Immune Checkpoint Inhibitors in NSCLC

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Chair, Comprehensive Cancer Center Zürich

Lugano, May 4, 2018
Disclosures

Consultant or Advisory Role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, Astra Zeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

Speaker Honoraria in the last two years
I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, MSD and Roche.

DMC in the last two years
Roche and Takeda
Treatment of locally advanced (stage III) NSCLC

- In multistation N2 or N3 disease, concurrent definitive CRT is preferred [I, A]. An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV, C]

- In the stage III disease treated with a CRT strategy, two to four cycles of concomitant ChT should be delivered [I, A].

- There is no evidence for further induction or consolidation ChT.

- Consolidation immunotherapy with durvalumab is likely to become the new treatment standard

ESMO guidelines: Postmus et al, Ann Oncol 2017
Randomized phase III comparison of standard-dose versus high-dose chemo-radiotherapy ± cetuximab for stage III NSCLC

**Schema**

<table>
<thead>
<tr>
<th>Stratify</th>
<th>RT Technique</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  2  3</td>
<td>3D-CRT IMRT</td>
<td>Arm A Concurrent chemotherapy RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Arm A Consolidation chemotherapy</td>
</tr>
<tr>
<td>Zubrod</td>
<td>1  2  3</td>
<td>Arm B Concurrent chemotherapy RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Arm B Consolidation chemotherapy</td>
</tr>
<tr>
<td>PET Staging</td>
<td>1  2</td>
<td>Arm C Concurrent chemotherapy* and Cetuximab RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Arm C Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td>Histology</td>
<td>1  2</td>
<td>Arm D Concurrent chemotherapy* and Cetuximab RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Arm D Consolidation chemotherapy* and Cetuximab</td>
</tr>
</tbody>
</table>

*Carboplatin and paclitaxel

One-sided log-rank p=0.0042

Median PFS 11 months

One-sided log-rank, p=0.2938

Bradley, Lancet Oncology 2015
PACIFIC: Consolidation durvalumab for 1 year after chemoradiotherapy of stage III NSCLC

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (28 countries)¹⁻³

Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting (N=702)

Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy

Primary endpoints³
- PFS, OS

Secondary endpoints³
- ORR, DoR, DSR
- Safety/tolerability
- PK, immunogenicity, QoL

Arm 1 (n=468): Durvalumab i.v. 10 mg/kg Q2w for up to 12 months

Arm 2 (n=234): Placebo i.v. Q2w

- 713 pts with stage III NSCLC after chemoradiotherapy
- 2:1 durvalumab 10 mg/kg Q2w for 12 months or placebo

No. of Events/ Total No. of Patients

No. of Patients

Median PFS from start of therapy @ 20 months

Paz-Ares, ESMO 2017; Antonia, NEJM 2017
What can we conclude for the first line therapy of advanced NSCLC without oncogenic driver mutation

• There is no single platinum-based doublet standard chemotherapy, however pemetrexed combinations are favoured in non-squamous NSCLC

• If platinum-based chemotherapy is indicated, a combination with bevacizumab is a treatment option in for patients with non-squamous NSCLC. In this case, carboplatin/paclitaxel is the preferred combination

• Pemetrexed maintenance therapy is an option for patients with non-squamous NSCLC without progression after first line therapy

• Immune checkpoint inhibition with pembrolizumab has become the preferred option for patients with tumors having strong PD-L1 expression

• Current developments in first line suggest superiority of on chemotherapy/IO or IO/IO combinations over chemotherapy alone. Whether IO this should be recommended in first line for all patients will be a matter of debate
Phase 3 ICB alone in 1L advanced NSCLC compared to chemotherapy

**Primary endpoints:**
- OS, PFS

**Nivolumab**
- **CHECKMATE 227**
  - Treatment-naïve or recurrent NSCLC
  - Platinum-based chemotherapy
  - N=1980
- **CHECKMATE 026**
  - Treatment-naïve non-squamous NSCLC
  - PD-L1-positive NSCLC
  - N=685
  - Primary endpoint: PFS
  - Nivolumab 3 mg/kg IV Q2W
  - ICC with potential for crossover

**Pembrolizumab**
- **KEYNOTE-042**
  - Treatment-naïve non-squamous NSCLC
  - PD-L1-positive NSCLC
  - N=1200
  - Primary endpoint: PFS
  - Pembrolizumab 200 mg IV Q2W

**Durvalumab**
- **MYSTIC**
  - Advanced NSCLC
  - N=575
- **NEPTUNE**
  - First-line metastatic NSCLC
  - N=1000
- **NEPTUNE**
  - SOC chemotherapy

**Atezolizumab**
- **Impower 110**
  - Stage IV non-squamous PD-L1+ NSCLC
  - N=480
- **Impower 111**
  - Stage IV squamous PD-L1+ NSCLC
  - N=480
  - Atezolizumab
  - Carboplatin or carboplatin + pemetrexed

**Pembrolizumab**
- **KEYNOTE-024**
  - Treatment-naïve non-squamous NSCLC
  - PD-L1–positive NSCLC
  - N=305
  - Primary endpoint: OS
  - Pembrolizumab 200 mg IV Q3W

≥ 5% PD-L1:
- Neg. PFS and OS
TPS ≥ 1%: Pos OS
TPS ≥ 50%: Pos. PFS and OS
CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent PD-L1 positive NSCLC
Impact of tumor mutation burden on the efficacy of first-line nivolumab in advanced NSCLC: PFS by mutation burden tertile

Data for patients with low and medium TMB were pooled in subsequent analyses. 

Peters, AACR 2017
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

**KEYNOTE-024 Study Design (NCT02142738)**

- **Key Eligibility Criteria**
  - Untreated stage IV NSCLC
  - PD-L1 TPS ≥50%
  - ECOG PS 0-1
  - No activating EGFR mutation or ALK translocation
  - No untreated brain metastases
  - No active autoimmune disease requiring systemic therapy

- **Randomization** R (1:1) N = 305

- **Pembrolizumab**
  - 200 mg IV Q3W (2 years)

- **Platinum-Douplet Chemotherapy**
  - 4-6 cycles

- **Key End Points**
  - Primary: PFS (RECIST v1.1 per blinded, independent central review)
  - Secondary: OS, ORR, safety
  - Exploratory: DOR

**PD-L1 Screening**

- 1934 patients entered screening
- 1729 submitted samples for PD-L1 assessment
- 1653 samples evaluable for PD-L1

- **500 TPS ≥50% (30%)**
- **1153 TPS <50%**

Reck, ESMO 2016
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as first-Line therapy for advanced NSCLC with a PD-L1 TPS ≥50%

PROGRESSION-FREE SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
<td>10.3</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>(0.37-0.68)</td>
<td></td>
</tr>
</tbody>
</table>

OBJECTIVE RESPONSE

Δ17%  
P = 0.0011

Reck, ESMO 2016 and NEJM 2016
KEYNOTE-024: Pembrolizumab vs platinum-based chemotherapy as for advanced NSCLC Updated results

Disposition of Study Treatment

305 patients randomly allocated

Pembrolizumab
- 154 allocated (ITT)
- 154 treated
- Median (range) treatment duration: 7.7 mo (1.0 to 29.8 mo)
- 114 discontinued

Chemotherapy
- 151 allocated (ITT)
- 100 treated
- Median (range) treatment duration: 3.5 mo (1.0 to 30.5 mo)
- 121 discontinued

82 crossed over to pembrolizumab on study
Median (range) treatment duration: 3.9 mo (1.0 to 23.7 mo)
12 received anti-PD-1 outside of crossover
62.2% effective crossover rate (ITT)

Median follow up: 25.2 mo

Overall Survival: Updated Analysis

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab*</td>
<td>73</td>
<td>0.63 (0.47–0.86)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
<td>P = 0.002*</td>
</tr>
</tbody>
</table>

Median (95% CI)
- Pembrolizumab: 30.0 mo (18.3 mo–NR)
- Chemotherapy: 14.2 mo (9.8 mo–19.0 mo)

Data cutoff: July 16, 2017

Brahmer, WCLC 2017
Pembrolizumab plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 Cohorts A-C

Cohort A: pembrolizumab plus carbo- paclitaxel

Cohort B: pembrolizumab plus carbo pac bevacizumab

Cohort C: pembrolizumab plus carbo pemetrexed

PD-L1 = programmed death ligand 1; SLD = sum of longest diameters; TPS = tumor proportion score.
†Patients with TPS ≥50%.

Gadgeel, AACR 2016
Randomized phase-2 study of carboplatin and pemetrexed with or without pembrolizumab as first line therapy of advanced NSCLC: Keynote-21 Cohort G: Updated results

**Overall Survival**

- Pembrolizumab + PC: 56.7% (Δ24.8%, 95% CI: 7.2%–40.9%; P = 0.0029)
- PC Alone: 31.7%

**Events, HR (95% CI)**
- Pembro + PC: 20/80 (HR = 0.59, 0.34–1.05; P = 0.03)
- PC alone: 31/63

*Median (95% CI)*
- NR (22.8–NR)
- 20.9 (14.9–NR)

Borghaei, ESMO2017
Phase 3 ICB in 1L advanced NSCLC: Chemotherapy combinations

**Anti-PD-1/PD-L1**

**Nivolumab**
- **CHECKMATE 227**
  - Treatment-naive or recurrent NSCLC
  - N=1980
  - Primary endpoints: OS, PFS

**Pembrolizumab**
- **KEYNOTE-189**
  - Treatment-naive non-squamous NSCLC
  - N=400
  - Primary endpoint: PFS

**Nivolumab**
- **CHECKMATE 026**
  - Treatment-naive non-squamous NSCLC PD-L1-positive NSCLC
  - N=85
  - Nivolumab 3 mg/kg IV Q2W
  - ICC\(^a\) with potential for crossover

**Pembrolizumab**
- **KEYNOTE-042**
  - Treatment-naive non-squamous NSCLC PD-L1-positive NSCLC
  - N=150
  - Pembrolizumab 200 mg IV Q2W
  - ICC\(^a\) with potential for crossover

**Pembrolizumab**
- **KEYNOTE-024**
  - Treatment-naive non-squamous NSCLC PD-L1-positive NSCLC
  - N=550
  - Pembrolizumab 200 mg IV Q2W
  - Platinum-based chemotherapy

**Durvalumab**
- **MYSTIC**
  - Advanced NSCLC
  - N=675
  - Durvalumab + Tremelimumab
  - SOC chemotherapy
  - Primary endpoint: OS, PFS

**Durvalumab**
- **NEPTUNE**
  - First-line metastatic NSCLC
  - N=800
  - Durvalumab
  - SOC chemotherapy
  - Primary endpoint: OS, PFS

**Atezolizumab**
- **Impower 110**
  - Stage IV non-squamous PD-L1+ NSCLC N=450
  - Atezolizumab + carboplatin or pemetrexed
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 111**
  - Stage IV squamous PD-L1+ NSCLC N=450
  - Atezolizumab
  - Gemcitabine + cisplatin or carboplatin
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 130**
  - Stage IV non-squamous NSCLC N=150
  - Atezolizumab + carboplatin + nab-paclitaxel
  - Carboplatin + nab-paclitaxel
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 133**
  - Stage IV squamous NSCLC N=1200
  - Atezolizumab + carboplatin + paclitaxel
  - Carboplatin + paclitaxel + carboplatin
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 150**
  - Stage IV non-squamous NSCLC N=1200
  - Atezolizumab + bevacizumab + paclitaxel + carboplatin
  - Bevacizumab + paclitaxel + carboplatin
  - Primary endpoint: PFS

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  - Stage IV squamous NSCLC
  - N=1200
  - Pembrolizumab + carboplatin + paclitaxel + carboplatin
  - Primary endpoint: PFS

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  - Pembrolizumab + carboplatin + nab-paclitaxel
  - Carboplatin + nab-paclitaxel
  - Primary endpoint: PFS

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  - Stage IV non-squamous NSCLC
  - N=1200
  - Pembrolizumab + confekt + paclitaxel + carboplatin
  - Confekt + paclitaxel + carboplatin
  - Primary endpoint: PFS

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  - Pemetrexed/platinum
  - Primary endpoint: PFS

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  - Primary endpoint: OS

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- **KEYNOTE-189**
  - Treatment-naive non-squamous NSCLC
  - N=400
  - Pembrolizumab + pemtrexed/platinum
  - Pemetrexed/platinum
  - Primary endpoint: PFS
Immune checkpoint inhibition combined with VEGF inhibition

Inhibition of VEGF reduced the expression of inhibitory checkpoints in the tumor microenvironment (colon cancer model)

Pembrolizumab and ramucirumab phase I trial

Voron, J Exp Med. 2015

77% of evaluable patients experienced a decrease in target lesions

Herbst, ESMO 2016
Primary PFS analyses of a randomized phase III study of carboplatin and paclitaxel +/- bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)

INV-assessed PFS in ITT-WT (Arm B vs Arm C)

Reck, ESMO IO 2017
Primary PFS analyses of a randomized phase III study of carboplatin and paclitaxel +/- bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150)

### PFS in key biomarker populations

<table>
<thead>
<tr>
<th>Population</th>
<th>n (%)</th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (including EGFR/ALK mutant +)</td>
<td>800 (100%)</td>
<td>Arm B: 8.3, Arm C: 6.8</td>
</tr>
<tr>
<td>EGFR/ALK mutant + onlyb</td>
<td>108 (14%)</td>
<td>0.59</td>
</tr>
<tr>
<td>ITT-WT</td>
<td>692 (87%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Teff-high (WT)</td>
<td>284 (43%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Teff-low (WT)</td>
<td>374 (57%)</td>
<td>0.76</td>
</tr>
<tr>
<td>PD-L1 IHC TC2/3 or IC2/3 (WT)</td>
<td>244 (35%)</td>
<td>0.48</td>
</tr>
<tr>
<td>PD-L1 IHC TC1/2/3 or IC1/2/3 (WT)</td>
<td>354 (51%)</td>
<td>0.50</td>
</tr>
<tr>
<td>PD-L1 IHC TC0 and IC0 (WT)</td>
<td>338 (49%)</td>
<td>0.77</td>
</tr>
<tr>
<td>PD-L1 IHC TC3 or IC3 (WT)</td>
<td>135 (20%)</td>
<td>0.39</td>
</tr>
<tr>
<td>PD-L1 IHC TC0/1/2 or IC0/1/2 (WT)</td>
<td>557 (80%)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*ITT, EGFR/ALK mutants and ITT-WT: excluded out of ITT (n = 800).

**Hazard Ratio**: In favour of Arm B: 1.0, In favour of Arm C: 1.25

Reck, ESMO IO 2017
KENOTE-189: Randomized double blind phase 3 study of pembrolizumab or placebo plus pemetrexed and platinum as 1L therapy for metastatic NSCLC
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**Progression-Free Survival, ITT (RECIST v1.1, BICR)**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrol/Pem/Plat</td>
<td>59.5%</td>
<td>0.52 (0.43-0.64)</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>80.6%</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI):
- Pembrol: 8.8 mo (7.6-9.2)
- Placebo: 4.9 mo (4.7-5.6)

KENOTE-189: Randomized double blind phase 3 study of pembrolizumab or placebo plus pemetrexed and platinum as 1L therapy for metastatic NSCLC
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Overall Survival in Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths/ No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>Subgroup</th>
<th>No. of Deaths/ No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Age</td>
<td>235/616</td>
<td>0.86 (0.79-0.94)</td>
<td>Overall</td>
<td>235/616</td>
<td>0.86 (0.79-0.94)</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>133/312</td>
<td>0.79 (0.68-0.92)</td>
<td>Baseline brain mets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>102/304</td>
<td>0.90 (0.76-1.06)</td>
<td>Yes</td>
<td>51/108</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>No</td>
<td>104/500</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143/363</td>
<td>0.82 (0.72-0.93)</td>
<td>PD-L1 TPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92/253</td>
<td>0.88 (0.76-1.03)</td>
<td>&lt;1%</td>
<td>84/190</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td>≥1%</td>
<td>135/388</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>74/266</td>
<td>0.90 (0.77-1.05)</td>
<td>1-49%</td>
<td>65/186</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>159/346</td>
<td>0.88 (0.77-1.02)</td>
<td>≥50%</td>
<td>70/202</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>Platinum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former</td>
<td>211/543</td>
<td>0.84 (0.76-0.94)</td>
<td>Carboplatin</td>
<td>176/445</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>24/73</td>
<td>0.91 (0.75-1.12)</td>
<td>Cisplatin</td>
<td>59/171</td>
<td></td>
</tr>
</tbody>
</table>

Ghandi, AACR 2018
PFS cross trial comparisons?
But: Disproportional hazards suggest landmark comparisons

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Medien PFS in months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TPS &lt; 1%</td>
</tr>
<tr>
<td>KN24</td>
<td>Pem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cb/Pem</td>
<td></td>
</tr>
<tr>
<td>KN189</td>
<td>Pem/Cb/Pem</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Cb/Pem</td>
<td>5.1</td>
</tr>
<tr>
<td>KN21G</td>
<td>Pem/Cb/Pem</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>Cb/Pem</td>
<td>9.3</td>
</tr>
<tr>
<td>IMP150</td>
<td>Atezo/Cb/Pc/Bev</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>Cb/Pc/Bev</td>
<td>6.6</td>
</tr>
</tbody>
</table>
Between trial comparison: HR and landmark results

HR 0.36

HR 0.50
KENOTE-189: Randomized double blind phase 3 study of pembrolizumab or placebo plus pemetrexed and platinum as 1L therapy for metastatic NSCLC

Adverse Events (All Cause): Frequency ≥20%

Data cutoff date: Nov 8, 2017.
KENOTE-189: Randomized double blind phase 3 study of pembrolizumab or placebo plus pemetrexed and platinum as 1L therapy for metastatic NSCLC.

**Immune-Mediated Adverse Events**

*Includes 3 grade 5 events. Data cutoff date: Nov 8, 2017.*
Safety and antitumour activity of durvalumab plus tremelimumab in non-small-cell lung cancer: a multicentre, phase 1b study

Durvalumab 20 mg/kg q4w + tremelimumab 1 mg/kg selected as the expansion-phase dose

Tumour shrinkage observed irrespective of PD-L1 tumour status

Antonia, Lancet Oncol 2016
NSCLC cohorts treated in first line with nivolumab alone or nivolumab combined with ipilimumab according to PD-L1 expression

Hellmann, Lancet Oncol 2016
Phase 3 ICB combinations in 1L advanced NSCLC:

**Nivolumab**
- **CHECKMATE 227**
  - Treatment-naïve or recurrent NSCLC
  - N=1980
  - Primary endpoints: OS, PFS

**Pembrolizumab**
- **KEYNOTE-189**
  - Treatment-naïve non-squamous NSCLC
  - N=580
  - Primary endpoint: PFS

**Nivolumab**
- **CHECKMATE 026**
  - Treatment-naïve non-squamous NSCLC
  - N=885
  - Primary endpoint: PFS

**Pembrolizumab**
- **KEYNOTE-042**
  - Treatment-naïve non-squamous NSCLC
  - N=1200
  - Primary endpoint: OS

**Pembrolizumab**
- **KEYNOTE-024**
  - Treatment-naïve non-squamous NSCLC
  - N=505
  - Primary endpoint: OS

**Durvalumab**
- **MYSTIC**
  - PD-L1+ NSCLC
  - N=675
  - Primary endpoint: OS

**Durvalumab**
- **NEPTUNE**
  - First-line metastatic NSCLC
  - N=800
  - Primary endpoint: OS

**Atezolizumab**
- **Impower 110**
  - Stage IV non-squamous PD-L1+ NSCLC
  - N=480
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 111**
  - Stage IV squamous PD-L1+ NSCLC
  - N=480
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 130**
  - Stage IV non-squamous NSCLC
  - N=150
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 131**
  - Stage IV squamous NSCLC
  - N=1200
  - Primary endpoint: PFS

**Atezolizumab**
- **Impower 150**
  - Stage IV non-squamous NSCLC
  - N=1200
  - Primary endpoint: PFS

- **TMB high: Pos. PFS**
- **PD-L1 ≥ 25%: Neg. PFS, OS pending**
Checkmate-227: Nivolumab + ipilimumab vs platinum-doublet chemotherapy as 1L treatment for advanced NSCLC

**CheckMate 227 Part 1 Study Design**

Key Eligibility Criteria:
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No known sensitizing EGFR/ALK alterations
- ECOG PS 0–1

Stratified by SQ vs NSQ

- N = 1189
- ≥1% PD-L1 expression
- R 1:1:1
- Nivolumab 3 mg/kg Q2W
  - Ipilimumab 1 mg/kg Q6W
    - n = 396
  - Histology-based chemotherapy
    - n = 397

- Nivolumab 240 mg Q2W
  - n = 396

- N = 550
- <1% PD-L1 expression
- R 1:1:1
- Nivolumab 3 mg/kg Q2W
  - Ipilimumab 1 mg/kg Q6W
    - n = 167
  - Histology-based chemotherapy
    - n = 169

- Nivolumab 360 mg Q3W + histology-based chemotherapy
  - n = 177

Patients for PD-L1 co-primary analysis:
- Nivolumab + Ipilimumab
  - n = 396
- Chemotherapy
  - n = 397

Patients for TMB co-primary analysis:
- Nivolumab + Ipilimumab
  - n = 139
- Chemotherapy
  - n = 160

Co-primary endpoints:
- Nivolumab + ipilimumab vs chemotherapy
  - OS in PD-L1-selected populations
  - PFS in TMB-selected populations

Hellmann, AACR 2018
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Selection of TMB ≥10 mut/Mb Cutoff for Nivolumab + Ipilimumab Using FoundationOne CDx™

- Retrospective testing from CheckMate 026, 012, and 568 informed selection of the TMB cutoff (≥10 mut/Mb)\(^1\)\(^3\)
- ORR increased in patients with higher TMB, and plateaued at TMB ≥10 mut/Mb

CheckMate 568: ROC for TMB by ORR irrespective of tumor PD-L1 expression (n = 98)

Checkmate-227: Nivolumab + ipilimumab vs platinum-doublet chemotherapy as 1L treatment for advanced NSCLC

TMB Analysis Using FoundationOne CDx™

- 58% of all randomized patients had TMB-evaluable samples\(^a\)

\[\text{TMB- evaluable patients (n = 1004)}\]

<table>
<thead>
<tr>
<th>TMB ≥10 mut/Mb</th>
<th>&lt;1%</th>
<th>≥1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>44%</td>
<td>29%</td>
<td>71%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TMB &lt;10 mut/Mb</th>
<th>&lt;1%</th>
<th>≥1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>56%</td>
<td>29%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Hellmann, AACR 2018
Checkmate-227: Nivolumab + ipilimumab vs platinum-doublet chemotherapy as 1L treatment for advanced NSCLC

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Nivo + ipi (n = 139)</th>
<th>Chemo (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>7.2</td>
<td>5.4</td>
</tr>
<tr>
<td>HR(^c)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>97.5% CI</td>
<td>0.41, 0.81</td>
<td></td>
</tr>
<tr>
<td>(P = 0.0002)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)\(^d\)

Hellmann, AACR 2018
Checkmate-227: Nivolumab + ipilimumab vs platinum-doublet chemotherapy as 1L treatment for advanced NSCLC

**ORR and DOR in Patients With High TMB (≥10 mut/Mb)**

**ORR (TMB ≥10 mut/Mb)**

- **Nivo + ipi**
  - 45.3%
  - 41.7 CR
  - 26.9 PR

- **Chemo**
  - 26.3%

**DOR (TMB ≥10 mut/Mb)**

- **Nivo + ipi** (n = 63)
  - Median DOR: 9.4 months (95% CI: 7.2, NR)
  - 1-y DOR: 68%

- **Chemo** (n = 43)
  - Median DOR: 5.4 months (95% CI: 4.2, 6.9)
  - 1-y DOR: 25%

- **No. at risk**
  - Nivo + ipi: 63, 56, 46, 32, 22, 10, 5, 0
  - Chemo: 43, 32, 15, 5, 2, 2, 1, 0

- Median time to response was 2.7 months with nivolumab + ipilimumab and 1.5 months with chemotherapy.

Heilman, AACR 2018
Checkmate-227: Nivolumab + ipilimumab vs platinum-doublet chemotherapy as 1L treatment for advanced NSCLC

Preliminary Overall Survival With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)

- Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored
- In the chemotherapy arm, 31.3% received subsequent immunotherapy (38.3% among those with disease progression)

Hellmann, AACR 2018
Checkmate-227: Nivolumab + ipilimumab vs platinum-doublet chemotherapy as 1L treatment for advanced NSCLC

# Safety Summary of Treatment-Related AEs

<table>
<thead>
<tr>
<th>TRAE, %</th>
<th>Nivolumab + ipilimumab (n = 576)</th>
<th>Chemotherapy (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>75</td>
<td>31</td>
</tr>
<tr>
<td>TRAE leading to discontinuationb</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Most frequent TRAEs (≥15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related deathsc</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

- Median duration (range) of therapy was 4.2 mo (0.03–24.0+) with nivolumab + ipilimumab and 2.6 mo (0.03–22.1+) with chemotherapy
- Median number of doses of nivolumab (Q2W) and ipilimumab (Q6W) received were 9 and 5, respectively
Biomarker development

- PD-L1 expression
- T effector signature
- Tumor mutation burden

**Dolled-Filhart,** *Arch Path Lab Med* 2016

**Fehrenbacher,** *Lancet Oncol* 2016

**Peters,** *AACR* 2017
Response rate with ICB therapy in 27 tumor types

Yarchoan, N Engl J Med 2017
Second and further line therapy for patients with NSCLC without oncogenic driver mutation – the shift to immunotherapy

- Docetaxel used to be the standard of care
- The addition of nintedanib to docetaxel (non-squamous NSCLC) and of ramucirumab to docetaxel (all NSCLC) is associated with small, but significant survival improvement over docetaxel alone
- Second line therapy with single agent immune checkpoint inhibitors (nivolumab, pembrolizumab or atezolizumab) provides survival advantage, fewer side effects and a better quality of life as compared to chemotherapy
- The observation of durable remissions with second or later line immune checkpoint inhibitor suggests a small proportion of patients might be cured by this approach
- The introduction of IO in first line opens the question on how to proceed from here
Systemic therapy of advanced NSCLC without oncogenic driver mutation: Immunotherapy as preferred second line therapy

Nivolumab

Pembrolizumab

Atezolizumab

Bramer, NEJM 2015; Borghai, NEJM 2015;
Horn, JCO 2017

Herbst, Lancet 2016

Rittmeyer, Lancet 2017
Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced NSCLC: Overall survival

54% pretreated with 3-5 therapies, 17% confirmed responses
Of the 16 pts surviving 5 years, 12 had a PR, 3 SD and 1 PD as best response

Brahmer, AACR 2017
Five-year follow-up from the CA209-003 study of nivolumab in previously treated advanced NSCLC: Outcome and subsequent treatment of the 16 long term survivors

- 12/16 patients remain without evidence disease progression
- 4 patients had subsequent therapy
  - 1 had surgical resection alone (and remains with no evidence of disease)
  - 1 had surgery followed by systemic therapies
  - 2 had systemic therapies

Brahmer, AACR 2017
What if 3rd line chemotherapy is the default? Will there be an improved response rate after immune checkpoint inhibition?

<table>
<thead>
<tr>
<th></th>
<th>No Prior CTx</th>
<th>≥1 Prior CTx</th>
<th>Carboplatin + pemetrexed</th>
<th>Docetaxel + ramucirumab</th>
<th>Vinorelbine</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=6</td>
<td>N=33</td>
<td>N=6</td>
<td>N=13</td>
<td>N=7</td>
<td>N=6*</td>
</tr>
<tr>
<td>CR/PR</td>
<td>3 (50%)</td>
<td>9 (27%)</td>
<td>3 (50%)</td>
<td>4 (31%)</td>
<td>2 (28%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (33%)</td>
<td>7 (21%)</td>
<td>2 (33%)</td>
<td>3 (23%)</td>
<td>1 (14%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (17%)</td>
<td>17 (52%)</td>
<td>1 (17%)</td>
<td>6 (46%)</td>
<td>4 (57%)</td>
<td>4 (66%)</td>
</tr>
</tbody>
</table>

Table 2: Objective response rates (ORR) to chemotherapy after an ICI. Responses are summarized by prior chemotherapy and by regimen. Many responses were durable, with a median time to progression (TTP) of 154 days among those with SD or better.

*Three patients received gemcitabine-based doublets with vinorelbine or docetaxel.

Grigg C et al. ASCO, 2017 #9082
Interaction of chemotherapy with the immune system

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

Tang, Ann Oncol 2018