SPRING 01 TRIAL
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A proof of concept Phase I/II study of the tri-therapy approach in advanced/metastatic NSCLC and correlative integrated genomics/transcriptomics

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Disclosures

• None
International Phase I/II Study of tri-therapy in NSCLC

• First trial investigating triple targeted therapy for metastatic/advanced non-small-cell lung cancer (NSCLC) in first line of treatment

• Study approved by the FDA and currently enrolling in USA, Europe, Israel

• Hypothesis: A triple targeted therapy approach will be able to achieve what targeted single agents have failed to do so far in precision oncology, stave off acquired resistance and prolong survival.
Academic Institutions, PIs and other partners

Razelle Kurzrock  
Senior Deputy Center Director  
Director, Center for Personalized Cancer Therapy, University of California San Diego Moores Cancer Center, USA

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Jair Bar  
Head of the Thoracic Oncology, Sheba Medical Center, Israel

Guy Berchem  
Medical Oncologist, Centre Hospitalier du Luxembourg

Pierre Saintigny  
Department of Translational Research, Centre Léon Bérard, France

Open sites:  
Pending sites:  
Other Partners:  
Industry partners:

- Pfizer
- Merck KGaA
- HTG Molecular
- Illumina
- Covance
Tumor and normal tissue undergo genomic and transcriptomic analysis and SIMS algorithm application.

Tumor and endobronchial mucosal biopsy

Treatment with avelumab, axitinib, and palbociclib

Response assessment and correlation with SIMS algorithm

Advanced/Metastatic NSCLC

- EGOG 0-1
- No EGFR, ALK; no ROS1 or MET if tested
- PDL1 positive or negative
- ≤2 prior lines (phase I) or untreated (phase II)
- Prior treated brain mets allowed
- Concurrent anticoagulation excluded
- Phase I n=30; Phase II n=100

Primary endpoint:
6-month objective response rate RR (by RECIST 1.1 criteria) as % of patients who achieve complete response, or partial response.

**SPRING 01 Phase 1 3+3 Dose Escalation**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>5 mg/kg</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Every 2 weeks</td>
<td>every 2 weeks</td>
<td>every 2 weeks</td>
<td>every 2 weeks</td>
<td>every 2 weeks</td>
</tr>
<tr>
<td>Axitinib</td>
<td>3 mg po bid</td>
<td>3 mg po bid</td>
<td>5 mg po bid</td>
<td>5 mg po bid</td>
<td>5 mg po bid</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>75 mg po qd 7 days OFF, 21 days ON</td>
<td>75 mg po qd 7 days OFF, 21 days ON</td>
<td>75 mg po qd 7 days OFF, 21 days ON</td>
<td>100 mg po qd 7 days OFF, 21 days ON</td>
<td>125 mg po qd 7 days OFF, 21 days ON</td>
</tr>
</tbody>
</table>

*Avelumab* is administered at the study center by intravenous infusion
*Axitinib and palbociclib* are taken orally at home
SPRING 01 Demographics (N=12)

<table>
<thead>
<tr>
<th>Number of patients enrolled by Site</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Avera Cancer Institute, Sioux Falls, SD, USA</td>
<td>2</td>
</tr>
<tr>
<td>UCSD Moores Cancer Center, La Jolla, CA, USA</td>
<td>2</td>
</tr>
<tr>
<td>VHIO, Barcelona, Spain</td>
<td>3</td>
</tr>
<tr>
<td>Centre Hospitalier du Luxembourg, Luxembourg</td>
<td>2</td>
</tr>
<tr>
<td>The Chaim Sheba Medical Center, Tel Hashomer, Israel</td>
<td>3</td>
</tr>
<tr>
<td>Centre Leon Berard, Lyon France</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior lines of therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>1 line</td>
<td>6</td>
</tr>
<tr>
<td>2 lines</td>
<td>5</td>
</tr>
</tbody>
</table>
SPRING 01 DLT

COHORT 1 N=3
Avelumab 10 mg/kg
Axitinib 3 mg
Palbociclib 75 mg
DLTs N=0

COHORT 2 N=6
Avelumab 10 mg/kg
Axitinib 5 mg
Palbociclib 75 mg
DLTs N=1
• G3 Infusion reaction

COHORT 3 N=3
Avelumab 10 mg/kg
Axitinib 5 mg
Palbociclib 100 mg
DLTs N=2
• G4 Resp failure
• G3 palmar-plantar erythrodysesthesia

Level 2 is the MTD
Level 3 is above MTD
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency</th>
<th>Grade</th>
<th>Attribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count decreased</td>
<td>25%</td>
<td>3</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25%</td>
<td>3</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>17%</td>
<td>3</td>
<td>Tri-therapy</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>17%</td>
<td>3</td>
<td>Avelumab and axitinib</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>8%</td>
<td>3</td>
<td>Avelumab</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>3</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesiae</td>
<td>8%</td>
<td>3</td>
<td>Axitinib</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8%</td>
<td>3</td>
<td>Tri-therapy</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>8%</td>
<td>3</td>
<td>Avelumab and axitinib</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8%</td>
<td>4</td>
<td>Tri-therapy</td>
</tr>
</tbody>
</table>
SPRING 01 Response Features

- 12 patients treated
- 4 Partial responses
  - 2 PR in Dose Level 1 (of 3 treated patients)
  - 2 PRs in Dose Level 2 (of 6 treated patients)
  - 2 PRs in patients with prior checkpoint inhibition
- Duration of PRs 11+, 7, 6, 3 months
### SPRING 01 Response RECIST 1.1

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>2</th>
<th>3</th>
<th>2</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>2</th>
<th>1</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>5</td>
<td>16</td>
<td>14</td>
<td>11</td>
<td>9</td>
<td>15</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Months in</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**% Change in tumor size by RECIST 1.1**

- Blue bars represent patients with a decrease in tumor size.
- Gray bars represent patients with no change in tumor size.
- Orange bars represent patients with an increase in tumor size.
SPRING 01 Case Report—Patient 2

• 52-year-old male with adenocarcinoma histology
• Dose level 1
• 1 prior line of therapy
  • 1\textsuperscript{st} line—pemetrexed, carboplatin, and pembrolizumab
• Partial response with 52\% reduction in target lesion measurements
• PFS=24 weeks
• Molecular data (DNA report)—KRAS G12V, FGFR (amp), Myc (amp), PIK3CB (amp), VEGF (amp), CCND3 (amp), MS stable, TMB 6 mut/MB
• PDL1=0\% (Dako 22C3)
SPRING 01 Case Report—Patient 2
52 y.o. male/adenoCA/Dose level 1/Best Response—52%↓/PFS 24 weeks
SPRING 01 Case Report—Patient 3

- 64-year-old female with adenocarcinoma histology
- Dose level 1
- No prior treatment
- Partial response with 80% reduction in target lesion measurements
- PFS=45+ weeks(ongoing)
- Molecular data (DNA report)—TP53 splice site 981_993+34del47; ERBB2: A775_G776insYVMA; ERRFI1: S138fs*8; ERRFI1: Q88*
- PDL1=60% (Dako 22C3)
SPRING 01 Case Report—Patient 3
64 y.o. female/adenoCA/Dose level 1/Best Response—80%↓/PFS 45+ weeks
72-year-old male with adenocarcinoma histology

Dose level 2

1 prior line of therapy

1st line—pemetrexed and carboplatin

Partial response with 50% reduction in target lesion measurements

PFS=31 weeks

Molecular data—No NGS data

PDL1=0% (Dako 22C3)
SPRING 01 Case Report—Patient 13
72 y.o. male/adenoCA/Dose level 2/Best Response—50%↓/PFS 31 weeks
SPRING 01 Phase I Conclusions

- Phase I: 12 patients treated. MTD determined.
- MTD may not be the RP2D because of long term tolerance
- PR rate of 33% including
  - 2 PRs in patients who failed prior pembrolizumab
  - 2 PRs on dose level 1
- Tri-therapy regimen of avelumab, axitinib, and palbociclib is tolerable
- Shows early evidence of activity including in NSCLC patients who failed a prior checkpoint inhibitor.
- Expansion cohorts are being added to optimize safety evaluation of a RP2D