PATIENT SELECTION
CORRELATION OF PD-L1 EXPRESSION AND OUTCOME?
THE ONCOLOGIST VIEW ON LUNG CANCER

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DISCLOSURES

• Honoraria for lectures from MSD, BMS, AstraZeneca, Merck, Roche, Lilly, Boehringer-Ingelheim, Celgene, Novartis, Pfizer

• Honoraria for consultancy from MSD, BMS, AstraZeneca, Merck, Roche, Lilly, Boehringer-Ingelheim, Celgene, Novartis, Pfizer
SOME THOUGHTS

• Biomarker have changed management of lung cancer
BIOMARKER HAVE IMPROVED TREATMENT OPTIONS AND OUTCOMES
SOME THOUGHTS

• Biomarker have changed management of lung cancer
• The problem of Biomarker in Lung Cancer
Many biomarkers have both predictive and prognostic value.

Controlled studies or meta-analyses are required to determine the prognostic and predictive contributions made by a particular marker.
SOME THOUGHTS

- Biomarker have changed management of lung cancer
- The problem of Biomarker in Lung Cancer
- Why do we need biomarkers in immunotherapy?
1. TO IDENTIFY PATIENTS WHO BENEFIT

29.04.2015

01.02.2017

> 22 months of response by immunotherapy in 75 year old patient with stage IV squamous cell NCLC and PDL-1 TPS score > 50%
2. TO IDENTIFY PATIENTS WHO DO NOT BENEFIT FROM IMMUNOTHERAPY

- Heavily pretreated
- High tumor burden (multipel metastases)
- Rapid progression
- Central location of tumor
- PD-L1 negative

Symptomatic Progression after 4 weeks of immunotherapy
SOME THOUGTHS

• Biomarker have changed management of lung cancer
• The problem of Biomarker in Lung Cancer
• Why do we need biomarkers in immunotherapy?
• What Biomarker do we have for immunotherapy?
MULTIPLE OPPORTUNITIES TO DEVELOP BIOMARKERS FOR IMMUNOTHERAPY

...however, so far only PD-L1 expression has been introduced to clinical practice

Topalian S, Nature Reviews Cancer 2016; e-published
PD-L1 AS A BIOMARKER: A NIGHTMARE IN COMPLEXITY

**Biology: PD-L1**
- Inter and intratumor heterogeneity
- Inducible and dynamic (IFN, post-treatment)
- Cell type (immune cell versus tumor versus both)
- Location (membrane versus cytoplasm)

**Technical: Assay**
- Epitope stability
- Distribution (patchy versus diffuse)
- Different antibodies and platforms
- Different thresholds for expression
- Interobserver readability

**Logistics: Tissue**
- Interval between tissue and treatment (archived versus fresh)
- Primary versus metastatic disease
- Some circumstances not amenable to obtaining any tissue
- Certain biopsy methods result in poor tissue quality/quantity

Challenges Surrounding Biomarker

Expression of PD-L1 is heterogeneous

Abs are not identical: >25% discordant

IFN = interferon; PD-L1 = programmed death ligand 1.

THE CHALLENGE IN PD-L1 TESTING: CURRENTLY FOUR TESTS IN DEVELOPMENT

<table>
<thead>
<tr>
<th></th>
<th>Merck</th>
<th>BMS</th>
<th>Roche</th>
<th>AZ</th>
<th>Pfizer</th>
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<tbody>
<tr>
<td>KEYTRUDA</td>
<td>pembrolizumab</td>
<td>Opdivo nivolumab</td>
<td>Atezolizumab</td>
<td>Durvalumab</td>
<td>Avelumab</td>
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<tr>
<td>Opdivo</td>
<td>28-8</td>
<td>SP142</td>
<td>SP263</td>
<td>–</td>
<td></td>
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<td>Clone</td>
<td>22C3</td>
<td>Dako</td>
<td>Ventana</td>
<td>Dako</td>
<td></td>
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<tr>
<td>Cutoffs</td>
<td>TC: ≥1, ≥50</td>
<td>TC: ≥1, ≥5, ≥10</td>
<td>TC: ≥1, ≥10, ≥50</td>
<td>TC: ≥25, ≥90</td>
<td>TC: ≥1</td>
</tr>
<tr>
<td>Prospective</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inter Observer</td>
<td>95.6 (50%)</td>
<td>97.8 (1%) 98.5 (5%)</td>
<td>&gt;90</td>
<td>96.7 (25%)</td>
<td>–</td>
</tr>
<tr>
<td>Inter Site</td>
<td>91.3 (50%)</td>
<td>90.2 (1%) 94.8 (5%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

However: So far PDL-1 expression is the only Biomarker, which correlates with efficacy.
THE PROBLEM OF PD-L1 TESTING

• The acquisition of adequate material remains a challenge
• PD-L1 Testing is not a perfect biomarker (no assessment of an oncogenic mutation)
CLINICAL IMPACT OF PD-L1 TESTING

- Pretreated patients
  - PD-L+ patients
CORRELATION OF PD-L1 EXPRESSION AND EFFICACY

Figure 6. 2-year OS rates overall and by PD-L1 expression level in CheckMate 057 (non-SQ NSCLC)

PDL-1 Expression

Subgroup
TC3 or IC3
TC2/3 or IC2/3
TC1/2/3 or IC1/2/3a
TC0 and IC0

0.41
0.67
0.74
0.75
0.73

Hazard Ratio

In favor of atezolizumab
In favor of docetaxel

CLINICAL IMPACT OF PD-L1 TESTING

• Pretreated patients
  • PD-L + patients
  • PD-L - patients
Efficacy of Immunotherapies in PDL-1 Negative Patients

Nivolumab – CM 57

<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>ORR.1 %</th>
<th>Median DOR, mos</th>
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<tbody>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>≥1%</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>≥5%</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>≥10%</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Not quantifiable</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

Response Rate lower in PD-L1 negative patients but there are responses.
Duration of response independent from PD-L1 status.

RR: 9%
DOR: 18.3 months

Atezolizumab - Oak

OS, PD-L1 expression on < 1% TC and IC
TC0 and IC0; 45% of patients

HR, 0.75
(95% CI, 0.59, 0.96)
P = 0.0205
Minimum follow up = 19 months

OS: 12.6 vs 8.9 months (HR 0.75)

OVERALL SURVIVAL
CHECKMATE 057: NIVOLUMAB VS. DOCETAXEL IN PREVIOUSLY TREATED NSQ NSCLC

Based on a February 18, 2016 database lock; minimum follow-up: 2 years

SINGLE BASELINE CHARACTERISTICS BY OS WITH NIVOLUMAB
CHECKMATE 057: NIVOLUMAB VS. DOCETAXEL IN PREVIOUSLY TREATED NSQ NSCLC

- No treatment related deaths in the first 3 months (progression)
- Imbalance of poor prognostic factors in the group of patients who died within the first three months
- Increased risk of death in patients with combination of poor prognostic factors and low/missing PD-L1 expression

Based on a March 18, 2015 database lock;

*Percentages of patients are based on numbers of patients with quantifiable PD-L1 expression at baseline; maint. = maintenance; mets = metastases; mut. = mutation; pos. = positive; resp. = response; TX = treatment
DIFFERENT OPPORTUNITIES IN SECOND LINE TREATMENT

Progression during or after platinum therapy

Chemotherapy
- Docetaxel
- Pemetrexed
- If not given previously
- Not suitable for squamous NSCLC
- If not given previously

EGFR TKI
- Erlotinib
- May be inferior to chemotherapy in WT patients
- Not suitable for squamous NSCLC

Antiangiogenics
- Nintedanib
- Ramucirumab
- If docetaxel not given previously
- Not suitable for SqCLC

Immune checkpoint inhibitors
- Nivolumab
- Atezolizumab
- US and EU approved for squamous and nonsquamous NSCLC
- Only approved for patients whose tumors express PD-L1

- Approved in EU only; bApproved in US only

1. NCCN Clinical Practice Guidelines for Non-Small Cell Lung Cancer, V.6.2015
4. Eli Lilly and Company. Alimta® (pemetrexed) prescribing information. Sep 2013
MOVING TO FIRST LINE – THE CHALLENGE!
FIRST-LINE PD1 / PD-L1 INHIBITION?

• Difficult environment:
  • Strong competitor (platin based chemotherapy)
• Burning Questions:
  • Will PD-L1 Inhibition overcome chemotherapy?
  • Are we able to identify suitable patients by PD-L1 expression?
CLINICAL IMPACT OF PD-L1 TESTING

First-Line patients
Monotherapy
  – PD-L1 + patients
Two „similar“ trials..

...but completely different outcomes!

CHECKMATE - 026

- PFS: 4.2 vs 5.9 m (chemo) (HR 1.15, p=0.25)
- RR: 26% vs 33% (chemo)
- OS: 13.2 vs 14.4 m (chemo) (HR 1.02)
- No difference in patients with PDL-expression =/> 50%
- TRAE 3/4: 18% vs 51% (chemo)
- Exploration of novel biomarker (TMB)
- Inhomogenities in patient populations
CLINICAL IMPACT OF PD-L1 TESTING

First-Line patients
Monotherapy
  – PD-L1 + patients
  – PD-L1++ (=/>50% TPS) patients
Two „similar“ trials..

...but completely different outcomes!

KEYNOTE - 024

- PFS: 10.3 vs 6.0 m (HR 0.5; p<0.001)
- RR: 45% vs 28% (chemo)
- OS: HR 0.6, p=0.005 (mature data today!)
- TRAE ¾: 26% vs 51% (update today!)
- Improvement in PRO scores (changes to baseline, time to deterioration)

UPDATE KEYNOTE 24: OVERALL SURVIVAL

Median OS: 30.0 vs 14.2 months
(HR 0.63, p=0.002)

Brahmer J, Reck M, WCLC 2017, abstr. OA 17.06
CLINICAL IMPACT OF PD-L1 TESTING

First-Line patients
Monotherapy
  – PD-L1 + patients
  – PD-L1++ (/>50% TPS) patients
Combination therapy
  – IO – IO combinations
IO-IO COMBINATIONS (PHASE I)  
(NIVOLUMAB/IPILIMUMAB – DURVALUMAB/TREMELIMUMAB)

- Response: 23-43%
- Conflicting Impact of PD-L1 expression:

CLINICAL IMPACT OF PD-L1 TESTING

First-Line patients
Monotherapy
  – PD-L1 + patients
  – PD-L1++ (=/>50% TPS) patients

Combination therapy
  – IO – IO combinations
  – IO – CT combinations
**KEYNOTE 21 G**

<table>
<thead>
<tr>
<th></th>
<th>Pembro + CT</th>
<th>CT</th>
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<tbody>
<tr>
<td>Pat.</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>RR</td>
<td>56.7%</td>
<td>31.7%</td>
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<tr>
<td>PFS</td>
<td>19.0 m</td>
<td>8.9 m</td>
</tr>
<tr>
<td>OS</td>
<td>nr</td>
<td>20.9 m</td>
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</tbody>
</table>

- **PFS**: HR 0.54, P = 0.0067
- **OS**: HR 0.59, P = 0.03

**Progression Free Survival**
- Median (95% CI): 19.0 (8.5–NR)
- 8.9 (6.2–11.8)

**Overall Survival**
- Median (95% CI): 20.9 (14.9–NR)

Borghaei H et al, ESMO 2017, abstract LBA 49
Objective Response Rate by PD-L1 Status
(RECIST v1.1 by Blinded, Independent Central Review)

Horizontal dotted lines represent the ORR in the total population.
Data cut-off: August 8, 2016.
Langer, C et al., ESMO 2016
### Table: Analysis of Progression-Free Survival (Primary Analysis)

Based on BICR Assessment per RECIST 1.1

**Cohort G1 Subjects with PD-L1 TPS ≥ 50% and TPS<50%**

*(ITT Population)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PD-L1 TPS ≥50%</th>
<th></th>
<th></th>
<th></th>
<th>PD-L1 TPS &lt;50%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N Events (%)</td>
<td>mPFS (months) (95% CI)</td>
<td>PFS Rate Month 6 (95% CI)</td>
<td>vs Control</td>
<td>HR (95% CI)</td>
<td>p-value§</td>
<td>N</td>
</tr>
<tr>
<td>pembro combo</td>
<td>20</td>
<td>6 (30.0)</td>
<td>NR (6.3,.)</td>
<td>79.4 (54.0,91.7)</td>
<td></td>
<td>0.26 (0.09, 0.76)</td>
<td>0.004</td>
<td>40</td>
</tr>
<tr>
<td>Control</td>
<td>17</td>
<td>9 (52.9)</td>
<td>6.2 (1.9,12.0)</td>
<td>73.1 (42.9,89.0)</td>
<td></td>
<td></td>
<td></td>
<td>46</td>
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</tbody>
</table>

Table made by the assessor from Table 14.2-19 and Table 14.2-20 of KN021 CSR; NR: Not reached; From product-limit (Kaplan-Meier) method for censored data; based on Cox regression model with treatment as covariate; § One-sided p-value based on log-rank test.

Database Cutoff Date: 08AUG2016

IMpower150 study design

The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit.

- Stage IV or recurrent metastatic non-squamous NSCLC Chemotherapy-naive
  Tumour tissue available for biomarker testing Any PD-L1 IHC status
  Stratification factors: • Sex • PD-L1 IHC expression • Liver metastases
  N = 1202

- Maintenance therapy (no crossover permitted)
  Treated with atezolizumab until PD by RECIST v1.1 or loss of clinical benefit AND/OR Treated with bevacizumab until PD by RECIST v1.1

Arm A
- Atezolizumab + Carboplatin + Paclitaxel
  4 or 6 cycles

Arm B
- Atezolizumab + Carboplatin + Paclitaxel + Bevacizumab
  4 or 6 cycles

Arm C (control)
- Carboplatin + Paclitaxel + Bevacizumab
  4 or 6 cycles

- Patients with a sensitising EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. Atezolizumab: 1200 mg IV q3w. Carboplatin: AUC 6 IV q3w. Paclitaxel: 200 mg/m² IV q3w. Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.
INV-assessed PFS in ITT-WT (Arm B vs Arm C)

HR, 0.617 (95% CI: 0.517, 0.737)

臂 B: atezolizumab + bevacizumab + chemotherapy
臂 C: bevacizumab + chemotherapy

P < 0.0001

 Minimum follow-up: 9.5 mo
 Median follow-up: ~15 mo
### PFS in key biomarker populations

<table>
<thead>
<tr>
<th>Population</th>
<th>n (%)</th>
<th>Median PFS, mo</th>
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</thead>
<tbody>
<tr>
<td><strong>ITT (including EGFR/ALK mutant +)</strong></td>
<td>800 (100%)</td>
<td></td>
</tr>
<tr>
<td><strong>EGFR/ALK mutant + only</strong></td>
<td>108 (14%)</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>ITT-WT</strong></td>
<td>692 (87%)</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Teff-high (WT)</strong></td>
<td>284 (43%)</td>
<td></td>
</tr>
<tr>
<td><strong>Teff-low (WT)</strong></td>
<td>374 (57%)</td>
<td>8.3</td>
</tr>
<tr>
<td><strong>PD-L1 IHC TC2/3 or IC2/3 (WT)</strong></td>
<td>244 (35%)</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>PD-L1 IHC TC1/2/3 or IC1/2/3 (WT)</strong></td>
<td>354 (51%)</td>
<td>11.0</td>
</tr>
<tr>
<td><strong>PD-L1 IHC TC0 and IC0 (WT)</strong></td>
<td>338 (49%)</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>PD-L1 IHC TC3 or IC3 (WT)</strong></td>
<td>135 (20%)</td>
<td>12.6</td>
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<tr>
<td><strong>PD-L1 IHC TC0/1/2 or IC0/1/2 (WT)</strong></td>
<td>557 (80%)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

**Hazard Ratio**

- In favour of Arm B: atezo + bev + CP
- In favour of Arm C: bev + CP

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*a* ITT, *EGFR/ALK* mutants, and ITT-WT % prevalence out of ITT (n = 800); Teff % prevalence out those tested in ITT-WT (n = 658); PD-L1 IHC % prevalence out of ITT-WT (n = 692).

*b* Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.

*c* Stratified HRs for ITT, ITT-WT and Teff-high WT populations; unstratified HRs for all other subgroups.

Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis.
CONCLUSION

• Assessment of PD-L1 Expression is not comparable to mutation testing
• PDL-1 Expression correlates with efficacy of immunotherapies in all lines of treatment
• Patients with high PD-L1 expression (≥/>50%) represent a unique group of patients
• Efficacy of immunotherapy is also seen in PDL-1 negative tumors
• Impact of PDL-1 Expression on combination approaches needs to be determined