Clinical/Translational Update

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Topics for Discussion

- Status of First Phase of NCI-MATCH
- Accrual to the Rare Variants Initiative of NCI-MATCH
- Plans for Follow-Up Trials Under the NCI-MATCH Umbrella
  - Phase II Trials
  - Additional NCI-MATCH Arms
- Cancer Immune Monitoring and Analysis Centers
Status and History of NCI-MATCH Trial

- Trial opened August 12, 2015, with 10 treatment arms.
- Trial temporarily closed to new accrual November 11, 2015 for built-in interim analysis.
- 795 patients screened between August 2015 opening and November 2015 temporary closure (3 month period).
- Original estimate of 50 screens per month greatly surpassed (>100/week during latter period).
- Over 1100 approved sites
- Trial re-opened May 31, 2016, with 24 treatment arms.
- 5/17: Closed to accrual requiring bx’s

Participation Rates by Site Type:
NCORPS ~ 90%
NCI Cancer Centers & LAPS ~ 80%
<table>
<thead>
<tr>
<th>Time period</th>
<th># enrolled</th>
<th># first samples submitted</th>
<th># first sample fail</th>
<th># assay complete</th>
<th># assigned to Rx</th>
<th># enrolled on Rx</th>
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</thead>
<tbody>
<tr>
<td>Total Pre Pause</td>
<td>794</td>
<td>739</td>
<td>116</td>
<td>645</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>Most Recent Week</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Total Post Pause</td>
<td>5603</td>
<td>5223</td>
<td>425</td>
<td>4912</td>
<td>937</td>
<td>660</td>
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<tr>
<td>Overall Total Screening Cohort</td>
<td>6397</td>
<td>5962</td>
<td>541</td>
<td>5557</td>
<td>991</td>
<td>687</td>
</tr>
<tr>
<td>Total Outside Assay</td>
<td>62</td>
<td>29</td>
<td>2</td>
<td>56</td>
<td>51</td>
<td>36</td>
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</table>
Current Status

- 30 treatment arms; ≈ 50% fully accrued; ≈ 25% well on the way; ≈ 25% will need additional accrual from ‘rare variant study’
- 6 more treatment arms approved for subsequent studies
- Assay success rate 94%
- Median assay turnaround time 16 days
- Toxicity acceptable
- Objective responses have been observed in 3 of the initial arms so far
Analysis Plan

• ORR, TTP, OS, toxicity in patients who received protocol therapy
• If the ORR is $\geq 5/31$ (16%) the agent will be worthy of further study: Protocol Defined
• 35 patients will need to be accrued to each arm to obtain 31 for each arm (with 10% ineligibility rate)
• Need $\approx 8$ mos median f/u to assess response
NCI-MATCH: Molecular Analysis for Therapy Choice (EAY131)

Rare Variant/
Outside Assay Initiative
### NCI-MATCH Remaining 15 of 30 Current Treatment Arms, By Prevalence Rate of Gene Abnormality

<table>
<thead>
<tr>
<th>Arm</th>
<th>Variant</th>
<th>Prevalence Rate %</th>
<th>Drug</th>
<th>Opened</th>
<th>Accrual Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>AKT</td>
<td>0.77</td>
<td>AZD5363</td>
<td>May ‘16</td>
<td>35</td>
</tr>
<tr>
<td>H</td>
<td>BRAF V600 E/K</td>
<td>0.69</td>
<td>Taflinar® Mekinist™</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>U</td>
<td>NF2 loss</td>
<td>0.69</td>
<td>Defactinib (VS-6063)</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>C2</td>
<td>MET exon 14</td>
<td>0.61</td>
<td>Xalkori®</td>
<td>May ‘16</td>
<td>35</td>
</tr>
<tr>
<td>C1</td>
<td>MET amplif.</td>
<td>0.51</td>
<td>Xalkori®</td>
<td>May ‘16</td>
<td>35</td>
</tr>
<tr>
<td>T</td>
<td>SMO/PTCH1</td>
<td>0.42</td>
<td>Erivedge®</td>
<td>Feb ‘16</td>
<td>35</td>
</tr>
<tr>
<td>L</td>
<td>mTOR</td>
<td>0.31</td>
<td>TAK-228</td>
<td>Mar ‘17</td>
<td>35</td>
</tr>
<tr>
<td>S2</td>
<td>GNAQ/GNA11</td>
<td>0.16</td>
<td>Mekinist™</td>
<td>Feb ‘16</td>
<td>35</td>
</tr>
<tr>
<td>E</td>
<td>EGFR T790M</td>
<td>0.11</td>
<td>AZD9291</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>V</td>
<td>cKIT</td>
<td>0.11</td>
<td>Sutent®</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>Z1E</td>
<td>NTRK</td>
<td>0.10</td>
<td>Larotrectinib</td>
<td>Mar ‘17</td>
<td>35</td>
</tr>
<tr>
<td>G</td>
<td>ROS1</td>
<td>0.05</td>
<td>Xalkori®</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>A</td>
<td>EGFR activating</td>
<td>0.05</td>
<td>Gilotrif®</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>F</td>
<td>ALK</td>
<td>0.03</td>
<td>Xalkori®</td>
<td>Aug ‘15</td>
<td>35</td>
</tr>
<tr>
<td>X</td>
<td>DDR2</td>
<td>0.00</td>
<td>Sprycel®</td>
<td>Feb ‘16</td>
<td>35</td>
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</tbody>
</table>
Rationale for Rare Variant/Outside Assay Initiative

- About 60% of screened patients on NCI-MATCH had less common/rare cancers (not colorectal, breast, NSCLC, prostate)
- Many of these arms have not completed accrual given the low frequency of certain mutations
- Tumor gene variants in less common cancers lower than expected (3.47 percent to 0)
- Need to accrue to these arms if possible
- NCI-MATCH provides treatment options for these patients
NCI-MATCH Collaboration with Commercial Labs

• Caris Life Sciences® and Foundation Medicine, Inc. will notify the treating physician at any one of the ~1100 sites when the results of their assay could make a patient eligible for a MATCH treatment arm.

• The labs do not specifically screen for the NCI-MATCH trial; it is only when the test is done for the purposes of clinical care.

• The results must be verified centrally by the NCI-MATCH Oncomine® assay.
NCI-MATCH Academic Laboratories

• In addition, we have engaged two academic labs that are already involved in the trial
  – MD Anderson Cancer Center
  – Memorial Sloan Kettering Cancer Center
• These labs will perform testing on their own patients, using their institutional assays
• MD Anderson uses the Oncomine® assay used in NCI-MATCH
• MSKCC uses a screening assay developed at their institution
• Patients will be considered for NCI-MATCH based on these results
• Request for proposals from other NGS providers posted in Federal Register in July 2017 to broaden patient base for completion of ongoing arms: Critical for Future Precision Oncology Studies
Future of MATCH: Considerations

Responsive Phenotypes

• For patients with the aMOI and evidence of a response (ORR>16% per study definition): **Phase II trial** for that drug to determine its true activity under NCI-MATCH umbrella

New Treatment Arms

• Activate 6 additional NCI-MATCH Arms (beyond Rare Variant Initiative) that have been approved by Pharma collaborators, and meet appropriate level of evidence, **IF** sufficient referral base of patients established using academic and commercial laboratories
## NCI-MATCH New Treatment Arms in Development for Addendum #11 – Possible Fall 2017 Activation

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Mutation Prevalence Rate in NCI-MATCH</th>
<th>Arm</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>3.47%</td>
<td>Z1F Follows arm I</td>
<td>copanlisib</td>
</tr>
<tr>
<td>PTEN loss by IHC</td>
<td>1.93%</td>
<td>Z1G Follows arm P</td>
<td>copanlisib</td>
</tr>
<tr>
<td>FGFR amplif.</td>
<td>1.86%</td>
<td>K1 Follows arm W</td>
<td>erdafitinib</td>
</tr>
<tr>
<td>PTEN</td>
<td>1.75%</td>
<td>Z1H Follows arm N</td>
<td>copanlisib</td>
</tr>
<tr>
<td>FGFR mut. or fusion</td>
<td>1.00%</td>
<td>K2 Follows arm W</td>
<td>erdafitinib</td>
</tr>
<tr>
<td>p53 and MYC</td>
<td>unavailable</td>
<td>Z1J</td>
<td>AZ1775</td>
</tr>
</tbody>
</table>
CIMAC: Cancer Immune Monitoring & Analysis Centers
Cancer Immune Monitoring and Analysis Centers (CIMACs)
Cancer Immunologic Data Commons (CIDC)

• Why CIMAC-CIDC network
  – To provide a standing, prefunded network of laboratories, along with a common data center, to perform biomarker assays and analysis for NCI-funded, early phase 1/2 clinical trials with immunotherapies, using standardized and state of the art assays
  – Data repository/center for biomarker results from CIMACs will foster a data integration/analysis platform for correlative studies within and across trials

• Funded under cooperative grant mechanisms (U24)
  – Current funding limited to early immunotherapy trials (phase I and phase II) under the NCI clinical trial networks or NCI grants (R01, SPORES, etc)
  – Covers comprehensive profiling for approximately 400 patient–timepoint per year

• Utilization of the CIMAC-CIDC resource is voluntary, but desired studies will require collaboration with CIMAC and approval by CTEP.

• FNLCR PD lab will collaborate with UCSF, Stanford, Mt. Sinai, MD Anderson, DFCI for assay development
Proposed CIMACs-CIDC Network Structure (Tentative)

- Each CIMAC is a multidisciplinary team (bioassays, statisticians, informatician, translational scientists, pathologists)
- Will be aligned with Clinical Trial Networks and Clinical trials – Collaboration in scientific planning, tissue accession, data analysis, and publication
- Triage of the work will be based on: Assay expertise; Overall workload; Established relationship with specific trials
- A given CIMAC may perform a specific assay for all CIMACs, depending on resource prioritization and expertise