma

▪ Better qualify instances in which NGS was utilized in order to understand incidence of mutations within a large population of Sarcoma patients
Results

- A Total of 117 patients were analyzed with assays performed between 2018 and 2020

- Patient Demographics and Clinical

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- Median (Range)</td>
<td>55 (20-94)</td>
</tr>
<tr>
<td>Male</td>
<td>57 (48%)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (52%)</td>
</tr>
<tr>
<td>Assays Per Patient (Range)</td>
<td>1 (1-4)</td>
</tr>
<tr>
<td>Histologic Subtypes</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>36 (31%)</td>
</tr>
<tr>
<td>STS NOS</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (31%)</td>
</tr>
</tbody>
</table>
Results

Mutation Prevalence

Actionable Mutations

<table>
<thead>
<tr>
<th>Histology</th>
<th>Mutation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewings Sarcoma</td>
<td>PTEN Loss</td>
<td>Copanlisib</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>ALK Fusion</td>
<td>Alectinib</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>MSI-H</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>IDH1</td>
<td>Ivosidenib</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>BRAF V600E</td>
<td>Encorafenib</td>
</tr>
<tr>
<td>STS NOS</td>
<td>CDK4 Amplification</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>STS NOS</td>
<td>CCND1 Amplification</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>STS NOS</td>
<td>NTRK Fusion</td>
<td>Larotrectinib</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>High TMB</td>
<td>Atezolizumab</td>
</tr>
</tbody>
</table>
Conclusions

34% of patients had potentially actionable Mutations

Treatment of 8% of patients was altered by NGS results

Incidence of actionable mutations increased over time

Partial responses in select refractory patients
Questions, Comments or More Information

https://www.cityofhope.org/research/find-a-clinical-trial
There is no profit in curing the body if in the process we destroy the soul.