Other Oncogenic Drivers (BRAF, MET, RET, HER2, NTRK)

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Department of Cancer Medicine
Gustave Roussy – Villejuif (France)
Disclosure Slide

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

- **Consulting, advisory role or lectures**: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, MSD Oncology, Novartis, Pfizer, prIME Oncology, Roche

- **Travel, Accommodations, Expenses**: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer
Great advances have been made in lung cancer therapy: targeting of oncogenic drivers

- **ALK (7%)**
- **EGFR other (4%)**
- **MET (3%)**
- **>1 mutation (3%)**
- **HER2 (2%)**
- **ROS1 (2%)**
- **BRAF (2%)**
- **RET (2%)**
- **NTRK1 (1%)**
- **PIK3CA (1%)**
- **MEK1 (<1%)**
- **KRAS (25%)**
- **EGFR sensitizing (17%)**

**Unknown oncogenic driver detected (31%)**

**EGFR sensitizing**
- Gefitinib; Erlotinib; Afatinib; Osimertinib; Dacomitinib

**ALK**
- Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib

**ROS1**
- Crizotinib; Cabozantinib; Ceritinib; Lorlatinib; Entrectinib; Ropotrectinib, DS-6051b

**BRAF**
- Vemurafenib; Dabrafenib; Dabrafenib + Trametinib

**MET**
- Crizotinib; Cabozantinib; Capmatinib; Savolitinib; Tepotinib; Merestinib; Glesatinib

**HER2**
- Trastuzumab emtansine; Afatinib; Neratinib-temsirolimus; Dacomitinib; Poziotinib; XMT-1522; TAK-788; DS-8201a

**RET**
- Cabozantinib; Alectinib; Apatinib; Vandetanib; sunitinib; Ponatinib; Lenvatinib; BLU-667; LOXO-292

**NTRK1**
- Entrectinib; LOXO-101 (larotrectinib); loxo-195; DS-6051b; ropotrectinib

**PIK3CA**
- LY3023414; PQR 309

**MEK1**
- Trametinib; Selumetinib; Cobimetinib
BRAF MUTATIONS IN NSCLC

France¹
NSCLC
(Biomarkers France [IFCT]; N=17,664)

US²
Adenocarcinoma
(Lung Cancer Mutation Consortium; N=733)

- NSCLC with BRAF V600E mutations has histological features suggestive of an aggressive tumor³
- Patients with BRAF V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy³,⁴

BRAF gene and protein structures with related biological aspects

18 exons and 17 introns spanning 200 Kb on the long arm of chromosome (7q34)
# BRAF-ASSOCIATED PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>ALK&lt;sup&gt;1–4&lt;/sup&gt;</th>
<th>EGFR&lt;sup&gt;1,3,4,7&lt;/sup&gt;</th>
<th>KRAS&lt;sup&gt;4,7&lt;/sup&gt;</th>
<th>BRAF&lt;sup&gt;5–8&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Younger (~50)</td>
<td>Older (~60)</td>
<td>Older (~60)</td>
<td>Older (~65)</td>
</tr>
<tr>
<td><strong>Male or female</strong></td>
<td>None</td>
<td>Female predominant</td>
<td>Female predominant</td>
<td>None</td>
</tr>
<tr>
<td><strong>Smoker or non-smoker</strong></td>
<td>Never or light</td>
<td>Never or light</td>
<td>Heavy</td>
<td>Smoker and non-smoker</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td><strong>Pattern of spread</strong></td>
<td>Pericardial,* pleural metastases,* liver,* intra- or extrathoracic lymph nodes,* CNS</td>
<td>Liver,* CNS</td>
<td>CNS</td>
<td>?</td>
</tr>
</tbody>
</table>


*Compared with triple-negative, wild-type patients
Inhibition of BRAF V600 Kinase

Dabrafenib
Vemurafenib

PI3K/AKT/mTOR pathway

BRAF V600

RAS

PI3K/AKT/mTOR pathway

BRAF
CRAF

MEK

ERK1/2

p90RSK
MSK1

Proliferation, Growth, Survival

RTKs
SOS
Grb2
SHC

P

Dabrafenib
Vemurafenib

BRAF
V600

CRAF

BRAF

ERK1/2

PI3K/AKT/mTOR pathway

Proliferation, Growth, Survival
Vemurafenib in **BRAF** mutant NSCLC

**AcSé trial**

Vemurafenib

**VE-Basket trial**

Vemurafenib

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79 **BRAF**\(^{V600}\) NSCLC

**ORR**: 43%. **PFS**: 5.2 mo

Mazières – WCLC 2018

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20 **BRAF**\(^{V600}\) NSCLC

**ORR**: 42%. **PFS**: 7.3 mo

Hyman – NEJM 2015
BRF113928 STUDY: DABRAFENIB IN BRAF MUTANT NSCLC IN 2ND LINE

Cohort A

84 BRAF<sup>V600E</sup> NSCLC

ORR: 33%

PFS: 5.5 months (95% CI 2.8, 6.9)

D. Planchard et al – lancet Oncol 2016
MECHANISM OF ACTION FOR DUAL MAPK PATHWAY INHIBITION WITH DABRAFENIB + TRAMETINIB TO OVERCOME ERK ESCAPE MECHANISM

Kristina M. Ilieva et al, mol cancer therapeutics
BRF113928 STUDY: MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 2ND LINE

Cohort B

**ORR: 66.7% (95% CI 52.9, 78.6)**

**mPFS: 10.9m (7.0-16.6)**

BRF113928 STUDY: MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

Cohort C

ORR: 64% (95% CI 46, 79)

mPFS: 10.2m (6.9-16.7)

The patient received the association:
Dabrafenib (150mg twice a day) + Trametinib (2mg/day)
## BRAF mutated patients

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Drug</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyman (BASKET-trial)</td>
<td>20</td>
<td>Vemurafenib</td>
<td>42%</td>
<td>7.3</td>
<td>NR</td>
</tr>
<tr>
<td>Gautschi (EU-RAF, retrospective)</td>
<td>35</td>
<td>Vemurafenib</td>
<td>53%</td>
<td>5</td>
<td>10.8</td>
</tr>
<tr>
<td>Mazières (AcSé Vemu)</td>
<td>100</td>
<td>Vemurafenib</td>
<td>44.9%</td>
<td>5.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Planchard (BRF cohort A)</td>
<td>78</td>
<td>Dabrafenib</td>
<td>33%</td>
<td>5.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Planchard (BRF cohort B)</td>
<td>57</td>
<td>Dabrafenib + trametinib</td>
<td>66.7%</td>
<td>10.9</td>
<td>12.7</td>
</tr>
<tr>
<td>Planchard (BRF cohort C)</td>
<td>36</td>
<td>Dabrafenib + trametinib 1L</td>
<td>64%</td>
<td>10.2</td>
<td>24.6</td>
</tr>
</tbody>
</table>

**EMA and FDA approvals 2017**

J. Mazieres, WCLC 2018
BRAF non V600 cohort (AcSé Vemu)

- Mean Bayesian Estimated Success rate: 5.9%; credibility 95% CI: [0.2%; 20.6%]
- Prob ORR < futility bound (10%): 81.5% - study stopped

Non V600 mutations
n = 17
G466A : n=1
G466V : n=3
G469A : n=3
G469V : n=1
N581S : n=3
G596R : n=1
K601E : n=3
K601N : n=2

Response rate: 0%

PFS: 1.8 m. [1.4;2.1]

J. Mazieres et al, WCLC 2018
**BRAF and immunotherapy**

45% of *BRAF*-mutant & high PD-L1 expression levels (≥ 50% by 22C3 IHQ)

10% of cases associated with high tumor mutational burden (≥20 Mb)

**ORR: 17%**

N=15

PFS / OS

V600E vs. Non-V600E: 6.1 mo. vs. 2.6 mo. (p=0.67) / NR vs. 33.9 (p=0.47)

Dudnik – WCLC 2017
**Immunotarget - 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>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>PDL1</td>
<td>Smoking</td>
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<tr>
<td>Total</td>
<td>19%</td>
<td>2.8</td>
<td>13.3</td>
<td></td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>KRAS</td>
<td>271</td>
<td>26%</td>
<td>3.2</td>
<td>13.5</td>
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<tr>
<td>EGFR</td>
<td>125</td>
<td>12%</td>
<td>2.1</td>
<td>10</td>
<td>+</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>
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<tr>
<td>HER2</td>
<td>29</td>
<td>7%</td>
<td>2.5</td>
<td>20.3</td>
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<td>+</td>
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<td>2.5</td>
<td>17</td>
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</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></td>
<td></td>
</tr>
</tbody>
</table>

Julien MAZIERES et al, ASCO 18
Stage IV lung carcinoma with **BRAF V600** mutation

- Dabrafenib/trametinib [III, A; MCBS 2] or Platinum-based ChT [IV, A]

  **Disease progression**

  - **Oligoprogession**
    - Local treatment
  - **Systemic progression**

  **Systemic progression**

- Dabrafenib/trametinib [III, A] or Platinum-based ChT [IV, A] (see Figure 2) if BRAF/MEK inhibitors received in first line. Consider immunochemotherapy as per Figure 2 if smoker [V, B]

D. Planchard et al, Annals Onco 2018
**MET aberrations in NSCLC**

**MET**
- Overexpression: 25-75%
- Amplification: 3-7%
- Exon 14 Skipping: 3%

**MET as a primary driver**
- Amplification
- Exon 14 alterations

**MET as a secondary/co-driver**
- EGFR mutation
- MET amplification


Drilon A et al, J Thoracic Oncol, 2016
### Type 1 MET Inhibitors

<table>
<thead>
<tr>
<th><strong>Good Drug</strong></th>
<th><strong>Criz</strong></th>
<th><strong>Tep</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>High ORR</td>
<td>✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Potent</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Selective</td>
<td>✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Tolerable</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>CNS Activity</td>
<td>✓</td>
<td></td>
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</table>

#### Crizotinib

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$ (nM) mean</th>
<th>Selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-MET</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>ALK</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>RON</td>
<td>298</td>
<td>34</td>
</tr>
<tr>
<td>Axl</td>
<td>294</td>
<td>34</td>
</tr>
<tr>
<td>Tie-2</td>
<td>448</td>
<td>52</td>
</tr>
<tr>
<td>Trk A</td>
<td>580</td>
<td>67</td>
</tr>
<tr>
<td>Trk B</td>
<td>399</td>
<td>46</td>
</tr>
<tr>
<td>Abl</td>
<td>1,159</td>
<td>166</td>
</tr>
</tbody>
</table>

#### Tepotinib

- Modest ORR
- Potent
- Selective
- Tolerable
- CNS Activity

---

Tumour shrinkage seen with crizotinib or capmatinib treatment in intermediate and high MET amplified

**Crizotinib**

<table>
<thead>
<tr>
<th>Low MET (≥1.8–≤2.2)</th>
<th>Intermediate MET (&gt; 2.2–&lt; 5)</th>
<th>High MET (≥5) MET/CEP7</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 2</td>
<td>n = 6</td>
<td>n = 6</td>
</tr>
</tbody>
</table>

- ORR: 33.3% (0.8–90.6) n = 3
- PFS: 1.8 (0.8–14.0) n = 3

- ORR: 14.3% (1.8–42.8) n = 14
- PFS: 6.7 (3.4–7.4) n = 14

- ORR: 40.0% (19.1–63.9) n = 20
- PFS: 6.7 (3.4–7.4) n = 20

**Capmatinib**

- ORR: 17% (2.1–48.4) n = 14
- PFS: 47% (21.3–73.4) n = 14

*UpDate ASCO D. Ross Camidge (Abst 9062)*


AcSé trial, Response rate MET amplification

Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

**ORR= 32 % (8/25) [15%; 54%], DCR=60 % (15/25) [39 ; 79%]**
Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

**Median PFS**: 3.4 months 95% CI [1.9; 5.5 months]

**Median OS**: 7.7 months 95% CI [4.6; 15.7 months]
Response to Combined EGFR- and MET-Directed Targeted Therapy (MET amplified)

• Capmatinib + Gefitinib
  • Phase 2 expansion cohort
  • EGFR-mutant lung cancers with acquired resistance and "MET-positive" NSCLCs

ORR:

- 15% in patients with MET gene copy number <6
- 25% in patients with MET gene copy number ≥6
- 50% in patients with MET gene copy number ≥6

Yi-Long Wu et al, JCO 2018
**TATTON (osimertinib+ Savolitinib)**

Preliminary anti-tumour activity in all MET-positive patients*, n = 64

<table>
<thead>
<tr>
<th>Objective response rate, n (%)</th>
<th>Prior 3rd Gen T790M directed EGFR-TKI (n = 30)</th>
<th>No prior 3rd Gen T790M directed EGFR-TKI</th>
<th>Total (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR†</td>
<td>10 (33)</td>
<td>6 (55)</td>
<td>14 (61)</td>
</tr>
</tbody>
</table>

Notes:
- 17 patients did not have central FISH confirmation of MET-positive status (n = 6 MET-negative; n = 11 unknown by central lab).
- Confirmed by a later scan performed at least 4 weeks after initial response observed.


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* Waterfall plot based on evaluable patients (n = 64): all patients dosed and with on-treatment assessment or discontinuation prior to first tumour assessment.

**Myung-Ju Ahn et al, IASLC 2017**

**TATTON Part B**

NCT02143466
57 year old female never smoker with NSCLC adenocarcinoma histology, ECOG PS 1

Diagnosis of adenocarcinoma T3N3M1b with brain metastasis; EGFR Ex19Del

Ex19Del, exon 19 deletion

First-line gefitinib 250 mg QD for 6 months
BOR: PR

Post-PD biopsy: T790M-, MET+ (FISH).
First dose on TATTON study

PR 6 week RECIST scan
Confirmed PR 12 week RECIST scan

Nov 2016
Jun 2017
Jul 2017
Sep 2017
Ongoing

Myung-Ju Ahn et al, IASLC 2017

TATTON Part B
NCT02143466
Receptor activation (Ras/MAPK, PI3K/Akt, Src, STAT3)

Receptor internalization

Receptor degradation

Exon 14 mutation/skipping

Loss of c-Cbl binding site
Decreased ubiquitination
Impaired receptor degradation

Increased MET signaling

Updated Antitumor Activity and Safety of Crizotinib in Patients With MET Exon 14-Altered Advanced NSCLC

ORR: 32% (95% CI*: 21, 45)

*Alterations in both splice donor and acceptor regions. †Includes alterations in the Splice Acceptor Region, Polypyrimidine Tract, and Branching Point. ‡Includes MET exon 14 alterations that are not associated with DNA coding region information. §White space in biomarker data rows indicates no available sample for testing, not analyzable or no results reported. bp, base pairs; UIF, uninformative.

Alexander Drilon et al, WCLC 2018
Progression-Free Survival (PFS) by Derived Investigator Assessment

- **Median PFS estimate:** 7.3m (5.4, 9.1)
- **OS data were not mature at time of data cutoff:** 34.8% patients had died; 40.6% still in follow-up
- **Median Overall Survival (OS) estimate, months (95% CI):** 20.5 (14.3, 21.8)

Shaded area in PFS Kaplan-Meier plot above represents 95% Hall-Wellner band. 95% CI estimates for PFS and OS based on Brookmeyer and Crowley method.

Alexander Drilon et al, WCLC 2018
AcSé trial, Response rate MET exon 14 mutation

Abstract ID: #12937. Activity of crizotinib in MET or ROS1 positive (+) NSCLC: results of the AcSé trial. D. Moro-Sibilot

Best response

ORR=40% (10 /25 ) [21%; 61%]
DCR=68% (17 / 25 ) [46%; 85%]
Response rate *MET* exon 14 mutation

**Median PFS**: 3.6 months 95% CI [1.6; 7 months]

**Median OS**: 9.5 months 95% CI [4.1; 13.4 months]
VISION: A Phase II, Single-arm Trial to Investigate Tepotinib in Advanced NSCLC with METexon14-Skipping Alterations

ORR: 23 (57.5%) [40.9, 73.0]

- BOR displayed at the end of the bar. NE*, BOR non-evaluable where ongoing patient has not had 2 post-baseline tumor assessments.
- BOR, best overall response; CR, complete response; L, liquid biopsy; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T, tumor biopsy.

n=39. Seven patients were excluded due to baseline/on-treatment measurement not being available.

Dr Enriqueta Felip, Vall d’Hebron University Hospital, Spain
Time on Treatment and Duration of Response (Investigator)

Median duration of response†
(95% CI)‡: 14.3 (3.7, nd) months

25/46 patients remain on-treatment

Dr Enriqueta Felip, Vall d'Hebron University Hospital, Spain

N=46. Time on treatment is the time from treatment initiation until treatment termination. Duration of response is measured from time of initial response until documented tumor progression. Patients denoted with an arrow remain on-treatment. BOR displayed at the end of the bar.
NE*, BOR non-evaluable where ongoing patient has not had two post-baseline tumor assessments. †From Kaplan-Meier survival analysis. ‡95% CI for the interval using the Brookmeyer and Crowley method.
BOR, best overall response; CR, complete response; L, liquid biopsy; nd, not determined; PD, progressive disease; PR, partial response; SD, stable disease; T, tumor biopsy.
Poor Response to Immunotherapy in MET exon 14-altered NSCLCs

$MET$ exon 14-altered cancers can express high levels of PD-L1

<table>
<thead>
<tr>
<th>PD-L1, Cell Signaling, Clone E1L3N assay, n=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 %</td>
</tr>
<tr>
<td>n, (%)</td>
</tr>
</tbody>
</table>

PMB is lower in patients with $MET$ exon 14 altered NSCLCs compared to other NSCLCs

ORR 6.7% (95% CI 0-32%)

No partial responses among the 6 patients with PD-L1 ≥ 50

Sabari et al, ASCO 2017
## 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>
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<tbody>
<tr>
<td></td>
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<td>Total</td>
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<tr>
<td>HER2</td>
<td>29</td>
<td>7%</td>
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<td>6%</td>
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<td>21.3</td>
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<tr>
<td>ROS1</td>
<td>7</td>
<td>17%</td>
<td>-</td>
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</tbody>
</table>

Julien MAZIERES et al, ASCO 18
## Resistance to MET-Directed Targeted Therapy

<table>
<thead>
<tr>
<th>Drug Administered</th>
<th>MET alteration</th>
<th>Putative resistance mechanism</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Crizotinib 8 mo of disease control</td>
<td>MET D1010H</td>
<td>MET D1228N (acquired second site mutation on tumor rebiopsy)</td>
<td>high total MET and phospho-MET IHC+ on post-PD biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MET D1228N (acquired second site mutation on tumor rebiopsy)</strong></td>
<td><strong>high total MET and phospho-MET IHC+ on post-PD biopsy</strong></td>
</tr>
<tr>
<td>Crizotinib 13 mo of disease control</td>
<td>MET D1010H</td>
<td>MET Y1230C (detected in ctDNA on PD)</td>
<td>thereafter responded to Glesatinib</td>
</tr>
<tr>
<td></td>
<td>(MET Y1230C)</td>
<td><strong>MET Y1230C (detected in ctDNA on PD)</strong></td>
<td><strong>thereafter responded to Glesatinib</strong></td>
</tr>
<tr>
<td>Crizotinib 8 mo of disease control</td>
<td>MET c.3028delG</td>
<td>MET Y1230H (acquired in tumor, MET amp + MET D1228N, Y1230H, Y1230S, and G1163R in plasma)</td>
<td>thereafter responded to Cabozatinib + Erlotinib</td>
</tr>
<tr>
<td>Savolitinib + Osimertinib 9 mo of disease control</td>
<td>MET amplification (+EGFR ex19 del)</td>
<td><strong>MET D1228V (acquired second site mutation on tumor rebiopsy)</strong></td>
<td><strong>thereafter responded to Cabozatinib + Erlotinib</strong></td>
</tr>
</tbody>
</table>

**Mechanisms of acquired resistance to MET TKIs in MET exon 14mutant NSCLC**

Presented Sunday, June 3, 2018. Mark M. Awad (Abst 9069)

- Secondary mutations in MET included H1094Y, G1163R, L1195F, L1195V, D1228N, Y1230H, and Y1230S.
- Bypass track activation: amplification of wild-type KRAS, BRAF, and/or EGFR.
- Acquired amplification of the mutated METex14 allele

In summary for MET NSCLC

Patients with METamp
- Crizotinib
- Capmatinib

Patients with MET exon14-skipping mutation
- Crizotinib
- Tepotinib

Savolitinib
Tepotinib
Cabozantinib
AMG337
Glesatinib
Merestinib

Second line MET TKI therapy post crizotinib ??
RET is a rare driver of multiple, diverse tumor types.

- Esophageal cancer
- Breast cancer
- Melanoma
- Colorectal cancer
- Leukemia
- Medullary thyroid cancer (>60% RET-mutations)
- Papillary thyroid cancer (~10% RET-fusions)
- Non-small cell lung cancer (~1-2% RET-fusions)

Other tumor types ≤1% RET-altered

**RET** rearrangements

- 1–2% of unselected NSCLCs
- Clinical features: young, never or former light cigarette smokers

### Multi-tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (nM) In vitro kinase</th>
<th>IC$_{50}$ (nM) Cellular kinase</th>
<th>IC$_{50}$ (nM) In vitro kinase RET V804M</th>
<th>Other targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib</td>
<td>1.5</td>
<td>*10</td>
<td>NR</td>
<td>VEGFR1-3, BRAF, c-kit, PDGF-b</td>
</tr>
<tr>
<td>Levantinib</td>
<td>1.5</td>
<td>48</td>
<td>NR</td>
<td>VEGFR1-3, FGFR1-3, c-kit, PDGF</td>
</tr>
<tr>
<td>Alectinib</td>
<td>4.8</td>
<td>?</td>
<td>53 V804L (32)</td>
<td>ALK (1.9 nM)</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>5.2</td>
<td>27-85</td>
<td>4094</td>
<td>VEGFR2, MET</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>7</td>
<td>0.7-11</td>
<td>12</td>
<td>Bcr-abl, FGFR1-4</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>30</td>
<td>40-164</td>
<td>55</td>
<td>VEGFR, PDGFR, c-kit, Flt-3</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>47</td>
<td>~20-50</td>
<td>12</td>
<td>RAF, VEGFR2-3, PDGFR, c-kit, Flt-3</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>100</td>
<td>NR</td>
<td>&gt; 10,000</td>
<td>VEGFR, EGFR</td>
</tr>
</tbody>
</table>

Global RET Registry

<table>
<thead>
<tr>
<th>RET inhibitor</th>
<th>Best response (%) ; 95% CI</th>
<th>Median DoT (range)</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>37% (16.3 - 61.6)</td>
<td>1.6 months (0.5 - 12.2)</td>
<td>3.6 months (1.3 - 7.0)</td>
<td>4.9 months (1.9 - 14.3)</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>18% (2.3 - 51.8)</td>
<td>2.9 months (0.8 - 7.1)</td>
<td>2.9 months (1.0 - 6.4)</td>
<td>10.2 months (2.4 - NR)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>22% (2.8 - 60.0)</td>
<td>2.2 months (0.7 - 6.6)</td>
<td>2.2 months (0.7 - 5.0)</td>
<td>6.8 months (1.1 - NR)</td>
</tr>
</tbody>
</table>

Gautschi et al, JCO 2017
Need of more potent drugs

**Cabozantinib**

- 7 PR (28%) in 25 cases

**Vandetanib**

- 3 PR (18%) in 17 cases

**Vandetanib**

- 9 PR (47%) in 19 cases

**mPFS: 5.5 months (95% CI 3.8–8.4)**

Drilon et al, Lancet Oncol, 2016

**mPFS: 5.5 months**

Lee et al, Ann Oncol, 2017

**mPFS: 4.7 months (95% CI 2.8–8.5)**

Yoh et al, Lancet Resp Med, 2017
BLU-667 designed to treat RET-altered cancers

**Subnanomolar potency**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Biochemical IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET wildtype</td>
<td>0.4</td>
</tr>
<tr>
<td>RET V804L</td>
<td>0.3</td>
</tr>
<tr>
<td>RET V804M</td>
<td>0.4</td>
</tr>
<tr>
<td>RET M918T</td>
<td>0.4</td>
</tr>
<tr>
<td>CCDC6-RET</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**More Potent than MKI**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Less Active than BLU-667</th>
<th>More Active than BLU-667</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT RET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET V804L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET V804M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET M918T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCDC6 RET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGFR-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Kinome selectivity for RET**

1. Subbiah V et al. *Cancer Discovery* April 15 2018
Broad anti-tumor activity against RET-altered cancers

Preliminary response rates
- ORR RET-fusion NSCLC 50%
- ORR RET-fusion MTC 40%

Vivek Subbiah et al, Cancer discovery 2018
Vivek Subbiah et al, AACR 2018
Durable activity

Vivek Subbiah et al, Cancer discovery 2018

Vivek Subbiah et al, AACR 2018
LOXO-292 is a potent and selective RET inhibitor

Subbiah et al. Ann Oncol 2018; Cabo = cabozantinib; PDX = patient-derived xenograft; NSCLC = non-small cell lung cancer; CRC = colorectal cancer; MTC = medullary thyroid cancer; BID = twice-daily; QD = once-daily
LOX-292: a new potent inhibitor of RET

- Enrolled: 38
- Eligible for response evaluation: 38

Overall Response Rate (95% CI):

- 26/38 (68%) (51% - 83%)
- 25/37 (68%) (50% - 82%)

Best Tumor Response (%)

- CR
- PR**
- SD
- PD
- NE

4/4 confirmed intracranial responses (1 CR, 3 PR) in patients with measurable (> 5 mm) intracranial lesions

Pending confirmation; * Excludes one patient with unconfirmed PR pending confirmation at time of data cut-off; ** 25 confirmed PR, 1 unconfirmed PR pending confirmation

Follow-up as of July 19, 2018.

Geoffrey R. Oxnard et al, WCLC 2018
Duration of LOXO-292 in RET fusion-positive NSCLC

- Median follow up for all patients: 8.5 months (0.3-14.1)
- Median follow up for all responders: 9.5 months (4.4-14.1)
- 24/26 (92%) responses ongoing, including 17 responses for ≥ 6 months


Geoffrey R. Oxnard et al, WCLC 2018
## RET: the next big target...

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>n</th>
<th>Response rate</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drilon A, 2016</td>
<td>Cabozantinib</td>
<td>25</td>
<td>28%</td>
<td>NR</td>
</tr>
<tr>
<td>Lin JJ, 2016</td>
<td>Alectinib</td>
<td>4</td>
<td>50%</td>
<td>Duration trt: 6m</td>
</tr>
<tr>
<td>Lee SH, 2017</td>
<td>Vandetanib</td>
<td>18</td>
<td>18%</td>
<td>4.5 m.</td>
</tr>
<tr>
<td>Yoh, K, 2017</td>
<td>Vandetanib</td>
<td>19</td>
<td>53%</td>
<td>4.7 m.</td>
</tr>
<tr>
<td>Velcheti, 2016</td>
<td>Lenvatinib</td>
<td>25</td>
<td>18%</td>
<td>7.3 m.</td>
</tr>
<tr>
<td>Gaustchi O, 2017</td>
<td>Various (registry)</td>
<td>53</td>
<td>18 to 37%</td>
<td>2.3 m.</td>
</tr>
<tr>
<td>Subbiah V, 2018 (ASCO)</td>
<td>Vandetanib + everolimus</td>
<td>13</td>
<td>54% (7/13)</td>
<td>4.4m</td>
</tr>
<tr>
<td>Subbiah V, 2018 (AACR)</td>
<td>BLU-667</td>
<td>53 (19 NSCLC)</td>
<td>50% (NSCLC)</td>
<td>Duration trt: 3.9m</td>
</tr>
<tr>
<td>Drilon A, 2018 (ASCO)</td>
<td>LOXO-292</td>
<td>82 (38 NSCLC)</td>
<td>68%</td>
<td>N.A</td>
</tr>
</tbody>
</table>

Targeting **HER2** aberrations

**HER2** mutations in ~1–4% and **HER2** amplifications in 2–5%

**Dacomitinib** (pan-**HER** inhibitor)

(*HER2*-mutated or amplified NSCLC)

- Only 3/26 of **HER2**-mutant patients had a response (**ORR** 12%)

**Neratinib** (pan-**HER** inhibitor)

± temsirolimus (mTOR inhibitor)

(*HER2*-mutated NSCLC)

- 21% **ORR** and mPFS of 4 months
- Patients had < 20% increase in tumour burden, but were considered PD due to the appearance of new lesions

Antibody-drug Conjugate Trastuzumab Emtansine (T-DM1) in Pts with Previously Treated HER2-Overexpressing

<table>
<thead>
<tr>
<th></th>
<th>IHC 2+ (n=29)</th>
<th>IHC 3+ (n=20)</th>
<th>All (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>2.6 (1.4, 2.8)</td>
<td>2.7 (1.4, 8.3)</td>
<td>2.6 (1.4, 2.8)</td>
</tr>
</tbody>
</table>

*Indicates positive HER2 amplification; U indicates unknown HER2 amplification; All other patients’ ISH status is negative

Thomas Stinchcombe et al, ASCO 2017
Phase 2 trial of ado-trastuzumab emtansine for pts withHER2 amplified or mutant cancers

**HER2 Mutant**
- ORR 44% (8/18, 95% CI 22-69%)

**HER2 amplified**
- ORR 50% (3/6)
- mPFS: 6m (95%CI 6-NR)

6 of 8 responders were heavily pre-treated, including response to prior HER therapy neratinib, afatinib, trastuzumab

Bob T Li et al, JCO 2018
Concurrent HER2 amplification observed in 2 of 18 (11%)

<table>
<thead>
<tr>
<th>NGS</th>
<th>FISH (HER2/CEP17)</th>
<th>IHC</th>
<th>Mass spectrometry (amol/ug)</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 20 p.A775_G776insYVMA</td>
<td>1.1 (2.7/2.5)</td>
<td>0</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Exon 20 p.A775_G776insYVMA</td>
<td>1.8 (8.1/4.5)</td>
<td>2+</td>
<td>642</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.A775_G776insYVMA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Exon 20 p.A775_G776insYVMA</td>
<td>1.4 (4.5/3.3)</td>
<td>1+</td>
<td>586</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.A775_G776insYVMA</td>
<td>1.9 (5.6/2.9)</td>
<td>1+</td>
<td>548</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.G778_P780dup</td>
<td>1.6 (7.8/4.8)</td>
<td>1+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.G778_P780dup</td>
<td>1.8(4.8/2.5)</td>
<td>2+</td>
<td>507</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.G778_P780dup</td>
<td>1.4 (5.8/4.2)</td>
<td>2+</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.G778-779 insCPG</td>
<td>1.6(4.3/2.7)</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Exon 20 p.G776_V777&gt;VCV</td>
<td>NA</td>
<td>NA</td>
<td>205</td>
<td>Yes</td>
</tr>
<tr>
<td>Exon 20 p.G776delinsVC</td>
<td>1.6 (5.7/3.8)</td>
<td>0</td>
<td>434</td>
<td>Yes</td>
</tr>
<tr>
<td>Exon 19 p.L755P</td>
<td>1.5 (3.2/2.1)</td>
<td>2+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Exon 19 p.L755P</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Exon 17 p.V659E</td>
<td>1.2 (2.4/2.0)</td>
<td>2+</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Exon 17 p.V659E</td>
<td>1.1 (2.3/2.0)</td>
<td>2+</td>
<td>688</td>
<td></td>
</tr>
<tr>
<td>Exon 8 p.S310F amplification fold change 2.8</td>
<td>4.1 (8.4/2.5)</td>
<td>2+</td>
<td>1495</td>
<td>Yes</td>
</tr>
<tr>
<td>Exon 8 p.S310F</td>
<td>1.8 (3.2/1.8)</td>
<td>0</td>
<td>902</td>
<td></td>
</tr>
<tr>
<td>Exon 8 p.S335C</td>
<td>2.4 (4.8/2.0)</td>
<td>2+</td>
<td>902</td>
<td></td>
</tr>
</tbody>
</table>

Bob T.Li et al, JCO 2018
Updated results of a phase 1 study of DS-8201a in HER2-expressing or -mutated advanced NSCLC

- DS-8201a was designed with the goal of improving critical attributes of an ADC

ADC, antibody drug conjugate.

Junji Tsurutani et al, WCLC 2018
Updated results of a phase 1 study of DS-8201a in HER2-expressing or -mutated advanced NSCLC

IHC by local laboratory testing.
E20, exon 20 insertion; EC, single base pair substitution at extracellular domain; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small cell lung cancer; NE, not examined or missing; TM, single base pair substitution in transmembrane domain.

Junji Tsurutani et al, WCLC 2018
## Efficacy Outcomes (Efficacy Evaluable Subjects)

Efficacy outcomes for HER2-expressing or HER2-mutated non-small cell lung cancer (NSCLC) are presented as follows:

<table>
<thead>
<tr>
<th></th>
<th>Confirmed ORR* (%) (n/N)</th>
<th>DCR, (%) (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-mutated NSCLC, N = 18</td>
<td><strong>58.8% (10/17)</strong></td>
<td><strong>83.3% (15/18)</strong></td>
<td><strong>9.9 (0.0+, 11.5)</strong></td>
<td><strong>1.4 (1.0, 4.2)</strong></td>
<td><strong>14.1 (0.9, 14.1)</strong></td>
</tr>
<tr>
<td>HER2-mutated NSCLC, n = 11</td>
<td><strong>72.7% (8/11)</strong></td>
<td><strong>100% (11/11)</strong></td>
<td><strong>11.5 (0.03+, 11.5)</strong></td>
<td><strong>1.4 (1.0, 4.2)</strong></td>
<td><strong>14.1 (4.0+, 14.1)</strong></td>
</tr>
</tbody>
</table>

Data cutoff, August 24, 2018.

*Confirmed response includes subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.

+ after value indicates censoring.

DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TTR, time to response.

Junji Tsurutani et al, WCLC 2018
Example CT Image from Responder to DS-8201a

- 23 years old
- Female
- Nonsmoker
- History of Type 1 Diabetes
- HER2 12 bp insertion in exon 20
- **January 2017**: presented with cough and SOB
  - Diagnosed with stage IV nonsquamous NSCLC
  - Carbo/Pem 1 cycle
- **February–June 2017**: switched to Carbo/Nab-paclitaxel due to LFT elevations
  - Best response SD
- **September–December 2017**: switched to Carbo/Pem due to progression
  - Four cycles
  - Best response SD
  - Last scan with slight increase in disease
  - Recommended HER2 targeted therapy; came to DFCI
- **February 2018**: started DS-8201a
  - Symptomatic with cough and DOE
  - Status: PR (confirmed)

Images courtesy of Dr. Pasi Jänne. Special thanks to Dr. Pasi Jänne and Dr. Ian Krop of DFCI.

bp, base pair; Carbo, carboplatin; CT, computed tomography; DFCI, Dana-Farber Cancer Institute; DOE, dyspnea on exertion; HER2, human epidermal growth factor 2; IV, intravenous; LFT, liver function test; Nab, nab-paclitaxel; NSCLC, non-small cell lung cancer; Pem, pemetrexed; PR, partial remission; SD, stable disease; SOB, shortness of breath.

Junji Tsurutani et al, WCLC 2018
Poziotinib is a selective (mut vs wt) inhibitor of EGFR and HER2 exon 20 mutations *in vitro*

**EGFR**

EGFR Ba/F3 Selectivity Index  
(N=20 cell lines)

**HER2**

MCF10A Selectivity Index  
(N=3 Cell lines)

Ratio to Poziotinib

<table>
<thead>
<tr>
<th></th>
<th>9.4</th>
<th>8.7</th>
<th>4.1</th>
<th>2.8</th>
<th>2.4</th>
<th>2.0</th>
</tr>
</thead>
</table>

Ratio to Poziotinib

<table>
<thead>
<tr>
<th></th>
<th>28.7</th>
<th>23.3</th>
<th>16.3</th>
<th>5.4</th>
<th>4.0</th>
<th>2.6</th>
</tr>
</thead>
</table>

JV Heymach, University of Texas MD Anderson Cancer Center, USA
A Phase II Trial of Poziotinib in EGFR and HER2 exon 20 Mutant Non-Small Cell Lung Cancer (NSCLC)

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC
(Evaluable patients n=44)

- Germline T790M mutation

**ORR (best response): 55%**

**ORR (confirmed): 43%**

Poziotinib efficacy in HER2 Exon 20 insertion mutant NSCLC
(All patients n=13)

Best response HER2
(Evaluable patients n=12)

**ORR: 50%**

Conclusions:

Encouraging activity has prompted a confirmatory, international, multicenter study in EGFR and HER2 exon 20 mutant NSCLC patients which is currently enrolling (NCT03318939) including a first-line cohort and development of a pan-tumor basket study.

Adapted from Heymach JV. OA 02.06 (WCLC 2018)
TRK fusions found in diverse cancer histologies

- Brain cancers (glioma, GBM, astrocytoma)
- Salivary (MASC)
- Thyroid cancer
- Lung cancer
- Secretory breast cancer
- Pancreatic Cholangiocarcinoma
- GIST
- Colon Melanoma
- Sarcoma (multiple)

- Gliomas
- Thyroid cancer
- Infantile fibrosarcoma
- Congenital nephroma
- Spitz nevi
- Sarcoma (multiple)

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Hyman ASCO 2017
**Entrectinib, first in class, antitumor activity in NTRK1/2/3 fusions**

<table>
<thead>
<tr>
<th>Fusion</th>
<th>Confirmed Responses (n)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK1/3</td>
<td>3/3</td>
<td>100%</td>
</tr>
<tr>
<td>ROS1</td>
<td>12/14</td>
<td>86%</td>
</tr>
</tbody>
</table>

A.Drilon et al, Can Disc 2017
TRK enrollment in STARTRK-2 has been consistent with the diffuse distribution pattern described in the literature

- Patients with TRK fusions enrolled across >15 different tumor types
- All of these patients were identified using next generation sequencing (NGS)

A. Drilon et al, Can Disc 2017
Larotrectinib (LOXO-101), a selective TRK inhibitor

Diversity of cancers treated - 17 unique types

- Peripheral nerve sheath tumor: 4%
- Sarcoma, NOS: 4%
- Myopericytoma: 4%
- Cholangiocarcinoma: 4%
- Spindle cell sarcoma: 5%
- GIST: 5%
- Melanoma: 7%
- Lung: 7%
- Colon: 7%
- Thyroid: 9%
- Infantile fibrosarcoma (IFS): 13%
- Inflammatory myofibroblastic kidney tumor: 2%
- Salivary gland: 22%
Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children

55 patients

ORR: 75% (95% CI, 61-85), independent review
ORR: 80% (95% CI, 67-90), investigator assessment

At 1 year, 71% of the responses ongoing
At 1 year, 55% of patients remained progression-free

A. Drilon et al, NEJM 2018
LOXO-195 to Address TRK Acquired Resistance

Larotrectinib (LOXO-101)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Fusion</th>
<th>Resistance mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Colorectal</td>
<td>LMNA-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>NSCLC</td>
<td>TPR-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>Sarcoma*</td>
<td>TPM3-NTRK1</td>
<td>TRKA G595R</td>
</tr>
<tr>
<td>IFS</td>
<td>ETV6-NTRK3</td>
<td>TRKC G623R</td>
</tr>
<tr>
<td>Cholangio*</td>
<td>LMNA-NTRK1</td>
<td>TRKA F589L* + GNAS Q227H</td>
</tr>
</tbody>
</table>

TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.

Hyman ASCO 2017, Drilon Can Disc 2017
A phase 1 study of the next-generation ALK/ROS1/TRK inhibitor ropotrectinib (TPX-0005) in patients with advanced ALK/ROS1/NTRK+ cancers (TRIDENT-1)
Presented Monday, June 4, 2018. Alexander E. Drilon (Abst 2513) 65 pts (28 ALK+, 29 ROS1+, and 8 NTRK+)

DS-6051b is an oral, small molecule receptor TKI with high affinity for ROS1 and NTRK kinases
First-in-human study of DS-6051b in patients (pts) with advanced solid tumors (AST) conducted in the US
Presented Monday, June 4, 2018. Kyriakos P. Papadopoulos (Abst 2514)
Stage IV NSCC: Molecular tests positive (ALK/BRAF/EGFR/ROS1)

- **ALK translocation** (refer to Figure 5)
  - Crizotinib [I, A; MCBS 4]
  - Alectinib [I, A; MCBS 4]
  - Ceritinib [I, B; MCBS 4]
  - Brigatinib [I, B]a

- **BRAF V600 mutation** (refer to Figure 7)
  - Dabrafenib/trametinib
    - [III, A; MCBS 2]

- **EGFR mutation** (refer to Figure 4)
  - Gefitinib [I, A]
  - Erlotinib [I, A]
  - +/- bevacizumab [II, B; MCBS 3]a
  - Afatinib [I, A]
  - Dacomitinib [I, A]b
  - Osimertinib [I, A]b
  - Gefitinib/carboplatin/pemetrexed [I, A]b

- **ROS1 translocation** (refer to Figure 6)
  - Crizotinib [III, A; MCBS 3]
In summary, promising new drugs for old or new targets...

1. Multidisciplinary discussion to determine optimal procedure for tissue procedure
2. Biopsy
3. Morphology
4. Review of patient and tumour data

**Molecular profiling**

- Integrated NGS-based assay to detect mutations, amplifications, and translocations

**Patient selection**

- EGFR
- ALK
- ROS1
- BRAF
- MET
- RET
- NTRK1/2/3
- HER2

**No actionable alterations**

**Treatment**

- Gefitinib, erlotinib, afatinib, dacomitinib, osimertinib
- Dabrafenib + trametinib
- Vemurafenib
- Crizotinib
- Ceritinib
- Lorlatinib
- Cabozantinib
- Entrectinib
- Ropotrectinib
- DS-6051b

- Crizotinib
- Cabozantinib
- Capmatinib
- Savolitinib
- Tepotinib
- Merestinib
- Merestinib
- Ponatinib
- Glesatinib

- Cabozantinib
- Vandetanib
- Sunitinib
- Lenvetanib
- Alectinib
- Ponatinib
- BLU-667
- LOXO-292
- NRG1
- ERBB3 inh

- Entrectinib
- Larotrectinib
- Cabozantinib
- Cabozantinib
- DS-6051b
- Ropotrectinib
- Trastuzumab
- TDM-1
- Neratinib+/- Temsirolimus
- Afatinib
- Dacomatinib
- Poziotinib
- XMT-1522
- TAK-788
- DS-8201a

Therapy switch/combination based on re-biopsies or liquid therapy

Chemotherapy

Or / and

immunotherapy

PD-L1, TMB

J. Maziere – ASCO Abst
THANK YOU!

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Laura MEZQUITA