NRG-LU004: Phase I study of AcceleRated vs. Conventionally fractionated radiotherapy with durvalumab in PD-L1 high expressing non-small cell lung cancer (ARCHON-1)

• **Hypothesis:** It is safe to combine radiotherapy alone (especially accelerated hypofractionated radiotherapy) with durvalumab concurrently and in maintenance in PD-L1 high locally-advanced NSCLC
Rationale Replacing Chemo With Immunotherapy

- Concurrent chemo-radiation was done at one point to improve on the terrible outcomes of radiation alone
- But, no consolidation chemo nor consolidation/maintenance targeted therapy trials in an unselected population have shown a survival benefit
- Current standard of care remains concurrent chemo-radiation followed by 1 year immunotherapy
- Concurrent chemo regimens do not achieve systemic therapy dosing and their main benefit may be to provide radiosensitization, with significant toxicities
- Ongoing studies demonstrate that immunotherapy can be a radiosensitizer but also have systemic effects, potentially even better in select patients (PD-L1 Hi)

- Replacing chemo is in-line with AZ strategic development (confirmed with US and Global leads)
# Replacing Chemotherapy With Immunotherapy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT</th>
<th>Phase of Trial</th>
<th>N</th>
<th>NSCLC Stage</th>
<th>Type of Radiation</th>
<th>Systemic Therapy</th>
<th>Biomarker Eligibility Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG LU004</td>
<td>03801902</td>
<td>I</td>
<td>24</td>
<td>IIA to IIIC</td>
<td>Accelerated hypofractionated and conventional fractionated</td>
<td>Durvalumab</td>
<td>PD-L1 IHC ≥ 50%</td>
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<tr>
<td>SPRINT</td>
<td>03523702</td>
<td>II</td>
<td>63</td>
<td>II to III</td>
<td>Conventional</td>
<td>PD-L1 IHC ≥ 50% receives Pembrolizumab while &lt; 50% receives concurrent chemotherapy</td>
<td>PD-L1 IHC status</td>
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<tr>
<td>MDACC</td>
<td>04013542</td>
<td>I</td>
<td>20</td>
<td>II to III</td>
<td>Conventional</td>
<td>Nivolumab-Ipilimumab</td>
<td>None</td>
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</tbody>
</table>

**Poor PS Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT</th>
<th>Phase of Trial</th>
<th>N</th>
<th>NSCLC Stage</th>
<th>Type of Radiation</th>
<th>Systemic Therapy</th>
<th>Biomarker Eligibility Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland Medical Center</td>
<td>03818776</td>
<td>I</td>
<td>27</td>
<td>IIA to IIIC</td>
<td>unsuitable for concurrent chemo-radiation</td>
<td>Proton beam (60 or 69 cGy)</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>PARIS</td>
<td>03245177</td>
<td>I</td>
<td>25</td>
<td>unsuitable for concurrent chemo-radiation</td>
<td></td>
<td>Conventional</td>
<td>Pembrolizumab</td>
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</table>

- ClinicalTrials.gov. NCT03801902; ClinicalTrials.gov. NCT03523702; ClinicalTrials.gov. NCT03818776; ClinicalTrials.gov. NCT03245177.
NRG-LU004: Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (durvalumab) in PD-L1 High Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (ARCHON-1)

Safety Cohorts

- Cohort 1, n = 3
  Durvalumab x 13 doses + Accelerated RT 60 Gy in 15 fx x 3 weeks
  - If Cohort 1 only is deemed safe, all patients will be registered to Cohort 3

- Cohort 2, n = 3
  Durvalumab x 13 doses + Standard RT 60 Gy in 30 fx x 6 weeks
  - If Cohort 2 only is deemed safe, all patients will be registered to Cohort 4
  - If both Cohorts 1 and 2 are deemed safe, patients will be randomized 1:1 to either Cohort 3 or 4

Expansion Cohorts

- Cohort 3, n = 9
  Durvalumab x 13 doses + Accelerated RT 60 Gy in 15 fx x 3 weeks
- Cohort 4, n = 9
  Durvalumab x 13 doses + Standard RT 60 Gy in 30 fx x 6 weeks

Primary: safety of adding durvalumab to 2 schedules of RT (60 Gy in 30 fx or 15 fx)
Secondary: feasibility, toxicities, PFS
Exploratory: tumor tissue/blood biomarkers, microbiome, TMB, PD-L1 IHC

- Durvalumab begins 2 weeks (day -14) before RT (+/- 48 hours) and is given 1500 mg IV Q4 weeks.
- ClinicalTrials.gov. NCT03801902.
Endpoints

Safety and Feasibility of durvalumab + RT in two flavors (accelerated RT vs conventional RT)

Primary endpoint: treatment related serious adverse events assessed using CTCAE v5.0

DLT observation period:
- ACRT + durva = 90 days from start of RT
- Standard RT + durva = 8 weeks from start of RT

DLT definition:
- Grade 4-5 non hematologic AEs within DLT window, significant dose delays, or permanent discontinuation of study drug if causatively related to drug
To move to phase II, treatment arm must be both “safe” and “feasible”

Safety: In the first part of study, if 0-1 of 6 evaluable pts develop any safety event after RT, then the regimen will be deemed safe, and that arm will continue to second part of study and enroll 6 additional pts
For each arm, after completing the entire study, if <=3 of the 12 evaluable pts experience a safety event, then the treatment will be considered “safe” or “tolerable”

Feasibility: Based on percentage of pts who received at least 80% of the planned dose of durvalumab during the first 8 weeks after durva. If 80% of the pts (10 of 12 per arm) receive at least 80% of the planned dose is considered to be “feasible”
LU004 status

Activated: January 4, 2019

Suspended: January 22, 2020 (Cohort 1)

Reopened: January 22, 2020 (Cohort 2)

Suspended: April 13, 2020 (Cohort 2)

Reopened: July 16, 2020 (Cohorts 3 and 4)

Closed: June 21, 2021 (Study)
Summary of safety of LU004

- Treatment with RT and durva was safe and well tolerated during and after treatment
- Toxicities were low (lower than what we see with chemoradiation)
- The reasons why 3 out of the 12 pts in the conventional RT + durva arm didn’t get second dose of durva had NOTHING to do with feasibility of combining durva with radiation, but patients had viral hepatitis reactivation, pneumonia and hemoptysis that were NOT related to treatment
- Efficacy results will be presented after two years of follow up
**COAST** (Combination Platform Study in Unresectable Stage III NSCLC; NCT03822351)

- Phase 2 study of durvalumab alone or combined with the anti-CD73 mAb oleclumab or anti-NKG2A mAb monalizumab as consolidation therapy

Oleclumab, anti-CD73,
Reduces extracellular adenosine production
Promotes antitumor immunity

Monalizumab blocks NKG2A
to reduce inhibition of NK and CD8+ T cells

- mAb, monoclonal antibody.
A planned sample size of 60 patients per arm was designed to provide acceptable precision in estimating antitumor activities in an early phase setting.

Between Jan 2019 and Jul 2020, 189 patients were randomized of whom 186 received D (n = 66), D+O (n = 59) or D+M (n = 61).
COAST Results Favor D+O and D+M for PFS With No Significant Increase in Toxicity

### Antitumor activity

<table>
<thead>
<tr>
<th></th>
<th>D (n = 67)</th>
<th>D+O (n = 60)</th>
<th>D+M (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR</td>
<td>17.9</td>
<td>30</td>
<td>35.5</td>
</tr>
<tr>
<td>DCR 16 weeks</td>
<td>58.2</td>
<td>81.7</td>
<td>77.4</td>
</tr>
<tr>
<td>Median DoR (months)</td>
<td>NR</td>
<td>12.9</td>
<td>NR</td>
</tr>
<tr>
<td>mPFS</td>
<td>6.3</td>
<td>NR</td>
<td>15.1</td>
</tr>
<tr>
<td>HR</td>
<td>-</td>
<td>0.44</td>
<td>0.65</td>
</tr>
</tbody>
</table>

### Incidence, n (%)

<table>
<thead>
<tr>
<th></th>
<th>D (n = 66)</th>
<th>D+O (n = 59)</th>
<th>D+M (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs</td>
<td>65 (98.5)</td>
<td>57 (96.6)</td>
<td>61 (100)</td>
</tr>
<tr>
<td>Grade 3 TEAEs</td>
<td>26 (39.4)</td>
<td>24 (40.7)</td>
<td>17 (27.9)</td>
</tr>
<tr>
<td>Study drug-related AEs</td>
<td>49 (74.2)</td>
<td>46 (78.0)</td>
<td>50 (82.0)</td>
</tr>
<tr>
<td>Study drug-related SAEs</td>
<td>6 (9.1)</td>
<td>7 (11.9)</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>11 (16.7)</td>
<td>9 (15.3)</td>
<td>9 (14.8)</td>
</tr>
<tr>
<td>Deaths*†</td>
<td>7 (10.6)</td>
<td>4 (6.8)</td>
<td>3 (4.9)</td>
</tr>
</tbody>
</table>

*All reported deaths within 90 days post-last dose, regardless of relationship to study drug; †In total, 4 deaths were related to study drug, 2 (pneumonitis and radiation pneumonitis) in the D arm, 1 (pneumonitis) in the D+O arm, and 1 (myocardial infarction) in the D+M arm.

NeoCoast-1: Tina Cascone AACR 2022

Stage I-IIIA NSCLC Unresectable
March 2019-Sept 2020 (N=84)

1 cycle (28 day)

- Durva alone
  - surgery
  - MPR: 11.1%
  - pCR: 3.7%

- + Durva + Monalizumab
  - surgery
  - MPR: 30%
  - pCR: 10%

- + Durva + Oleclumab
  - surgery
  - MPR: 19%
  - pCR: 9.5%

- + Durva + danvatirsen
  - surgery
  - MPR: 31.3%
  - pCR: 12.5%
Aligning with AZ strategy in future development

**PACIFIC-9 Study design**

Phase III, double-blind, multicenter international study of durvalumab + oleclumab and durvalumab + monalizumab for the treatment of patients who have not progressed following concurrent chemoradiation treatment for locally-advanced, stage III, unresectable NSCLC.

**Patient Population**
- Patients with unresectable stage III NSCLC who have not progressed following definitive platinum-based CRT

**Stratification Factors**
- Stage (IIIA: IIIB/IIIC)
- Histology (Squamous: Non-squamous)
- PD-L1 (<1%: 1% - 49%: ≥ 50%)

**Arm A**
- N=333
- Durvalumab 1500mg on day 1 of each 28-day cycle + Oleclumab 3000mg on day 1 and 15 of first two cycles then on day 1 of each subsequent cycle
- Total Treatment: 12 mos

**Arm B**
- N=333
- Durvalumab 1500mg day 1 of each 28-day cycle + Monalizumab 1500mg day 1 of each cycle + placebo on day 15 of first two cycles
- Total Treatment: 12 mos

**Arm C**
- N=333
- Durvalumab 1500mg day 1 of each 28-day cycle + placebo day 1 and 15 of first two cycles then day 1 of each subsequent cycle
- Total Treatment: 12 mos

**Primary Endpoints**
- PFS (BCR) Arm A vs Arm B
- PFS (BCR) Arm B vs Arm C

**Secondary endpoints**
- OS Arm A vs Arm C
- OS Arm B vs Arm C
- Safety/tolerability
CTEP approved amendment to LU004

LA-NSCLC PD-L1 ≥50%

60 Gy in 30 Fractions + Durva + Monalizumab

Durvalumab + Monalizumab x 1 year

Initial 6 → safety window of 8 weeks; Additional 6 patients

60 Gy in 30 Fractions + Durva + Oleclumab

Durvalumab + Oleclumab x 1 year

Initial 6 → safety window of 8 weeks; Additional 6 patients
LA-NSCLC PD-L1 ≥50%

60 Gy in 30 Fractions + Durva + Monalizumab

Durvalumab + Monalizumab x 1 year (N=12)

60 Gy in 30 Fractions + Durva + Oleclumab

Durvalumab + Oleclumab x 1 year (N=12)

Followed by proposal to be approved by NRG RSC and TMSC submission

60 Gy in 30 Fractions + Chemo

Durvalumab x 1 year

60 Gy in 30 Fractions + Durva + Oleclumab

Durvalumab + Olec x 1 year

60 Gy in 30 Fractions + Durva + Monalizumab

Durvalumab + Mona x 1 year

Randomized Phase 2/3

LA-NSCLC PD-L1 ≥50%

LU004 amendment w/ two added cohorts (N=24)

Control “PACIFIC arm”

Experimental “triple combo” Oleclumab

Experimental “triple combo” Monalizumab

Planned approach