Developmental Therapeutics in Lung Cancer

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Disclosure Information
Developmental Therapeutics Symposium
Christine Bestvina

I have the following financial relationships to disclose:

Consultant for: AbbVie, AstraZeneca, Genentech, Pfizer
Honoraria from: OncLive

I will discuss investigational products in my presentation.
Objectives

▪ To introduce an investigator initiated trial of ipilimumab, nivolumab, and stereotactic body radiotherapy in NSCLC

▪ To discuss targeted clinical trials available for non-small cell lung cancer (NSCLC)

▪ To review clinical trials incorporating immunotherapy with chemotherapy and radiation in the Stage III curative setting
Workup of Metastatic Non-Small Cell Lung Cancer

HISTOLOGIC SUBTYPE
- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

TESTING
- Molecular testing
  - EGFR mutation testing (category 1)
  - ALK testing (category 1)
  - ROS1 testing
  - BRAF testing
  - Testing should be conducted as part of broad molecular profiling
- PD-L1 testing (category 1)

TESTING RESULTS
- Sensitizing EGFR mutation positive (see NSCL-18)
- ALK positive (see NSCL-21)
- ROS1 positive (see NSCL-24)
- BRAF V600E positive (see NSCL-25)
- PD-L1 ≥50% and EGFR, ALK negative or unknown (see NSCL-27)
- EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1 <50% or unknown
Systemic therapy for NSCLC, no targetable mutations

**PD-L1 ≤ 49%**
- PS 0, 1
  - Carboplatin/Pemetrexed/Pembrolizumab (Adeno)
  - Carboplatin/Paclitaxel/Pembrolizumab (Squamous)

**PD-L1 ≥ 50%**
- Pembrolizumab (Adeno or Squamous)
  - Carboplatin/Pemetrexed/Pembrolizumab (Adeno)
  - Carboplatin/Paclitaxel/Pembrolizumab (Squamous)
Radiation and Immunotherapy

- A minority of unselected patients respond to anti-PD1 therapy.
- SBRT can stimulate innate and adaptive immunity to potentially augment immunotherapy.
- Anti-PD1 treatment outcomes are improved with lower disease burden.
- Multi-site radiation is an emerging paradigm for eradicating metastatic disease.
- Based on earlier work, the combination of pembrolizumab and SBRT has a reasonable safety profile.

Concurrent or Sequential Ipilimumab, Nivolumab, and SBRT in Patients with Stage IV NSCLC

Metastatic NSCLC naive to immunotherapy regardless of PD-L1 expression

RANDOMIZE Biospecimen collection

SEQUENTIAL ARM (I)

SBRT to 2-4 metastases

Biospecimen collection + Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

CONCURRENT ARM (II)

Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W + SBRT to 2-4 metastases

Biospecimen collection

Imaging with cycle 2 and every other cycle afterwards until discontinuation from trial
Targeted Therapies: Lung Adenocarcinoma Genomic Subtypes

A Distribution of major drivers in full genotyping cohort (n = 423)

- KRAS: 25%
- sEGFR: 15%
- ALK Rearrangement
- BRAF V600E
- RET Rearrangement
- ERBB2
- oEGFR
- MET Amplification
- NRAS
- BRAF (non-V600E)
- Doubleton

*MET exon 14: 5%
*NTRK: 0.2%

Aisner CCR 2018
LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers


1Memorial Sloan Kettering Cancer Center, New York, NY; 2MD Anderson Cancer Center, Houston, TX; 3Dana-Farber Cancer Institute, Boston, MA; 4Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; 5Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; 6START Midwest, Grand Rapids, MI; 7Institut Gustave Roussy, Villejuif, France; 8Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 9University of Chicago, Chicago, IL; 10City of Hope Comprehensive Cancer Center, Duarte, CA; 11START Madrid CIOCC Hospital Universitario Sanchinarro, Madrid, Spain; 12The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong; 13Peter MacCallum Cancer Centre, East Melbourne, Australia; 14Loxo Oncology, Stamford, CT; 15The Ohio State University Comprehensive Cancer Center, Columbus, OH; 16Massachusetts General Hospital Cancer Center, Boston, MA

PRESENTED AT: 2018 ASCO ANNUAL MEETING  #ASCO18
PRESENTED BY: Dr. Alexander Drilon
RET is activated by two major mechanisms in cancer

**RET fusions**

- Non-small cell lung cancer (2%)
  - Papillary and other thyroid cancers (10–20%)
  - Pancreatic cancer (<1%)
  - Salivary gland cancer (<1%)
  - Spitz tumors (<1%)
  - Colorectal cancer (<1%)
  - Ovarian cancer (<1%)
  - Myeloproliferative disorders (<1%)
  - Many others (<1%)

**KIF5B** (most common in lung cancer)

**CCDC6 or NCOA4** (most common in thyroid cancer)

**RET mutations**

- Medullary thyroid cancer
  - Sporadic (>60%)
  - Hereditary (>90%)

- Activation by ligand-independent dimerization
- Direct kinase activation
- Covalent disulfide bonds in cysteine-rich region
- Kinase domain mutation

Common mutation: **RET M918T**

LOXO-292 is a potent and selective RET inhibitor

**Kinome selectivity**
Highly selective for RET

**Xenograft models**
Multiple fusions/mutations/histologies

**Orthotopic brain model**
CCDC6-RET orthotopic brain PDX

**Change in tumor size (%)**
- Vehicle
- Cabo
- LOXO-292

**Survival (%)**

**Tumor models**
- KIF5B-RET (PDX-NSCLC)
- CCDC6-RET (PDX-CRCA)
- CCDC6-RET-V804M (PDX-CRCA)
- KIF5B-RET (NIH-3T3)
- KIF5B-RET-V804M (NIH-3T3)
- RET C634W (TT cell line-MTC)
- CCDC6-RET (LC-2/ad cell line-NSCLC)

**Treatments**
- Vehicle
- LOXO-292 30 mg/kg BID → Day 52 → 3 mg/kg BID
- Ponatinib 20 mg/kg QD → Day 52 → 2 mg/kg QD

Subbiah et al. Ann Oncol 2018 (accepted manuscript/available online); Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRCA = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily
## Clinical activity of LOXO-292 in RET-altered cancers

<table>
<thead>
<tr>
<th></th>
<th>RET fusion-positive cancers</th>
<th>RET-mutant MTC</th>
<th>No known activating RET alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>NSCLC</td>
<td>Other¹</td>
</tr>
<tr>
<td>Enrolled</td>
<td>49</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>Eligible for response evaluation²</td>
<td>39</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td><strong>Overall Response Rate (95% CI)³</strong></td>
<td>77% (61% – 89%)</td>
<td>77% (58% – 90%)</td>
<td>78% (40% – 97%)</td>
</tr>
<tr>
<td>Confirmed Overall Response Rate³,⁴</td>
<td>74%</td>
<td>74%</td>
<td>71%</td>
</tr>
<tr>
<td>CR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>uCR⁵</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>uPR⁵</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Not evaluable⁶</td>
<td>3</td>
<td>3</td>
<td>–</td>
</tr>
</tbody>
</table>

1. Patients eligible for response evaluation include thyroid cancer (n=7), pancreatic cancer (n=2). 2. Excludes patients recently enrolled that remain on treatment, but have not had a first post-baseline response assessment. 3. Response status per RECIST 1.1. Overall response rate = CR+uCR+PR+uPR. Overall response rate, Confirmed overall response rate: all RET fusion-positive (30/39, 25/34), RET fusion-positive NSCLC (23/30, 20/27), RET fusion-positive other (7/9, 5/7), RET-mutant MTC (10/22, 6/18). 4. Excludes patients with unconfirmed CR/PR pending confirmation at time of data cut-off. 5. Unconfirmed responses in patients that remain on treatment awaiting a confirmatory response assessment. 6. Patients that discontinued treatment prior to a first post-baseline response assessment.
Protocol M16-438

A Phase 1 Study Evaluating the Safety, Pharmacokinetics, and Anti-Tumor Activity of ABBV-321 in Subjects with Advanced Solid Tumors Associated with Overexpression of the Epidermal Growth Factor Receptor (EGFR) or Its Ligands
ABBV-321: Antibody-Drug Conjugate

- ABT-806 targets a cryptic epitope within EGFR that is hypothesized to be exposed in particular pathologic settings:
  - Avoids targeting EGFR receptors in healthy tissue (e.g., skin)
- Antibody Drug Conjugate: Pyrrolobenzodiazepines (PBDs) as Cytotoxins
Phase I: Trial Design

- GBM
  - ABBV-321 IV q4w at RP2D
  - N=40

- Solid tumor Basket Study (EGFR+)
  - ABBV-321 IV q4w at RP2D
  - N=40
  - Of Interest: HNC, NSCLC
TAK-788 (AP32788): Oral EGFR/HER2 Exon 20 Inhibitor

Primary endpoint: RP2D
Secondary endpoints: MTD, safety, tolerability, DLTs, PK parameters + active metabolites

RP2D: Jan 2018
Phase 2 expansion
(Open, enrolling)

Cohort 1
EGFR exon 20 insertion
No CNS metastases

Cohort 2
HER2 exon 20 insertion or point mutation
No CNS metastases

Cohort 3
EGFR exon 20 insertions or HER2 exon 20 insertions or point mutations
With CNS metastases

Cohort 4
Other EGFR mutations: +/- T790M, uncommon EGFR
With or without CNS metastases

Doebele ASCO 2018
Figure 5. Antitumor Activity in All Patients Treated with TAK-788 at a Total Daily Dose ≥80–160 mg

- Progressive disease
- Stable disease
- Partial response
- Complete response

Best Change in Target Lesions (%)

Prior TKI:

| N | Y | Y | N | Y | N | N | N | N | N | N | N | N | N | N | N | Y | N |

Prior IO:

| N | N | N | Y | Y | Y | Y | N | N | N | Y | Y | Y | N | N | N | Y | N |

- HER2 mutation
- EGFR exon 20 ins

1 Includes 40 mg bid, 80 mg qd, 60 mg bid, 120 mg qd, and 160 mg qd dose groups

2 Per RECIST v1.1

* Response awaiting confirmation
Targeted Clinical Trials for Stage IV

- LIBRETTO-001: LOXO-292 for RET Fusion-Positive Solid Tumors
- TAK-788: AP32788 EGFR/HER2 Inhibitor
- JNJ-61186372: Bispecific EGFR and cMET Antibody
M7824

- M7824 is an innovative first-in-class bifunctional fusion protein
  - Antibody component
    - Fully human IgG1 mAb against human PD-L1
  - TGF-β-neutralizing trap component
    - Extracellular domain of human TGF-βRII
    - Binds TGF-β1, -β2, and -β3
    - Fused to CH₃-C terminus of the IgG via a flexible glycine-serine linker
  - Dual targeting of the PD-L1 and TGF-β pathways
    - Possibility of synergistic antitumor activity

PD-L1 binding region

M7824 (MW: 177 kDa)

TGF-β trap

Independent and complementary anti-immunosuppressive functions

Presented at: ASCO Annual Meeting '17 | #ASC017
Presented by James L. Gulley
M7824 + Concurrent ChemoXRT

Arm 1: M7824 + Concurrent ChemoXRT
- SD, PR, CR

Arm 2: Placebo + Concurrent ChemoXRT
- SD, PR, CR

Primary End Point: Progression Free Survival

Stage III Unresectable Non-Small Cell Lung Cancer

R(1:1) N=350

M7824

Durvalumab
Stage III Clinical Trials

- Neoadjuvant: Nivolumab plus Ipilimumab or Nivolumab plus Platinum-Doublet Chemotherapy versus Platinum-Doublet Chemotherapy in Early Stage NSCLC
- Tislelizumab (BGB-A317) Plus Chemoradiotherapy Followed by Tislelizumab Monotherapy in Newly Diagnosed Unresectable NSCLC
- M7824 with Concurrent Chemoradiation Followed by M7824 versus Concurrent Chemoradiation plus Duvalumab in Unresectable Stage III NSCLC
Conclusions

- The combination of ipilimumab, nivolumab, and SBRT is being studied as first-line treatment for Stage IV NSCLC.

- A variety of targeted clinical trials are available in the Stage IV setting for those with RET fusions, HER2/EGFR including Exon 20, MET, and others.

- Immunotherapy is being incorporated for patients with Stage III NSCLC in an attempt to improve cure rates.