Cours du GOLF 2019
Nouvelles molécules
(nouveaux mécanismes d’actions hors immunothérapie)

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Head of the Cancer Medicine Department, Gustave Roussy
Head of the EORTC Lung Cancer Group
Disclosures

• **No personal financial disclosures**

• **Sponsored Research at Gustave Roussy Cancer Center**
  Abbvie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, Pharma Mar, Sanofi, Spectrum Pharmaceuticals, Takeda, Tiziana Pharma.

• **Investigator or co-investigator of trials**
  Nerviano, GSK, Pfizer, Roche-Genentech, Lilly, OSE Pharma, MSD, Celgene, Stemcentrx, Ignyta, Abbvie, Loxo Oncology, AstraZeneca, Blueprint Medicines.
New drugs

• Molecular selection
Personalised treatment

N=17,664 (76% ADC). 6 cancer-associated genes

N=860 ADC. ≥ 300 cancer-associated genes

21% Potentially actionable alterations. 11 days

87% Potentially actionable alterations. 28 days

Courtesy of J. Remon

Barlesi – Lancet 2015 * Jordan- Cancer Discovery 2017
MOSCATO trial

Adults n= 1035

Molecular portrait n=843 (81%)

Actionable target n=411 (40%)

Matched treatment N=199 (19%)

Evaluable PFS2/PFS1 n=193 (19%)
I want de-addiction

B-RAF inhibitor in NSCLC
(V600E BRAF mutation) ESMO 2014

EGFR inhibitor in NSCLC
(EGFR mutation) Lancet Oncol 2012

ROS1 inhibitor in NSCLC
(ROS1 rearrangement) NEJM 2014

MOSCATO Cancer Dis 2017

Most of the targets are ‘SOFT’
Physician and expert assessment (OncoKB.org) about actionable alteration differ suggesting that utility and physicians ability to interpret data merits further improvement

Schram – Ann Oncol 2017
37% targetable alterations and 11% of patients were enrolled on genomically matched clinical trials

Courtesy of J.Remon

Zehir- Nature Medicine 2017
Biomarkers in NSCLC

2004
Discovery activating mutations

2019
NGS ~10s genes
PDL1

2034
NGS ~100s genes
With pathways

TMB
New drugs

- Molecular selection
- TKI & family
Dose your TKI

- 41 patients and 51 samples
- Median time of exposure: 20.3 months (2.9-67.8)
- Median age: 65 Ic95 [51.79 – 78.21]

### Frequency of Low plasmatic exposure

<table>
<thead>
<tr>
<th>Characteristics, No. (%)</th>
<th>Overall (n=41)</th>
<th>Low-PC</th>
<th>Standard-PC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Samples</strong></td>
<td>31 (61%)</td>
<td>20 (39%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28 (68.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (31.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4 (9.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>28 (69.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop</td>
<td>9 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TKI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>7 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>3 (7.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>9 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>10 (26.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osimertinib</td>
<td>9 (21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>3 (7.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant PPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (31.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28 (68.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Geraud - WCLC 2019
Dose your TKI

- 18 patients treated with 1st-generation EGFR-TKI
- 4 (22%) developed T790M resistance mutation

Geraud - WCLC 2019
Crizotinib: exposure - response

48% of patients (n=23) median $C_{min}$ below threshold

Median PFS: 5.7 vs. 17.4 months (p = 0.08, log-rank)

Multivariable Cox regression: HR 1.79 (95% CI 0.90 – 3.59, p=0.10) corrected for WHO performance status and number of prior lines of therapy

Groenland - ESMO 2019
Alectinib: exposure - response

37% of patients (n=19) median $C_{\text{min}}$ below threshold

Median PFS: 12.8 months vs. not reached ($p = 0.04$, log-rank)

Multivariable Cox regression: HR 3.86 (95% CI 1.19 – 12.58, $p=0.025$) corrected for WHO performance status and prior treatment with ALK-inhibitor(s)

Groenland - ESMO 2019
Efficacy regardless of tumor type

David Hyman at 2017 ASCO Annual Meeting

**RESPONSE RATE 78%**

**1-year PFS: 63%**

Larotrectinib (LOXO101)

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.
**RET**

**BLU-667**
Praseltinib

- **ORR**: 58%
- **PFS**: data not mature

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**LOXO-667**
Selpercatinib

- **ORR**: 68%
- **PFS**: 18.4 months

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Gainor ASCO 2019 – Drilon WCLC 2019
KRAS

Frequency of KRAS mutations (%)

- Never Smokers (n=81)
  - 15%

- Former Smokers (n=316)
  - 22%

- Current Smokers (n=85)
  - 25%

Current/Former Smokers

- G12A (7)
- G12C (46)
- G12D (12)
- G12R (2)
- G12S (3)
- G12V (19)
- G13C (1)
- G13D (5)
- L9F (1)
- Q61H (6)
- Q61L (1)

Never Smokers

- G12A (6)
- G12C (6)
- G12D (20)
- G12S (1)
- G13C (1)
- G13D (1)

Riely et al. CCR 2008; Redig et al. ASCO 2016
KRAS - Target

KRAS inhibition

MRTX849

A – GTP-bound state
B – GDP-bound state
C – RAS Guanine nucleotide exchange factor (GEF)
D – upstream inputs that regulate RAS-GEPs

Patricelli KRAS Cancer Disc 2016, Janne ESMO 2019
Efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>All evaluable patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Evaluable patients treated with 960 mg&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response – n (%)</td>
<td>11 (48)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Stable disease – n (%)</td>
<td>11 (48)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Progressive disease – n (%)</td>
<td>1 (4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Objective response rate – %</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>Disease control rate&lt;sup&gt;c&lt;/sup&gt; – %</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease.

<sup>a</sup>Evaluable patients: patients who have been followed up for at least 6 weeks; <sup>b</sup>One patient discontinued study due to PD prior to the 1<sup>st</sup> assessment, and the post-baseline tumor burden data are missing; <sup>c</sup>PR or SD at week 6; <sup>d</sup>Patient had complete response to the target lesions.

AMG510: de-addiction?

B-RAF inhibitor in NSCLC
(V600E BRAF mutation) ESMO 2014

EGFR inhibitor in NSCLC
(EGFR mutation) Lancet Oncol 2012

ROS1 inhibitor in NSCLC
(ROS1 rearrangement) NEJM 2014

AMG510 ESMO 2016

~1-2% NSCLC

~12% NSCLC
KRAS G12C

Efficacy in NSCLC

Time to Response and Duration of Treatment

- First Response (PR or better)
- Best Overall Response
- Disease progression
- Ongoing on-study
- Death

Evaluable NSCLC Patients, N = 23

Patients with PR, N = 11
- Median duration of treatment – weeks (range)
  - 15.1 (4.1 – 42.3)
- 8/11 patients continuing study

Patients with SD, N = 11
- Median duration of treatment – weeks (range)
  - 10.0 (4.1 – 35.1)
- 8/11 patients continuing study

Planned dose: 180 mg, 360 mg, 720 mg, 960 mg

*The graph was plotted based on the data received from the participating sites as of the data cutoff; duration of treatment data for this patient might be missing from the study site. Evaluable patients: patients who had the first 6-week scan or early progressive disease; NSCLC: non-small cell lung cancer; PR: partial response; SD: stable disease.
### KRAS G12C

<table>
<thead>
<tr>
<th>All TRAEs</th>
<th>Any Grade N = 34, n (%)</th>
<th>Grade 3 N = 34, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAE</td>
<td>12 (35.3)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (11.8)</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Blood alkaline phosphate increased</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

#### All TRAEs

<table>
<thead>
<tr>
<th></th>
<th>Any Grade N = 34, n (%)</th>
<th>Grade 3 N = 34, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (2.9)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

- 3 of 34 patients (8.8%) reported two grade 3 treatment-related AEs: diarrhea and anemia
- There were no grade 4 or higher treatment-related AEs.
### KRAS G12C – AMG510

#### All Dose Levels

<table>
<thead>
<tr>
<th>Efficacy outcomes with all dose levels</th>
<th>NSCLC, evaluable patients N = 23</th>
<th>CRC, evaluable patients N = 29</th>
<th>Other tumor types, evaluable patients N = 3</th>
</tr>
</thead>
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<tr>
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<td>1 (3)</td>
<td>1 (33)(^c)</td>
</tr>
<tr>
<td>Stable disease – n (%)</td>
<td>11 (48)</td>
<td>22 (76)</td>
<td>1 (33)(^d)</td>
</tr>
<tr>
<td>Progressive disease – n (%)</td>
<td>1 (4)</td>
<td>6 (21)</td>
<td>1 (33)(^e)</td>
</tr>
<tr>
<td><strong>Objective response rate</strong>(^a)</td>
<td><strong>48%</strong></td>
<td><strong>3%</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Disease control rate</strong>(^b)</td>
<td><strong>96%</strong></td>
<td><strong>79%</strong></td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### 960mg Dose

<table>
<thead>
<tr>
<th>Efficacy outcomes with 960mg dose</th>
<th>NSCLC, evaluable patients N = 13</th>
<th>CRC, evaluable patients N = 12</th>
<th>Other tumor types, evaluable patients N = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response – n (%)</td>
<td>7 (54)</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stable disease – n (%)</td>
<td>6 (46)</td>
<td>10 (83)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Progressive disease – n (%)</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>1 (100)(^c)</td>
</tr>
<tr>
<td><strong>Objective response rate</strong>(^a)</td>
<td><strong>54%</strong></td>
<td>8%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Disease control rate</strong>(^b)</td>
<td>100%</td>
<td>92%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## KRAS G12C – AMG510

### All Dose Levels

<table>
<thead>
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</tr>
<tr>
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</tr>
<tr>
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<td><strong>3%</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Disease control rate</strong>b</td>
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<td><strong>79%</strong></td>
<td>N/A</td>
</tr>
</tbody>
</table>

### 960mg Dose

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<td><strong>92%</strong></td>
<td>N/A</td>
</tr>
</tbody>
</table>

Arkenau ESMO 2019 – Govingam ESMO 2019
New drugs

• Molecular selection
• TKI & family
• Other targets
PARPi

• Poly(ADP(ribose) polymerase (PARP) signals the presence of DNA damage and facilitates DNA repair

• Single agent in DNA repair deficient tumors

• Germline or tumor mutations in BRAC1 and BRCA2

Edelman ASCO 2019
Tested activity of single agent PARP inhibitor in a population defined by any deleterious mutation in study-defined HRR genes [ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCF, FANCM, NBN (NBS1), PALB2, RAD51, RAD51B (RAD51L1), RAD54L, RPA1]. Failed to achieve prespecified single agent activity defined by RR. PFS and OS also not impressive.
PARPi – S1400G

Ovarian Cancer – randomisation in patients with CR or PR after paclitaxel-carboplatin

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Biomarker</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIEL3</td>
<td>Rucaparib</td>
<td>BRCAmut</td>
<td>0.23 [0.16; 0.34]</td>
<td>0.23</td>
<td>[0.16; 0.34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HRD+</td>
<td>0.32 [0.24; 0.42]</td>
<td>0.32</td>
<td>[0.24; 0.42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All population</td>
<td>0.36 [0.30; 0.45]</td>
<td>0.36</td>
<td>[0.30; 0.45]</td>
</tr>
<tr>
<td>NOVA</td>
<td>Niraparib</td>
<td>gBRCA</td>
<td>0.27 [0.17; 0.41]</td>
<td>0.27</td>
<td>[0.17; 0.41]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HRD+/ non-gBRCA</td>
<td>0.38 [0.24; 0.59]</td>
<td>0.38</td>
<td>[0.24; 0.59]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-gBRCA</td>
<td>0.45 [0.34; 0.61]</td>
<td>0.45</td>
<td>[0.34; 0.61]</td>
</tr>
<tr>
<td>SOLO2</td>
<td>Olaparib</td>
<td>gBRCA</td>
<td>0.30 [0.22; 0.41]</td>
<td>0.30</td>
<td>[0.22; 0.41]</td>
</tr>
</tbody>
</table>

0C, Ovarian Cancer; P.S.R. Platinum Sensitive Recurrence; G. Olaparib; N. Niraparib; R, Rucaparib; gBRCA, germline BRCA; BRCA mut, BRCA1 and/or BRCA2 mutation; HRD, Homologous Recombination Deficiency.
Study design

Newly diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer

FIRST LINE
- Surgery (upfront or interval)
- Platinum–taxane based chemotherapy
- ≥3 cycles of bevacizumab

N=806

Randomization

Maintenance therapy
- Olaparib (300 mg BID) x2 years
  + bevacizumab
- Placebo x2 years
  + bevacizumab

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)
Sensitivity analysis
PFS by BICR
Secondary endpoints
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

Stratification
- Tumour BRCAm status
- First-line treatment outcome

Ray-Coquard ESMO 2019
PARPi – PAOLA ovarian cancer

PFS by investigator assessment: ITT population

Median time from first cycle of chemotherapy to randomization = 7 months

HRD negative
n=277; 34%

HRD positive
n=387; 48%

HRD positive, excluding tBRCAm
n=152; 19%

HRD status unknown
n=142; 18%
PARPi – PAOLA ovarian cancer

The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less than 50% maturity.
PARPi – ORION study

Study Population
Stage IV NSCLC
1L (no prior treatment for stage IV disease)
ECOG PS 0-1
RECIST v1.1 evaluable Tumours lacking EGFR mutations and ALK fusions

Patients with CR, PR or SD

Initial Phase
Durvalumab+Investigator’s choice of platinum-based double therapy for 4 cycles

Maintenance Phase
Durvalumab+Olaparib
Durvalumab+Placebo

R

1L, first-line; ALK, anaplastic lymphoma kinase; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PR, partial response; PS, performance status; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
Apoptosis
Apoptosis
KRAS/NRAS mutant cancers
Phase I - Trametinib (MEKi) + navitoclax (BLC-XL)

Potential disease-specific differences in efficacy

Colorectal Cancer

Patient Number

0% Response Rate (n=9)
22% Disease Control Rate

Gynecologic Cancer

Patient Number

31% Confirmed Response Rate (n=13)
69% Disease Control Rate

Corcoran et al, Cancer Cell 2013

Corcoran ESMO 2019
New drugs

- Molecular selection
- TKI & family
- Other targets
- ADCs
ADC - Antibody drug conjugates

Xie, JTO 2019
ADC - Antibody drug conjugates

= SMART CHEMO
ADC - Antibody drug conjugates

= SMART CHEMO VECTORIZED CHEMO
ADC - Antibody drug conjugates

= 

SMART CHEMO
VECTORIZED CHEMO
NEXT-GEN CHEMO
ADC - Antibody drug conjugates

= SMART CHEMO
VECTORIZED CHEMO
NEXT-GEN CHEMO
TARGETED CHEMO
Anti-HER2 : DS-8201a

<table>
<thead>
<tr>
<th>Condition</th>
<th>Confirmed ORR, % (n/N)</th>
<th>DOR, median (range), months</th>
<th>TTR, median (range), months</th>
<th>PFS, median (range), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-expressing or HER2-mut. NSCLC - N = 18</td>
<td>58.8% (10/17)</td>
<td>9.9 (0.0+, 11.5)</td>
<td>1.4 (1.0, 4.2)</td>
<td>14.1 (0.9, 14.1)</td>
</tr>
<tr>
<td>HER2-mutated NSCLC n = 11</td>
<td>72.7% (8/11)</td>
<td>11.5 (0.03+, 11.5)</td>
<td>1.4 (1.0, 4.2)</td>
<td>14.1 (4.0+, 14.1)</td>
</tr>
</tbody>
</table>
MET
telisotuzumab vedotin (teliso-v)

- Telisotuzumab vedotin (ABBV-399; teliso-v): c-Met–targeted, humanized monoclonal antibody (ABT-700) conjugated to monomethyl auristatin E (MMAE)
  - Teliso-v is internalized, MMAE released → mitosis inhibition and cell death

Resistant to EGFR TKIs

C-Met+: central lab IHC H-score ≥150 or local lab MET amplification (MET/CEN7 ≥2)
**MET**

telisotuzumab vedotin (teliso-v)

**Efficacy**

*Data cutoff: June 21, 2019*

<table>
<thead>
<tr>
<th></th>
<th>EGFR M+ (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Objective response rate,</em> % (95% CI)</em>*</td>
<td>33.3 (17.3, 52.8)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td><strong>Median duration of response, mo (95% CI)</strong></td>
<td>NR (2.8, NE)</td>
</tr>
<tr>
<td><strong>Median PFS, mo (95% CI)</strong></td>
<td>5.9 (3.7, NE)</td>
</tr>
<tr>
<td><strong>Median follow-up, mo (range)</strong></td>
<td>6.3 (1.4 – 13.4)</td>
</tr>
<tr>
<td><strong>Median treatment duration, mo (range)</strong></td>
<td></td>
</tr>
<tr>
<td>Teliso-v</td>
<td>4.9 (0.7 – 10.4)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>5.9 (0.7 – 25.4)</td>
</tr>
</tbody>
</table>

**Objective response rate by subgroup of interest, n (%)**

| Received prior third-generation EGFR TKI | 6/17 (35.3) |
| c-Met amplified, copy number gain, or polysomy | 5/8 (62.5) |
| EGFR TKI-containing regimen as last-line therapies | 8/20 (40.0) |

*RECIST version 1.1.

CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; M, mutation; mo, months; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor.

Camidge WCLC 2019
**MET**

telisotuzumab vedotin (teliso-v)

<table>
<thead>
<tr>
<th>TEAE With Incidence ≥20%, n (%)</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All treated patients in the cohort</strong></td>
<td>42 (100)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Patients who experienced ≥1 event</td>
<td>42 (100)</td>
<td>27 (64)</td>
</tr>
<tr>
<td>Peripheral neuropathy SMQ</td>
<td>22 (52)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>16 (38)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (36)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>14 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13 (31)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (31)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (21)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (21)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Camidge WCLC 2019
HER3
U3-1402

Conjugation chemistry
The drug-linker is conjugated to the antibody via cysteine residues

Payload (DXd)
Exatecan derivative
Topoisomerase I Inhibitor

Percentage of patients with TEAEs (≥10%; N = 23)

- Nausea
- Fatigue
- Vomiting
- Decreased appetite
- Platelet count decreased
- Alopecia
- Epistaxis
- Gastroesophageal reflux disease
- Diarrhea
- Constipation
- Skin ulcer
- Memory impairment
- Dysarthria
- Hypokalemia
- Weight decreased

Janne ASCO 2019
HER3
U3-1402

Post EGFR TKI

N = 16

EGFR activating mutations:
- L858R
- L858R
- L858R
- L858R
- Ex19del
- Ex19del
- Ex19del
- L858R
- Ex19del
- Ex19del
- Ex19del
- Ex19del
- L858R
- Ex19del
- Ex19del

EGFR resistance mutations:
- NE
- NE
- NE
- NE
- NE
- NE
- T790M
- NE
- NE
- NE
- NE
- NE
- T790M
- NE
- NE
- NE
- NE
- NE
- c797s
- NE
- NE
- NE
- NE
- NE
- CDK4
- CDK4
- HER2
- NE

Amplifications:
- NE
- NE
- NE
- NE
- CDK4
- CDK4
- HER2
- NE

Janne ASCO 2019
DS-1062a structure: TROP2-targeting antibody-drug conjugate\(^1\) with a novel topoisomerase I inhibitor (DXd)\(^2,3\)

Conjugation chemistry
- Tetrapeptide linker bound to a cysteine residue of the antibody
- DS-1062a is a selective DAR4 conjugate

DS-1062a Antitumor activity in lung cancer xenograft mouse models:
Stronger antitumor activity in TROP2-positive tumors\(^1,4\)

46 NSCLC
- Failed prior immune checkpoint inhibitors (86.5%)
- 12 PRs (10 confirmed; 2 too early to confirm)

Clear dose-effect on frequency of response

Durable responses seen at multiple dose levels

Data cut-off: July 3, 2019.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor, HER2; human epidermal growth factor receptor 2; PD, progressive disease; PR, partial response; Pt, patient; SD, stable disease.
### TROP2

#### DS-1062a

<table>
<thead>
<tr>
<th>TEAEs, regardless of causality, (in ≥10% of pts), n (%) (N=52)</th>
<th>All Grades</th>
<th>Grade ≥3</th>
<th>All grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>48 (92.3)</td>
<td>22 (42.3)</td>
<td>7 (13.5)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (36.5)</td>
<td>2 (3.8)</td>
<td>7 (13.5)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (36.5)</td>
<td>0</td>
<td>7 (13.5)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15 (28.8)</td>
<td>0</td>
<td>6 (11.5)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (26.9)</td>
<td>0</td>
<td>6 (11.5)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (23.1)</td>
<td>0</td>
<td>5 (9.6)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis/mucosal inflammation</td>
<td>12 (23.1)</td>
<td>2 (3.8)</td>
<td>5 (9.6)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (23.1)</td>
<td>0</td>
<td>5 (9.6)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>11 (21.2)</td>
<td>0</td>
<td>5 (9.6)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (15.4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Adverse Events

- **Any TEAE**: 48 (92.3) vs. 22 (42.3)
- **Constipation**: 7 (13.5) vs. 0
- **Fatigue**: 19 (36.5) vs. 2 (3.8)
- **Cough**: 7 (13.5) vs. 0
- **Nausea**: 19 (36.5) vs. 0
- **Diarrhea**: 7 (13.5) vs. 0
- **Alopecia**: 15 (28.8) vs. 0
- **ALT increased**: 6 (11.5) vs. 0
- **Decreased appetite**: 14 (26.9) vs. 0
- **Weight decreased**: 6 (11.5) vs. 0
- **Anemia**: 12 (23.1) vs. 0
- **Dehydration**: 5 (9.6) vs. 0
- **Stomatitis/mucosal inflammation**: 12 (23.1) vs. 2 (3.8)
- **Dyspnea**: 5 (9.6) vs. 1 (1.9)
- **Vomiting**: 12 (23.1) vs. 0
- **Headache**: 5 (9.6) vs. 0
- **Infusion related reaction**: 11 (21.2) vs. 0
- **Pain**: 5 (9.6) vs. 1 (1.9)
- **Rash**: 8 (15.4) vs. 0

#### Data Cut-off

- **Data cut-off**: July 3, 2019.

- **DLT**: reached at 10 mg/kg;**a** MTD at 8 mg/kg is also RDE, median exposure duration was 10.6 (range 3.0–43.1) weeks
- **Serious TEAEs**: occurred in 14 (26.9%) pts and death in 3 (5.8%) pts; no deaths were related to study drug
- **TEAEs associated with dose reduction, interruption, or discontinuation**: in 5 (9.6%), 5 (9.6%), and 2 (3.8%) pts, respectively
- **One pt (1.9%)** with disease progression treated with the 6.0 mg/kg dose developed a pulmonary adverse event of special interest of respiratory failure (grade 5), adjudicated as not an ILD

- Including cases post-data cutoff, 4 not-yet adjudicated possible ILD reports were observed (1 grade 2 pneumonitis [6.0 mg/kg], 1 grade 2 organizing pneumonia [8 mg/kg], 1 grade 2 pneumonitis [8 mg/kg], and 1 grade 5 [respiratory failure in a pt with disease progression; 8.0 mg/kg])

**a**2 DLTs occurred at the 10-mg/kg dose; 1 pt with mucosal inflammation and another pt with stomatitis. One DLT occurred at the 6-mg/kg dose in a pt with rash maculopapular.

**b**The most frequent TEAE leading to dose reduction was mucosal inflammation (2 pts [3.8%], 10-mg/kg group).

**c**TEAEs leading to drug discontinuation (1 pt each) were pleural effusion (0.27 mg/kg) and pain (2.0 mg/kg).

ALT, alanine aminotransferase; DLT, dose-limiting toxicity; ILD, interstitial lung disease; MTD, maximum tolerated dose; PD, progressive disease; Pt, patient; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event.

Heist WCLC 2019
New drugs

- Molecular selection
- TKI & family
- Other targets
- ADCs
- Bispecific antibodies
Bispecific Antibodies

**Effectorsite**
- **Molecules:** antigens, enzymes, drugs, cytokines, toxins, radionucleotides, plasma proteins.
- **Cells:** T-cells, Natural Killer cells, macrophages, neutrophils.

**Target site**
- **Molecules:** cytokines, growth factors
- **Cellular targets:** Receptors, adhesion molecules
- **Organisms:** Viruses, bacteria, parasites

- Targeting 2 epitopes on a single target
- Targeting 2 antigens on the same tumor cell
- Targeting 2 antigens on different cells (example: tumor cell and T-cell)

*Courtesy of S. Champiat*
Bispecific Antibodies

Effect site:
- Molecules: antigens, enzymes, drugs, cytokines, toxins, radionucleotides, plasma proteins
- Cells: T-cells, Natural Killer cells, macrophages, neutrophils

Target site:
- Molecules: cytokines, growth factors
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- Organisms: Viruses, bacteria, parasites

Targeting 2 epitopes on a single target
Targeting 2 antigens on the same tumor cell
Targeting 2 antigens on different cells (example: tumor cell and T-cell)

Courtesy of S.Champiat
Blinatumomab: Bispecific T-Cell Engager Antibody

- **Blinatumomab**[1]
  - Bispecific T-cell engager antibody construct that directs cytotoxic T cells to CD19-positive cells[2]
  - CD19: highly specific and expressed in >90% of B-cell lineage cancers[3]
  - Blinatumomab was approved in December 2014 by the FDA to treat pts with Ph- precursor B-cell ALL


*Courtesy of S. Champiat*
Bispecific Antibodies

**Effect site**
- **Molecules:** antigens, enzymes, drugs, cytokines, toxins, radionucleotides, plasma proteins.
- **Cells:** T-cells, Natural Killer cells, macrophages, neutrophils.

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- Targeting 2 antigens on the same tumor cell
- Targeting 2 antigens on different cells (example: tumor cell and T-cell)

*Courtesy of S.Champiat*
EGFR-cMet bispecific antibody
JNJ-61186372 (JNJ-372)

- Fully humanized, bispecific IgG1 antibody
- Targets EGFR and cMet receptors through unique mechanisms of action
EGFR-cMet bispecific antibody
JNJ-61186372 (JNJ-372)

Inhibition of EGFR and cMet Signaling

Receptor Degradation

ADCC Function

Moores et al. 2016 Cancer Res; 76 (13)

Haura ASCO 2019
EGFR-cMet bispecific antibody
JNJ-61186372 (JNJ-372)

32/108 (30%) patients with best response of PR across diverse EGFR mutations:

- Exon 21 L858R
- Exon 19 deletion
- Exon 20 insertion
- Exon 20 T790M
- Exon 18 G719A
- Exon 19 deletion
- Exon 20 insertion

Primary:
Secondary:
- T790M
- C797S
- cMet amplification

EGFRmut+ and 700–1400 mg
N=108
# EGFR-cMet bispecific antibody

## JNJ-61186372 (JNJ-372)

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>140 mg (n=3)</th>
<th>350 mg (n=3)</th>
<th>700 mg (n=10)</th>
<th>1050 mg (n=86)</th>
<th>1400 mg (n=40)</th>
<th>Total (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion related reaction (IRR)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>9 (90)</td>
<td>46 (54)</td>
<td>28 (70)</td>
<td>88 (62)</td>
</tr>
<tr>
<td>Rash a</td>
<td>0</td>
<td>2 (67)</td>
<td>3 (30)</td>
<td>55 (64)</td>
<td>19 (48)</td>
<td>79 (56)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>0</td>
<td>1 (33)</td>
<td>2 (20)</td>
<td>28 (33)</td>
<td>6 (15)</td>
<td>37 (26)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>2 (20)</td>
<td>22 (26)</td>
<td>5 (13)</td>
<td>31 (22)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
<td>2 (20)</td>
<td>20 (23)</td>
<td>5 (13)</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (33)</td>
<td>2 (20)</td>
<td>14 (16)</td>
<td>10 (25)</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (33)</td>
<td>0</td>
<td>2 (20)</td>
<td>14 (16)</td>
<td>9 (23)</td>
<td>26 (18)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>16 (19)</td>
<td>4 (10)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
<td>13 (15)</td>
<td>7 (18)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
<td>2 (20)</td>
<td>11 (13)</td>
<td>7 (18)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (67)</td>
<td>0</td>
<td>2 (20)</td>
<td>11 (13)</td>
<td>3 (8)</td>
<td>18 (13)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>10 (12)</td>
<td>6 (15)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1 (10)</td>
<td>8 (9)</td>
<td>8 (20)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (33)</td>
<td>0</td>
<td>2 (20)</td>
<td>3 (4)</td>
<td>4 (10)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Pneumonitis/ILD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (5)</td>
<td>3 (2)</td>
</tr>
</tbody>
</table>

- Grade ≥3 TEAEs reported in 49 (35%) patients
- Treatment-related grade ≥3 AEs reported in 12 (9%) patients
- AEs leading to treatment discontinuations=8% (4% related)
- AEs leading to dose reduction=4%

Haura ASCO 2019
Réaction à la perfusion

Hypersensibilité

Allergique
IgE médié

Non-Allergique
Non IgE médié

À partir de la 2ème perfusion

À la 1ère perfusion

Dès la 1ère perfusion Si charge tumorale importante

Réaction à la perfusion

Syndrome de relargage cytokinique

Lymphocyte

cellules NK

Cellule dendritique

Macrophage

Courtesy of S.Champiat
EGFR-cMet bispecific antibody
JNJ-61186372 (JNJ-372)

IRR Severity (n=88)
- Grades 1–2 (98%)
- Grade 3 (2%)

IRR-associated TEAEs (≥15%)
- Chills (20%)
- Dyspnea (20%)
- Nausea (19%)
- Flushing (17%)

- IRR commonly observed but primarily limited to first infusion
- Split first dose: 350 mg on C1D1, with remainder on C1D2
Bispecific Antibodies

Effect site:
Molecules: antigens, enzymes, drugs, cytokines, toxins, radionucleotides, plasma proteins,

Cells: T-cells, Natural Killer cells, macrophages, neutrophils

Target site:
Molecules: cytokines, growth factors

Cellular targets: Receptors, adhesion molecules

Organisms: Viruses, bacteria, parasites

Targeting 2 epitopes on a single target
Targeting 2 antigens on the same tumor cell
Targeting 2 antigens on different cells (example: tumor cell and T-cell)

Courtesy of S. Champiat
HER2-HER2 bispecific antibody
ZW25

=Trastuzumab
=Pertuzumab

T = Trastuzumab, K = T-DM1, P = Pertuzumab, L = Lapatinib
*Radiologic Progression; ▼Clinical Progression
Disease control rate defined as percentage of patients with complete response (CR), partial response (PR), or stable disease (SD) per RECIST 1.1
† 3 of the 46 response-evaluable patients had no post-baseline disease assessment of their target lesions

Meric-Bernstam ASCO 2019
New drugs

- Molecular selection
- TKI & family
- Other targets
- ADCs
- Bispecific antibodies
- Chemo!
IO + Chemotherapy in Non-Squamous

**KEYNOTE 189**
- Unresected stage IV non-squamous NSCLC
- No concurrent EGFR or ALK inhibition
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No prior systemic therapy

**IMPOWER 150**
- Tumor tissue available for biomarker testing
- Any PD-L1 IC1 status
- Stratification factors:
  - Sex
  - PD-L1 IHC expression
  - Liver metastasis
  - N = 1202

**Papadimitakoupolou – WCLC 2018**
- Crossover not allowed
But ~31% in arm C received ICI

**Cappuzzo – ESMO 2018**
- Crossover allowed 41% (ICI 59.2%)
IO + Chemotherapy in Non-Squamous: PFS

**KEYNOTE 189**
Platinum/Pem +/- Pembrolizumab

- Hazard ratio for disease progression or death: 0.52 (95% CI, 0.43–0.64) \(p<0.001\)
- RR: 47.6% vs. 18.9%, \(p<0.001\)
- Median, 8.8 mo.
- 4.9 mo.
- RR: 47% vs. 32%

**IMPOWER 150**
CBDCA/Taxol/BVZ +/- Atezolizumab (B vs. C)

- Median, 6.8 mo.
- Median, 8.3 mo. (95% CI: 7.7, 9.8)
- RR: 63.5% vs. 48%
- HR², 0.59 (95% CI: 0.50, 0.70) \(p<0.0001\)
- Median follow-up: ~20 mo

**IMPOWER 132**
Platinum/Pem +/- Atezolizumab

- RR: 47.6% vs. 18.9%, \(p<0.001\)
- Median, 8.8 mo.
- 4.9 mo.
- RR: 47% vs. 32%

**IMPOWER 130**
CBDCA/nab-Paclitaxel +/- Atezolizumab

- Median, 5.2 mo. (95% CI: 4.3, 5.6)
- Median, 7.6 mo. (95% CI: 6.6, 8.5)

WE NEED NEW CHEMO FOR NEXT LINES!

*Courtesy of J. Remon* Gandhi – NEJM 2018 * Papadimitakoupolou – WCLC 2018

Socinski – NEJM 2018 * Cappuzzo – ESMO 2018
Le cocktail anti-cancéreux du XXIème siècle

Roy HERBST
ASCO 2001

Immunotherapy revolution unseen!!
Le cocktail anti-cancéreux du XXIème siècle

Chemotherapy and ADC

Immunotherapy
Hard (CAR-T...)
vs. Soft (BITEs, ICI)

TKIs
New targets,
ext gen. drugs

Local treatments everywhere

Integrated cares (IPA...)

AI everywhere
(maybe too much)

Strategy tools
Connected tools...