Targeted therapy beyond EGFR/ALK
Focus on ROS1, RET, NTRK, BRAF, MET

Byoung Chul Cho, M.D., Ph.D.
DISCLOSURE

- Research funding: Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD

- Consulting role: Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD

- Stock ownership: TheraCanVac Inc
Potentially Actionable Oncogenic Drivers in Lung Adenocarcinoma

ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers

- Enriched in adenocarcinoma, typically in younger never or light smokers
- No overlap with other oncogenic drivers
- ROS1 and ALK kinase domains do not only share structure homology (>80% sequence identity in ATP-binding site), but also mutational hotspots and TKI sensitivity

Molecular Testing Guideline for ROS1 Fusion

**ESMO**

ROS1 testing should be systemically carried out in advanced non-squamous NSCLC. FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing. NGS is an emerging technology.

**CAP/IASLC/AMP**

ROS1 testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics. ROS1 IHC may be used as a screening test. However, positive IHC results should be confirmed by molecular or cytogenetic method.

**NCCN**

ROS1 rearrangement discovered prior to first-line systemic therapy

- Crizotinib\(^{in}\) (preferred) or Ceritinib\(^{in}\)
  - Progression

ROS1 rearrangement positive

ROS1 rearrangement discovered during first-line systemic therapy

- Complete planned systemic therapy, including maintenance therapy, or interrupt, followed by crizotinib (preferred) or ceritinib
  - Progression
Clinical detection of ROS1 fusions

- **ROS1 break-apart FISH** (positive if at least 15% split or isolated 3’ signals)
  - Used in the global crizotinib study
  - Challenges - technique and interpretation
- **IHC** (clone D4D6)
  - Various ROS1 staining patterns
  - Background staining (pneumocytes, alveolar macrophages, etc)
  - False positivity
- **NGS** (ArcherDx, Oncomine Dx, FoundationOne CDx)
- **RT-PCR** (AmoyDx)

All are imperfect assays!
Korean nationwide phase II study of ceritinib in ROS1+ NSCLC (KCSG-LU 13-08)

- Advanced NSCLC
- **ROS1 Fusion-positive confirmed by Abbott split-apart FISH (≥ 15% positive cells)**
- Age ≥ 20 years, PS 0-2
- At least one prior chemo
- N= 30 (Screen ~3,000)

Ceritinib 750 mg/day orally, once daily, until PD or unacceptable toxicity

Primary endpoint: ORR (RECIST v.1.1)

Some discordant cases Concordance rate 86.2%

Abbott FISH

Central Lab (Prof. Shim HS)

NGS IHC
Proposed diagnostic algorithm using ROS1 IHC

Subsequent FISH analysis is recommended for >75% tumor cell expression, intensity 2+ or 3+ or H-score >100

Shim HS. PlosOne 2017
Discordance between FISH and NGS

<table>
<thead>
<tr>
<th>Patient</th>
<th>FISH</th>
<th>IHC</th>
<th>RCS1 Fusion Variant</th>
<th>Best Overall Response</th>
<th>PFS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Positive</td>
<td>Positive</td>
<td>CD74-ROS1</td>
<td>PR</td>
<td>≈ 31.8</td>
</tr>
<tr>
<td>3</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>SD</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>CD34A2-ROS1</td>
<td>Positive</td>
<td>PR</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>PR</td>
<td>≈ 20.7</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>PR</td>
<td>≈ 20.6</td>
</tr>
<tr>
<td>19</td>
<td>Positive</td>
<td>Positive</td>
<td>EZR-ROS1</td>
<td>CR</td>
<td>6.01</td>
</tr>
<tr>
<td>20</td>
<td>Positive</td>
<td>Positive</td>
<td>EZR-ROS1</td>
<td>FR</td>
<td>≈ 17.3</td>
</tr>
<tr>
<td>21</td>
<td>Positive</td>
<td>Positive</td>
<td>EZR-ROS1</td>
<td>FR</td>
<td>≈ 16.4</td>
</tr>
<tr>
<td>22</td>
<td>Positive</td>
<td>Positive</td>
<td>EZR-ROS1</td>
<td>NA</td>
<td>0.25</td>
</tr>
<tr>
<td>23</td>
<td>Positive</td>
<td>Positive</td>
<td>CD74-ROS1</td>
<td>PR</td>
<td>≈ 14.2</td>
</tr>
<tr>
<td>27</td>
<td>Positive</td>
<td>Positive</td>
<td>EZR-ROS1</td>
<td>FR</td>
<td>13.6</td>
</tr>
<tr>
<td>29</td>
<td>Positive</td>
<td>Positive</td>
<td>SLC34A2-ROS1</td>
<td>PR</td>
<td>4.4</td>
</tr>
<tr>
<td>32</td>
<td>Positive</td>
<td>Positive</td>
<td>EZR-ROS1</td>
<td>FR</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; NA, not available; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Living in a Imperfect World

NGS, Foundation Medicine

Lim SM, Cho BC. JCO 2017
67/F Lung Adenocarcinoma, stage IV

Discordant Result:
ROS1 (+) by IHC & FISH
ROS1 (-) by Archer FusionPlex™ Assay

Repotrectinib
40 mg QD
Clinical ROS1 Inhibitors

Crizotinib
MW 450.34
Approved

Entrectinib
MW 560.65
Ph2

Lorlatinib
MW 406.42
Ph2

Ceritinib
MW 558.14
Ph2

Brigatinib
MW 584.10
Ph2

TPX-0005
(Repotrectinib)
Ph1
Phase 1 PROFILE 1001: Crizotinib for *ROS1*+ metastatic NSCLC

<table>
<thead>
<tr>
<th></th>
<th>2014: N = 50(^1)</th>
<th>2016 (latest results): N = 53(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%) (95% CI)</td>
<td>72 (58–84)</td>
<td>70 (56–82)</td>
</tr>
<tr>
<td>PFS (months) (95% CI)</td>
<td>19.2 (14.4–NR)</td>
<td>19.3 (14.8–NR)</td>
</tr>
<tr>
<td>DoR (months) (95% CI)</td>
<td>17.6 (14.5–NR)</td>
<td>NR (15.2–NR)</td>
</tr>
</tbody>
</table>

## Summary of ROS1+ crizotinib studies

The FDA and EMA approved crizotinib for the treatment of ROS1+ NSCLC (March and August 2016, respectively).

<table>
<thead>
<tr>
<th></th>
<th>PROFILE 1001</th>
<th>OxOnc</th>
<th>EUROS1</th>
<th>AcSé</th>
</tr>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective</td>
<td>Prospective</td>
<td>Retrospective</td>
<td>Prospective</td>
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<tr>
<td><strong>Number</strong></td>
<td>53</td>
<td>127</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Global (42% Asian)</td>
<td>East Asian (China, Japan, South Korea, Taiwan)</td>
<td>Europe</td>
<td>France</td>
</tr>
<tr>
<td><strong>ROS1 detection method</strong></td>
<td>Break-apart FISH</td>
<td>Amoy RT-PCR</td>
<td>Break-apart FISH</td>
<td>Break-apart FISH</td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>70%</td>
<td>71.7%</td>
<td>80%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>PFS (m)</strong></td>
<td>19.3m</td>
<td>15.9m</td>
<td>9.1m</td>
<td>9.1m</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(update WCLC 5.5m)</td>
<td></td>
</tr>
<tr>
<td><strong>mDoR (m)</strong></td>
<td>17.6m</td>
<td>19.7m</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Shaw AT. NEJM 2014; Mazieres J. JCO 2015; Wu YL. JCO 2018; Moro-Sibilot D. WCLC 2015, WCLC 2018
All ROS1+ Tumors Invariably Develop Acquired Resistance to Crizotinib

Gainor JF. JCO Precis Oncol. 2017

Patil T. JTO 2018
Activity of ROS1 Inhibitors against Crizotinib-resistant Mutations

<table>
<thead>
<tr>
<th>ALK</th>
<th>C1156Y</th>
<th>L1196M</th>
<th>G1202R</th>
<th>D1203N</th>
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<tr>
<td>WT</td>
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<td></td>
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<tr>
<td>G2032R</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>S1986F</td>
<td></td>
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<tr>
<td>S1986F</td>
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<td></td>
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<tr>
<td>D2033N</td>
<td></td>
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<tr>
<td>D2033N</td>
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<table>
<thead>
<tr>
<th>ROS1</th>
<th>S1986Y/F</th>
<th>L2026M</th>
<th>G2032R</th>
<th>D2033N</th>
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<tr>
<td>Crizotinib</td>
<td></td>
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<tr>
<td>Ceritinib</td>
<td></td>
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<tr>
<td>Lorlatinib</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Entrectinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repotrectinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Solvent-front”

Lin JJ. JTO 2017; Gainor JF. JCO Precis Oncol. 2017; Facchinetti F. CCR 2016
Ceritinib in \textit{ROS1+} NSCLC
(Korean Nationwide Phase II Study)

- 25% had brain metastasis at baseline
- iORR 25%, iDCR 63%

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>All ((n=32; 2) crizotinib-pretreated)</th>
<th>Crizotinib-naïve ((n=30))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>DoR, months ((95% CI))</td>
<td>18.4 (8.0, 18.4)</td>
<td></td>
</tr>
<tr>
<td>PFS, months ((95% CI))</td>
<td>10.0 (2.5-17.4)</td>
<td>20.7 (4.7, NE)</td>
</tr>
</tbody>
</table>

*Two crizotinib-pretreated pts showed PD to ceritinib

**PROFILE 1001 \((n=53)\)**
- ORR 70%
- mPFS 19.3 mo
(Shaw A, et al. ESMO 2016)

Lim SM, Cho BC. JCO 2017; https://www.nccn.org
Entrectinib (CNS-Active, ROS1/TRK/ALK Inhibitor) in ROS1+ NSCLC (ROS1+ crizotinib-naïve)

- ORR 77.4%
  - 73.9% CNS(+) vs 80.0% CNS(-)

- mPFS 19.0 months
  - 13.6m CNS(+) vs 26.3m CNS(-)

- intracranial ORR 55%
- intracranial mDOR 12.9 months

Doebele RC, Cho BC. WCLC 2018
### Lorlatinib (CNS-Active, ALK/ROS1 Inhibitor) in \textit{ROS1}+ NSCLC (ROS1+ with any prior treatment)

- 53% had brain metastasis at baseline
- 72% had received prior crizotinib

<table>
<thead>
<tr>
<th></th>
<th>EXP6 (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n/N (%) (95% CI)</strong></td>
<td>17/47 (36)</td>
</tr>
<tr>
<td></td>
<td>(23, 52)</td>
</tr>
<tr>
<td><strong>IC ORR, n/N (%) (95% CI)</strong></td>
<td>14/25 (56)</td>
</tr>
<tr>
<td></td>
<td>(35, 76)</td>
</tr>
<tr>
<td><strong>Median DOR, mo (95% CI)</strong></td>
<td>13.8 (11.1, NR)</td>
</tr>
<tr>
<td><strong>DOR ≥6 mo, n⁰/n (%)</strong></td>
<td>12/17 (71)</td>
</tr>
<tr>
<td><strong>Median PFS, mo (95% CI)</strong></td>
<td>9.6 (4.7, NR)</td>
</tr>
</tbody>
</table>

**Best Change From Baseline (%)**

- Complete response
- Partial response
- Stable disease
- Progressive disease (PD)
- Indeterminate

CI, confidence interval; DOR, duration of response; mo, months; NR, not reached

Solomon BJ. WCLC 2017
Lorlatinib is preclinically and clinically minimally effective against ROS1 G2032R Kinase Domain Mutation.

5 had SD with short duration (2.0, 9.6 mo).

Solomon BJ. ESMO 2018
Repotrectinib (TPX-0005, ROS1/ALK/TRK Inhibitor) in ROS1+ NSCLC

Drilon A, Ou SI, Cho BC, Shaw AT. Cancer Discov 2018
Repotrectinib is more potent than other ROS inhibitors against G2032R mutation.

YU1079, CD74-ROS1G2032R Crizotinib-resistant patient-derived cells

Yun MR
Efficacy of Repotrectinib in TKI-naïve and TKI-pretreated ROS1+ NSCLC

Lin JJ, Cho BC. WCLC 2018

TKI-naïve
cORR 80%
iORR 100%

TKI-pretreated

cORR 18%
iORR 25%

G2032R

SD  PR
Not all ROS1 patients treated equally?

Case 1
- Entrectinib
- PD to Ceritinib/crizotinib

Case 2
- Ceritinib
- PR to Repotrectinib

Case 3
- Crizotinib
- PD to Ceritinib
- PR to Cabozantinib
Suggested Approach to the Treatment of ROS1+ NSCLC

Lin JJ, Shaw AT. JTO 2017
The future?

How should we optimally sequence these ROS1 inhibitors?
Oncogenic RET Fusions in NSCLC

**RET**
- TM: Transmembrane domain
- TK domain
- E12

**KIF5B-RET**
- Kinesin motor
- Colled-coil
- TK domain
- E12

**KIF5B**
- Kinesin motor
- Colled-coil
- E15

**Ligand-independent homodimerization**

- PI3K/AKT
- RAS/MAPK
- JAK/STAT

**Cell survival**

**Proliferation**

**Migration**

**NSCLC 2%**
(younger, never or light smokers)

- Papillary and other thyroid cancers (10-20%)
- Pancreatic cancer (<1%)
- Salivary gland cancer (<1%)
- Spitz tumors (<1%)
- Colorectal cancer (<1%)
- Ovarian cancer (<1%)

Ferrara R. JTO 2017
Efficacy of Multikinase Inhibitors
Far less than expected…

**Vandetanib**
LURET, PhII, N=17
- ORR 47%, PFS 4.7 mo

**Vandetanib**
Korean, PhII, N=18
- ORR 18%, PFS 4.5 mo

**Vandetanib**
PhII, N=25
- ORR 28%, PFS 5.5 mo

**RXDX-105**
Phlb, N=31
- ORR 19%
Differential Activity of Multikinase Inhibitors by Upstream Partners

- Vandetanib¹: 8.3 months
- RXDX-105
- Cabozantinib: 7.5 months
- Vandetanib²
- Lenvatinib: 9.1 months, 3.6 months

### Anti-RET Multikinase Inhibitors IC50 and Major Targets

<table>
<thead>
<tr>
<th>Compound</th>
<th>Anti-RET IC50 (nM)</th>
<th>Principal Kinase Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib</td>
<td>100</td>
<td>VEGFR, EGFR, RET</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>5-20</td>
<td>VEGFR2, MET, AXL, c-KIT, FLT3, TIE2, RET</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>1.5</td>
<td>VEGFR1-3, FGFR1-4, PDGFRA, c-KIT, RET</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>15-150</td>
<td>VEGFR1-3, PDGFRB, c-KIT, FLT3, RET</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>220-1300</td>
<td>VEGFR1-3, PDGFRB, c-KIT, FLT3, RET, BRAF, c-RAF</td>
</tr>
<tr>
<td>Alectinib</td>
<td>4.8</td>
<td>ALK, LTK, CHEK2, FLT3, RET</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>25.8</td>
<td>BCR-ABL, FLT3, SRC, c-KIT, FGFR, VEGFR, PDGFR, RET</td>
</tr>
<tr>
<td>Dovitinib</td>
<td>20</td>
<td>PDGFRB, c-KIT, FGFRs, VEGFRs, FLT3, RET</td>
</tr>
<tr>
<td>Apatinib</td>
<td>13</td>
<td>VEGFR2, PDGFRB, SRC, c-KIT, RET</td>
</tr>
<tr>
<td>AD80</td>
<td>9</td>
<td>ERK, AKT, S6K, RET</td>
</tr>
<tr>
<td>Sitavatinib</td>
<td>44</td>
<td>VEGFR, MET, AXL, NTRK, DDR1-2, AXL, PDGFRA, KIT, FLT3, RET</td>
</tr>
</tbody>
</table>

**Different clinical activity**

**Higher toxicities (hypertension, rash, diarrhea...)**

Ferrara R. JTO 2017
LOXO-292 is a potent and selective RET inhibitor

**Kinome selectivity**
- Highly selective for RET

**Xenograft models**
- Multiple fusions/mutations/histologies

**CLIP1-RET** fusion NSCLC

**Baseline**

**Week4**

**LIBRETTO-001 Phase I**

**ORR 77% in NSCLC (n=38)**

**Minimum change in tumor size (%)**

**KIF5B**
- ORR, %
- 81%

**Non-KIF5B**
- ORR, %
- 82%

**Tumor type**
- NSCLC
- Thyroid
- Pancreatic

**RET fusion partner**
- KIF5B
- CCDC68
- CLIP1
- NCOA4
- ERCC1
- RUFY2
- JPH
- PRKAR1A

**Minimum change in target tumor size (%)**

**Prior multi-line therapy**
- Yes
- No

Drilon A. ASCO 2018
BLU-667 is Highly Potent, Selective RET Inhibitor

**Kinome selectivity**

<table>
<thead>
<tr>
<th>Protein</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; BLU-667</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT RET</td>
<td>More active than BLU-667</td>
<td>Less active than BLU-667</td>
</tr>
<tr>
<td>RET V904L</td>
<td>RXDX-105</td>
<td>Vandetanib</td>
</tr>
<tr>
<td>RET V804M</td>
<td>Calozaantinib</td>
<td></td>
</tr>
<tr>
<td>RET M918T</td>
<td></td>
<td></td>
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<tr>
<td>CCDC6 RET</td>
<td></td>
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<tr>
<td>VEGFR2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KIF5B-RET NSCLC**

Baseline vs First assessment (Month 2)

**Maximum Reduction from Baseline (%)**

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Evaluable Patients (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n, (%)</td>
</tr>
<tr>
<td>CR*</td>
<td>1 (3)</td>
</tr>
<tr>
<td>PR**</td>
<td>17 (43)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (50)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

C, prior chemotherapy; CR, complete response; I, prior immunotherapy; M, prior MKI therapy; MKI, multikinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease

Subbiah V. AACR 2018
**TRK fusions found in diverse cancer histologies**

- GBM (NTRK1 1%)
- Salivary MASC (NTRK3 ~100%)
- Thyroid cancer (NTRK1 11.8%, NTRK3 14.5%)
- Lung cancer (NTRK1 0.12-3.3%, NTRK2 0.02%, NTRK3 0.08%)
- Secretory breast cancer (NTRK3 92%)
- Cholangiocarcinoma (NTRK1 3.6%)
- Pediatric glioma (NTRK1/2/3 10%)
- Astrocytoma (NTRK2 3.1%)
- Fibrosarcoma (NTRK3 91–100%)
- Congenital nephroma (NTRK3 83–92%)

NTRK fusions occur in NSCLC across gender, age, smoking history and histology

Hyman ASCO 2017; Farago AF. JCO Precis Oncol 2018; Vaishnavi A. Cancer Discov 2014
TRK fusions in Lung Cancer

MPRIP-NTRK1 fusion

NTRK fusion frequency
0.23% (11/4872)

Vaishnavi A. Nature Med 2013; Farago AF. JCO Precis Oncol 2018
# TRK inhibitors in Clinical Trials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Company</th>
<th>Population</th>
<th>Disease</th>
<th>Phase</th>
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<tbody>
<tr>
<td>LOXO-101</td>
<td>NTRK1/2/3</td>
<td>Loxo Oncology</td>
<td>Pediatric</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>NTRK1/2/3, ALK, ROS1</td>
<td>Ignyta</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>II</td>
</tr>
<tr>
<td>LOXO-195</td>
<td>NTRK1/2/3</td>
<td>Loxo Oncology</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>I, II</td>
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<tr>
<td>TSR-011</td>
<td>NTRK1/2/3, ALK</td>
<td>Tesaro</td>
<td>Adult</td>
<td>Solid tumor Lymphoma</td>
<td>I</td>
</tr>
<tr>
<td>PLX-7486</td>
<td>NTRK1/2/3, CSF1R</td>
<td>Plexxikon</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>MGCD-516</td>
<td>NTRK1/2/3, KDR, MET, KIT, KDR,</td>
<td>Mirati Therapeutics</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>DS-6051b</td>
<td>NTRK1/2/3, ROS1</td>
<td>Daiichi Sankyo</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>DCC-2701</td>
<td>MET, TRK, VEGFR2, TIE2</td>
<td>Deciphera Pharmaceuticals</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>NTRK2, RET, KIT, FLT3, MET, KDR,</td>
<td>Exelixis</td>
<td>Adult</td>
<td>NSCLC</td>
<td>II</td>
</tr>
<tr>
<td>Merestinib</td>
<td>NTRK1/2/3, MET, AXL, ROS1, MKNKI</td>
<td>Eli Lilly</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>II</td>
</tr>
</tbody>
</table>
Entrectinib (RXDX-101), a CNS-active Pan-TRK, ALK and ROS1 inhibitor

25 TKI-naïve patients in ALKA-372-001 and STARTRK-1

- Intracranial ORR 63% (5/8)
- CR in SQSTM1-NTRK1 rearranged NSCLC
Larotrectinib (LOXO-101), a Selective TRK Inhibitor

High potency against TRKA, TRKB and TRKC
$IC_{50} = 5–11 \text{ nM}$ in cellular assays

**Adult phase 1**
- Age $\geq 18$ years
- Advanced solid tumors

**Pediatric phase 1/2**
- Age $\leq 21$ years
- Advanced solid tumors

**Adult/adolescent Basket**
- Age $\geq 12$ years
- Advanced solid tumors

$N=55$
Patients harboring $NTRK$ gene fusions

- Patients with TRK fusions enrolled across 17 unique cancer types
- TRK fusions were identified using NGS and FISH

Diversity of Cancers treated - 17 unique types (n=55)
Efficacy of Larotrectinib in TRK Fusion+ Cancers (Age- and Tumor-agonistic)

55 patients

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

Drilon A. NEJM 2018
Resistance to TRK inhibitors eventually occurs

**Entrectinib**

- **Solvent-front**
  - TRKA G595R, TRKC G623R

**Larotrectinib**

- **Gatekeeper**
  - TRKA F589L
- **Activation loop**
  - TRKA G667S, TRKC G696A

**Kinase domain mutations**
Repotrectinib and LOXO-195 to Address TRK Solvent-Front Mutations

**TRKC G623R**

**TRKA G595R**

**LMNA-NTRK1 G595R**

Colorectal cancer

**ETV6-NTRK3 G623E**

MASC

Drilon A. Cancer Discov 2017; Drilon A. Cancer Discov 2018
Chasing TRK fusion

- Larotrectinib
- Entrectinib
- (FDA approval pending)

- DS605-1b
- Merestinib
- Repotrectinib
- Foretinib
- LOXO-195
**BRAF Mutation**

- Ser-Thr kinase linking RAS GTPase to downstream family of MAPK family
- Mostly adenoCa (1-3%), ~50% V600E
- V600E mutation was more prevalent in current or former smokers\(^1\) (an equal distribution in never smokers in a study by Kinno T et al\(^3\))
- V600E is associated with aggressive histotype (micropapillary features) & poor survival\(^2\)
- **The fourth actionable genomic biomarker in metastatic NSCLC**

\(^1\)Paik PK. JCO 2011; \(^2\)Marchetti A. JCO 2011; \(^3\)Kinno T. Ann Oncol 2013
Study design: Phase II study BRF113928

Stage IV NSCLC
BRAF V600E
ECOG 0-2
Prior Tx

Cohort A:
dabrafenib: 150 mg BID
(n = 84)

Cohort B:
dabrafenib: 150 mg BID +
trametinib: 2 mg QD
(n = 59)

Cohort C:
dabrafenib: 150 mg BID +
trametinib: 2 mg QD
(n=34)

Stage IV NSCLC
BRAF V600E
ECOG 0-2
No Prior Tx

ORR 33%, mPFS 5.5 mo
(Lancet Oncol 2016)

Non-randomized

Non-randomized

Non-randomized

Dabrafenib in patients with BRAF<sup>V600E</sup>-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

Dabrafenib plus trametinib in patients with previously treated BRAF<sup>V600E</sup>-mutant metastatic non-small-cell lung cancer: an open-label, multicentre phase 2 trial

Lancet Oncol 2016

Lancet Oncol 2017
Rationale for Dual MAPK Pathway Inhibition

Dabrafenib

Reversible, small molecule BRAF inhibitor
BRAF V600E: IC$_{50}$ 0.65 nM

Trametinib

Reversible, small molecule MEK1 and MEK2 allosteric inhibitor
MEK1 and MEK2: IC$_{50}$ 0.7 and 0.9 nM

Loss of Negative Feedback

- RAS
- CRAF
- MEK
- ERK
- RAS$^{mut}$
- MEK$^{mut}$
- COT
Dabrafenib + trametinib provided a greater clinical activity compared with dabrafenib monotherapy for patients with BRAF V600E–mutant NSCLC

<table>
<thead>
<tr>
<th>Based on Investigator Assessment</th>
<th>Previously treated(^1) (n = 57)</th>
<th>Previously untreated(^2) (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI), %</td>
<td>63 (49-76)</td>
<td>64 (46-79)</td>
</tr>
<tr>
<td>Disease control rate (95% CI), %</td>
<td>79 (66-87)</td>
<td>75 (58-88)</td>
</tr>
<tr>
<td>PFS, median (95% CI), mo</td>
<td>9.7 (6.9-19.6)</td>
<td>10.9 (7.0-16.6)</td>
</tr>
<tr>
<td>DOR, median (95% CI), mo</td>
<td>9.0 (6.9-18.3)(^a)</td>
<td>10.4 (8.3-17.9)</td>
</tr>
</tbody>
</table>

MET aberrations in Lung Cancer

MET Overexpression 25-75%
MET Amplification 5-25%
MET Exon14 skipping 3%

MET as a Codriver

MET as a Primary Driver

Drilon A. JTO 2016
MET Amplification as a Codriver in NSCLC

- Frequency 5-25% for 1st G vs. unknown for 3rd G EGFR TKI
- Coupling of MET to HER3 leads to sustained activation of PI3K/AKT signaling
- Clinically meaningful MET amplification vs. poysomy?
- Standardization of screening methods (FISH, NGS..)?

MET exon 14 skipping represents a unique subset of NSCLC

- Significantly older than EGFR/KRAS mutant patients (~60% smoker)
- Occur predominantly in adenocarcinoma; enriched in sarcomatoid carcinoma (~20%)
- Up to 20% with concurrent high-level MET amplification
- Mutually exclusive with other oncogenic drivers (EGFR/KRAS/ERBB2)
- Diagnosis: DNA-based NGS

Awad MM. JCO 2016; Liu SY. JTO 2016; Liu X. JCO 2016
<table>
<thead>
<tr>
<th>Compound</th>
<th>Modality</th>
<th>Target(s)</th>
<th>Company</th>
<th>Cancer Type</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilotumumab (AMG 102)</td>
<td>Antibody</td>
<td>HGF</td>
<td>Amgen</td>
<td>Gastric, lung, colon, brain, ovary, renal</td>
<td>2/3</td>
</tr>
<tr>
<td>Ficlatuzumab (AV-299)</td>
<td>Antibody</td>
<td>HGF</td>
<td>AVEO Pharmaceuticals</td>
<td>Lung</td>
<td>1/2</td>
</tr>
<tr>
<td>HuL2G7 (TAK701)</td>
<td>Antibody</td>
<td>HGF</td>
<td>Galaxy Biotech</td>
<td>Solid tumors</td>
<td>1</td>
</tr>
<tr>
<td>Onartuzumab (MetMab)</td>
<td>Antibody</td>
<td>MET</td>
<td>Genentech/Roche</td>
<td>Lung, colon, breast</td>
<td>2/3</td>
</tr>
<tr>
<td>AMG 337</td>
<td>Small molecule</td>
<td>MET</td>
<td>Amgen</td>
<td>Solid tumors</td>
<td>½</td>
</tr>
<tr>
<td>Capmatinib (INC 280)</td>
<td>Small molecule</td>
<td>MET</td>
<td>Novartis/Incyte</td>
<td>Renal, brain, liver, lung, melanoma, head and neck</td>
<td>2</td>
</tr>
<tr>
<td>Tepotinib (EMD 1214063)</td>
<td>Small molecule</td>
<td>MET</td>
<td>Merck</td>
<td>Lung, liver</td>
<td>2</td>
</tr>
<tr>
<td>Savolitinib (AZD6094)</td>
<td>Small molecule</td>
<td>MET</td>
<td>AstraZeneca/Chimedin</td>
<td>Lung, renal, gastric</td>
<td>1</td>
</tr>
<tr>
<td>Crizotinib (PF-2341066)</td>
<td>Small molecule</td>
<td>MET, ALK</td>
<td>Pfizer</td>
<td>Lung, lymphoma</td>
<td>2/3</td>
</tr>
<tr>
<td>Cabozantinib (XL 184)</td>
<td>Small molecule</td>
<td>MET, VEGFR2, RET, KIT, AXL, FLT3</td>
<td>Exelixis/Bristol-Myers Squibb</td>
<td>Lung</td>
<td>2/3</td>
</tr>
</tbody>
</table>

*Yilong Zhang. Biomedicines 2015*
# Efficacy of Crizotinib and Capmatinib in MET amplified Lung Cancer

## Crizotinib
**Camidge DR. ASCO 2018**

<table>
<thead>
<tr>
<th>MET Level</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MET (≥1.8-≤2.2) (n=3)</td>
<td>33.3% (0.8, 90.6)</td>
<td>1.8 mo (0.8, 14.0)</td>
</tr>
<tr>
<td>Intermediate (&gt;2.2-&lt;4.0) (n=14)</td>
<td>14.3% (1.8, 42.8)</td>
<td>1.9 mo (1.3, 5.5)</td>
</tr>
<tr>
<td>High (≥4.0) (n=20)</td>
<td>40% (19.1, 63.9)</td>
<td>6.7 mo (3.4, 7.4)</td>
</tr>
</tbody>
</table>

## Capmatinib
**Schuler M. ASCO 2016**

<table>
<thead>
<tr>
<th>GCN Level</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCN &lt;4 (n=17)</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>GCN ≥4 and &lt;6 (n=12)</td>
<td>17.0% (2.1, 48.4)</td>
<td>-</td>
</tr>
<tr>
<td>GCN ≥6 (n=15)</td>
<td>70% (21.3, 73.4)</td>
<td>7.4 mo (3.84, 22.11)</td>
</tr>
</tbody>
</table>
Response to Combined EGFR and MET Inhibition in MET-amplified EGFR mutant NSCLC

**Capmatinib (INC280) + Gefitinib**
- Phase I/II
- EGFRm, MET-amplified NSCLC with acquired resistance to EGFR-TKI

**Savolitinib + Osimertinib**
- TATTON Phase Ib
- EGFRm, MET-amplified NSCLC with acquired resistance to EGFR-TKI
- MET diagnostic criteria: MET gene copy ≥5 or MET/CEP7 ratio ≥2
- ORR 33% in pts previously treated with 3rd G EGFR TKI
- ORR 55% (T790M+) and 61% (T790M-) in pts without prior 3rd G EGFR TKI

Wu YL, et al ASCO 2016

Ahn MJ, et al WCLC 2017
Patient Selection Determines Outcome!

**MET 2+/3+ by IHC or MET GCN ≥5 and/or MET/CEP7 ratio ≥2**

**MET 3+ by IHC**

**ORR 68.4% vs. 33.3%**

**Wu YL. ESMO 2018**
Efficacy of Crizotinib and Tepotinib in MET exon 14 skipping

PROFILE 1001 (n=69)
ORR 57.5% (95% CI: 40.9, 73.0)
DoR 14.3 mo (95% CI: 3.7, ND)

VISION Ph II (n=69)
ORR 32% (95% CI: 21, 45)
DoR 9.1 mo (95% CI: 6.4, 12.7)

Drilon A. WCLC 2018; Felip E. WCLC 2018
Capmatinib (INC280)

**Cohort 5B 2/3L (N=69)**

- **IC\textsubscript{50}** 0.6 nM for METex14
- ORR 39.1\% (27.6-51.6)

**Cohort 4 1L (N=25)**

- ORR 72.0\% (50.6-87.9)

Wolf J. ESMO 2018
## Comparison of Common Adverse Events

<table>
<thead>
<tr>
<th>All grade (Grade ≥3), %</th>
<th>Crizotinib (n=30)</th>
<th>Tepotinib (n=46)</th>
<th>Capmatinib (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>47 (3)</td>
<td>58.7 (4.3)</td>
<td>40.4 (6.3)</td>
</tr>
<tr>
<td>Vision disorder</td>
<td>40 (0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (0)</td>
<td>21.7 (0)</td>
<td>32.8 (1.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30 (0)</td>
<td>37.0 (2.2)</td>
<td>11.6 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (0)</td>
<td>-</td>
<td>19.2 (2.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (0)</td>
<td>15.2 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>23 (1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>13 (0)</td>
<td>17.4 (2.2)</td>
<td>13.2 (3.3)</td>
</tr>
<tr>
<td>Blood Cr elevation</td>
<td>-</td>
<td>21.7 (0)</td>
<td>19.2 (0)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>10 (3)</td>
<td>10.9 (4.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

Drilon A. WCLC 2016; Felip E. WCLC 2018; Wolf J. ESMO 2018
Poor outcome to ICI in MET ex14 altered NSCLCs

Proportion of never-smokers ranges from 8% to 36%\(^1-4\)

\(\text{PD-L1, Clone E1L3N assay (n=111)}\)

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>0%</th>
<th>1-49%</th>
<th>≥50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>41 (37)</td>
<td>24 (22)</td>
<td>46 (41)</td>
</tr>
</tbody>
</table>

ORR 17%

\(^1\text{Sabari JK. Ann Oncol 2018; }^2\text{Liu JY. JTO 2016; }^3\text{Liu X. JCO 2016; }^4\text{Awad MM. JCO 2016;}\)
ESMO Biomarker Guidelines

**ROS1 rearrangement**

ROS1 testing should be systemically carried out in advanced non-squamous NSCLC [A]. FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing. NGS is an emerging technology.

**BRAF mutation**

BRAF mutation testing should be systemically analyzed in advanced non-squamous NSCLC [A]. Any adequately sensitive method is valid.

**MET alteration**

Targeting MET amplification/METex14 variants is not routinely recommended [C].

**RET rearrangement**

Targeting RET fusions is not recommended [C].

**NTRK rearrangement**

Targeting NTRK fusions is not recommended [C].

Planchard D. Ann Oncol 2018
ESMO Clinical Practice Guideline
Too many drugs for so small targets!

<table>
<thead>
<tr>
<th>Target</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS1 fusion (1-4%)</td>
<td>Crizotinib [A], Ceritinib, Brigatinib, Entrectinib, Lorlatinib, TPX0005</td>
</tr>
<tr>
<td>RET fusion (1-2%)</td>
<td>Cabozantinib [C], Vandetanib [C], Sunitinib [C], Sorafenib [C], Alectinib [C], Lenvatinib [C], Nintedanib [C], Ponatinib [C], Regorafenib [C], BLU-667 [C], LOXO-292 [C]</td>
</tr>
<tr>
<td>NTRK1-3 fusion (&lt;1%)</td>
<td>Larotrectinib (LOXO-101) [C], Entrectinib (RXDX-101) [C]</td>
</tr>
<tr>
<td>MET ex14 mutation (3-4%)</td>
<td>Crizotinib [C]</td>
</tr>
<tr>
<td>BRAF V600E (1-2%)</td>
<td>Dabrafenib/Trametinib [A]</td>
</tr>
</tbody>
</table>

Grades of recommendation
A: Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
C: Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages, optional

Planchard D. Ann Oncol 2018