FIRST-LINE TREATMENT OF NON-ONCOGENE ADDICTED ADVANCED NSCLC

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CIBERONC
There are still more than 1.1 billion smokers

It has been predicted that there will be 1 billion deaths attributable to tobacco this century

Ever cigarette smoking is the principal risk factor for cancer burden

In 2012, the tobacco industry spent over 40 times more on tobacco advertising and promotion in the USA than the NIH spent on lung cancer research ($9.6 billion tobacco industry versus $2333 million NIH)\(^1\)
LUNG CANCER MORTALITY:
MAJOR GLOBAL HEALTH BURDEN

Leading cause of cancer deaths worldwide (1.8 M deaths/yr); responsible for over a fifth of all cancer deaths in the EU

Global cancer burden projected to double by 2050 and lung cancer is expected to remain the leading cause of all cancer deaths

Lung cancer has become the first cause of cancer death in women in several countries and is still expanding in Western and Southern Europe

Stage matters: the lower the stage, the better the 5-year survival

- More than 40% of patients are still diagnosed with Stage IV

CURRENT OPTIONS FOR UPFRONT TREATMENT IN STAGE IV NSCLC

Smoking cessation highly encouraged
Systemic therapy offered to all PS 0–2 patients
Decisions based on histology and molecular pathology, age, PS, comorbidities and patients’ preferences
Options:
  - Chemotherapy + anti-angiogenic therapy
  - Targeted therapy (TKI) molecular diagnosis is required (EGFR, ALK, ROS and BRAF)
  - Immunotherapy (ICPI) + chemotherapy
CHEMOTHERAPY

Unique treatment option for ECOG 0–2 stage IV NSCLC patients for many years
CHEMOTHERAPY BENEFIT?

NSCLC Collaborative Group (BMJ 1995)¹
Data from 778 patients included in 8 RCTs comparing supportive care with supportive care plus CT
Cisplatin-based trials showed a benefit of chemotherapy with
- HR 0.73 (p<0.0001), a reduction in the risk of death of 27%
- Equivalent to an absolute improvement in survival of 10% (5% to 15%) at 1 year

NSCLC Meta-Analyses Collaborative Group (JCO 2008)²
Data were obtained from 2714 patients from 16 RCTs
Significant benefit of chemotherapy
- HR 0.77; 95% CI: 0.71, 0.83; p≤0.0001
- Equivalent to an absolute improvement in survival of 9% at 12 months
- Increasing survival from 20% to 29%

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WHAT DO WE HAVE TO KNOW ABOUT CHEMOTHERAPY?

Number of CT agents?
- No survival benefit when comparing three agents vs. doublets (Delbaldo C, JAMA 2004;292(4):470-484)

Type of CT regimen?
- Platinum-containing regimens are better than non-platinum combinations (Pujol JL, Cancer 2006;51(3):335-345)

Cisplatin- or carboplatin-based regimen?
- Different toxicity profile

Number of CT cycles?
- Six cycles of platinum-based CT does not improve OS compared with 3 or 4 cycles (Park JO, J Clin Oncol. 2007;25(33):5233-9.; Rossi A, Lancet Oncol 2014;15(11):1254-1262)
BEST PLATINUM REGIMEN COMBINATION?

Several platinum-based regimens with third-generation cytotoxics (paclitaxel, gemcitabine, docetaxel, vinorelbine) have shown comparable efficacy.

HISTOLOGIC SUBTYPE MATTERS

Pemetrexed and bevacizumab restricted to non-squamous NSCLC

Pemetrexed/CDDP:
Better efficacy results in Non Sq (Scagliotti, JCO 2008)

Pemetrexed/Cis vs Gem/Cis in 1st-line NSCLC:
Prospective Analysis of Histology and OS

Bevacizumab + CT:
Higher toxicity risk in Sq (Johnson, JCO 2004)

Phase II trial of bevacizumab plus CP in NSCLC

- This ‘proof of principal’ trial demonstrated that bevacizumab therapy is feasible and effective in patients with NSCLC
- The addition of bevacizumab to CP was generally well tolerated
- Severe, pulmonary haemorrhage was a concern in 6/66 (9%) patients receiving bevacizumab
  - apparent risk factors
    - squamous-cell histology (4/6)
    - centrally located cavitory or necrotic tumours (5/6)
- Based on these observations, patients with predominantly squamous-cell carcinoma were excluded from future trials

ROLE OF MONOCLONAL ANTIBODIES IN COMBINATION WITH FIRST-LINE CHEMOTHERAPY
ANTI-EGFR AND CT: LIMITED CLINICAL IMPROVEMENT

CETUXIMAB
FLEX study showed superior OS when cetuximab added to CT (Pirker R, Lancet 2009)
- Selected population: EGFR expression in at least one positively stained tumour cell by IHC
- Modest benefit in OS (median 11.3 vs. 10.1 months; HR 0.871; p=0.044)
- No benefit in PFS and increased toxicity (acne-like rash 10% grade 3)

NECITUMUMAB
No benefit in non-squamous (INSPIRE trial) when added to CDDP/Pem (Paz-Ares L, Lancet 2015)
- Median OS 11.3 vs. 11.5 months (HR 1.1; p=0.06)
Benefit in squamous (SQUIRE trial) in combination to CDDP-Gem (Thatcher N, Lancet Oncol 2015)
- Median OS 11.5 vs. 9.9 months (HR 0.84; p=0.01)

Potential role for biomarkers? (Garrido P, Ann Oncol 2016)
ROLE OF BEVACIZUMAB ADDED TO 1 L CT IN NON-SQUAMOUS NSCLC

Bevacizumab improves

- OS when combined with paclitaxel/carboplatin regimens (Sandler A, NEJM 2006)
- PFS but not OS when added to CDDP/Gem (Reck M, JCO 2009; Ann Oncol 2010)
- Systematic review and meta-analysis of randomised, Phase II/III trials (Soria J-C, Ann Oncol 2013)
- Compared with chemotherapy alone, bevacizumab significantly prolonged OS (HR 0.90; p=0.03), and PFS (0.72; p<0.001)

MAINTENANCE TREATMENT

Pemetrexed
CDDP/Pem followed by Pem (PARAMOUNT trial) (Paz-Ares L, J Clin Oncol 2013; 31(23): 2895-2902)
- Reduced the risk of disease progression vs placebo (HR 0.62; p<0.001)
- Improved OS (HR 0.78; p=0.0195); median OS: pemetrexed, 13.9 months; placebo, 11.0 months

Bevacizumab
Positive RCT included Bev + CT followed by Bev as maintenance.

Pemetrexed + Bevacizumab
AVAPERL study (Barlesi F, J Clin Oncol 2013; 31(24):3004-11)
- Benefit in PFS but not in OS using maintenance with Bev + Pem vs. Bev alone after CDDP/Pem/Bev

POINTBREAK study (Patel JD, J Clin Oncol 2013; 31(34): 4349-57)
- OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev

Gemcitabine
- Continuation maintenance with Gem after 4 cycles of CDDP/Gem reduces PFS with a non-significant OS improvement
ESMO GUIDELINES
STAGE IV SCC

STAGE IV NSCC

IMMUNOTHERAPY IN NSCLC

Cancer evades immune cell recognition and destruction

Immunotherapy is not focused on cancer cells but on the immune system, facilitating the recognition of cancer cells by our own immune system

Different toxicity profile

Long-term survival ≈ 20–30% patients

RECOMMENDATIONS AND CONTRAINDICATIONS

To use programmed death-ligand 1 (PD-L1) in the first-line setting in specific situations

Contraindications:

- In patients with history of organ transplantation because of non-negligible risk of organ rejection and death
- If a woman is or becomes pregnant
  - PD-L1 is constitutively expressed by the placenta to prevent maternal immunity from rejecting the foetus, and therefore PD-L1 blockade would be expected to be incompatible with pregnancy

Concerns

- Severe and/or symptomatic autoimmune diseases
- Pulmonary fibrosis and interstitial lung disease

There is no longer concern about using PD-L1 blockade in patients with chronic viral infections such as hepatitis B and C and HIV

- PD-1 blockade is now approved for use in viral hepatitis-related hepatocellular cancers

ICPIs IN NSCLC CURRENTLY MEANS

PD-1/PD-L1
- Nivolumab
- Pembrolizumab
- Atezolizumab
- Durvalumab

CTLA-4
- Ipilimumab
- Tremelimumab
MONOTHERAPY
THREE RCTs TESTING ICPI VERSUS CT AS FIRST LINE

PD-L1 >50%
   - KEYNOTE-024

PD-L1 >1%
   - KEYNOTE-042
   - CHECKMATE 026
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

Key endpoints
- 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%
KEYNOTE-024: UPDATED OVERALL SURVIVAL

Overall survival¹

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>6 mo survival, %</th>
<th>12 mo survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>44</td>
<td>NR</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>64</td>
<td>NR</td>
<td>72</td>
<td>54</td>
</tr>
</tbody>
</table>


DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab.
KEYNOTE-042 STUDY DESIGN

Key eligibility criteria
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥1%
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification factors
- Region (East Asia vs. Rest of the World)
- ECOG PS (0 vs. 1)
- Histology (squamous vs. non-squamous)
- PD-L1 TPS (≥50% vs. 1–49%)

Endpoints
- Primary: OS in PD-L1 TPS ≥50%, ≥20%, and ≥1%
- Secondary: PFS and ORR in TPS ≥50%, ≥20%, and ≥1%; safety in TPS ≥1%

Pembrolizumab 200 mg Q3W for up to 35 cycles

Carboplatin AUC 5 or 6 Q3W + paclitaxel 200 mg/m² Q3W⁹
OR
Carboplatin AUC 5 or 6 Q3W + pemetrexed 500 mg/m² Q3W⁹ for up to 6 cycles

⁹Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

OVERALL SURVIVAL: TPS ≥1%

Data cutoff date: Feb 26, 2018
OVERALL SURVIVAL

Overall survival: TPS ≥50%

Overall survival: TPS ≥1–49% (exploratory analysis)

Data cutoff date: Feb 26, 2018


CHECKMATE 026: NEGATIVE STUDY
Nivolumab vs. platinum-based CT in patients

Progression-free survival

Overall survival

Patients with advanced NSCLC and PD-L1 expression >50%:

- Pembrolizumab is considered a **standard first-line option** for patients who do not otherwise have contraindications to use of immunotherapy [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 5]

Patients with advanced NSCLC and PD-L1 expression >1% (KEYNOTE-042):

- Overall, the **preponderance of the OS benefit was driven by patients with 50%**, while no significant increase was seen in those patients with 1%–49% PD-L1 expression (HR 0.92; 95% CI: 0.77, 1.11)
- Regulatory approval for pembrolizumab monotherapy at TPS ≥1% threshold is expected in some countries, although clinical use of this approach is expected (and recommended) to be limited (Peters S. Ann Oncol 2019)
IO + CT IN THE FIRST LINE SETTING
KEYNOTE-189 STUDY DESIGN (NCT02578680)

Key eligibility criteria
- Untreated stage IV nonsquamous NSCLC
- No sensitising EGFR or ALK alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification factors
- PD-L1 expression (TPS<1% vs ≥1%)
- Platinum (cisplatin vs. carboplatin)
- Smoking history (never vs. former/current)

R (2:1)

n=410

Pembrolizumab 200 mg + pemetrexed 500 mg/m² + carboplatin AUC 5 OR cisplatin 75 mg/m² Q3W for 4 cycles

Placebo (normal saline) + pemetrexed 500 mg/m² + carboplatin AUC 5 OR cisplatin 75 mg/m² Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles + pemetrexed 500 mg/m² Q3W

Placebo (normal saline) for up to 31 cycles + pemetrexed 500 mg/m² Q3W

n=206

Pembrolizumab 200 mg Q3W for up to 35 cycles

PD

aPercentage of tumour cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. bPatients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Gandhi, KN189; AACR 2018.
KEYNOTE-189: OVERALL SURVIVAL, ITT

Data cut-off date: Nov 8, 2017.
KEYNOTE-189: OVERALL SURVIVAL BY PD-L1 TPS

<table>
<thead>
<tr>
<th>TPS &lt;1%</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>38.6%</td>
<td>0.59</td>
<td>0.0095</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>55.6%</td>
<td>(0.38-0.92)</td>
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</table>

<table>
<thead>
<tr>
<th>TPS 1-49%</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>28.9%</td>
<td>0.55</td>
<td>0.0081</td>
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<tr>
<td>Placebo/Pem/Plat</td>
<td>48.3%</td>
<td>(0.34-0.90)</td>
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</table>

<table>
<thead>
<tr>
<th>TPS ≥50%</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>25.8%</td>
<td>0.42</td>
<td>0.0001</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>51.4%</td>
<td>(0.26-0.68)</td>
<td></td>
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</tbody>
</table>

*Nominal and one-sided. Data cut-off date: Nov 8, 2017.
**IMpower132 STUDY DESIGN**

Chemotherapy-naive patients with Stage IV non-squamous NSCLC without *EGFR* or *ALK* genetic alteration

Stratification factors:
- Sex
- Smoking status
- ECOG PS
- Chemotherapy regimen

N=578

Induction therapy:
- **Arm APP**
  - Atezolizumab + carboplatin or cisplatin + pemetrexed
  - 4 or 6 cycles

Maintenance therapy:
- Atezolizumab + pemetrexed

Maintenance treatment until PD by RECIST v1.1 or loss of clinical benefit

Survival follow-up

- Co-primary endpoints: INV-assessed PFS and OS
- Secondary endpoints: INV-assessed ORR and DOR, PRO and safety measures
- Exploratory analyses: clinical and biomarker subgroup analyses
  - Biomarker-evaluable tissue not mandatory for enrollment (was available from 60% of patients)


PRO, patient-reported outcomes.

*Atezolizumab: 1200 mg IV Q3W; Carboplatin: AUC 6 mg/mL/min IV Q3W; Cisplatin: 75 mg/m² IV Q3W; Pemetrexed: 500 mg/m² IV Q3W.

Barlesi F, et al. ESMO 2018*
**IMpower132: INTERIM OS ANALYSIS**

HR: 0.81 (95% CI: 0.64, 1.03; p=0.0797)

Minimum follow-up: 11.7 mo
Median follow-up: 14.8 mo

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>APP</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-mo OS, %</td>
<td>59.6</td>
<td>55.4</td>
</tr>
</tbody>
</table>

APP, atezolizumab + carboplatin/cisplatin + pemetrexed; PP, carboplatin/cisplatin + pemetrexed.

Data cut-off: May 22, 2018. Frequency of OS events: 44% and 49% in arms APP and PP respectively.

Barlesi F, et al. ESMO 2018, IMpower132: efficacy of atezolizumab + carboplatin/cisplatin + pemetrexed as 1L treatment in key subgroups with stage IV non squamous NSCLC.

By permission of Prof Fabrice Barlesi
**IMpower132: FINAL INVESTIGATOR-ASSESSED PFS, ORR AND DOR**

**Progression-Free Survival (%)**

- **Minimum follow-up:** 11.7 mo
- **Median follow-up:** 14.8 mo

**HR 0.60 (95% CI: 0.49, 0.72; p<0.0001)**

**6-mo PFS**
- **APP:** 59.1%
- **PP:** 40.9%

**12-mo PFS**
- **APP:** 33.7%
- **PP:** 17.0%

**ORR, %**
- **APP:** 47%
- **PP:** 32%

**CR**
- **APP:** 2
- **PP:** 1

**PR**
- **APP:** 45%
- **PP:** 32%

**Median DOR, mo**
- **APP:** 10.1
- **PP:** 7.2

**Ongoing response, %**
- **APP:** 42%
- **PP:** 30%

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APP, atezolizumab + carboplatin/cisplatin + pemetrexed; CR, complete response; DOR, duration of response; HR, hazard ratio; IRF, independent review facility; ORR, objective response rate; PP, carboplatin/cisplatin + pemetrexed; PR, partial response.

Data cut-off: May 22, 2018. IRF-assessed median PFS was 7.2 mo with APP and 6.6 mo with PP (stratified HR: 0.758 [95% CI: 0.623, 0.923] p=0.055)

Barlesi F, et al. ESMO 2018, IMpower132: efficacy of atezolizumab +carboplatin/cisplatin + pemetrexed as 1L treatment in key subgroups with stage IV non squamous NSCLC.

By permission of Prof Fabrice Barlesi
IMPOWER150 STUDY DESIGN

Stage IV or recurrent metastatic nonsquamous NSCLC
Chemotherapy-naive\(^a\)
Tumour tissue available for biomarker testing
Any PD-L1 IHC status

Stratification factors:
• Sex
• PD-L1 IHC expression
• Liver metastases

\(N = 1202\)

**Arm A**
Atezolizumab\(^b\) + Carboplatin\(^c\) + Paclitaxel\(^d\)
4 or 6 cycles

**Arm B**
Atezolizumab\(^b\) + Carboplatin\(^c\) + Paclitaxel\(^d\)
+ Bevacizumab\(^e\)
4 or 6 cycles

**Arm C (control)**
Carboplatin\(^c\) + Paclitaxel\(^d\)
+ Bevacizumab\(^e\)
4 or 6 cycles

**Maintenance therapy**
(no crossover permitted)

Atezolizumab\(^b\)

Atezolizumab\(^b\) + Bevacizumab\(^e\)

Bevacizumab\(^e\)

Treated with atezolizumab until PD per RECIST v1.1 or loss of clinical benefit
AND/OR
Treated with bevacizumab until PD per RECIST v1.1

IMpower150: OS

Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs. chemo + bev in 1L nonsquamous (NSQ) NSCLC. By permission of Prof Mark A. Socinski.
**IMpower150: ALL PD-L1 SUBGROUPS IN THE ITT-WT (ARM B VS. ARM C)**

**PD-L1–High**
TC3 or IC3

- HR\textsuperscript{a}, 0.70
- (95% CI: 0.43, 1.13)
- 15.0 mo
- 25.2 mo

**PD-L1–Low**
TC1/2 or IC1/2

- HR\textsuperscript{a}, 0.80
- (95% CI: 0.55, 1.15)
- 16.4 mo
- 20.3 mo

**PD-L1–Negative**
TC0 and IC0

- HR\textsuperscript{a}, 0.82
- (95% CI: 0.62, 1.08)
- 14.1 mo
- 17.1 mo

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Socinski M, ASCO 2018 Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs. chemo + bev in 1L nonsquamous (NSQ) NSCLC.

By permission of Prof Mark A. Socinski.
IMpower130 STUDY DESIGN

- Co-primary endpoints: investigator-assessed PFS and OS (ITT-WT population)
  - ITT-WT population: randomised patients excluding those with EGFR or ALK genomic alterations
  - Key secondary endpoints: OS and PFS (ITT population and by PD-L1 expression), ORR and safety
  - Exploratory analyses: clinical and biomarker subgroup analyses
    - ITT population could be formally tested for OS/PFS if ITT-WT OS was positive

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a Measurable (RECIST v1.1) stage IV non-squamous NSCLC; b one patient died before randomisation, but was assigned to a treatment group; this patient was excluded from the intention-to-treat population; c CnP = carboplatin: AUC 6 Q3W; nab-paclitaxel: 100 mg/m² IV QW

IMpower130:
INVESTIGATOR ASSESSED PFS AND OS (ITT-WT)

KEYNOTE-407 STUDY DESIGN (NCT02775435)

Key eligibility criteria
- Untreated stage IV nonsquamous NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification factors
- PD-L1 expression (TPSa <1% vs. ≥1%)
- Choice of taxane (paclitaxel vs. nab-paclitaxel)
- Geographic region (East Asia vs. Rest of World)

Endpoints
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

a Percentage of tumour cells with membranous PD-L1 staining assessed using the PD-L1 IHC-22C3 pharmDx assay;

b Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

KEYNOTE-407: OVERALL SURVIVAL AT IA2, ITT

Data cut-off date: Apr 3, 2018.
KEYNOTE-407: OVERALL SURVIVAL AT IA2 BY PD-L1 TPS

Data cut-off date: Apr 3, 2018.
IMpower131: STUDY DESIGN

Stage IV squamous NSCLC
- Chemotherapy-naive
- ECOG PS 0 or 1
- Any PD-L1 IHC status

Stratification factors:
- Sex
- PD-L1 IHC expression
- Liver metastases
N=1021

Arm A
Atezolizumab + carboplatin + paclitaxel
4 or 6 cycles

Arm B
Atezolizumab + carboplatin + nab-paclitaxel
4 or 6 cycles

Arm C (control)
Carboplatin + nab-paclitaxel
4 or 6 cycles

Maintenance therapy
(no crossover permitted)

Until PD per RECIST v1.1 or loss of clinical benefit

Co-primary endpoints
- Investigator-assessed PFS per RECIST v1.1 (ITT)
- OS (ITT)

Secondary endpoints
- PFS and OS in PD-L1 subgroups
- ORR, DOR; safety

*Patients with sensitising EGFR mutation or ALK translocation must have disease progression or intolerance to treatment with ≥1 approved targeted therapies. Testing for EGFR mutation or ALK translocation was not mandatory. Atezolizumab: 1200 mg IV Q3W; carboplatin: AUC 6 IV Q3W; nab-paclitaxel 100 mg/m² IV QW; paclitaxel: 200 mg/m² IV Q3W

IMpower131

Investigator-assessed PFS in the ITT population (Arm B vs. Arm C)

- Arm B: atezo + CnP
- Arm C: CnP

<table>
<thead>
<tr>
<th></th>
<th>Arm B: atezo + CnP</th>
<th>Arm C: CnP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>6.3 (5.7, 7.1)</td>
<td>5.6 (5.5, 5.7)</td>
</tr>
<tr>
<td>HR* (95% CI)</td>
<td>0.71 (0.60, 0.85)</td>
<td>0.0001</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Minimum follow-up: 9.8 mo
Median follow-up: 17.1 mo

*Stratified HR.
Data cut-off: January 22, 2018
**IMpower131**

First interim OS in the ITT population (Arm B vs. Arm C)

<table>
<thead>
<tr>
<th></th>
<th>Arm B: atezo + CnP</th>
<th>Arm C: CnP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mo</td>
<td>14.0 (12.0, 17.0)</td>
<td>13.9 (12.3, 16.4)</td>
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<tr>
<td>HR* (95% CI)</td>
<td>0.96 (0.78, 1.18)</td>
<td>0.6931</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>0.621</td>
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</table>

*Stratified HR.
Data cut-off: January 22, 2018
OPEN QUESTIONS ABOUT SELECTING THE BEST STRATEGY

No head-to-head comparison
Best decision in patients with PD-L1 TPS >50%?

- Many experts tend to favour pembrolizumab monotherapy:
  - Similar 1-year OS when comparing across KEYNOTE-024, KEYNOTE-189, and KEYNOTE-407 at the PD-L1 TPS ≥50% threshold (70.3%, 69.2%, and 65.2%, respectively)
  - Improved tolerability and improved health-related quality of life compared with chemotherapy
- In highly symptomatic patients with PD-L1 TPS ≥50%, it is quite reasonable to use pembrolizumab + CT
  - No evidence of chemotherapy detracting from the potential benefit of PD-1 blockade (or vice versa)
  - Response rate is higher with combos (pembrolizumab monotherapy, 39.5% and 45.5% [KEYNOTE-042 PD-L1 TPS ≥50% and KEYNOTE-024, respectively] vs. pembrolizumab combination therapy, 47.6% and 57.9% [KEYNOTE-189 PD-L1 TPS ≥50% and KEYNOTE-407 PD-L1 TPS ≥50%, respectively])

IO + IO COMBINATION
PD-1 AND CTLA-4 RATIONALE FOR COMBINATION

PD-1 and CTLA-4 have complementary, distinct roles in T cells

PD-1 and CTLA-4 blockade is synergistic in preclinical models

There is no evidence that CTLA-4 monotherapy has efficacy in NSCLC, notwithstanding evaluation in a number of studies

Based on the efficacy seen in melanoma, the combination of PD-(L)1 plus CTLA-4 blockade has been studied in NSCLC:

- CheckMate 227
- Mystic trial
CHECKMATE 227: 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

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

Histology-based chemotherapy

Nivolumab 3 mg/kg Q2W
Ipiilimumab 1 mg/kg Q6W
n=396

Histology-based chemotherapy
n=397

Nivolumab 240 mg/kg Q2W
n=396

Nivolumab 3 mg/kg Q2W
Ipiilimumab 1 mg/kg Q6W
n=187

Histology-based chemotherapy
n=186

Nivolumab 360 mg/kg 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

Chemotherapy for patients with NSCLC consisted of pemetrexed (500 mg/m^2 BSA) plus cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6), Q3W for up to 4 cycles, with optional maintenance therapy with pemetrexed (500 mg/m^2) after chemotherapy or with nivolumab (360 mg Q3W) plus pemetrexed (500 mg/m^2) after nivolumab plus chemotherapy. Chemotherapy for patients with squamous NSCLC consisted of gemcitabine (1000 or 1250 mg/m^2) plus cisplatin (75 mg/m^2), or gemcitabine (1000 mg/m^2) plus carboplatin (AUC 5), Q3W for up to 4 cycles;

TMB co-primary analysis was conducted in the subgroup of patients assigned to nivolumab plus ipilimumab or chemotherapy who had a TMB of at least 10 mutations per megabase.

PFS IN CHECKMATE 227 PART 1
NIVOLUMAB + IPILIMUMAB IN TMB >10 MB

NEGATIVE OS RESULTS IN TMB HIGH COHORT CHECKMATE 227*

Preliminary OS with nivolumab+ipilimumab vs. chemotherapy with high TMB (≥10 mut/Mb)

- Updated OS data* (IO combo vs. CT):
  - TMB ≥10 mut/Mb: median OS 23.03 months vs. 16.72 months (HR 0.77; 95% CI: 0.56, 1.06)
  - TMB <10 mut/Mb, median OS 16.20 months vs. 12.42 months (HR 0.78; 95% CI: 0.61, 1.00)

Database lock: March 15, 2018; minimum follow-up: 14.2 months; 53% of patients were censored.
Hellmann MD, et al. AACR 2018. By permission of Prof Hellmann
MYSTIC STUDY DESIGN

- Stage IV NSCLC
- All-comers population (i.e. irrespective of PD-L1 status)
- No sensitising EGFR mutation or ALK rearrangement
- ECOG PS 0/1
- Immunotherapy- and CT-naïve
  N=1118 randomised

Durvalumab (n=374)
20 mg/kg q4w until disease progression

Durvalumab + tremelimumab (n=372)
D 20 mg/kg q4w until disease progression +
T 1 mg/kg q4w for up to 4 doses

Platinum-based chemotherapy (n=372)
- Paclitaxel + carboplatin OR
- Gemcitabine + cisplatin/carboplatin (squamous) OR
- Pemetrexed + cisplatin/carboplatin (non-squamous)†
  for up to 6 cycles

Primary endpoints (PD-L1 TC ≥25%*):
- PFS‡ (D+T vs CT)
- OS (D vs CT)
- OS (D+T vs CT)

Key secondary endpoints:
- PFS‡ (D vs CT; PD-L1 TC ≥25%*)
- OS (D+T vs CT; PD-L1 TC ≥1%*)
- ORR‡
- DoR
- Safety and tolerability

Key exploratory endpoints:
- OS by additional PD-L1 TC cutoffs
- OS by blood TMB

Stratified by PD-L1 TC (<25% vs ≥25%*) and histology

MYSTIC TRIAL: NEGATIVE OS RESULTS

Durvalumab vs. chemotherapy: No statistical significance improvement in OS was observed
- HR 0.76 (97.54% CI: 0.564, 1.019; p=0.036)
- 2-year OS: 38.3% vs. 22.7%

Durvalumab + tremelimumab vs chemotherapy: OS was not improved
- HR 0.85 (98.77% CI: 0.611, 1.173; p=0.202)

Exploratory analysis
- High bTMB (≥16 mut/Mb cut-off) was associated with better OS for durvalumab + tremelimumab vs. chemotherapy
- HR 0.62 (95% CI: 0.451, 0.855); 2-year OS: 39% vs. 18%
ESMO GUIDELINES
TREATMENT ALGORITHM FOR STAGE IV NSCC, MOLECULAR TESTS NEGATIVE (ALK/BRAF/EGFR/ROS1)

In absence of contraindications and conditioned by the registration and accessibility of anti-PD-(L)1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 <50%. Alternatively, if TMB can accurately be evaluated, and conditioned by the registration and accessibility, nivolumab plus ipilimumab should be preferred to platinum-based standard ChT in patients with NSCLC with a high TMB.

Not EMA-approved.

ALK, anaplastic lymphoma kinase; BSC, best supportive care; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; IO, immuno-oncology; Mb, megabase; MCBS, ESMO-Magnitude of Clinical Benefit Scale; nab-P, albumin-bound paclitaxel; PS, performance status; TMB, tumour mutation burden.

TREATMENT ALGORITHM FOR STAGE IV SCC

Molecular testing is not recommended in SCC, except in those rare circumstances when SCC is found in a never-, long-time ex- or light-smoker (<15 pack-years), bin absence of contraindications and conditioned by the registration and accessibility of anti-PD-L1 combinations with platinum-based ChT, this strategy will be preferred to platinum-based ChT in patients with PS 0-1 and PD-L1 <50%. Alternatively, if TMB can accurately be evaluated, and conditioned by the registration and accessibility, nivolumab plus ipilimumab should be preferred to platinum-based standard ChT in patients with NSCLC with a high TMB.

Not EMA-approved.

ALK, anaplastic lymphoma kinase; BSC, best supportive care; ChT, chemotherapy; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; IO, immuno-oncology; Mb, megabase; MCBS, ESMO-Magnitude of Clinical Benefit Scale; nab-P, albumin-bound paclitaxel; PS, performance status; TMB, tumour mutation burden.
CONCLUSIONS

PD-L1 blockade, as mono-immunotherapy or combined with other anticancer agents, is now a routine part of the care of most patients, ideally with newly-diagnosed metastatic NSCLC.

Long-term disease control is observed in only a subset of selected patients, and the percentage of unselected patients who achieve durable benefit from immunotherapy remains low.

It is crucial to refine the predictive value of known biomarkers, as well as exploring other biomarkers to better select patients to be treated with each potential strategy.
THANK YOU!