COURS DU GOLF 2017

Quelles associations avec l’immunothérapie ?

Prof Benjamin Besse
Head of the Thoracic Oncology Group, Gustave Roussy
Head of the EORTC Lung Cancer Group
Disclosures

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  – AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS, Onxeo, OncoMed, Inivata, OSE Pharma
Summary

- **Immunotherapy impact on cancer outcomes**
  - Example of tail
  - Opportunities to expand population benefit

- **Rational combination strategies**
  - IO-IO
  - IO-Chemo
  - IO-Targeted therapies
  - IO-Radiation

- **The future**
Summary

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  - IO-Radiation
- The future
About the Tail – Example of Melanoma

- The tail starts at 3 years
- Long responders may experience CR/PR but also SD or PD
- Right definition for pt with OS >5 years?

Cured?

EAP ipilimumab
n = 4846
3-year OS = 21% (95% CI, 20% to 22%)

# IO: EMA Approval Status

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>MELANOMA</th>
<th>LUNG (NSCLC)</th>
<th>GU (BLADDER)</th>
<th>H&amp;N</th>
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<tbody>
<tr>
<td>ADJUVANT therapy</td>
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<tr>
<td>First line</td>
<td>IPILIMUMAB</td>
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<td>IPILIMUMAB</td>
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*EMA status: Nivolumab approved (June 2); Atezolizumab (July 21), and pembrolizumab (July 21) CHMP recommended.*
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<td><strong>IPILIMUMAB NIVOLUMAB PEMBROLIZUMAB</strong></td>
<td><strong>NIVOLUMAB PEMBROLIZUMAB only PD-L1+ ≥1% ATEZOLIZUMAB</strong></td>
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*Notes: Nivolumab approved (June 2); Atezolizumab (July 21), and pembrolizumab (July 21) CHMP recommended.*
Summary

• **Immunotherapy impact on cancer outcomes**
  – Example of tail
  – Opportunities to expand population benefit

• **Rational combination strategies**
  – IO-IO
  – IO-Chemo
  – IO-Targeted therapies
  – IO-Radiation

• **The future**
Immunotherapies in Combination
May Enable Better Long-Term Survival

- Immunotherapy +
  - Chemotherapy,
  - Targeted therapy, and/or
  - Other Immunotherapies

- Targeted therapies or chemotherapies

- Immunotherapy

- Control
Curves cross, suggesting a deleterious effect in a subgroup of patients

Hyperprogressive Disease in Lung Cancer

*HPD: 16% of NSCLC
26% of H&N
25% of bladder*
Summary

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- **Rational combination strategies**
  - IO-IO
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  - IO-Targeted therapies
  - IO-Radiation

- The future
Iconic Combo in Melanoma

- Ipilimumab + nivolumab
- Each single agent
- Restricted to PD-L1–?

Nivolumab 16.3%
Ipilimumab 27.3%
Combo 55%

Iconic Combo in Melanoma

PD-L1 Expression Level <1%

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1% PD-L1</td>
<td>NR (NR)</td>
<td>23.5 (13.0-NR)</td>
<td>18.6 (13.7-23.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (26.5-NR)</td>
<td>18.6 (13.7-23.2)</td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI) vs NIVO
0.74 (0.52-1.06) ─ ─

• ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

PD-L1 Expression Level ≥1%

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>NIVO+IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1% PD-L1</td>
<td>NR (NR)</td>
<td>22.1 (17.1-NR)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NR)</td>
<td>22.1 (17.1-NR)</td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI) vs NIVO
1.03 (0.72-1.48) ─ ─

• ORR of 65.2% for NIVO+IPI and 55.0% for NIVO

Patients at risk:

- NIVO+IPI: 155
- NIVO: 171
- IPI: 164

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td><strong>47</strong> (31, 64)</td>
<td><strong>39</strong> (23, 55)</td>
<td><strong>23</strong> (13, 37)</td>
</tr>
<tr>
<td>Median duration of response, mo (95% CI)</td>
<td>NR (11.3, NR)</td>
<td>NR (8.4, NR)</td>
<td>NR (5.7, NR)</td>
</tr>
<tr>
<td>Median length of follow-up, mo (range)</td>
<td>12.9 (0.9–18.0)</td>
<td>11.8 (1.1–18.2)</td>
<td>14.3 (0.2–30.1)</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Stable disease</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Progressive disease</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Unable to determine</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>8.1 (5.6, 13.6)</td>
<td>3.9 (2.6, 13.2)</td>
<td>3.6 (2.3, 6.6)</td>
</tr>
<tr>
<td>1-year OS rate, % (95% CI)</td>
<td>NC</td>
<td>69 (52, 81)</td>
<td>73 (59, 83)</td>
</tr>
</tbody>
</table>

NC = not calculated (when >25% of patients are censored); NR = not reached
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock except for OS data, which are based on an August 2015 database lock

Hellman, ASCO 2016
Nivolumab Plus Ipilimumab in First-line NSCLC:
Checkmate 012

Combo catches the PDL1- NSCLC patient?

Goldman, ASCO 2017
irAEs are NOT so rare when used in combination

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

- Nivolumab: 7.7%
- Ipilimumab: 18.6%
- Nivo+Ipi: 39.6%

Neptune and mystic:

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

N=800

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

Primary Endpoint: OS

N=1092

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

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

*PD-L1 positivity defined as ≥25% of tumor cells with membrane staining as determined by the Ventana PD-L1 IHC assay.
Immune Checkpoint Blockade for Therapeutic Action Against Multiple Cancer Clones

αPD-1
αPD-L1
αCTLA4
αOX40
α4-1BB
αCD47
αKIR
αCD40
αLAG-3
αTIM-3
αGITR
Rising Stars . . . or Not

**IDO1 epacadostat + pembrolizumab**

H&N, N = 38

- Complete response: HPV, human papillomavirus; PD, progressive disease; PR, partial response; SD, stable disease.
- For 8 efficacy-evaluable patients, data are shown for the 32 with ≥1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per progressive disease (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan.
- Overall response is PD (SD per target lesions, PD per new lesions). * Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

Rising Stars . . . or Not

**IO-CT**

**Immunogenic cell death**
CT, RT

**Up-regulation of MHC-I**
Paclitaxel, gemcitabine, erlotinib

**DC maturation**
Paclitaxel, docetaxel, bevacizumab

**Up-regulation of PD-L1**
Paclitaxel, etoposide

**T-Reg inhibition**
Cisplatin, paclitaxel, bevacizumab

**Down-regulation of PD-L1**
Pi3K? MEKi? crizotinib

CT, chemotherapy; DC, dendritic cell; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; RT, radiotherapy; TReg, T regulatory cells

Chemotherapy Efficacy & the Immune System

**BALB/c Wildtype Mice**

- PBS
- MTX

**BALB/c nu/nu Mice (Immunodeficient)**

- PBS
- MTX

*P<.05; n = 10 mice per group; means ± SEM are shown.

TX, mitoxantrone; PBS, phosphate-buffered saline (control).

**KEYNOTE-021 Cohort G**

**Key Eligibility Criteria**
- Untreated stage IIIB or IV nonsquamous NSCLC
- No activating *EGFR* mutation or *ALK* translocation
- Provision of a sample for PD-L1 assessment
- ECOG PS 0-1
- No untreated brain metastases
- No ILD or pneumonitis requiring systemic steroids

Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

Indefinite maintenance therapy with pemetrexed 500 mg/m² Q3W permitted.

**End Points**
- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

**Treatment**
- Pembrolizumab 200 mg Q3W for 2 years + Carboplatin AUC 5 mg/mL/min + Pemetrexed 500 mg/m² Q3W for 4 cycles
- Carboplatin AUC 5 mg/mL/min + Pemetrexed 500 mg/m² Q3W for 4 cycles
- Pembrolizumab 200 mg Q3W for 2 years
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Pembro + Chemo</th>
<th>Chemo Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), y</strong></td>
<td>62.5 (40-77)</td>
<td>66.0 (37-80)</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>38 (63)</td>
<td>37 (59)</td>
</tr>
<tr>
<td><strong>ECOG PS 1, n (%)</strong></td>
<td>35 (58)</td>
<td>34 (54)</td>
</tr>
<tr>
<td><strong>Adenocarcinoma histology, n (%)</strong></td>
<td>58 (97)</td>
<td>55 (87)</td>
</tr>
<tr>
<td><strong>Stage IV disease, n (%)</strong></td>
<td>59 (98)</td>
<td>60 (95)</td>
</tr>
<tr>
<td><strong>Smoking status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former</td>
<td>45 (75)</td>
<td>54 (86)</td>
</tr>
<tr>
<td>Never</td>
<td>15 (25)</td>
<td>9 (14)</td>
</tr>
<tr>
<td><strong>Stable brain metastases, n (%)</strong></td>
<td>9 (15)</td>
<td>6 (10)</td>
</tr>
<tr>
<td><strong>PD-L1 TPS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>21 (35)</td>
<td>23 (37)</td>
</tr>
<tr>
<td>1%-49%</td>
<td>19 (32)</td>
<td>23 (37)</td>
</tr>
<tr>
<td>≥50%</td>
<td>20 (33)</td>
<td>17 (27)</td>
</tr>
</tbody>
</table>

Data cut-off: August 8, 2016.
Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Pembro + Chemo Responders n = 33</th>
<th>Chemo Alone Responders n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>55% (45, 65)</td>
<td>29% (17, 42)</td>
</tr>
<tr>
<td>∆26%</td>
<td>P = 0.0016</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TTR, mo median (range)</th>
<th>1.5 (1.2-12.3)</th>
<th>2.7 (1.1-4.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR, mo median (range)</td>
<td>NR (1.4+13.0+)</td>
<td>NR (1.4+15.2+)</td>
</tr>
<tr>
<td>Ongoing response, a</td>
<td>29 (88)</td>
<td>14 (78)</td>
</tr>
</tbody>
</table>

- Pembrolizumab
- Chemotherapy

Assessed per RECIST v1.1 by blinded, independent central review.

Data cut-off: August 8, 2016.

DOR = duration of response; TTR = time to response.
aAlive without subsequent disease progression.
Progression-Free Survival

**Assessed per RECIST v1.1 by blinded, independent central review.**

**Data cut-off: August 8, 2016.**
Objective Response by PD-L1 TPS

Pembrolizumab + Chemotherapy

Chemotherapy Alone

<table>
<thead>
<tr>
<th>PD-L1 TPS Range</th>
<th>Pembrolizumab + Chemotherapy</th>
<th>Chemotherapy Alone</th>
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<tbody>
<tr>
<td>&lt;1%</td>
<td>57%</td>
<td>13%</td>
</tr>
<tr>
<td>≥1%</td>
<td>54%</td>
<td>38%</td>
</tr>
<tr>
<td>1%-49%</td>
<td>26%</td>
<td>39%</td>
</tr>
<tr>
<td>≥50%</td>
<td>80%</td>
<td>35%</td>
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- 0% to 100% on the y-axis represents the ORR, % (95% CI).
- Horizontal dotted lines represent the ORR in the total population.
- Data cut-off: August 8, 2016.
- ORR assessed per RECIST v1.1 by blinded, independent central review.
Primary endpoint: ORR

Key eligibility criteria:
- Untreated stage IV NSCLC
- ANY PD-L1


Pembrolizumab Q3W for 2 years + Carboplatin + Pemetrexed Q3W for 4 cycles
- Pembrolizumab 200 mg Q3W for 2 years
- Carboplatin + Pemetrexed Q3W for 4 cycles

FDA approved
- For PD-L1+ >50% (~30%)
- Pembro alone might be enough
- Risk: overtreatment
Atezolizumab clinical development programme in first-line NSCLC

Non-squamous
N=1202

Arm A
Atezo + Carbo/Pac

Arm B
Atezo + Carbo/Pac/Bev

Arm C
Carbo/Pac/Bev

Non-squamous
N=724

Arm A
Atezo + Carbo/Nab-Pac

Arm B
Carbo/Nab-Pac

Non-squamous
N=568

Arm A
Atezo + Carbo/Cis + Pem

Arm B
Carbo/Cis + Pem

Squamous
N=1025

Arm A
Atezo + Carbo/Pac

Arm B
Atezo + Carbo/Nab-pac

Arm C
Carbo/Nab-pac
IO + Antiangiogenic

Phase I: Pembrolizumab + ramucirumab
41% PD-L1 (≥50%: 26%)

RR: 30%. DCR: 56%
Grade 3 TRAE: 7%
PFS: 9.7 mo (PDL1-: 9.4)

NCT02856425: Phase I trial of pembro + ninted
NCT03074513: Phase II trial of atezolizumab + BVZ
The median duration of response was not reached.

6 of 29 evaluable patients had a post-baseline assessment.

Patient with a 37% reduction in target lesion classified as SD. ^ Patient with a 100% reduction in target lesion classified as SD. ¤ Patient with a 30% reduction in target lesion classified as PD.

Lenalidomide + Anti-PD-1 in Multiple Myeloma

ORR = 76% (13/17)


Pomalidomide/dexamethasone with or without pembrolizumab

phase 3 KEYNOTE-183 study (NCT02576977)
Lenalidomide + Anti-PD-1 in Multiple Myeloma

ORR = 76% (13/17)


phase 3 KEYNOTE-183 study (NCT02576977)

Pomalidomide/dexamethasone with or without pembrolizumab

HR for OS = 1.61 (95% CI, 0.91-2.85), translating into a >50% increase in the relative risk of death.


diagram content:

- Percent Change From Baseline in Level of M Protein or Free Light Chains
- 94% of patients achieving complete or very good partial remission
PEMBROLIZUMAB – NECITUMUMUMAB (Ab EGFR)

Table 1. Best Percent Change from Baseline in Tumor Size

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>Squamous</th>
<th>On treatment</th>
<th>Weak Positive</th>
<th>Strong Positive</th>
<th>Negative</th>
<th>Unknown</th>
</tr>
</thead>
</table>

ORR = 23%

N=64

PDL1- 50% / ~50% squamous

Survival Probability

Note: PDL1 status Unknown group was not included in this plot because this group does not provide any relevant interpretation.
Immunotherapy 1st line in EGFR-mutant

- Erlotinib and Atezolizumab phI (NCT02013219)
  - N=20. ORR: 75%. PFS 11.3 mo. Grade 3-4 AE’s: 39%

- Osimertinib + Immune checkpoint inhibitors?
  - TATTON phI (NCT02143466), CAURAL phIII (NCT02454933)
  - TATTON:
    - ORR T790M + vs. -: 67% vs. 21%, and 70% in 1st line treatment,
    - 26% and 64% of ILD in 2nd and 1st line, respectively.

EGFR TKI alone as 1st line treatment in ph III, ORR: ~ 70%, PFS: ~ 9-13 months

IO-RT: Lung

- In situ vaccination
- T-cell priming
- Trafficking, infiltration, and killing

IO-RT: Lung

LDI <1 Gy

MDI 1-10 Gy

HDI >10 Gy

M2 phenotype

M1 phenotype

M2 phenotype

M1 markers
TNFα, iNOS, IL-1β, IL-2, IL-6, IL-8, IL-12, IL-23
IFN, ROS, NO, CXCL10, HLA-DR.

M1 phenotype

Bactericidal activity
Inflammation
Immunostimulation

ANTI-TUMORAL activity

M2 phenotype

Tissue repair
Matrix remodeling
Angiogenesis
Immunosuppression

PRO-TUMORAL activity

Abscopal Effect in a Patient With Hodgkin Lymphoma Treated by PD-1 Antibody

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial


Radiotherapy

Site: Bone metastases
Dose: 8 Gy, single fraction
Time: Radiotherapy within 2 days from ipilimumab, then anytime during ipilimumab

Study powered to detect a 4 month difference in median overall survival (15.8 months versus 12.0 months)

Study Design

Powell, ASCO 2017

**IO – RT in H&N**

**Treatment Dose and Schedule**
- Cisplatin 40 mg/m² weekly (6 planned doses)
- Pembrolizumab 200 mg every 3 weeks (8 planned doses)
- Radiation therapy at 2 Gy once daily for 35 fractions (total 70 Gy)

**Primary end points:**
- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

**Secondary end points:** PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)
## IO – RT in H&N

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>26 (96%)</td>
<td>12 (44%)</td>
<td>None</td>
</tr>
<tr>
<td>Mucositis (oral/pharyngeal)</td>
<td>26 (96%)</td>
<td>8 (30%)</td>
<td>None</td>
</tr>
<tr>
<td>Dermatitis radiation</td>
<td>22 (81%)</td>
<td>4 (15%)</td>
<td>None</td>
</tr>
<tr>
<td>Weight loss</td>
<td>22 (81%)</td>
<td>4 (15%)</td>
<td>None</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17 (63%)</td>
<td>9 (33%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>25 (93%)</td>
<td>4 (15%)</td>
<td>None</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (41%)</td>
<td>2 (7%)</td>
<td>None</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>20 (74%)</td>
<td>5 (19%)</td>
<td>None</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>17 (63%)</td>
<td>1 (4%)</td>
<td>None</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>12 (44%)</td>
<td>4 (15%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>
IO + RT NSCLC

NICOLAS Trial

Primary endpoint: Grade ≥ 3 pneumonitis

NCT02402920. phase I. N=80 LD/ED-SCLC.
CTRT + Pembrolizumab
The Future

- Better use of IO
  - Learn the sequence IO vs other treatment (academic study)
  - Learn when to stop and de-escalade
Sequence with TKI? EORTC Phase II Study 1612-MG

Unresectable or metastatic (7th edition AJCC stage IIIC/IV) melanoma, BRAF V600E mut (N = 270)

R (1:1)

12 weeks (4 infusions, Q3W)
Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg

Nivolumab 480 mg IV Q4W until up to 2 years /progression (PFS1)

Investigator’s choice until PFS2

12 weeks
Encorafenib 450 mg QD + Binimetinib 45 mg BID

4 infusions, Q3W
Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg

Nivolumab 480 mg IV Q4W until up to 2 years /progression (PFS1)

Encorafenib 450 mg QD + Binimetinib 45 mg BID Until PFS2

Endpoint: PFS by RECIST
PI: C. Robert
SAFIR02 Lung – IFCT 1301

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

LC metastatic or locally advanced
- EGFR mutation
- ALK translocation

N= 650

platinum
Based regimen
4 cycles

CR/ PR or SD

Targetable molecular alteration

N=230

YES

R 2:1

SUBSTUDY

Arm A1: Targeted therapy
- AZD2014
- AZD4547
- AZD5363
- AZD8931
- Vandetanib
- Selumetinib

Arm B1: Maintenance Arm
- Pemetrexed

SUBSTUDY

Arm A2: MEDI4736

N=180

SUBSTUDY

Arm B2: Maintenance Arm
- Pemetrexed

N=650

No EGFR mutation
No ALK translocation

PIs: B Besse & F Barlesi

Sponsor: UNICANCER-IFCT
Partnership: AstraZeneca & French Charity Fondation ARC
EORTC 1643

Cohort 1 – non squamous

Cohort 2 – squamous

Stratification factors will be:
- response to induction CT (SD vs CR/PR)
- ECOG PS (0 vs 1)
- Disease stage (TNM8 IIIB-IVB vs IVB)

Arm A: Durvalumab + Tremelimumab

Arm B: Pemetrexed

Arm A: Durvalumab + Tremelimumab

Arm B: observation

R 1:1

PD

PD (crossover)

Investigators choice chemotherapy

PD

PD (crossover)
The Future

- Better use of IO
  - Learn the sequence IO vs other treatment (academic study)
  - Learn when to stop and de-escalade
CheckMate 153: Continuous vs 1-Year Nivolumab (NSCLC, second-line+, n = 168)

PFS From Randomization

<table>
<thead>
<tr>
<th></th>
<th>Median, months (95% CI)</th>
<th>PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
<td>80</td>
</tr>
<tr>
<td>1-year tx</td>
<td>10.3 (6.4, 15.2)</td>
<td>69</td>
</tr>
</tbody>
</table>

OS From Randomization

<table>
<thead>
<tr>
<th></th>
<th>Median, months (95% CI)</th>
<th>OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous tx</td>
<td>NR (NR)</td>
<td>97</td>
</tr>
<tr>
<td>1-year tx</td>
<td>23.2 (23.2, NA)</td>
<td>95</td>
</tr>
</tbody>
</table>

HR: 0.42 (95% CI: 0.25, 0.71)

Toxicity progression

# 15 + 28 = 43%

Randomization 1:1
Patients:
- PD-L1+ as centrally assessed
- with disease control

At 6 months

Arm A
Nivolumab 3mg/kg q2w + Ipilimumab 1mg/kg q6w

Arm B
Observation

Platinum-based doublet recommended

Primary objective: PFS from randomization (non-inferiority study)

Identification factors:
- Histology (SCC vs. Non-SCC)
- Smoking status (ever smoker vs. never smoker)
- 1 centrally-assessed IHC: ≥ 50% vs. < 50%

IFCT-1701 – DICIPLE
Double Immune Checkpoint Inhibitors in PD-L1-positive stage IV non-small Lung Cancer
The Future

- Better use of IO
  - Learn the sequence IO vs other treatment (academic study)
  - Learn when to stop and de-escalade
- Next gen IO: personalized IO (CAR-T, individual vaccine)
Personalized IO

- Personalized vaccine development against tumor-specific antigens
- Overexpressed tumor antigens

Biopsy
- For deep tumor cell analysis
- For leukocyte assessment

Mandal R, Chan TA. Cancer Discov. 2016;6(7):703-713.
Personalized IO

- Select best immune checkpoint inhibitors
- Understand resistance
- Select second-line IO

Biomarkers

- Personalized vaccine development against tumor-specific antigens
- Overexpressed tumor antigens
- Biopsy and sequence tumor
- Identify patient- and tumor-specific antigens
- Quantify mRNA and protein expression levels
- Characterize patient genome

- Personalized engineered CARs/TCRs against tumor-specific antigens
  - in vitro testing
- Adoptive cell transfer
- Genomic instability
  - High microsatellite instability
  - High mutational burden
- Checkpoint inhibitors

Mandal R, Chan TA. *Cancer Discov.* 2016;6(7):703-713.
HUDSON Schema
AZ Basket Trial

Screening Protocol
Molecular profiling
NGS, IHC

Translational Science
Tissue and plasma

Biomarker positive
- HRRm: Olaparib/durvalumab
- ATM deficiency: AZD6738/durvalumab
- LKB1: Olaparib/durvalumab
- RICTOR, TSC1,2: AZD2014/durvalumab

IO-refractory
- Olaparib/durvalumab
- AZD9150/durvalumab
- AZD6738/durvalumab

IO-resistant
- Olaparib/durvalumab
- AZD9150/durvalumab
- AZD6738/durvalumab

Non-matched
- AZD6738/durvalumab

PARP/PD-L1
ATR/PD-L1
PARP/PD-L1
TOR1,2/PD-L1
PARP/PD-L1
STAT3/PD-L1
PARP/PD-L1
ATR/PD-L1
PARP/PD-L1
STAT3/PD-L1
ATR/PD-L1
Personalized IO

Analyze tumor antigens
- Personalized vaccine

- Biopsy and sequence tumor
  Identify patient- and tumor-specific antigens
  Quantify mRNA and protein expression levels
  Characterize patient genome

- Personalized vaccine development against tumor-specific antigens
  Overexpressed tumor antigens

- Therapeutic vaccination

- Personalized engineered CARs/TCRs against tumor-specific antigens
  in vitro testing

- Adoptive cell transfer

- Checkpoint inhibitors

- Genomic instability
  High microsatellite instability
  High mutational burden

Mandal R, Chan TA. Cancer Discov. 2016;6(7):703-713.
Personalized IO

Leukocyte engineering

- CARs – Chimeric antigen receptor-engineered T cells
- TCRs – Recombinant T-cell receptors

Mandal R, Chan TA. Cancer Discov. 2016;6(7):703-713.
Conclusion

YES WE CAN CURE

LET'S KILL THE HEALTH SYSTEMS ERA

BEGINNING ERA

CANCER MANAGEMENT TIMELINES

CHEMOTOSSIC ERA

BEGINNING ERA

VERY VERY BEGINNING ERA

YES WE CAN CURE

BEGINNING ERA
Deux nouveaux chapitres dans le manuel des internes :
Immunothérapie & Enfants et adolescents

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[Manuel pratique d'oncologie de Gustave Roussy]