Immunotherapy in advanced NSCLC patients
Changing the course of the disease

Jordi Remon Masip
Thoracic Oncology Unit
Outline

1. Introduction
2. Immunotherapy in 2\textsuperscript{nd} Line treatment
3. Immunotherapy in 1\textsuperscript{st} Line treatment
4. Who (not) to give immunotherapy?
5. Toxicity
6. Conclusions
Introduction
New revolution in cancer treatment

2013

Science
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack

2015

nature
Immune-checkpoint blockade in cancer

Science
Cancer Immunology and Immunotherapy
Comprehensive analysis of the IO landscape

The tail effect with immunotherapy

5y OS IN 8TH TNM for M1c: 0%

5y OS with Nivolumab in phase I trial

Nivolumab up to 96 weeks

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI), mo</th>
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<tbody>
<tr>
<td>Overall (N = 129)</td>
<td>9.9 (7.8, 12.4)</td>
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PD-L1 > 50% (N=13)
5-yOS: 43%

New treatment perspective

TRADITIONAL ONCOLOGY VIEW
A CANCER THAT GROWS

IMMUNO-ONCOLOGY VIEW
A BODY THAT LETS A CANCER GROW

Courtesy of Pr Besse
How does cancer induce immnosurveillance?

Chen Immunity 2013
How does cancer induce immunosurveillance?
Immune checkpoint inhibitors

**Anti-CTLA-4**
- Ipilimumab (BMS-7340)
- Tremelimumab (CP-675,206)

**Anti-PD1**
- Nivolumab (BMS-936558)
- Pembrolizumab (MK3475)

**Anti-PDL1**
- Atezolizumab (MPDL3280A)
- Durvalumab (MEDI4736)
- Avelumab (PF-06834635, MSB0010718C)
Outline

2. Immunotherapy in 2nd Line treatment
Past, present, future treatment approaches

**FIRST-LINE TREATMENT**

PAST

Chemotherapy

**SECOND-LINE TREATMENT**

Chemotherapy  VS  Immunotherapy

Courtesy Prof. Soria (modified)
2nd line treatment with ICI in NSCLC patients

**Nivolumab – CheckMate 017 (PIII)**
- 2nd Line, squamous, PD-L1 All-Comer
  - Stage IIIb/IV SQ NSCLC
  - 1 prior platinum doublet-based chemotherapy
  - ECOG PS 0-1
  - Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis
  - n=272
  - Nivolumab
    - 3 mg/kg IV Q2W until PD or unacceptable toxicity
    - n=135
  - Docetaxel
    - 75 mg/m² IV Q3W until PD or unacceptable toxicity
    - n=137
  - Patients stratified by region and prior Paclitaxel use

**Nivolumab – CheckMate 057 (PIII)**
- 2nd Line, non-squamous, PD-L1 All-Comer
  - Stage IIIb/IV non-SQ NSCLC
  - Pre-treatment (archival or recent) tumor samples required for PD-L1
  - ECOG PS 0-1
  - Failed 1 prior platinum doublet
  - Prior maintenance therapy allowed
    - therapy allowed for translocation or on
    - n=202
  - Docetaxel
    - 75mg/m² IV Q3W
    - n=200
  - Patients stratified by prior maintenance therapy and line of therapy (2nd- vs. 3rd-line)

**Pembrolizumab - Keynote 010 (PII/III)**
- 2nd+ Line, PD-L1 TPS ≥1%
  - NSCLC
  - At least 2 cycles of platinum-containing doublet chemotherapy
  - PD-L1+ (central laboratory review)
  - ECOG PS 0-1
  - n=1034
  - Pembrolizumab high dose (10 mg/kg) iv q3w
    - n=346
  - Pembrolizumab low dose (2 mg/kg) iv q3w
    - n=345
  - Docetaxel
    - n=343

**Atezolizumab – OAK (P III)**
- 2nd Line, PD-L1 All-comer
  - Locally Advanced or Metastatic NSCLC
  - 1–2 prior lines of chemo including at least 1 platinum based
  - Any PD-L1 status
  - N = 1,225 enrolled
  - Stratification factors
    - PD-L1 expression
    - Histology
    - Prior chemotherapy regimens
  - Atezolizumab
    - 1200 mg IV q3w
  - Docetaxel
    - 75 mg/m² q3w
  - PD or loss of clinical benefit

2nd line treatment with ICI in NSCLC patients: OS

**CheckMate 017 (SQ NSCLC)**

- **Nivolumab (n = 135)**
- **Docetaxel (n = 137)**

HR (95% CI): 0.62 (0.48, 0.80)

1-y OS: 42%
2-y OS: 23%
3-y OS: 16%
1-y OS: 24%
2-y OS: 8%
3-y OS: 6%

**CheckMate 057 (non-SQ NSCLC)**

- **Nivolumab (n = 292)**
- **Docetaxel (n = 290)**

HR (95% CI): 0.73 (0.62, 0.88)

1-y OS: 51%
2-y OS: 29%
3-y OS: 18%
1-y OS: 39%
2-y OS: 16%
3-y OS: 9%

**PDL1 ≥ 50%**

- **Pembrolizumab 10 mg/kg QW**
  - Events: 203/488
  - Median mo (95% CI): 13.4 (9.1-17.0)
  - Hazard Ratio (95% CI): 0.59 (0.48-0.71)
  - P-value: < 0.0001
  - 25-mo rate: 29.5 (24.4-34.6)

- **Pembrolizumab 2 mg/kg QW**
  - Events: 254/544
  - Median mo (95% CI): 16.5 (9.6-12.4)
  - Hazard Ratio (95% CI): 0.78 (0.62-0.97)
  - P-value: 0.00024
  - 25-mo rate: 29.1 (17.4-27.1)

- **Docetaxel**
  - Events: 219/543
  - Median mo (95% CI): 7.6 (7.2-8.6)
  - Hazard Ratio (95% CI): --
  - P-value: --
  - 25-mo rate: 12.3 (9.8-15.6)

**Overall Survival (%)**

- **Pembrolizumab**
- **Docetaxel**

TC3/IC3: 20.5 vs. 8.9

**PDL1 ≥ 50%**

- **14.9 vs. 17.3 vs. 8.2**
- HR 0.54, HR 0.50

2nd line treatment with ICI in NSCLC patients

Updated CheckMate017 & 057 (2-years follow-up)

Any grade 68% vs. 88%.
Grade 3-4: 10% vs. 55%

Horn – JCO 2017
2nd line treatment with ICI in NSCLC patients: OS

**CheckMate 017 (SQ NSCLC)**
- Nivolumab (n = 135)
- Docetaxel (n = 137)
- 1-y OS = 49%
- 3-y OS = 23%
- OS = 8%
- OS = 6%
- HR 0.48, (0.48, 0.80)

**CheckMate 057 (non-SQ NSCLC)**
- Nivolumab (n = 292)
- Docetaxel (n = 290)
- 1-y OS = 33%
- 3-y OS = 29%
- 1-y OS = 16%
- 3-y OS = 18%
- HR 0.73 (0.62, 0.88)

TC3/IC3: 20.5 vs. 8.9

PDL1 ≥ 50%:
- 14.9 vs. 17.3 vs. 8.2
- HR 0.54, 0.50

In PD-L1 ≥1% tumours

APPROVED by FDA & EMA

Past, present, future treatment approaches

**FIRST-LINE TREATMENT**

- **PAST**
  - Chemotherapy

- **PRESENT AND FUTURE**
  - Chemotherapy

**SECOND-LINE TREATMENT**

- **PAST**
  - Chemotherapy

- **PRESENT AND FUTURE**
  - PD(L)-1 Antibody
Outline

3. Immunotherapy in 1st Line treatment
Benefit of monotherapy with ICI is limited

Delayed separation of curves
- Early progressors?
- Later time to response?
- Poorly immunogenic tumor?

Important to improve number of patients who may get benefit and duration of benefit
Different strategies to improve outcome

ICI+ICI

ICI+CT

ICI in PD-L1≥50%

ICI+VEGF

Attili – Critical Rev in Oncol Hematol 2017 (modified)
1st Line treatment with ICI in NSCLC: OS

ICI+ICI

ICI+CT

KEYNOTE 189

APPROVED by FDA

ICI in PD-L1 ≥50%

ICI+VEGF

IMPOWER 150

APPROVED by FDA & EMA

Past, present, future treatment approaches

**FIRST-LINE TREATMENT**
- **PAST**
  - Chemotherapy

**SECOND-LINE TREATMENT**
- **PRESENT AND FUTURE**
  - Chemotherapy
  - PD(L)-1 Antibody

PDL1 ≥50%

Courtesy Prof. Soria (modified)
New treatment paradigm in NSCLC

**Oncogene addiction**

- **PDL1 / TMB Molecular**
  - **EGFR**
  - **ALK**
  - **ROS1**
  - **BRAF V600E**
  - **HER2**
  - **NTRK**
  - **MET**

**1ST LINE**

- **PD-L1≥ 50%**
  - Pembrolizumab*,#
  - CBDCA+Taxol +/- BVZ*#
  - And maintenance; Platin/Pem/Pembr*

- **PD-L1< 50%**
  - Crizotinib*,#
  - Dabrafenib + Trametinib*#
  - Entrectinib*,# LOXO101* TDM1@…

**2ND LINE**

- **T790M + → Osimertinib**# (if not received as 1st Line)
- **T790M – or 1st Line Osimertinib → Pem / Platinum**

- **Crizotinib**#
  - **Ceritinib**#
  - **Entrectinib**#

- **Platinum based-CT**
  - **Nivolumab**#
  - **Atezolizumab**#
  - **Pembrolizumab**#

- **Squamous**
  - **Non-Squamous**

*FDA approved
#EMA approved
@Not yet approved

Algorithm by Jordi Remon
New treatment paradigm in NSCLC

Oncogene addiction

PDL1 status Molecular

**EGFR, ALK, ROS1, BRAF**

PD-L1< 50%

PD-L1≥ 50%

TMB High

1ST LINE

TARGETED THERAPIES

EGFR, ALK, ROS1, BRAF

CHIMIO

~15%

~85%

Algorithm by Jordi Remon & Prof Besse
Outline

4 Who (not) to give immunotherapy?
Who (not) to give?

SELECT THE RIGHT PATIENT FOR EFFICACY

AVOID A DETRIMENTAL EFFECT

AVOID TOXICITIES IN NON-RESPONDERS

Courtesy of Prof Besse

Who (not) to give?

SELECT THE RIGHT PATIENT FOR EFFICACY

PD-L1 expression

Tumor Mutational Burden (TMB)
measurement of the overall number of genomic alterations seen in a cancer
Who to give?: PD-L1 expression

In NSCLC, PD-L1 expression correlates with RR and OS

Khunger – JCO Precision Oncology 2017 * Horn – J Clin Oncol 2017
Who to give?: PD-L1 expression

PD-L1 expression is heterogeneous

Blueprint PD-L1 IHC Diagnostic Assays

PD-L1 is a reality in daily clinical practice

**KEYNOTE 024 in PD-L1 ≥ 50% by 22C3**

**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

**Primary endpoint: PFS**
(Squamous ~18%)

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

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

- Pemetrexed + carboplatin
- Pemetrexed + cisplatin
- Paclitaxel + carboplatin
- Gemcitabine + carboplatin
- Gemcitabine + cisplatin

**Events, n**

- Pembrolizumab: 73
  - HR (95% CI): 0.63 (0.47–0.86)
  - Median (95% CI): 30.0 mo (18.3 mo–NR)
- Chemotherapy: 96
  - HR (95% CI): 0.002
  - Median (95% CI): 14.2 mo (9.8 mo–19.0 mo)

Who to give?: High TMB

NSCLC are cancers with highest TMB

Correlation between TMB and RR (p<0.001)

Who to give?: High TMB

Check Mate 227

Nivolumab 3 mg/kg Q2W
Ipilimumab 1 mg/kg Q6W
n = 386

Histology-based chemotherapy\(^a\)
\(n = 397\)

Nivolumab 240 mg Q2W
\(n = 396\)

Nivolumab + ipilimumab
\(n = 139\)

Chemotherapy\(^a\)
\(n = 160\)

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

TMB ≥ 10 Mb

Median PFS,\(^b\) mo

<table>
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<tr>
<th></th>
<th>Nivo + ipi (n = 139)</th>
<th>Chemo (n = 160)</th>
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<tbody>
<tr>
<td>HR(^c)</td>
<td>0.58</td>
<td>0.41, 0.81</td>
</tr>
<tr>
<td>97.5% CI</td>
<td></td>
<td></td>
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<tr>
<td>P</td>
<td>0.0002</td>
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1-y PFS = 43%
Nivolumab + ipilimumab

1-y PFS = 13%
Chemotherapy

Hellmann - NEJM 2018
Who (not) to give?

AVOID A DETREMENTAL EFFECT

AVOID TOXICITIES IN NON-RESPONDERS

HyperPD (NSCLC ???)

Before IO

PD

PR

PseudoPD

1st Cycle

Time

ORR%
Hyperprogressive disease under IO

Urothelial carcinoma 49 yo male
COMBO anti-PDL1 + other immunotherapy
C1J1 18/10/2016

Baseline 06/10/2016
Hyperprogressive disease under IO

Urothelial carcinoma 49 yo male
COMBO anti-PDL1 + other immunotherapy
C1J1 18/10/2016

Baseline 06/10/2016

@3 wks - 09/11/2016
Hyperprogressive disease

14% HPD with IO vs. 5% with CT

Ferrara – WCLC 2017
Early deaths (<3 mo.): characteristics

Single Baseline Characteristics by OS With Nivolumab
CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

Patients with factor in OS subgroup (%)

Rapid PD

High Tumor Burden

Prior therapy

Baseline disease site

Smoking status

ECOG PS

PD-L1 expression

EGFR mut.-pos.

<3 mo from last TX

PD best resp.

No maint. TX

>5 sites with lesions

Bone mets

Liver mets

Current/former

Never

0

1

<1%

≥1%

≥5%

≥10%

<1%

≥1%

≥5%

≥10%

Peters – WCLC 2016
Baseline autoimmune disorders in NSCLC

In a SEER database, from **14% to 25%** of NSCLC patients have ≥ 1 autoimmune diseases

**Patients’ Characteristics with autoimmune disease**

- **< 75 / ≥ 75**: 12.3, 28.5%
- **Female / Male**: 16.8, 10.7%
- **I-II / III-IV**: 32.7, 25%

**Most common Autoimmune diseases**

- Giant cell arteritis
- Ulcerative colitis
- Lupus
- Addison disease
- Polymyalgia
- Psoriasis
- Reumathoid arthritis

In lung cancer patients, AD not associated higher mortality

Khan – JAMA Oncol 2016 * Khan – Lung Cancer 2018
ICI in patients with baseline autoimmune diseases

41% had disease exacerbation during ICIs therapy, No difference in onset of AE’s in patients with active vs. inactive baseline AD.

Melanoma and Ipilimumab

- In phase II&III, mOS: 11.4 mo
- 30 melanoma with baseline AD:
  - 43% receiving IS therapy
  - 27% had exacerbations
  - 33% of grade 3-5 ir-AE’s
  - Response Rate 20%

Median OS: 12.5 mo.
Baseline steroids and ICI

66 out of 244 patients (27%) received steroids at baseline

Martinez – ESMO 2017
Ir-AE’s are NOT so rare when used in combination

Grade 3-4 immune related Adverse Events with anti-CTLA4 + anti-PD-1

- 7.7% for nivolumab
- 18.6% for ipilimumab
- 39.6% for nivo+ipi


Courtesy of Dr. Champiat
Aetiology

Increasing T-cell activity against antigens that are present in tumors and healthy tissue

Increasing levels of preexisting autoantibodies

Enhanced complement-mediated inflammation due to direct binding of an anti-CTLA-4 antibody with CTLA-4 expressed on normal tissue, such as the pituitary gland

Increase in the level of inflammatory cytokines

Postow - NEJM 2018
It’s not about the frequency…it’s about diversity!

Courtesy of Dr. Champiat
It’s not about the frequency…it’s about diversity!
New

Diverse

Uncommon

ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Adrenal insufficiency
Diabetes

GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis

LIVER
Hepatitis

SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson

REPRODUCTIVE
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis

RENAL
Nephritis

NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia

BLOOD
Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

MUSCULOSKELETAL
Arthritis
Dermatomyositis

Champiat – Ann Oncol 2015
Atypical autoimmune side effects

Long Tail of irAE

20%

- Rash/pruritus
- Diarrhea
- Endocrinopathies, arthralgia
- Pneumonitis

Myocarditis, rare neurologic syndromes*, cholangitis*, vasculitic neuropathy*, atrophic exocrine pancreatic insufficiency*, sclerodermoid reaction*, others...

Friedman - Ann Oncol 2017
Immunotherapy toxicity management

Champiat et al., Annals of Oncology, 2015
Onset of irAE’s in NSCLC patients

Horn – J Clin Oncol 2017
General management strategies for irAEs

1. Symptomatic therapy
   - Consider oral steroids
   - Start IV steroids
   - Hold IO agent

2. Consider organ specialist referral & other immunosuppressive therapy

3. Outside skin or endocrine disorders where immunotherapy can be maintained
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. B. A. G. Haanen, F. Carbonnel, C. Robert, K. M. Kerr, S. Peters, J. Larkin & K. Jordan, on behalf of the ESMO Guidelines Committee

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline


Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

Onset of ir-AE’s and survival in NSCLC

OAK trial: OS was in favor of atezo arm pts with irAEs vs those without irAEs (10.6 vs. 29.7 months, HR 0.56 in atezolizuamb arm without vs. with-irAE’s (Von-Pawel. ESMO 2017).
Conclusions

1. Introduction: ICI are treatment options in almost all cancers
2. 1st Line: Almost all patients will receive ICI alone +/- combos
3. 2nd Line: We need new treatment options in PD to 1st Line IO
4. Biomarkers: PD-L1 remains gold-standard. TMB next one?
5. Toxicity: Why not a multidisciplinary board about ICI toxicity?
The Dangers Of Sitting And The Benefits of Moving

PAST TIME IN NSCLC TREATMENT

PRESENT TIME IN NSCLC TREATMENT. WHAT ELSE?