Patients should be selected based on predictive biomarkers

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DISCLOSURES

Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Clinical trials research: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer
Prognostic vs. predictive markers

Prognostic

Predictive

Prognostic + Predictive

Paesmans, Breathe 2012
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib
2008 (IPASS Trial; T.Mok et al, NEJM)

Treatment by subgroup interaction test, p<0.0001
Progression-free survival

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>609</td>
<td>608</td>
</tr>
<tr>
<td>Events</td>
<td>453 (74.4%)</td>
<td>497 (81.7%)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.741 (0.651, 0.845)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.7</td>
<td>5.8</td>
</tr>
<tr>
<td>4 months progression-free</td>
<td>61%</td>
<td>74%</td>
</tr>
<tr>
<td>6 months progression-free</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>12 months progression-free</td>
<td>25%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Gefitinib

Mok et al 2008
ISEL Trial

Overall population

- Gefitinib
- Placebo

Proportion surviving

Time (months)

p=0.087

BR.21 Trial

P<0.001 by stratified log-rank test
Hazard ratio, 0.70 (95% CI, 0.58–0.85)

Patients (%)

Months

Nick Thatcher et al, Lancet 2005

Frances A. Shepherd et al, NEJM 2005
Why we need biomarkers?

**BENEFIT**

PROVIDE DRUGS ONLY TO PATIENTS WHO COULD BENEFIT FROM THEM

**RISK**

AVOID TO EXPOSE PATIENTS TO TOXICITY WHEN THERE ARE NO CHANCES OF EFFICACY

Efficacy with IO (PDL1 80%)

Toxicity

Hyperprogressive disease

A consistent but limited benefice in OS 2\textsuperscript{nd} line

**Checkmate 017 (SQ)\textsuperscript{1}**

- Nivolumab
- Docetaxel

2-yr OS = 23%
2-yr OS = 8%

**Checkmate 057 (NSQ)\textsuperscript{1}**

- Nivolumab
- Docetaxel

2-yr OS = 29%
2-yr OS = 16%

**KEYNOTE-010 (≥1% PD-L1)\textsuperscript{3}**

- Pembro 2 mg/kg
- Pembro 10 mg/kg
- Docetaxel

30-mo OS = 29.5%
30-mo OS = 22.1%
30-mo OS = 12.3%

**OAK\textsuperscript{4}**

- Atezolizumab
- Docetaxel

18-mo OS = 40%
18-mo OS = 27%

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Herbst et al., 2017, ASCO.\textsuperscript{3}

Borghaei et al., 2016, ASCO.\textsuperscript{1}

Rittmeyer et al., 2017, Lancet.\textsuperscript{4}
UNSELECTED PATIENTS
OS in all nivolumab-treated patients (CM 003, 063, 017 and 057 studies)

No Benefit: Progressive disease (HDP?)
Primary resistance

Transitory benefit/stable disease
Acquired resistance

Major benefit: Partial/complete responses
Predictive bioM

No. at risk
Nivolumab 664 430 299 214 164 123 104 92 82 28 16 16 13 4 2 1 1 0

Julie Brahmer et al, AACR 2019
5-Year Estimates of OS
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

Squamous (n=54)

- 1-year OS, 41%
- 2-year OS, 24%
- 3-year OS, 20%
- 5-year OS, 16%

Nonsquamous (n=74)

- 1-year OS, 42%
- 2-year OS, 24%
- 3-year OS, 17%
- 5-year OS, 15%

Julie Brahmer et al, AACR 2016
Long Term Survival
OS (3 Years’ Minimum Follow-up)

CheckMate 017 (SQ NSCLC)

CheckMate 057 (non-SQ NSCLC)

Enriqueta Felip et al, ESMO 2017
NEED TO ENRICH PATIENTS WITH HIGH ORR ANTI-PD(L)1 SURVIVAL BASED ON RESPONSE TYPE

Data from patients treated with an anti–PD-(L)1 monotherapy in a phase I trial at Gustave Roussy were retrospectively analyzed over a period of 5 years.

Impact on practice for PR/SD patients?

Landmark analysis of OS by response category status at 6 months (CM 017 and 057)\textsuperscript{a}

### Nivolumab

- Median OS (95% CI), mo
  - CR/PR: 16.1 (10.2, 23.5)
  - SD: 9.1 (6.2, 11.4)
- HR (95% CI), vs PD
  - CR/PR: 0.18 (0.12, 0.27)
  - SD: 0.52 (0.37, 0.71)

### Docetaxel

- Median OS (95% CI), mo
  - CR/PR: 17.1 (11.1, 28.7)
  - SD: 8.0 (6.6, 10.4)
- HR (95% CI), vs PD
  - CR/PR: 0.43 (0.29, 0.65)
  - SD: 0.80 (0.61, 1.04)

\textsuperscript{a}In all randomized patients from CheckMate 017 and 057 studies alive at the 6-month landmark; 65.6% and 61.8% patients in the nivolumab and docetaxel treatment arms, respectively, were included in this analysis.

Julie Brahmer et al, AACR 2019
NEED TO AVOID PD OR HPD

TGR: Tumour growth rate

Possible deleterious effect
ON treatment TGR
> TGR BEFORE treatment

No change on tumor kinetics
ON treatment TGR
= TGR BEFORE treatment

Evidence of tumor activity
ON treatment TGR
< TGR BEFORE treatment

Time

TGR: Tumour growth rate of the SLD of target lesions

+ 50%

+ 30%

+ 10%

- 32%

BEFORE treatment

ON treatment
13.8% of the patients

- N = 406 advanced NSCLC patients, ICIs
- n = 59 patients in chemo cohort
- Only 5.1% in chemo cohort
PD-L1 a good bioM? 
Comparison of PD-L1 assays in NSCLC

<table>
<thead>
<tr>
<th>Immunotherapy (I/O)</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Durvalumab</th>
<th>Avelumab</th>
<th>Atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection antibody</td>
<td>28-8</td>
<td>22C3</td>
<td>SP263</td>
<td>73-10</td>
<td>SP142</td>
</tr>
<tr>
<td>IHC platform</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
<td>Dako</td>
<td>Ventana</td>
</tr>
<tr>
<td>Cell types scored for NSCLC</td>
<td>TC</td>
<td>TC</td>
<td>TC</td>
<td>TC &amp; IC</td>
<td></td>
</tr>
<tr>
<td>Cut-off definitions for positivity (complementary vs companion)</td>
<td>&gt;5%</td>
<td>First line: PD-L1+ ≥90% Late lines PD-L1+ ≥25%</td>
<td>&gt;25%</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Blueprint phase 1

NCCN study

French study

AstraZeneca study

✓ Comparables: 22C3, 28-8 and SP263

✓ Weaker: SP142 lower sensitivity

Courtesy of Julien Adam

High PD-1 expression associated with higher responses and outcomes

- **NSCLC**
- **Single-agent**
- **PD(L)-1 inh**

**PD-L1 IHC cut-off value**

Garon, NEJM 2015; Brahmer, NEJM 2015; Borghaei, NEJM 2015; Spira ASCO 2015; Besse ECC 2015; Higgs, ECC 2015
Limitations for PD-L1

.. is heterogeneous

... is dynamic

McLaughlin et al, JAMA Oncol 2016; Gainor et al, CCR 2016
OS with nivolumab versus docetaxel by tumor PD-L1 expression in CM017 and 057

Should we exclude <1% tumours from anti-PD(L1) therapy?

PD-L1 expression <1%

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 163)</th>
<th>Docetaxel (n = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mo</td>
<td>9.7 (7.6, 13.3)</td>
<td>7.8 (6.7, 10.5)</td>
</tr>
</tbody>
</table>

PD-L1 expression ≥1%

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 185)</th>
<th>Docetaxel (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mo</td>
<td>13.4 (10.0, 17.7)</td>
<td>8.5 (7.0, 9.3)</td>
</tr>
</tbody>
</table>

Nivolumab (n = 185) Docetaxel (n = 179)

PD-L1 can predict long term survival
Patients with non-squamous histology and low/no PD-L1 expression did not derive benefit

CheckMate 057

<table>
<thead>
<tr>
<th>PD-L1 expression level</th>
<th>Overall survival</th>
<th>Unstratified HR</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>High PD-L1 expression</td>
<td>123</td>
<td>123</td>
<td>0.59</td>
</tr>
<tr>
<td>Low/no PD-L1 expression</td>
<td>108</td>
<td>101</td>
<td>0.90</td>
</tr>
<tr>
<td>PD-L1 not quantifiable at baseline</td>
<td>95</td>
<td>86</td>
<td>0.43</td>
</tr>
<tr>
<td>≥1%</td>
<td>136</td>
<td>138</td>
<td>1.01</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>86</td>
<td>79</td>
<td>0.40</td>
</tr>
<tr>
<td>≥5%</td>
<td>145</td>
<td>145</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>61</td>
<td>66</td>
<td>0.91</td>
</tr>
</tbody>
</table>

PD-L1 expression measured retrospectively on TCs using Dako 28-8 IHC assay in prospectively collected, pretreatment (archival or recent) tumour specimens

Two „similar“ trials...

...but completely different outcomes!

**OS (≥5% PD-L1+)**

**CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 211)</th>
<th>Chemotherapy (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>4.2 (3.0, 5.3)</td>
<td>5.9 (5.4, 6.9)</td>
</tr>
<tr>
<td>1-year PFS rate, %</td>
<td>23.6</td>
<td>23.2</td>
</tr>
</tbody>
</table>

HR = 1.15 (95% CI: 0.91, 1.45), *P* = 0.2511

- 60.4% in the chemotherapy arm had subsequent nivolumab therapy
- 43.6% in the nivolumab arm had subsequent systemic therapy

KN-024: Patients with advanced NSCLC and PD-L1 expression ≥50%

PFS

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

OS

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>73</td>
<td>0.63</td>
<td>(0.47-0.86)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
<td>51.5%</td>
<td>34.5%</td>
</tr>
<tr>
<td></td>
<td>30.0 mo (18.3 mo–NR)</td>
<td>70.3%</td>
<td></td>
</tr>
</tbody>
</table>

≈30% PD-L1 ≥50% EGFR/ALK WT
Overall Survival

TPS ≥1%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>371 (58.2%)</td>
<td>0.81 (0.71-0.93)</td>
</tr>
<tr>
<td>Chemo</td>
<td>438 (68.8%)</td>
<td></td>
</tr>
</tbody>
</table>

≥50%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>157 (52.5%)</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>Chemo</td>
<td>199 (66.3%)</td>
<td></td>
</tr>
</tbody>
</table>

≥1-49% (Exploratory analysis)

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>214 (63.3%)</td>
</tr>
<tr>
<td>Chemo</td>
<td>239 (70.9%)</td>
</tr>
</tbody>
</table>

The PD-L1 ≥50% Subgroup Is the Main Driver of OS Benefit in PD-L1-Pos Cases

Small but important early death rate with Pembro

5-years long-term OS for patients with advanced NSCLC treated with pembrolizumab

KN-001

**Treatment-Naive Patients**

<table>
<thead>
<tr>
<th>PD-L1 TPS</th>
<th>Events, n/N</th>
<th>Median (95% CI) OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS ≥50%</td>
<td>17/27</td>
<td>35.4 (20.3–63.5)</td>
</tr>
<tr>
<td>TPS 1%–49%</td>
<td>43/52</td>
<td>19.5 (10.7–26.3)</td>
</tr>
</tbody>
</table>

**Previously Treated Patients**

<table>
<thead>
<tr>
<th>PD-L1 TPS</th>
<th>Events, n/N</th>
<th>Median (95% CI) OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS ≥50%</td>
<td>104/138</td>
<td>15.4 (10.6–18.8)</td>
</tr>
<tr>
<td>TPS 1%–49%</td>
<td>146/168</td>
<td>8.5 (6.0–12.6)</td>
</tr>
<tr>
<td>TPS &lt;1%</td>
<td>83/90</td>
<td>8.6 (5.5–10.6)</td>
</tr>
</tbody>
</table>

5-Year OS, % (95% CI)

- **Treatment-Naive Patients**
  - 29.6 (7.7–56.1)
  - 15.7 (7.3–26.9)

- **Previously Treated Patients**
  - 25.0 (18.0–32.5)
  - 12.6 (7.9–18.5)
  - 3.5 (0.7–10.0)
Pembro alone remains a reasonable choice for PD-L1≥50% patients

**KN-189**  
(up-date OS ASCO 19)  

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro/Pem/Plat</td>
<td>43.9%</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>60.0%</td>
</tr>
</tbody>
</table>

**KN-024**  
(up-date OS)  

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96</td>
</tr>
</tbody>
</table>

**KN-042**  
(up-date OS ELCC)  

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

HR: 0.59

HR: 0.63

HR: 0.71
PD-L1 IHC can be used to determine chemotherapy sparing.
CT adds toxicity in combination with IO

Grade ≥3 treatment-related AEs

- KEYNOTE-024 PEMBRO
- CheckMate 026 NIVO
- CheckMate 227 IPI-NIVO
- KEYNOTE-189 PEMBRO + CT
- IMpower150 ATEZO + CT + BEVA

Reck NEJM 16, Carbone NEJM 17, Hellmann NEJM 18, Gandhi NEJM 18, Socinski NEJM 18
PD-L1 IHC determines who should have chemotherapy or not

TMB?

A minority of mutation produce neoantigens

Accumulation of mutation increasing its likelihood to be recognized

High probability of neoantigens

Lawrence, Nature 2015; Alexandrov, Nature 2013
TMB correlates with tumor response in several tumor types

High TMB Melanoma

Snyder et al., NEJM, 2014

Van Allen et al., Science, 2015

Urothelial cancer

TMB and outcome

Cohort 2
Platinum-treated mUC

Cohort 1
1L cisplatin-ineffable mUC

High TMB NSCLC

Le et al., NEJM, 2015

Rizvi et al., Science, 2015

MSI-High Colorectal Cancer
Evidence for correlation of response to TMB across tumour types

Correlation coefficient = 0.74, meaning that 55% of the differences in the ORR across cancer types may be explained by variations of TMB.

Yarchoan et al, NEJM 2017
Correlation of WES and targeted sequencing panels in NSCLC

FoundationOne
N= 315 genes

MSK-IMPACT
N= 341-468 genes

Peters, AACR 2017; Rizvi, JCO 2018
TMB is predictive of OS benefit across tumour types

Clinical and genomic (MSK-IMPACT) data of 1,622 advances pts treated with ICI
In 352 (31.5% of ITT) matched patient specimens, tTMB values positively correlated with bTMB values.

Spearman’s rho = 0.6
Pearson’s r = 0.7

In 352 matched patient specimens, tTMB values positively correlated with bTMB values.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>64% (95% CI: 54–74%)</td>
</tr>
<tr>
<td>NPA</td>
<td>88% (95% CI: 83–92%)</td>
</tr>
</tbody>
</table>
Enrolled (N = 153) → ITT \(^a\) (n = 152) → bTMB not evaluable\(^b\) (n = 4) → MSAF\(<1\%\)\(^c\) (n = 29) → BEP MSAF \(\geq 1\%\) (n = 119) → bTMB low, < 16 (n = 91) → bTMB high, \(\geq 16\) (n = 28)

- Excludes one patient who was never treated.
- Assay QC failures.
- The MSAF < 1% population was considered as non-biomarker evaluable (non-BEP).

Overall Response Rate, %

- ITT \(^b\) (N = 152)
- BEP (n = 119)

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n = 28)</td>
<td>28.6%</td>
</tr>
<tr>
<td>Low (n = 91)</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

bTMB Subgroup

- \(\geq 16\) cutoff
- ITT \(^b\) (N = 152)
- BEP (n = 119)

<table>
<thead>
<tr>
<th>Group</th>
<th>Overall Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>14.5%</td>
</tr>
<tr>
<td>Low</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

P = 0.0002

Progression-Free Survival (%)

- High bTMB: 4.6 mo
- Low bTMB: 3.7 mo

Kim ESMO 2018
BFAST: Trial Schema

**Screening Inclusion/Exclusion Criteria***
- Age $\geq$ 18 yo
- Unresectable, Stage IIIB or IV NSCLC
- Measurable disease
- Treatment naïve
- PS 0-2

*Blood to FMI for ctDNA testing for mutations and bTMB

*All cohorts have additional, treatment-specific inclusion/exclusion criteria

**Real World Data Cohort**

- Patients not enrolled in Treatment Cohorts

**Treatment Cohorts**

- **ALK+**
  - Alectinib 600 mg PO BID until PD (n = 78)
  - Alectinib PO at 900, 1,200, or 750 mg PO BID until PD (n = 50-62; dose finding in BFAST and/or IST)

- **RET+**
  - Alectinib PO at 900, 1,200, or 750 mg PO BID until PD (n = 50-62; dose finding in BFAST and/or IST)

- **bTMB+**
  - Atezolizumab 1,200 mg IV q3w until PD or loss of clinical benefit
  - Randomized 1:1, n = 440
  - Platinum-based chemotherapy for 4 or 6 cycles

- **ALK+**
  - Entrectinib 600 mg PO daily until PD (n = 50)

- **ROS1+**
  - Entrectinib 600 mg PO daily until PD (n = 50)
Correlation of TMB and ORR

Nivo + Ipilimumab (CM-227)

ORR (TMB ≥10 mut/Mb)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + ipi</td>
<td>3.6</td>
<td>26.9</td>
</tr>
<tr>
<td>Chemo</td>
<td>41.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Durva+Tremelimumab (MYSTIC)

Objective response rate

- **D**
- **D+T**
- **CT**

<table>
<thead>
<tr>
<th>TMB Category</th>
<th>D (N=63)</th>
<th>D+T (N=43)</th>
<th>CT (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bTMB evaluable</td>
<td>23.1%</td>
<td>24.3%</td>
<td>28.6%</td>
</tr>
<tr>
<td>bTMB ≥20 mut/Mb</td>
<td>29.9%</td>
<td>48.4%</td>
<td>21.4%</td>
</tr>
<tr>
<td>bTMB &lt;20 mut/Mb</td>
<td>20.6%</td>
<td>16.7%</td>
<td>31.4%</td>
</tr>
</tbody>
</table>

Matthew D. Hellmann et al, AACR 2018

Peters.S and al, AACR 2019
Overall Survival in ITT and Blood TMB Evaluable Populations (MYSTIC Trial)

**ITT population**

<table>
<thead>
<tr>
<th></th>
<th>D (n=374)</th>
<th>D+T (n=372)</th>
<th>CT (n=372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months</td>
<td>12.3 (10.1–14.9)</td>
<td>11.2 (9.5–12.9)</td>
<td>11.8 (10.5–13.3)</td>
</tr>
<tr>
<td>HR vs CT</td>
<td>0.96 (0.81–1.13)</td>
<td>0.94 (0.79–1.10)</td>
<td>–</td>
</tr>
</tbody>
</table>

**bTMB evaluable population**

<table>
<thead>
<tr>
<th></th>
<th>D (n=286)</th>
<th>D+T (n=268)</th>
<th>CT (n=255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months</td>
<td>11.1 (9.3–14.9)</td>
<td>9.7 (8.0–11.6)</td>
<td>10.8 (9.5–12.5)</td>
</tr>
<tr>
<td>HR vs CT*</td>
<td>0.87 (0.72–1.05)</td>
<td>0.94 (0.78–1.14)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Unadjusted; data cut-off October 4, 2018

Peters.S and al, AACR 2019
**OS in Patients With Blood TMB ≥20 and <20 mut/Mb (MYSTIC Trial)**

### bTMB ≥20 mut/Mb

<table>
<thead>
<tr>
<th></th>
<th>D (n=77)</th>
<th>D+T (n=64)</th>
<th>CT (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months</td>
<td>12.6 (95% CI 7.8–18.6)</td>
<td>21.9 (95% CI 11.4–32.8)</td>
<td>10.0 (95% CI 8.1–11.7)</td>
</tr>
<tr>
<td>HR vs CT* (95% CI)</td>
<td>0.72 (0.50–1.05)</td>
<td>0.49 (0.32–0.74)</td>
<td>–</td>
</tr>
<tr>
<td>HR vs D* (95% CI)</td>
<td>–</td>
<td>0.74 (0.48–1.11)</td>
<td>–</td>
</tr>
</tbody>
</table>

### bTMB <20 mut/Mb

<table>
<thead>
<tr>
<th></th>
<th>D (n=209)</th>
<th>D+T (n=204)</th>
<th>CT (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, months</td>
<td>11.0 (95% CI 8.9–14.9)</td>
<td>8.5 (95% CI 6.7–9.8)</td>
<td>11.6 (95% CI 9.6–13.1)</td>
</tr>
<tr>
<td>HR vs CT* (95% CI)</td>
<td>0.93 (0.74–1.16)</td>
<td>1.16 (0.93–1.45)</td>
<td>–</td>
</tr>
<tr>
<td>HR vs D* (95% CI)</td>
<td>–</td>
<td>1.22 (0.98–1.52)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Unadjusted; data cut-off October 4, 2018*
PFS in Patients With Blood TMB ≥20 and <20 mut/Mb (MYSTIC Trial)

**bTMB ≥20 mut/Mb**

<table>
<thead>
<tr>
<th></th>
<th>D (n=77)</th>
<th>D+T (n=64)</th>
<th>CT (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, *months</td>
<td>2.7 (1.8–4.4)</td>
<td>4.2 (2.8–NR)</td>
<td>4.4 (4.1–5.4)</td>
</tr>
<tr>
<td>HR vs CT† (95% CI)</td>
<td>0.77 (0.52–1.13)</td>
<td>0.53 (0.34–0.81)</td>
<td>–</td>
</tr>
<tr>
<td>HR vs D† (95% CI)</td>
<td>– (0.50–1.15)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**bTMB <20 mut/Mb**

<table>
<thead>
<tr>
<th></th>
<th>D (n=209)</th>
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<th>CT (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, *months</td>
<td>2.8 (2.2–3.1)</td>
<td>2.0 (1.7–2.8)</td>
<td>5.0 (4.2–5.5)</td>
</tr>
<tr>
<td>HR vs CT† (95% CI)</td>
<td>1.19 (0.94–1.50)</td>
<td>1.55 (1.23–1.94)</td>
<td>–</td>
</tr>
<tr>
<td>HR vs D† (95% CI)</td>
<td>– (1.02–1.57)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Blinded independent central review per RECIST v1.1; †Unadjusted; data cut-off June 1, 2017

mPFS, median progression-free survival; NR, not reported; RECIST, Response Evaluation Criteria for Solid Tumors.

Peters.S and al, AACR 2019
Co-primary endpoint (CM227): PFS with nivolumab+Ipilimumab vs chemotherapy with high TMB (≥10 mut/Mb)

7.2 vs 5.4 mos

IO combo TMB (≥10 mut/Mb) or IO-ChemoT?

**CM227**

TMB (≥10 mut/Mb)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS, mo</th>
<th>HR[^a]</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + ipi (n = 139)</td>
<td>7.2</td>
<td>0.58</td>
<td>0.41, 0.81</td>
</tr>
<tr>
<td>Chemo (n = 160)</td>
<td>5.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^a]: HR = hazard ratio

---

**MYSITC**

bTMB ≥20 mut/Mb

<table>
<thead>
<tr>
<th></th>
<th>D (n=77)</th>
<th>D+T (n=64)</th>
<th>CT (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS[^b] months (95% CI)</td>
<td>2.7 (1.8–4.4)</td>
<td>4.2 (2.8–NR)</td>
<td>4.4 (4.1–5.4)</td>
</tr>
<tr>
<td>HR vs CT[^c] (95% CI)</td>
<td>0.77 (0.52–1.13)</td>
<td>0.53 (0.34–0.81)</td>
<td>–</td>
</tr>
<tr>
<td>HR vs D[^d] (95% CI)</td>
<td>–</td>
<td>0.76 (0.50–1.15)</td>
<td>–</td>
</tr>
</tbody>
</table>

[^b]: mPFS = median progression-free survival
[^c]: HR = hazard ratio
[^d]: D = nivolumab + ipilimumab
[^e]: D+T = nivolumab + ipilimumab + chemotherapy

---

Peters S and al, AACR 2019

Would consider use of nivolumab plus ipilimumab, particularly in pts PD-L1–negative with high TMB, durable outcomes may exceed chemotherapy plus pembrolizumab (1-year PFS: 45%...vs ≈ 20%)

NSCLC ANTI-PD1 COMBINATIONS FOR IO NAIVE PATIENTS

+CHEMO IN PDL1$^{\text{HIGH}}$

Median DOR: 11.2 months

+ANTI-CTLA-4 IN TMB$^{\text{HIGH}}$

Median DOR: Not Reached


Impact of chemo on lymphocytes

Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer

SURVIVAL PITFALLS

We need Follow Up+++ Duration of Response as a surrogate Endpoint for OS benefits

A.Marabelle, Gustave Roussy 2019
TMB but not PD-L1 expression is predictive of response duration and of long term benefit from anti-PD(L)-1 therapy

Benefit lasting ≥18mo

- NSCLC pts treated with anti-PD-(L)1 based therapy (n = 766)
  - No LTR (progressed < 18mo) (n = 704, 92%)
  - LTR (benefit lasting ≥ 18mo) (n = 62, 8%)

- Short-term response, STR (PR with PFS < 18mo) (n = 54, 8%)
- CR or PR (n = 47, 76%)
- SD (n = 15, 24%)

TMB assessed with MSK-IMPACT

76% (CR or PR) 24%(SD)

Rizvi H et al, ASCO 2018
PD-L1 and Blood TMB are Independent Biomarkers (MYSTIC Trial)

- bTMB values did not correlate with PD-L1 expression levels

*Spearman’s rho = 0.05
Pearson’s r = 0.01
N=809

Blood TMB (GuardantOMNI)

Tumor cells staining positive for PD-L1 (%)

- bTMB ≥20 mut/Mb
  N=211
  (19%*)
- PD-L1 TC ≥25%
  N=488
  (44%*)

N=100
(9%*)
LIMITED OVERLAP BETWEEN bTMB ≥16 AND PD-L1 EXPRESSION\(^a\) (OAK BEP)

- Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, \(P = 0.62\))
  - 19.2\% of tumors with bTMB ≥16 were also TC3 or IC3
  - 29.1\% of tumors with TC3 or IC3 also had bTMB ≥16

<table>
<thead>
<tr>
<th></th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bTMB ≥16</td>
<td>0.64 (0.46, 0.91)</td>
<td>0.64 (0.44, 0.93)</td>
</tr>
<tr>
<td>TC3 or IC3</td>
<td>0.62 (0.41, 0.93)</td>
<td>0.44 (0.27, 0.71)</td>
</tr>
<tr>
<td>bTMB ≥16 and TC3 or IC3</td>
<td>0.38 (0.17, 0.85)</td>
<td>0.23 (0.09, 0.58)</td>
</tr>
</tbody>
</table>

\(^a\) PD-L1 expression was evaluated by immunohistochemistry (IHC) using the VENTANA SP142 assay; TC3 or IC3, ≥50\% of TC or ≥10\% of IC express PD-L1. BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cell; TC, tumor cell.
PD-L1 IHC determines who should have chemotherapy or not

TMB determines who should have IO-IO combination

Other IO BioM?
STK11/LKB1 mutations drive resistance to PD-1 inhibitors in KRAS mutant NSCLC

- Loss of LKB1 can drive production of G-CSF, CXCL7, and IL-6 by the tumor, which promotes neutrophil recruitment, which can block anti-tumoral cytotoxic T cells.
- Loss of p53 can modulate the immune microenvironment by regulating NF-kB signaling. This results in increased cytokine production by tumor cells and recruitment and activation of immune cells, such as macrophages

**Graphs:***
- KRAS/STK11 vs. KRAS only
- KRAS/TP53
- KRAS mutated LUAC

**Tables:**

<table>
<thead>
<tr>
<th>Group</th>
<th>KL</th>
<th>KP</th>
<th>K-only</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>7.4% (4/54)</td>
<td>35.7% (20/56)</td>
<td>28.6% (18/65)</td>
</tr>
</tbody>
</table>

**References:**

- Scheffler M et al, JTO 2019
- Skoulidis F, Cancer Discov 2018
**LIPI: Lung Immune Prognostic Index**

**Neutrophil recruitment can block anti-tumoral cytotoxic T cells**

### Lung Immune Prognostic Index

<table>
<thead>
<tr>
<th>No factor</th>
<th>dNLR ≤3 and LDH≤ULN</th>
<th>Good</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 factor</td>
<td>dNLR&gt;3 or LDH&gt;ULN</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2 factors</td>
<td>dNLR&gt;3 and LDH&gt;ULN</td>
<td>Poor</td>
</tr>
</tbody>
</table>

\[dNLR > 3 \text{ [neutrophils/(leucocytes-neutrophils)]}\]

- **N=466 advanced NSCLC patients treated with PD(L)1 inh**
- **8 European centers**

**A** OS in the immunotherapy pooled cohort

16.5 vs. 10.0 vs. 4.8

15%

**B** PFS in the immunotherapy pooled cohort

6.3 vs. 3.7 vs. 2.0

**Predictive for IO ! (not for chemotherapy)**
Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, TKI Naïve Patients

Best Response for Target Lesions by Patient While on Trial

No responses seen in EGFR+ patients

*PD due to dural thickening on MRI
†PD due to non-target progression

Lisberg et al, JTO 2018
Hazard ratios of OS by EGFR mutational status in 3 Phase III trials comparing ICI with docetaxel

KEYNOTE-010
Pembrolizumab

CheckMate 057
Nivolumab

Oak
Atezolizumab
**Driver +: PD-L1, Immune TME**

**Constitutive PD-L1 expression**

*Ota et al CCR 2015*

**Immunotarget, ≥1% PD-L1 expression**

<table>
<thead>
<tr>
<th>Driver</th>
<th>N</th>
<th>PD-L1 + (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>95</td>
<td>66.4%</td>
</tr>
<tr>
<td>EGFR</td>
<td>49</td>
<td>63.2%</td>
</tr>
<tr>
<td>BRAF</td>
<td>11</td>
<td>70.0%</td>
</tr>
<tr>
<td>MET</td>
<td>20</td>
<td>75.5%</td>
</tr>
<tr>
<td>HER2</td>
<td>15</td>
<td>53.3%</td>
</tr>
<tr>
<td>ALK</td>
<td>11</td>
<td>63.3%</td>
</tr>
<tr>
<td>RET</td>
<td>8</td>
<td>75.0%</td>
</tr>
<tr>
<td>ROS1</td>
<td>5</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Mazières, ASCO 2018*

These subgroups have not routinely benefited from immunotherapy.
## Immunotarget Cohort

Low benefit of immunotherapy in case of molecular alteration...need for specific studies

<table>
<thead>
<tr>
<th>Driver</th>
<th>n</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>Impact (+/X) on PFS of</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PDL1</td>
<td>Smoking</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>19%</td>
<td>2.8</td>
<td>13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>271</td>
<td>26%</td>
<td>3.2</td>
<td>13.5</td>
<td>+X</td>
<td>X</td>
</tr>
<tr>
<td>EGFR</td>
<td>125</td>
<td>12%</td>
<td>2.1</td>
<td>10</td>
<td>+X</td>
<td>X</td>
</tr>
<tr>
<td>BRAF</td>
<td>43</td>
<td>24%</td>
<td>3.1</td>
<td>13.6</td>
<td>X</td>
<td>+</td>
</tr>
<tr>
<td>MET</td>
<td>36</td>
<td>16%</td>
<td>3.4</td>
<td>18.4</td>
<td>NA</td>
<td>X</td>
</tr>
<tr>
<td>HER2</td>
<td>29</td>
<td>7%</td>
<td>2.5</td>
<td>20.3</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>ALK</td>
<td>23</td>
<td>0</td>
<td>2.5</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET</td>
<td>16</td>
<td>6%</td>
<td>2.1</td>
<td>21.3</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ROS1</td>
<td>7</td>
<td>17%</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Julien MAZIERES et al, ASCO 18
The best place for IO

IMMUNOGENECITY

IMMUNOGENECITY

IMMUNOGENECITY

TARGETABILITY

TARGETABILITY

TARGETABILITY

Targeted therapy

Immunotherapy

Chemo, Chemo/IO

Courtesy of Prof. Mazières, ELCC 2019
Carbo+Pacli+Atezolizumab, potentiel new option in EGFR-mutant post TKIs (Impower 150)

Reck, M et al; lancet resp 2019
So IO alone or combo...need to take in account many factors

Biomarkers for IO

CANCER CELL - TISSUE
- PD-L1 IHC
- Neo-antigens
- Driver mutations
- MSI
- TMB

BLOOD
- sPD-L1
- CTCs
- ctDNA
  1. bTMB
  2. AF dynamic
- Leukocytes ratio

MICROENVIRONMENT
- Immune phenotype
- TCR sequencing
- Cytokines signature

IMMUNE INFILTRATING CELLS
- TILs
- Immuno score

Adapted from Schumacher T, Nature 2016 and Sacher J Thorac Oncol. 2017

IHC: immunohistochemistry; MSI: microsatellite instability; TMB: tumor mutational burden; TILs: Tumor infiltrating lymphocytes; AF: Allelic Fraction
Strong evidences that bacteria in the gut may influence responses to cancer immunotherapy

CANCER IMMUNOTHERAPY

91 Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors
B. Routy et al.

97 Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients
V. Gopalakrishnan et al.

104 The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients
V. Matson et al.

► PERSPECTIVE P. 32

Science Volume 359(6371):91-97-104-32 January 5, 2018
Precision medicine using microbiota

1. Cancer Screening
   - Microbiota specific medical history:
     - Weight, Diet, Smoking
     - ATB 30 days before
     - PPI, Metformin
     - Apendectomy

2. Cancer Diagnosis
   - Diagnostic Kit: Cancer signature
     - No
     - Yes
     - Perform adequate testing:
       - CT scan
       - Mammography
       - PSA, CEA, LDH

3. Investigations
   - Immune atlas on Tumor biopsy
   - Selection of ICB monotherapy vs combination
     - PD-L1
     - PD-1
     - LAG3
     - CTLA-4
     - TIM-3

4. Immunotherapy + oncomicrobiotherapy
   - Proceed to immunotherapy alone
   - Specific antibiotics
   - Diet
   - Fecal transplant from healthy volunteer vs patients in complete response
   - Oncomicrobiotics: Consortium of bacteria
   - Metabolites
Concomitant medications at baseline to IO

**Antibiotics**

- Derosa, Annals of Oncol 2018

**Steroids**

- Arbour & Mezquita, J Clin Oncol 2018

Retrospective cohorts & probably comorbidities associated
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

- N=86 MMRD patients
- 12 different solid tumors (no lung)
- Pembrolizumab ≥ 2nd line
  - ORR 53% (21% CR)
- Median OS NR
  - 1y-OS 76%; 2y-OS 64%

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA’s first tissue/site-agnostic approval.
4 US centers, n=78 (23 non-smokers)
PD-L1 IHC

*Is still the king*

- Growing evidence that TMB is predictive of immunotherapy efficacy in NSCLC

- Relevant challenges:
  - methodology standardization
  - Definition of high/low TMB
  - Turn-around time
  - Clinical validation
  - Reimbursement/cost

-Several new biomarkers* under development: microbiom, genomic markers, epigenetic markers

-still a lot of work to be done
Biomarker selection for 1st line

- **TMB high**
  - PD-L1 high
    - Pembrolizumab
    - Nivolumab+Ipilimumab
    - Durvalumab+Tremelimumab
  - PD-L1 Low
    - Nivolumab+Ipilimumab
    - Durvalumab+Tremelimumab

- **TMB Low**
  - PD-L1 high
    - Pembrolizumab
  - PD-L1 Low
    - Chemotherapy
    - Chemotherapy

Need TMB data

IO+chemotherapy
IO combo tomorrow…
we need bioM !!!
THANK YOU!

Acknowledgments

Benjamin BESSE
Thierry LE CHEVALIER
Jean-Charles SORIA
Charles NALTET
Anas GAZZAHA
Pernelle LAVAUD
Cécile LE PECHOUX
Angéla BOTTICELLA
Antonin LEVY
Laura MEZQUITA

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