Lung Cancer Combination Immunotherapies

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Disclosure slide

- Bayer Health Care
- Biodesix
- Biothera
- Boehringer Ingelheim
- Bristol Myers-Squibb (BMS)
- Clovis Oncology
- Eisai Inc.
- Genentech/Roche
- GlaxoSmithKline (GSK)
- MedImmune
- Merck
- Novartis
- Peregrine Pharmaceuticals, Inc.
- Pfizer
- Synta Pharmaceuticals Corp.

This includes receipt of grants/research support, receipt of honoraria or consulting fees, and participation in company sponsored speaker’s bureaus.
I-O agents have a unique MoA, offering the opportunity for combination with other agents

Examples of ongoing combination trials with I-O therapies, many more in development

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Targeted</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (anti-PD-1)</td>
<td>+ cisplatin/gemcitabine, cisplatin/pemetrexed or carboplatin/paclitaxel (NCT01454102)</td>
<td>NR</td>
<td>+ bevacizumab or erlotinib</td>
<td>+ ipilimumab (NCT01454102) + anti-KIR (NCT01714739) + anti-LAG3 (NCT01968109)</td>
</tr>
<tr>
<td></td>
<td>+ paclitaxel/carboplatin ± bevacizumab (NCT02039674)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (anti-PD-1)</td>
<td>+ cisplatin/pemetrexed or carboplatin/paclitaxel (NCT01840579)</td>
<td>NR</td>
<td>+ gefitinib or erlotinib</td>
<td>+ ipilimumab (NCT02039674) + INCB024360 (NCT02178722)</td>
</tr>
<tr>
<td></td>
<td>+ paclitaxel/carboplatin ± bevacizumab (NCT02039674)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEDI-4736 (anti-PD-L1)</td>
<td></td>
<td>NR</td>
<td>+ gefitinib (NCT02088112)</td>
<td>+ tremelimumab (NCT02000947, NCT02141347)</td>
</tr>
<tr>
<td>MPDL3280A (anti-PD-L1)</td>
<td></td>
<td>NR</td>
<td>+ erlotinib (NCT02013219)</td>
<td>+ ipilimumab (NCT02174172)</td>
</tr>
<tr>
<td></td>
<td>+ stereotactic radiosurgery* (NCT02107755, NCT02239900)</td>
<td>+ stereotactic radiosurgery* (NCT02221739)</td>
<td>+ erlotinib or crizotinib (NCT01998126)</td>
<td>+ nivolumab (NCT01454102) + pembrolizumab (NCT02039674)</td>
</tr>
<tr>
<td>Ipilimumab (anti-CTLA-4)</td>
<td>+ ionizing radiation (NCT02221739)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremelimumab (anti-CTLA-4)</td>
<td></td>
<td>NR</td>
<td>+ gefitinib (NCT02040064)</td>
<td>+ MEDI-4736 (NCT02000947)</td>
</tr>
</tbody>
</table>

*Trial in patients with melanoma with metastatic disease to a visceral organ (lung, liver, brain, adrenal, nodal station outside the regional lymph drainage of the primary, vertebral bodies).
NR = no trials reported.
I-O agents have a unique MoA, offering the opportunity for combination with other agents.

Response Patterns for Immunotherapy Compared With Targeted Therapy

Combining Immunotherapy and Conventional Therapies

Is the immune system relevant in tumors with “driver oncogenes”?
Immune system and MYC

Rakhra and Felsher, Cancer Cell, 2010
Restoration of DLL-1 in Bone Marrow Inhibits Tumor Growth

Huang and Carbone, Cancer Research 2011
Induction of Mutant p53-Specific Immune Response by Clustered DLL1

Huang and Carbone, Cancer Research 2011
Clustered DLL1 improves progression-free survival after oncogene-targeted therapy

Tumor volume, mm^3

Days

Dikov and Carbone, in revision
CA209-012 Study Design: Nivolumab in Combination With Erlotinib

Stage IIIB/IV, EGFR MT, non-squamous NSCLC, no prior chemotherapy for advanced NSCLC and ECOG PS 0 or 1<sup>a,b</sup>

Nivolumab 3 mg/kg IV Q2W + erlotinib 150 mg/day PO until disease progression or unacceptable toxicity<sup>c</sup>

Primary objective: safety and tolerability
Secondary objectives: ORR (by RECIST v1.1)<sup>d</sup> and PFS rate at 24 wks
Exploratory objective: OS

<sup>a</sup>Site-determined EGFR mutation test
<sup>b</sup>Prior use of EGFR TKIs was allowed
<sup>c</sup>Pts were permitted to continue study treatment beyond RECIST v1.1-defined progression if they were considered to be deriving clinical benefit and tolerating study treatment
<sup>d</sup>Response was assessed at the beginning of wks 11, 17, 23, and every 3 months thereafter until disease progression
ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; OS = overall survival; PO = oral administration; Q2W = every two wks; RECIST = Response Evaluation Criteria In Solid Tumors; wks = weeks
## Tumor response in NSCLC pts treated with nivolumab plus erlotinib

<table>
<thead>
<tr>
<th></th>
<th>Prior treatment with erlotinib (n = 20)</th>
<th>No prior treatment with erlotinib (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, n (%) [95% CI]</strong></td>
<td>4 (19) [5, 42]</td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing responders, n (%)</strong></td>
<td>2 (67)</td>
<td>1 (100)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR(^a)</td>
<td>3 (15)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (45)</td>
<td>0</td>
</tr>
<tr>
<td>PD(^b)</td>
<td>8 (40)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Response duration by pt, wks</strong></td>
<td>60.1, 64.6+, 70+</td>
<td>83.7+</td>
</tr>
<tr>
<td><strong>SD duration by pt, wks</strong></td>
<td>9.9+, 15.7, 22.3, 22.7+, 29.4, 35.9, 49.4, 52.7, 53.0</td>
<td>–</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS rate at 24 wks, % (95% CI)</td>
<td>50 (27, 70)</td>
<td></td>
</tr>
<tr>
<td>Median PFS, wks (range)</td>
<td>29.4 (4.6, 93.1+)</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-month OS rate, % (95% CI)</td>
<td>64 (39, 81)</td>
<td></td>
</tr>
<tr>
<td>Median OS, wks (range)</td>
<td>NR (10.7+, 110.3+)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)All PRs were confirmed by a subsequent tumor assessment per RECIST v1.1

\(^b\)Includes one pt with an unconventional “immune-related” response

+= censored; CI = confidence interval; NR = not reached
### Characteristics of Pts With Tumor Regression on Nivolumab Plus Erlotinib

<table>
<thead>
<tr>
<th>Pt</th>
<th>EGFR MT</th>
<th>Prior erlotinib</th>
<th>Prior afatinib/ cetuximab</th>
<th>Rebiopsy</th>
<th>Treatment duration (wks)</th>
<th>PFSb (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEL19</td>
<td>90</td>
<td>n/a</td>
<td>T790M+</td>
<td>66+</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>DEL19</td>
<td>40</td>
<td>15</td>
<td>T790M−</td>
<td>61</td>
<td>80+</td>
</tr>
<tr>
<td>3c</td>
<td>L858R</td>
<td>26</td>
<td>n/a</td>
<td>T790M−</td>
<td>108+</td>
<td>69</td>
</tr>
<tr>
<td>4d</td>
<td>L858R/ S768I</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>104+</td>
<td>93+</td>
</tr>
<tr>
<td>5e</td>
<td>L858R</td>
<td>55</td>
<td>34</td>
<td>T790M+</td>
<td>104+</td>
<td>9</td>
</tr>
</tbody>
</table>

- **Pt**: Patient
- **EGFR MT**: EGFR mutation type
- **Prior erlotinib**: Duration of prior erlotinib treatment (weeks)
- **Prior afatinib/ cetuximab**: Duration of prior afatinib/cetuximab treatment (weeks)
- **Rebiopsy**: T790M status
- **Treatment duration (wks)**: Duration of nivolumab plus erlotinib treatment (weeks)
- **PFSb (wks)**: Investigator-reported progression-free survival (weeks)

**Notes**:
- a: Investigator-reported PFS
- b: Tumor assessments were performed until disease progression, including after discontinuation of treatment
- c: Pt continues trial therapy after excision of solitary site of growth, with sustained response at other sites
- d: Erlotinib-naïve pt
- e: Pt with PD by RECIST v1.1; however, this pt exhibited an unconventional “immune-related” response, with a 51% reduction in target lesions (maximum decrease) after initial progression in non-target lesions
  + = ongoing; n/a = not available
Results (cont)

Characteristics of Response in NSCLC Pts Treated With Nivolumab Plus Erlotinib

Pt
1
2
3
4

Time (Weeks)
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120 126 132

- Blue bar: Time to and duration of response on treatment
- ▶: Ongoing response
- ○: Time to response
- *: Duration of study drug exposure at time of data analysis
- Red bar: Response duration following latest reported dose of therapy

a Erlotinib-naïve pt
b T790M-positive pt
Percent Changes in Target Lesion Tumor Burden in NSCLC Pts Treated With Nivolumab Plus Erlotinib

Percent Change in Target Lesions From Baseline

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a One pt exhibited an unconventional “immune-related” response (ongoing), with a 51% reduction in target lesions (maximum decrease) after initial progression in non-target lesions (included here as having PD).

b Only includes pts with baseline target lesion(s) and at least one complete post baseline target lesion assessment.
Percent Changes in Target Lesion Tumor Burden in NSCLC Pts Treated With Nivolumab Plus Erlotinib

Best percent change in target lesion tumor burden from baseline

- One pt exhibited an unconventional “immune-related” response (ongoing), with a 51% reduction in target lesions (maximum decrease) after initial progression in non-target lesions (included here as having PD)
- Only includes pts with baseline target lesion(s) and at least one complete post baseline target lesion assessment
PFS and OS in NSCLC Pts Treated With Nivolumab Plus Erlotinib

**PFS**
- Nivolumab 3 mg/kg + erlotinib (mPFS 29.4 wks)
- PFS rate at 24 weeks = 50%

**OS**
- Nivolumab 3 mg/kg + erlotinib (mOS NR)
- 18-month OS rate = 64%

**Number of Pts at Risk**

<table>
<thead>
<tr>
<th>Time Since First Dose (Weeks)</th>
<th>B/L</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + erlotinib</td>
<td>21</td>
<td>14</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Number of Pts at Risk**

<table>
<thead>
<tr>
<th>Time Since First Dose (Weeks)</th>
<th>B/L</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
<th>96</th>
<th>108</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + erlotinib</td>
<td>21</td>
<td>20</td>
<td>20</td>
<td>16</td>
<td>15</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

B/L = baseline; mOS = median OS; mPFS = median PFS
Safety

- Most treatment-related adverse events (AEs) were low grade
- No grade 4 or 5 AEs were reported
- One pt (5%) had grade 1 pneumonitis
- Treatment-related diarrhea (n = 2, both grade 3), increased aspartate aminotransferase (AST) (n = 1, grade 3), increased alanine aminotransferase (ALT), flushing, and tubulointerstitial nephritis (n = 1 each, grade 2) led to discontinuation of study medication in 4 pts (19%)
  - One pt had both grade 3 diarrhea and grade 2 flushing
- At the time of analysis, 9 pts had died, including 8 due to disease progression and 1 due to an unknown cause
Erlo-Nivo combination conclusions

- Treatment with nivolumab plus erlotinib may provide durable clinical benefit in chemotherapy-naïve, EGFR MT pts previously treated with EGFR TKI therapy
  - Observed duration of response and prolonged SD are encouraging relative to other available therapies for such pts
  - Responses were seen across EGFR MT subtypes, including pts with/without T790M mutations

- Nivolumab in combination with erlotinib was associated with a safety profile that reflected additive toxicities of the individual agents and was manageable using safety algorithms

- These findings support further evaluation of anti-PD-1 and EGFR inhibitor combinations in this pt population
I-O agents have a unique MoA, offering the opportunity for combination with other agents.

Anti-CTLA-4 plus chemotherapy as 1st-line treatment: ipilimumab plus carboplatin/paclitaxel as an example

CA184-041: phase 2 study results, no prior therapy for lung cancer, stage IIIIB/IV NSCLC, ECOG PS ≤1, all histologies

Ipilimumab + concurrent chemotherapy

Ipilimumab + phased chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Events/patients</th>
<th>Median irPFS, months</th>
<th>95% CI</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>56/66</td>
<td>4.63</td>
<td>4.14, 5.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>55/70</td>
<td>5.52</td>
<td>4.17, 6.74</td>
<td>0.81</td>
<td>0.13</td>
</tr>
</tbody>
</table>

CA209-012 (CheckMate 012) Study Design: Nivolumab in Combination With Chemotherapy

Chemotherapy-naïve patients with stage IIIB or IV NSCLC

- **Squamous**
  - Nivolumab 10 mg/kg IV Q3W + Gem 1250 mg/m² + Cis 75 mg/m² (four 21-day cycles)
  - Nivolumab 10 mg/kg IV Q3W until disease progression or unacceptable toxicity

- **Non-squamous**
  - Nivolumab 10 mg/kg IV Q3W + Pem 500 mg/m² + Cis 75 mg/m² (four 21-day cycles)
  - Nivolumab 10 mg/kg IV Q3W + Pac 200 mg/m² + Carb AUC 6 (four 21-day cycles)

- **Any histology**
  - Nivolumab 5 mg/kg IV Q3W + Pac 200 mg/m² + Carb AUC 6 (four 21-day cycles)
  - Nivolumab 5 mg/kg IV Q3W until disease progression or unacceptable toxicity

Primary objective: safety and tolerability
Secondary objectives: ORR and PFS rate at 24 weeks
Exploratory objective: OS

Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; ORR = objective response rate; OS = overall survival; Pac = paclitaxel; Pem = pemetrexed; PFS = progression-free survival; Q3W = every three weeks
## Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 10 mg/kg</th>
<th>Nivolumab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem/Cis (n = 12)</td>
<td>Pem/Cis (n = 15)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>SD, %</td>
<td>58</td>
<td>47</td>
</tr>
<tr>
<td>18-month OS rate, %</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>Median OS, weeks</td>
<td>51</td>
<td>83</td>
</tr>
</tbody>
</table>

NR = not reached
Best Percent Change in Target Lesions

<table>
<thead>
<tr>
<th>Change in Baseline Target Lesions (%)</th>
<th>Nivolumab 10 mg/kg + Gem/Cis</th>
<th>Nivolumab 10 mg/kg + Pem/Cis</th>
<th>Nivolumab 10 mg/kg + Pac/Carb</th>
<th>Nivolumab 5 mg/kg + Pac/Carb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Percent Change in Target Lesions

Nivolumab 10 mg/kg + Gem/Cis

Nivolumab 10 mg/kg + Pem/Cis

Nivolumab 10 mg/kg + Pac/Carb

Nivolumab 5 mg/kg + Pac/Carb

Change From Baseline (%)

Time Since First Dose (Weeks)

Squamous
Non-squamous
Responses Can Persist Following Treatment Discontinuation

- Nivolumab 10 mg/kg + Gem/Cis (squamous)
- Nivolumab 10 mg/kg + Pem/Cis (non-squamous)
- Nivolumab 10 mg/kg + Pac/Carb (any histology)
- Nivolumab 5 mg/kg + Pac/Carb (any histology)

Response duration following last reported dose of therapy

Ongoing response

Time (Week)
# Efficacy Endpoints According to Baseline PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>Baseline PD-L1 expression$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD-L1$^+$</td>
</tr>
<tr>
<td>Samples sufficient for analysis, n</td>
<td>17</td>
</tr>
<tr>
<td>ORR,$^b$ %</td>
<td>53</td>
</tr>
<tr>
<td>18-month OS rate, %</td>
<td>59</td>
</tr>
<tr>
<td>Median OS, weeks</td>
<td>88</td>
</tr>
</tbody>
</table>

$^a$Positivity defined as tumor cell membrane staining with $\geq5\%$ expression in a minimum of 100 evaluable cells

$^b$Confirmed PRs or CRs only (per RECIST v1.1)
Overall Survival by Treatment Arm

<table>
<thead>
<tr>
<th>Regimen</th>
<th>mOS (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 10 mg/kg + Gem/Cis</td>
<td>51</td>
</tr>
<tr>
<td>Nivolumab 10 mg/kg + Pem/Cis</td>
<td>83</td>
</tr>
<tr>
<td>Nivolumab 10 mg/kg + Pac/Carb</td>
<td>65</td>
</tr>
<tr>
<td>Nivolumab 5 mg/kg + Pac/Carb</td>
<td>NR</td>
</tr>
</tbody>
</table>

mOS = median OS
Chemo-Nivo conclusions

- ORR for nivolumab plus chemotherapy in 1\textsuperscript{st}-line treatment of patients with advanced NSCLC are similar to those previously reported for chemotherapy alone

- Nivolumab 5 mg/kg Q3W in combination with paclitaxel/carboplatin may provide clinical benefit beyond nivolumab monotherapy or single modality chemotherapy
  - Encouraging 18-month OS rate of 86% with a lack of progressive disease at first restaging

- Responses were observed regardless of tumor PD-L1 expression

- Nivolumab plus chemotherapy demonstrates a manageable safety profile, reflecting additive toxicities of individual agents

- These data support further evaluation of nivolumab 5 mg/kg Q3W in combination with chemotherapy
Epigenetic Priming for Chemotherapy and PD-1 Blockade
Tumor-intrinsic effects of combination epigenetic therapy

Normal

Open promoter chromatin (euchromatic state)

Closed promoter chromatin (heterochromatic state)

Cancer

p16, VHL, E-cad, etc.

Entinostat

Azacitidine

Synergy
Romodepsin-induced T cell chemokine expression is NF-κB-dependent (mouse LKR-13 lung cancer cell line)

Amer Beg, unpublished
Romidepsin enhances response to anti-PD-1 (day 15, 17, 19)

Amer Beg, unpublished
Epigenetic lung cancer study - trial schema

- Single-arm phase II
- Simon two-stage design
- 5AC dosing = 40 mg/m² SQ daily on days 1-6 and 8-10
- Entinostat dosing = 7 mg PO days 3 & 10
- Cycle length = 28 days
- 3% RR, Median Survival 8.6 months

Juergens R et al Cancer Disc 2011
Immunotherapy After Epigenetic Therapy

Change in Target Lesions from Baseline (%)

Duration of Immunotherapy (weeks)

- Ongoing therapy
- Discontinued therapy
- Radiographic tumor assessment
- Adenocarcinoma
- Squamous cell carcinoma

24 weeks
Pt 010-6084 – History 64 y/o Diagnosed with IIIB adenoca Rx with XRT+ Tax/carbo, pemetrexed + carbo, Entinostat + 5aza x 6 cycles
Synergy between Epigenetic Modulation and PD-1 pathway blockade - Unleashing the Perfect Storm against Tumors

**AZA/HDACi Rx**

Tumor

Intratumoral pro-inflammatory responses: IL-1, IL-18, IFN pathway, HLA

De novo antigen expression: ie C-T Antigens

De-repression of \( \gamma \)-IFN promoter in tolerant T cells

PD-1 Blockade

Enhanced Anti-tumor Response

Adaptive Resistance: ↑ PD-L1

↑ PD-1 from promoter demethylation
Epigenetic Priming Study Design

Study population

Metastatic NSCLC
1 – 2 prior therapies
ECOG PS 0 - 1

Epigenetic priming

Azacitidine
40 mg/m2 SC d 1-6, 8-10
Entinostat
7mg PO
days 3 + 10
28 day cycle × 2

CC-486
300 mg PO
d1-21
28 day cycle × 2

Nivolumab

3 mg/kg IV q 2 weeks
Until progression

Biopsy
I-O agents have a unique MoA, offering the opportunity for combination with other agents.
Mechanism of Action of PD-1 and CTLA-4 Blockade

MHC = major histocompatibility complex; TCR = T-cell receptor

CA209-012 Study Design: Nivolumab Plus Ipilimumab

Stage IIIb or IV NSCLC, no prior chemotherapy for advanced NSCLC, and Eastern Cooperative Oncology Group performance status 0 or 1

Primary objective: safety and tolerability
Secondary objectives: ORR (by RECIST v1.1)\(^b\) and PFS rate at 24 wks
Exploratory objective: OS

\(^a\)Pts were permitted to continue study treatment beyond RECIST v1.1-defined progression if they were considered to be deriving clinical benefit and tolerating study treatment

\(^b\)Response was assessed at wks 10, 17, and 23, and every 3 months thereafter until disease progression

non-sq = non-squamous; Q2W = every two wks; Q3W = every three wks; RECIST = Response Evaluation Criteria In Solid Tumors; sq = squamous; wks = weeks
Best Percent Change in Target Lesion Tumor Burden From Baseline in NSCLC Pts Treated With Nivolumab Plus Ipilimumab

Only includes pts with baseline target lesion and ≥1 post-baseline target lesion assessment with non-missing value
Characteristics of Response by Treatment Arm in NSCLC Pts Treated With Nivolumab Plus Ipilimumab

- **Nivolumab 1 mg/kg + ipilimumab 3 mg/kg**
- **Nivolumab 3 mg/kg + ipilimumab 1 mg/kg**

- Time to response
- Duration of response while on treatment
- Ongoing response
- Duration of study drug exposure at time of data analysis
- Response duration following latest reported dose of therapy
Percent Changes in Target Lesion Tumor Burden From Baseline in NSCLC Pts Treated With Nivolumab Plus Ipilimumab

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg

Nivolumab 3 mg/kg + ipilimumab 1 mg/kg

+ first appearance of new lesion
PFS and OS in NSCLC pts Treated With Nivolumab Plus Ipilimumab

**PFS**
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (mPFS 16.1 wks)
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (mPFS 14.4 wks)

**OS**
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (mOS NR)
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (mOS 47.9 wks)

PFS rate at 24 wks = 44%
PFS rate at 24 wks = 33%

1-year OS rate = 65%
1-year OS rate = 44%

**Number of Pts at Risk**
- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg: 24, 10, 8, 6, 3, 1, 0
- Nivolumab 3 mg/kg + ipilimumab 1 mg/kg: 25, 14, 8, 4, 3, 2, 0

mOS = median OS; mPFS = median PFS
Percent Changes in Target Lesion Tumor Burden and PFS by PD-L1 Status in NSCLC Patients Treated With Nivolumab Plus Ipilimumab

A. Best percent change in target lesion tumor burden

PD-L1 Status (5% cut-off)
- Negative
- Positive

B. PFS

PD-L1 Status (5% cut-off)
- Negative (mPFS 13.6 wks)
- Positive (mPFS 14.4 wks)

*Only includes pts with baseline target lesion and at least on-baseline target lesion assessment with missing value
Safety

- Adverse events (AEs) were managed using well established safety guidelines
- The majority of toxicity occurred during the induction phase (nivolumab + ipilimumab Q3W for four cycles) as compared with the maintenance phase
  - Across arms, grade 3–4 AEs were reported in 32–50% of pts and 21–27% of pts during induction and maintenance, respectively
Ipi-Nivo conclusions

- Treatment with nivolumab plus ipilimumab was associated with a safety profile that was managed using well-established safety guidelines.

- The nivolumab plus ipilimumab regimen provided durable responses as first-line treatment for pts with advanced NSCLC, regardless of histology.

- Activity was observed with nivolumab plus ipilimumab in PD-L1\(^+\) and PD-L1\(^-\) pts.

- The safety and clinical activity of nivolumab plus ipilimumab will be further assessed at additional specified doses and schedules.
I-O agents have a unique MoA, offering the opportunity for combination with other agents.

Radiation and Immunotherapy

Cancer Immunology Research: Cancer Immunology at the Crossroads

21-22 November 2014, Geneva, Switzerland

www.esmo.org

Tang et al, Cancer Immunol Res, 2(9); 831–8. 2014
Potential of anti-CTLA-4 plus radiation: ipilimumab in one patient with melanoma as an example

- The target and other lesions regressed
- Regression of distant lesions may be due to an enhanced systemic response

STIMILI: A randomized phase II trial of consolidation ipilimumab vs placebo in limited-stage SCLC after chemoradiotherapy

- Biomarker collaboration: G Coukos, Lausanne
Early Stage disease

Combination with surgery
Early Stage Disease: Neoadjuvant therapy

If no progression is seen at D20 CT, an additional 2 cycles are given before surgery.
Combinations and new directions

- Combinations are being studied with
  - PD-1 and anti-CTLA4 or other immune modulators
  - PD-1 and chemotherapies, first and later lines
  - PD-1 and targeted therapies, up-front or upon resistance
  - Neoadjuvant/Adjuvant
  - Radiation therapy
  - Vaccines
  - Other biologics, e.g. bevacizumab
Summary

• Immunotherapy has clear activity in lung cancer as a single agent

• Modest and manageable side-effects that differ from other therapies enable the testing of combinations

• Many combinations are being tested with promising results