Targeted therapy beyond EGFR/ALK Focus on RET, NTRK, 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, Abbvie, Medpacto, GIInnovation, Eli Lilly
- Consulting role: Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, Janssen
- Stock ownership: TheraCanVac Inc, Gencurix Inc, Bridgebio therapeutics, KANAPH Therapeutic Inc
- Scientific Advisory Board: KANAPH Therapeutic Inc
- Royalty: Champions Oncology
Potentially Actionable Oncogenic Drivers in Lung Adenocarcinoma

- **EGFR** sensitizing 19.4%
- **EGFR** T790M 5.5%
- **EGFR** exon20 2.1%
- **EGFR** WT amp 1.0%
- **ALK** fusion 3.8%
- **ROS1** fusion 2.6%
- **RET** fusion 1.7%
- **BRAF** V600E 2.1%
- **MET** splice 3.0%
- **MET** amp 1.4%
- **ERBB2** amp 1.4%
- **BRCA1/2** loss 1.3%
- **TSC1/2** loss 0.7%
- **NRAS** 1.2%
- **PIK3CA** 2.0%
- **MAP2K1** 0.7%
- **ERBB2** mut 2.3%

Other drivers 2.9%
- **PTEN** loss 0.7%
- **CDKN2A** loss 1.9%
- **BRAF** non-V600E 1.3%
- **NF1** loss 1.9%

No mutations 1.2%
UMD 12.0%
Oncogenic RET Fusions in NSCLC

**RET**

- TM
- TK domain

**KIF5B-RET**

- Kinesin motor
- Colled-coil
- TK domain

**KIF5B**

- Kinesin motor
- Colled-coil

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

Cabozantinib
PhII, N=25
ORR 28%, PFS 5.5 mo

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

### 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>220-1300</td>
<td>VEGFR1-3, PDGFRB, c-KIT, FLT3, RET</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>15-150</td>
<td>VEGFR1-3, PDGFB, 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>Sitravatinib</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
Frequency of Brain Metastasis and Multikinase Inhibitor Outcomes in RET-rearranged Lung Cancer

Intracranial ORR 18%

Drilon A, et al. JTO 2018
Selpercatinib* (LOXO-292) is a potent and selective RET Inhibitor

Kinome selectivity
Highly selective for RET

Xenograft models
Multiple fusions/mutations/histologies

Orthotopic brain model
CCDC6-RET orthotopic brain PDX

Change in tumor size (%)

Vehicle
Cabo
LOXO-292

Survival (%)

Day

Tumor models
- KIF5B-RET (PDX-NSCLC)
- CCDC6-RET (PDX-CRCA)
- CCDC6-RET-V804M (PDX-CRCA)
- KIF5B-RET (NIH-3T3)
- KIF5B-RET-V804M (NIH-3T3)
- RET C634W (TT cell line-MTC)
- CCDC6-RET (LC-2/ad cell line-NSCLC)

Treatments
- Vehicle
- LOXO-292 30 mg/kg BID → Day 52 → 3 mg/kg BID
- Ponatinib 20 mg/kg QD → Day 52 → 2 mg/kg QD

*PINN, pending USAN approval.
Efficacy of Selpercatinib in RET-altered patients with prior platinum chemotherapy (n=105)

Investigator response assessments as of June 17th, 2019. 5 patients not shown in waterfall plot: 3 discontinued prior to any post-baseline imaging assessments, 1 did not have measurable disease at baseline, and 1 deemed not evaluable on study by the Investigator. NE—Not evaluable, n=5 patients: 3 discontinued prior to any post-baseline imaging assessments, 1 deemed not evaluable on study by the Investigator, and 1 discontinued after a single post-baseline imaging assessment showing SD, less than 6 weeks after starting treatment. Total % may be different than the sum of the individual due to rounding. *N=105 dataset includes 2 unconfirmed PRs awaiting confirmatory response assessments. **Patients with CNS target lesions at baseline.

Prior therapy
- Chemo
- ICI
- MKI

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=105)</th>
<th>CNS** (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>68% (58%–76%)*</td>
<td>91% (59%–100%)</td>
</tr>
<tr>
<td>CR</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>66%</td>
<td>73%</td>
</tr>
<tr>
<td>SD</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>PD</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
**Durability of Selpercatinib Efficacy**

**Duration of response**
- Median DOR: 20.3 months* (95% CI: 13.8–24.0)
- Number of events: 16/69
- Median follow-up: 8.0 months

**Progression-free survival**
- Median PFS: 18.4 months* (95% CI: 12.9–24.9)
- Number of events: 33/105
- Median follow-up: 9.6 months

- Of 28 patients in the PAS that progressed, 23 continued treatment post-progression, for 0.2–16.4+ months
- ORR, DOR, PFS similar regardless of prior therapy (e.g. anti-PD-1/PD-L1, MKIs)

Data cut-off: June 17th, 2019. Shading in PAS Kaplan-Meier curves indicates the 95% confidence band. *Medians are not statistically stable due to a low number of events.
# Selpercatinib Safety Profile

### LIBRETTO-001 Safety Database, n=531

<table>
<thead>
<tr>
<th>Treatment-emergent AEs (≥15% overall)</th>
<th>Treatment-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>29%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>17%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
</tr>
<tr>
<td>Constipation</td>
<td>19%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>14%</td>
</tr>
</tbody>
</table>

Data cut-off: June 17th, 2019. AE — adverse event; Total % for any given AE may be different than the sum of the individual grades, due to rounding.
Pralsetinib (BLU-667) Potently and Selectively Inhibits RET Alterations and Resistance Mutants

Pralsetinib (BLU-667) : High kinome selectivity for RET

- 90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

Pralsetinib (BLU-667) vs pharmacologically relevant kinases:

- 90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

### In vivo models of implanted, engineered Ba/F3 cells

| Pralsetinib (BLU-667) cellular activity in KIF5B-RET |
|-----------------|-----------------|-----------------|-----------------|
| Pralsetinib (BLU-667) | 10.1 nM (1x) | 8.1 nM (0.8x) | 14.1 nM (1.4x) | 8.1 nM (0.8x) |

In vivo models of implanted, engineered Ba/F3 cells

---

2. Blueprint internal data.

---

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines).

2. Blueprint internal data.

---

Erica K. Evans, et al. the International Association for the Study of Lung Cancer 2019
Pralsetinib (BLU-667) Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC

Pralsetinib (BLU-667) Starting Dose 400 mg QD

Maximum % Reduction from Baseline Sum of Diameters of Target Lesions

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All (N=48)</th>
<th>Prior Platinum (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>58% (43–72)</td>
<td>60% (42–76)</td>
</tr>
<tr>
<td>CR*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR*</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>SD</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td>96% (86–99)</td>
<td>100% (90–100)</td>
</tr>
</tbody>
</table>

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

CI, confidence interval; CR, complete response; DCR, disease control rate (best response of SD or better); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19. Response-evaluable population includes patients with measurable disease at baseline and ≥1 evaluable post-treatment disease assessment, and excludes 4 patients who previously received >1 cycle of a selective RET inhibitor.

Pralsetinib (BLU-667) Demonstrated Anti-tumor Activity in Patients with CNS Involvement

KIF5B-RET NSCLC

Baseline
First assessment (Month 2)

- CNS involvement
- No CNS involvement
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>
</tr>
</thead>
<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>
</tr>
<tr>
<td>TSR-011</td>
<td>NTRK1/2/3, ALK</td>
<td>Tesaro</td>
<td>Adult</td>
<td>Solid tumor, Lymphoma</td>
<td>I, II</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, PDGFR, DDR2</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, FLT1, FLT4, AXL</td>
<td>Exelisix</td>
<td>Adult</td>
<td>NSCLC</td>
<td>II</td>
</tr>
<tr>
<td>Merestinib</td>
<td>NTRK1/2/3, MET, AXL, ROS1, MKNK1, MKNK2, FLR3, TEK, DDR1, DDR2</td>
<td>Eli Lilly</td>
<td>Adult</td>
<td>Solid tumor</td>
<td>II</td>
</tr>
</tbody>
</table>
Entrectinib preclinical data show broad pan-tumour TRK inhibition and antitumour activity, including CNS.

KM12-Luciferase (TPM3-NTRK1; CRC)

Subcutaneous

Intracranial

Entrectinib (mg/kg, qd)

Day

Veh 10 30

Body weight change (%)

Tumor volume (mm³)

Days after grouping

Percent survival (%)

Days after grouping

Demetri GD. ESMO 2018
Efficacy of Entrectinib in NTRK fusion-positive Solid Tumors (STARTRK-2, STARTRK-1² & ALKA-372-001²)

Demetri GD. ESMO 2018
Entrectinib activity in \textit{NTRK} fusion-positive solid tumours: Duration of response, PFS and OS

Demetri GD. ESMO 2018
Larotrectinib (LOXO-101), a Selective TRK Inhibitor

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

- **Adult phase 1**
  - Age ≥18 years
  - Advanced solid tumors

- **Pediatric phase 1/2**
  - Age ≤21 years
  - Advanced solid tumors

- **Adult/adolescent Basket**
  - Age ≥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)

- Lung: 7% (N=4)
- Salivary gland: 22%
- Infantile fibrosarcoma (IFS): 13%
- Thyroid: 9%
- Colon: 7%
- Melanoma: 7%
- GIST: 5%
- Spindle cell sarcoma: 5%
- Myopericytoma: 4%
- Cholangiocarcinoma: 4%
- Sarcoma, NOS: 4%
- Peripheral nerve sheath tumor: 4%
- Inflammatory myofibroblastic kidney tumor: 2%
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**

- TRKA G595R, TRKC G623R

**Larotrectinib**

- TRKA F589L
- TRKA G667S, TRKC G696A

**Kinase domain mutations**

- **Solvent-front**
  - TRKA G595R, TRKC G623R
- **Gatekeeper**
  - TRKA F589L
- **Activation loop**
  - TRKA G667S, TRKC G696A
Repotrectinib and LOXO-195 to Address TRK Solvent-Front Mutations

ETV6-NTRK3<sup>G623E</sup> MASC

LMNA-NTRK1<sup>G595R</sup> Colorectal cancer

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

Larotrectinib
Entrectinib
(FDA approval)

DS605-1b
Merestinib

Repotrectinib

Foretinib

LOXO-195
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
## MET inhibitors in Clinical Trials

<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>½대</td>
</tr>
<tr>
<td>Capmatinib (INC 280)</td>
<td>Small molecule</td>
<td>MET</td>
<td>Novartis/Icyte</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/Chimed</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>
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 (mo)</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 (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 (1.3, 5.5)</td>
</tr>
<tr>
<td>High (≥4.0) (n=20)</td>
<td>40% (19.1, 63.9)</td>
<td>6.7 (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 (mo)</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 (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**

ORR 45.2% vs. 33.3%

**MET 3+ by IHC**

ORR 68.4% vs. 33.3%

**MET GCN ≥5 and/or MET/CEP7 ratio ≥2**

ORR 66.7% vs. 42.9%

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

PROFILE 1001 (n=69)

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

DoR 9.1 mo (95% CI: 6.4, 12.7)

VISION Ph II (n=69)

ORR 57.5% (95% CI: 40.9, 73.0)

DoR 14.3 mo (95% CI: 3.7, ND)

29 May 2018
FDA Breakthrough Therapy Designation

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

**IC$_{50}$ 0.6 nM for METex14**

**Cohort 5B 1L (N=28)**
- ORR 67.9% (47.6, 84.1)

**Cohort 4 2/3L (N=69)**
- ORR 40.6% (28.9, 53.1)
## 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%  

**Table: 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>

**Graphs:**
- Mutations per million bases (Mutations/MB)
  - METex14 (n=78)
  - NSCLC (n=1769)

**Legend:**
- PD
- SD
- PR

**Change from baseline (%)**
- PD
- SD
- PR

**Statistics:**
- **ORR 17%**
- **P < 0.001**

References:
## ESMO Clinical Practice Guideline

### Too many drugs for so small targets!

<table>
<thead>
<tr>
<th>RET fusion (1-2%)</th>
<th>FDA New Drug Application submission planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib [C], Vandetanib [C], Alectinib [C], Lenvatinib [C], Nintedanib [C], Ponatinib [C], Regorafenib [C], BLU-667 [C], LOXO-292</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NTRK1-3 fusion (&lt;1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larotrectinib(VITRAKVI), Entrectinib (ROZLYTREK)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MET ex14 mutation (3-4 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib [C], Capmatinib (INC280), Tepotinib</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

---

Modified from Planchard D. Ann Oncol 2018
LOXO-292 is a potent and selective RET inhibitor

LIBRETTO-001 Phase I

ORR 77% in NSCLC (n=38)

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>NSCLC</th>
<th>Thyroid</th>
<th>Pancreatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum change in tumor size (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KIF5B Non-KIF5B

ORR, % 81% 82%

CLIP1-RET fusion NSCLC

Baseline

Week4
BLU-667 (Pralsetinib) is Highly Potent, Selective RET Inhibitor

Kinome selectivity

KIF5B RET NSCLC

BLU-667 IC_{50} vs. WT RET Kinase Panel

Baseline

First assessment (Month 2)

Maximum Reduction from Baseline (%)

Best Response | Evaluable Patients (N=40) n, (%)
--- | ---
CR* | 1 (3)
PR** | 17 (43)
SD | 20 (50)
PD | 2 (5)

Non-small cell lung cancer
Medullary thyroid cancer
Papillary thyroid cancer

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
FDA approves larotrectinib for solid tumors with NTRK gene fusions

On November 26, 2018, the Food and Drug Administration granted accelerated approval to larotrectinib (VITRAKVI, Loxo Oncology Inc. and Bayer) for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

This is the second tissue-agnostic FDA approval for the treatment of cancer.

Approval was based on data from three multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH). NTRK gene fusions were inferred in three pediatric patients with infantile fibrosarcoma who had a documented ETV6 translocation by FISH. The major efficacy outcome measures were overall response rate (ORR) and response duration, as determined by a blinded independent review committee according to RECIST 1.1.

Efficacy was evaluated in the first 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion enrolled across the three trials. All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Twelve patients were less than 18 years of age. A total of 12 cancer types were represented, with the most common being salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%).

FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC

On August 15, 2019, the Food and Drug Administration granted accelerated approval to entrectinib (ROZLYTREK, Genentech Inc.) for adults and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.

Today, FDA also approved entrectinib for adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.

Efficacy in NTRK-positive tumors was investigated in 54 adult patients who received entrectinib at various doses and schedules in one of three multicenter, single-arm, clinical trials: ALKA, STARTTRK-1 (NCT02097810) and STARTTRK-2 (NCT02568267); 94% received entrectinib 600 mg orally once daily. Identification of positive NTRK gene fusion status was determined in local laboratories or a central laboratory using nucleic acid-based tests prior to enrollment.

Among 54 adult patients, the overall response rate as determined by independent review was 57% (95% CI: 43, 71). Response duration was 6 months or longer for 68% of patients and 12 months or longer for 45% of patients. The most common cancers were sarcoma, NSCLC, mammary analogue secretory carcinoma, breast, thyroid, and colorectal.

Efficacy in ROS1-positive metastatic NSCLC was investigated in 51 adult patients who received entrectinib at various doses and schedules in the same three trials; 90% received entrectinib 600 mg orally once daily. The overall response rate was 78% (95% CI: 65, 89) and response duration was 12 months or longer for 55% of patients.