Future Directions in the Treatment of NSCLC

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@jsoriamd
Disclosure Slide

- Consultancy fees from AstraZeneca, Astex, Covagen, Clovis, GSK, GammaMabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Takeda.

- Company scientific co-founder Gritstone
Outline

- Non-IO phase 2-3 trials
- IO-based phase 3 trials
  - IO-IO
  - IO-chemotherapy
  - IO-targeted therapies
  - IO-radiotherapy
SAFIR02 Lung – IFCT 1301

PI: JC Soria
Co-PI: F Barlesi

NSCLC metastatic or locally advanced
No EGFR mutation
No ALK translocation

N=650

Biopsy or primitive frozen specimen
- NGS
- CGH array/SNP array

CR/PR or SD

Targetable molecular alteration

N=230

YES

R 2:1

Arm A1: Targeted therapy
AZD2014
AZD4547
AZD5363
AZD8931
Vandetanib
Selumetinib

N=180

SUBSTUDY 1

Arm B1: Maintenance Arm
Pemetrexed

SUBSTUDY 2

Arm A2: MEDI4736

Targetable molecular alteration

N=650

platinum Based regimen
4 cycles

Arm B2: Maintenance Arm
Pemetrexed

Sponsor: UNICANCER-IFCT
Dacomitinib vs. Gefitinib (Phase 3)

**Key eligibility:**
- Stage IIIb/IV NSCLC
- EGFR-activating mutation
- ECOG PS 0/1

**Stratification:**
- Race
- EGFR-mutation status (19 vs. 21)

**Randomize**

- Dacomitinib 45 mg QD
- Gefitinib 250 mg QD

**Primary endpoint:**
- PFS*

**Secondary endpoints:**
- OS
- OS at 30 months
- PFS by investigator assessment
- Response
- Safety
- PROs

**N = 440**

ASCO 2017
Tuesday, June 6, 2017, 9:45 am – 12:45 pm
Dacomitinib versus gefitinib for the first-line treatment of advanced EGFR mutation positive non-small cell lung cancer (ARCHER 1050): A randomized, open-label phase III trial. Abstract LBA9007

* Per blinded IRC review. Ha: HR≤ 0.667(50%↑)

www.clinicaltrials.gov: NCT01774721
SWOG-S1403 Phase 2/3 Study Design

Estimated enrollment: 605

- Stage IV or recurrent NSCLC
- EGFR exon 19 del or exon 21 L858R
- EGFR T790M or other mutation allowed if accompanied by exon 19 or exon 21 mutation
- No prior systemic treatment for advanced or metastatic disease

Primary endpoint
OS (Phase 3)

Secondary endpoints include
PFS, ORR, time to treatment discontinuation, time to treatment failure, toxicity

Afatinib + cetuximab

Afatinib

Clinicaltrials.gov. Accessed June 2017 (NCT02438722)
Phase II Trial of T-DM1 in HER2-Positive Locally Advanced or Metastatic NSCLC

- HER2-overexpressing NSCLC
- Previously treated with platinum-based therapy

**T-DM1**
3.6 mg/kg
D1 q3wk
(n = 49)

**Response rates (median follow-up 16.3 mo)**
- IHC2+ (n = 29): 0%
- IHC3+ (n = 20): 20% (4 PR)
- Median DoR: 7.3 mo

**Median PFS**
- IHC2+ 2.6 mo
- IHC3+ 2.7 mo

Stinchcombe T et al. ASCO 2017;Abstract 8509.
Phase II Basket Trial of T-DM1 in HER2 Amplified or Mutant Cancers

**COHORTS**

- Lung cancers - HER2 mutant (n = 18)
- Lung cancers - HER2 amplified
- Bladder/urinary tract cancers - HER2 amplified
- Other solid tumors - HER2 amplified

T-DM1 3.6 mg/kg D1 q3wk

**ORR**: 33% (5/15)
**Median DoR**: Not reached
**Median PFS**: 4 mo

- There were 10 HER2 exon 20 insertions and 8 point mutations
- Responders were observed across mutation subtypes

Li BT et al. ASCO 2017;Abstract 8510.
**JUNIPER Phase 3 Study Design**

**Estimated enrollment: 450 (closed)**

- Stage IV NSCLC
- Previous progression after platinum-based therapy
- KRAS mutant

- **Abemaciclib** 200 mg PO q12h d1-28 + BSC
- **Erlotinib** 150 mg PO q24h d1-28 + BSC

**Primary endpoint**
OS

**Secondary endpoints include**
PFS, ORR, safety/tolerability, QoL

NCT02152631
ClinicalTrials.gov. Available at: [https://clinicaltrials.gov/ct2/show/NCT02152631](https://clinicaltrials.gov/ct2/show/NCT02152631)
PD-L1 expression and response to immunotherapy in patients with MET exon 14-altered NSCLC

• 41 patients with MET exon 14 skipping alterations (METΔ14) and PD-L1 expression analysis

• Substantial portion of patients with METΔ14 NSCLC express PD-L1 (TPS ≥50% = 44%; TPS 1%-49% = 17%)

• Immunotherapy administered to 15 patients:
  • Nivolumab n = 5
  • Ipilimumab + nivolumab n = 4
  • Pembrolizumab n = 3
  • Atezolizumab n = 2
  • Durvalumab n = 1

• ORR = 2/15 (13%)
• ORR for TPS ≥50% = 1/3 (33%)

Sabari JK et al. ASCO 2017;Abstract 8512.
Outline

- Non-IO phase 3 trials
- IO-based phase 3 trials
  - IO-IO
  - IO-chemotherapy
  - IO-targeted therapies
  - IO-radiotherapy
Combination strategies are necessary to address broad patient populations

I-O = immuno-oncology.
Phase I CheckMate 012: Response

**ORR (all):** 18/38 (47%)
**ORR (PD-L1 ≥1%):** 12/21 (57%)

Treatment-related AEs prompting treatment discontinuation: 4/38 (11%)

**ORR (all):** 15/39 (38%)
**ORR (PD-L1 ≥1%):** 13/23 (57%)

Treatment-related AEs prompting treatment discontinuation: 5/39 (13%)

Key Eligibility Criteria

• Chemotherapy-naïve patients with stage IV or recurrent NSCLC
• No EGFR/ALK mutations sensitive to available targeted inhibitor therapy
• ECOG PS 0–1

Fully enrolled*

Nivolumab monotherapy
240 mg Q2W

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

Platinum-doublet chemotherapy

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

Platinum-doublet chemotherapy

Platinum-doublet chemotherapy

Treatment until disease progression or unacceptable toxicity

*R Stratification factor at randomization: histology (squamous versus non-squamous).

ALK=anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; I-O=immuno-oncology; NSCLC=non-small cell lung cancer; PD-L1=programmed death ligand 1; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; R=randomized.

Neptune and Mystic:

Phase 3, open-label trials of anti–PD-L1 ± anti–CTLA-4 vs Pt-based doublet chemotherapy for first-line treatment of stage IV NSCLC

**NEPTUNE**¹,²

N=960

- **Key Inclusion Criteria**
  - Treatment naïve, stage IV NSCLC
  - No activating EGFR or ALK rearrangement
  - PD-L1 positive* or negative

- **Primary Endpoint:** OS

- **R 1:1**
  - Durvalumab + tremelimumab
  - Histology-based Pt doublet chemotherapy

- **Patients achieving disease control may restart combination treatment upon evidence of PD**

**MYSTIC**³,⁴,⁵

N=1118

- **Key Inclusion Criteria**
  - Treatment naïve, stage IV NSCLC
  - No activating EGFR or ALK rearrangement

- **Primary Endpoints:** PFS and OS of durva + treme (PD-L1+ and all-comers) and durva monotherapy (PD-L1+ only)

- **R 1:1:1**
  - Durvalumab
  - Durvalumab + tremelimumab
  - Histology-based Pt doublet chemotherapy

- **Patients achieving disease control may restart combination treatment upon evidence of PD**

*PD-L1 positivity defined as ≥25% of tumor cells with membrane staining as determined by PD-L1 IHC assay.
Study JVDF (NCT02443324) Phase 1A/B Study Design

**Phase 1a: DLT Assessment (n=6 to 12)**

- **Primary:** Safety and tolerability
- **Secondary:** PK

**Schedule 1:** Gastric/GEJ, BTC
- 3+3 design (n= 3 to 6 patients)
- Ram 8 mg/kg, Day 1 and 8
- Pembro 200 mg fixed, Day 1
- Both IV every 3 weeks

**Schedule 2:** Gastric/GEJ, NSCLC, UC
- 3+3 design (n= 3 to 6 patients)
- Ram 10 mg/kg, Day 1
- Pembro 200 mg fixed, Day 1
- Both IV every 3 weeks

**Phase 1b: Cohort Expansion (n=155)\(^a\)**

- **Primary:** Safety and tolerability
- **Secondary:** PK and preliminary efficacy
- **Exploratory:** Biomarkers and immunogenicity

- **Cohort A:** 15 Gastric/GEJ (2nd-3rd Line)
- **Cohort A1:** 25 BTC (2nd-3rd Line)\(^b\)
- **Cohort A2:** 25 Gastric/GEJ (1st Line)\(^b\)
- **Cohort B:** 15 Gastric/GEJ (2nd-3rd Line)
- **Cohort C:** 25 NSCLC (2nd-4th Line)
- **Cohort D:** 25 UC (2nd-4th Line)
- **Cohort E:** 25 NSCLC (1st Line)\(^b\)

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\(^a\) Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason. 
\(^b\) Protocol was recently amended to add cohorts A1, A2 and E; cohorts are currently enrolling.

DLT dose-limiting toxicity; PK pharmacokinetics; Ram ramucirumab; Pembro pembrolizumab

Study JVDF (NCT02443324) Cohort C: Interim clinical activity


**ITT Population**

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>Patients</th>
<th>Events</th>
<th>Median PFS, Mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>27</td>
<td>8</td>
<td>NR (3.98, —)</td>
</tr>
<tr>
<td>Negative</td>
<td>10</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Weak positive</td>
<td>4</td>
<td>2</td>
<td>3.98 (2.76, —)</td>
</tr>
<tr>
<td>Strong positive</td>
<td>7</td>
<td>2</td>
<td>NR</td>
</tr>
<tr>
<td>Not reported</td>
<td>6</td>
<td>2</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Objective response rate, n (%)**

- All patients: 8 (30%)

**Disease control rate, n (%)**

- All patients: 23 (85%)
Atezolizumab clinical development programme in first-line and adjuvant NSCLC
Upcoming randomized immunotherapy trials in 1\textsuperscript{st} line NSCLC and \textit{projected} read-out timelines

2016

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Nivolumab monotherapy  
  PDL1+  
  CheckMate-026  
  Q3 2016

2017

- Pembrolizumab + platinium / pemetrexed (non-squamous)  
  Keynote 189  
  Q3 2017

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab + platinium / pemetrexed (non-squamous)  
  Keynote 189  
  Q3 2017

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

2018

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

2019

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

2020

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

- Pembrolizumab monotherapy >50% PDL1+  
  Keynote 024  
  Q2 2016

- Pembrolizumab monotherapy >1% PDL1+  
  Keynote 042  
  Q2 2018

Legend

- PD1/PDL1 Monotherapy
- PD1 or PDL1  
  CT Combo
- CTLA4 + PD1

Durvalumab ± tremelimumab vs SoC  
MYSTIC  
Q1 2017

Atezolizumab + chemo  
± bevacizumab vs chemo + bevacizumab  
IMpower 150  
Q1 2017

Nivolumab mono vs  
Niv + Ipi vs  
Niv + Pt doublet vs Pt doublet  
CheckMate-227  
Q1 2018

Atezolizumab + chemo  
IMpower 130 (non-SCC)  
IMpower 131 (SCC)  
Q3 2018

Durvalumab ± tremelimumab vs SoC  
NEPTUNE  
Q4 2018
Other candidate combination Targets across Lung cancer

- **TGF-B**
- **T-cell Checkpoints** (e.g., CD137, CD27, GITR, OX40, LAG3, TIGIT, CD73)
- **IDO**
- **CCR4**
- **Cytokines** (e.g., IL2)
- **PI3K**
- **ALK**
- **cMET**
- **PARP**
- **EGFR**
- **BCR-ABL**
- **NK Cell Modulation** (e.g., SLAMF7, KIR)
- **Oncolytic Viruses**
- **Vaccines**
- **Antibody-Drug Conjugates**
- **Epigenetic Modifiers (HDAC)**
- **Glypican-3**

- **Immune Stimulation/Modulation**
- **Tumor Cell Targeted Pathways**
Key trials with I-O therapies: Combinations

Combinations of pembrolizumab, ipilimumab, nivolumab, atezolizumab, and tremelimumab and other therapies are currently not approved for advanced/metastatic NSCLC.