Are there new targets in advanced NSCLC?

New targets relevant after the era of EGFR and ALK

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Disclosures

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Evolution of cancer treatment

Nowadays

Clinical Oncology → Pathologic Oncology → Molecular Oncology

Disease guided approach → Pathologic guided approach → Molecular approach

Few therapeutic options:
- Surgery
- Radiotherapy
- Chemotherapy

Increased therapeutic options allows specific treatments for different tumor types

Targeted agents that work in specific molecular alterations:
- Broad knowledge of molecular tumor biology
- Development of molecular analysis
Evolution of cancer treatment

Reclassification of disease
- Cancer genome atlas
- Pangenomics

Technology development and genomics
- Multiplexing
- Next Generation Sequencing

Change in paradigm of biomarker-drug development
- Clinical trials in small p populations

New clinical trials in Personalized medicine

Organisers:
- IASLC
- ESMO

Partners:
- ESTRO
Targetable oncogenes in lung ADC

- Unknown ≈ 50%
- KRAS 26.9%
- EGFR 9.4%
- ALK 4%
- MET 4%
- RET 1.9%
- ROS1 1.7%
- BRAF 1.6%
- HER2 0.9%
- PIK3CA 2.6%

Minuti Exp Opin Biol Ther 13

15-18 April 2015, Geneva, Switzerland
97% of mutations mutually exclusive

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</table>

Number of patients with variants in indicated combination of genes, 3% (14/516)

15-18 April 2015, Geneva, Switzerland

Lung Cancer Mutation Consortium
Mechanisms of acquired resistance to EGFR TKIs

- **MET amplification**: 3%
- **Small cell + MET**: 1%
- **Small cell**: 1%
- **Small cell + T790M**: 2%
- **MET + T790M**: 3%
- **HER2 + T790M**: 4%
- **Unknown**: 18%
- **T790M**: 60%
Potentially targetable mutations in SCC

New targets relevant after the era of EGFR and ALK

Outline

- ROS1
- HER2
- BRAF
- RET
- NTRK1
- MET
- FGFR1
- DDR2
ROS1 in NSCLC

- 50 advanced NSCLC patients with ROS1 rearrangement received crizotinib
- RR 72% with 3 CR and 33 PR
- Median duration of response 17.6 mo
- Median PFS 19.2 mo
- Safety profile of crizotinib similar to that seen in patients with ALK-rearranged NSCLC
- Crizotinib showed marked antitumor activity in patients with advanced ROS1-rearranged NSCLC
ROS1 in NSCLC

- Retrospective study of stage IV lung ADC patients with ROS1 rearrangement (FISH) who had received crizotinib (individual off-label use)
- 32 patients
  - Median age 50.5 yrs
  - 64.5% women
  - 67.7% never-smokers
  - RR 80%
  - Median PFS 9.1 months
  - No unexpected AEs observed
- Crizotinib highly active in lung cancer patients with ROS1 rearrangement, suggesting that patients with lung ADC should be tested for ROS1
ROS1 in lung cancer, next steps

- IHC, high sensitivity and specificity for detecting ROS1 rearrangements *(Boyle Clin Lung Cancer 15)*

- Cabozantinib overcomes crizotinib resistance in ROS1+ *(Katayama CCR 15)*

- PF-06463922, a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations *(Zou PNAS 15)*

- Clinical trials
  - Cabozantinib in p with RET fusion+ advanced NSCLC and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity
  - LDK378 in p with NSCLC harboring ROS1 rearrangement
  - PF-06463922 in p with advanced NSCLC with ALK+ or ROS1+
HER2 in NSCLC

- Somatic mutations of HER2 kinase domain in lung ADC (*Shigematsu Cancer Res 05*)

- HER2 mutation and response to trastuzumab (*Cappuzzo NEJM 06*)

- 16 p receiving HER2-tageted therapies; 22 evaluable individual anti-HER2 treatments, 50% RR (majority received trastuzumab+CT) (*Mazières JCO 13*)

- Dacomitinib (*Kris WLCC Sydney 13*)
  - 26 p with HER2 mutation
    - 3 PR (13%), duration of response 4+, 13, 14 mo
    - Median PFS 3 mo, median OS 10 mo
  - 4 p with HER2 amplification, no responses
HER2 in NSCLC

• Afatinib
  – Induced regressions in transgenic mouse models, effect increased with rapamycin (mTOR inhibitor) (Perera PNAS 09)
  – PR in 3 / 3 evaluable p with HER2-mut (De Grève Lung Cancer 12)

• Neratinib
  – Phase I neratinib/temsirolimus, 7 NSCLC p with HER2 mutations (2 previously treated with trastuzumab): 2 PR / no PD (Gandhi JCO 14)

• Trastuzumab emtansine
  – Rapid response to trastuzumab emtansine in a p with HER2-driven lung cancer (Weiler JTO 15)
Neratinib with/without temsirolimus in p with NSCLC carrying HER2 somatic mutations

- 13 p received neratinib, 14 p neratinib/temsirolimus
- Neratinib arm: 54% SD / 46% PD; PFS 2.9 mo
- Neratinib/temsirolimus: 21% PR / 79% SD; PFS 4.0 mo
- G3 toxicity neratinib/temsirolimus: vomiting 21%; diarrhea 14%

Besse ESMO 14
HER2 in lung cancer, next steps

- RR in HER2 mutated p treated prospectively with HER2 inhibitors seems lower to that observed in other oncogenic-driven subsets

- Other predictive markers?
  - Insertions vs other
  - p95HER2

- Ongoing treatment strategies
  - Neratinib/temsirolimus combination, further study
  - Afatinib phase II ETOP trial
  - TDM1 phase II trial
BRAF in NSCLC

• BRAF mutations occurred in 2.2% of advanced-stage lung ADC, most commonly V600E (Villaruz Cancer 15)

• Vemurafenib, case reports
  – P with BRAF V600E lung ADC responding to vemurafenib (Gautschi JTO 12)
  – Dramatic response induced by vemurafenib in a BRAF V600E mutated lung ADC (Peters JCO 13)
  – Lung ADC with BRAF G469L mutation refractory to vemurafenib (Gautschi Lung Cancer 13)

• Dabrafenib
  – Preliminary efficacy data from 20 BRAF V600E p promising, 60% DCR (Planchard ASCO 13)
Dabrafenib in p with BRAF V600Emutant advanced NSCLC: a phase II trial

- 78 previously treated p; median age 66 yrs, 50% female, 15% ECOG 2, 37% never-smoker
- 32% PR / 24% SD > 12 weeks / 29% PD / 14% NE
- Disease control rate: 51% independent review vs 56% investigator
- Median duration of response 11.8 mo
- PFS 5.5 mo
- Tolerable treatment-related toxicity, special attention to cutaneous squamous cell-carcinoma needed
BRAF in NSCLC, next steps

• Identification of acquired resistance mechanisms to BRAF inhibitors
  – After PR with dabrafenib, biopsy at PD showed KRAS G12D mutation (Rudin JTO 13)
  – BRAF V600E NSCLC cells acquire resistance to BRAF inhibition (Lin PNAS 14)
    • Simultaneous loss of full-length BRAF V600E, and aberrant BRAF pathway expression
    • Engagement of EGFR signaling pathway

• Combination of targeted therapies
  – Cohort B with dabrafenib/trametinib actively recruiting
Lung ADC with RET fusion: early experience with diagnosis and targeted therapy

- 529 tumor samples analyzed in 12 mo
- 12 (2%) tumors RET-positive by FISH
- No coincident mutations in EGFR, HER2, KRAS, BRAF, ALK, or ROS1
- 4 p with RET fusion received one or more RET inhibitors; PR seen with cabozantinib and vandetanib
Patients with targeted therapy

Patient 1: sunitinib  →  vinorelbine
SD   SD   SD
56+ mts alive

Patient 2: vandetanib  →  cabozantinib  →  ponatinib
PR   SD   PD   PD
50+ mts alive

Patient 3: vandetanib  →  cabozantinib
PR   PD   PR   PD
36 mts after diagnosis

Patient 4: vandetanib  →  cabozantinib
PD   PR   PD
34 mts after diagnosis

Months from RET-TKI start
0  3  6  9  12

15-18 April 2015, Geneva, Switzerland

Gautschi ELCC 14
RET in NSCLC, next steps

- Responses to cabozantinib in p with RET fusion-positive lung ADC (*Drilon Cancer Discov 13*)

- Clinical trials
  - Cabozantinib in p with RET fusion+ advanced NSCLC and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity
  - Vandetanib in advanced NSCLC with RET rearrangement
  - Ponatinib in advanced NSCLC with RET translocation
  - Safety and activity of lenvatinib (E7080) in subjects with KIF5B-RET+ ADC of the lung
NTRK1 in NSCLC

- NTRK1 rearrangements, which encode TRKA protein, identified in tumor samples from 3/91 (3%) p (never-smokers) with lung cancer without known oncogenic alterations (Vaishnavi Nat Med 13)

- In preclinical models, kinase inhibitors with activity against TKRA—including ARRY-470, lestaurtinib (CEP-701), and crizotinib induced cell-cycle arrest and inhibited proliferation

- Clinical trials:
  - Phase I study of RXDX-101, an oral Pan-Trk, ROS1, and ALK inhibitor (De Braud ESMO 14)
  - Cabozantinib in p with RET fusion+ advanced NSCLC and those with other genotypes: ROS1 or NTRK fusions or increased MET or AXL activity
MET: study A8081001 with crizotinib

Part 1: Dose escalation

- Cohort 1 (n=3) 50 mg QD
- Cohort 2 (n=4) 100 mg QD
- Cohort 3 (n=8) 200 mg QD
- Cohort 4 (n=7) 200 mg BID
- Cohort 5 (n=6) 300 mg BID
- Cohort 6 (n=9) 250 mg BID MTD/RP2D

Part 2: Molecularly enriched cohorts

ALK, MET, ROS1

NCT00519535 15-18 April 2015, Geneva, Switzerland
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose
**MET amplification cohorts determined by FISH**

- **Low MET level**
  - MET/CEP7 ratio ≥1.8 – ≤2.2
  - Mean MET cell: 9.0
  - Mean CEP 7 cell: 4.7
  - Ratio: 1.9

- **Intermediate MET level**
  - MET/CEP7 ratio >2.2 – <5.0
  - Mean MET cell: 7.0
  - Mean CEP 7 cell: 2.1
  - Ratio: 3.3

- **High MET level**
  - MET/CEP7 ratio ≥5
  - Mean MET cell: 15.7
  - Mean CEP 7 cell: 2.8
  - Ratio: 5.6
### Objective response rate

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<th>Low MET, n=2</th>
<th>Intermediate MET, n=6</th>
<th>High MET, n=6</th>
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<tr>
<td><strong>ORR, % (95% CI)</strong>(^b)</td>
<td>0 (0–84)</td>
<td>17 (0–64)</td>
<td>67 (22–96)</td>
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<tr>
<td><strong>Best response, n (%)</strong></td>
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<tr>
<td>Complete response</td>
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<td>1 (17)</td>
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<tr>
<td>Partial response</td>
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<td>Stable disease</td>
<td>0</td>
<td>4 (67)</td>
<td>1 (17)</td>
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<tr>
<td>Objective progression</td>
<td>2 (100)</td>
<td>1 (17)</td>
<td>1 (17)</td>
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<tr>
<td><strong>Median duration of response, weeks (range)</strong>(^c)</td>
<td>–</td>
<td>16 (24.1–128.0)</td>
<td>73.6</td>
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<tr>
<td><strong>Duration of stable disease, n (%)</strong>(^d)</td>
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<tr>
<td>0–&lt;3 months</td>
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<td>3 (75)</td>
<td>0</td>
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<tr>
<td>3–&lt;6 months</td>
<td>–</td>
<td>1 (25)</td>
<td>1 (100)</td>
</tr>
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</table>

- Lung Cancer Mutation Consortium (*Varella-Garcia ASCO 12*) MET gene amplification defined by ratio mean MET/mean CEP7>2 in 4% of ADC

15-18 April 2015, Geneva, Switzerland
c-MET Inhibition in SCC: crizotinib

c-Met amplified SCC

Before

After

Schwab Lung Cancer 2014
MET amplification, a mechanism of AR to EGFTKIs

• Phase Ib/II of cabozantinib +/- erlotinib, encouraging activity in erlotinib-pretreated population, including PR in one p with MET amplification *(Wakelee ASCO 12)*

• Phase Ib/II trial of INC280/gefitinib in p with EGFR mutation and MET-positive (IHC) *(Wu ASCO 14)*
  – PR seen in 8/46 (17%) evaluable p
  – All responding p had high MET status by IHC or FISH

• Phase I of EGF816 in combination with INC280 in NSCLC p with EGFR mutation and AR

15-18 April 2015, Geneva, Switzerland
**FGFR inhibition in SCC, BGJ398**

- Phase I dose-escalation study of p with any *FGFR* genetically altered tumor, progressed at least 1 line, including platinum (SCC cohort: N=21)
  - FGFR 1-amplified tumors by FISH/CISH
- **Results:** 17 evaluable p
  - 2 PR
  - 2 additional PRs after the data cutoff date
  - 3 additional p had SD with tumor regression (up to 11% reduction)
- **Safety:**
  - Manageable and reversible hyperphosphatemia, stomatitis, decreased appetite, and fatigue
- **Conclusion:**
  - These data encourage further development of BGJ398 in *FGFR1*-amplified SCC and efforts to optimize predictive biomarkers for FGFR inhibitor sensitivity

*Nogova J Clin Oncol 2014*
FGFR Inhibition in SCC, AZD4547

- Phase I expansion of AZD4547 in previously-treated p with FGFR1 amplified SCC

**Results:**
- 15 p: 1 PR, 4 SD, 9 PD (7 progressions and 2 deaths)
  - The PR observed in a p with high FGFR1 amplification

**Safety:**
- Most common related AEs were GI and dermatologic
- Grade ≥ 3 related AEs in 3 p (20%) (central serous retinopathy, hyponatremia, dehydration)

**Conclusion:**
- AZD4547, well-tolerated in p with FGFR1 amplified SCC but pre-specified efficacy endpoint in terms of ORR for continuation not met

Paik J Clin Oncol 2014
## FGFR inhibitors in clinical trials in NSCLC

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<th>DRUG</th>
<th>TARGET</th>
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<td>Dovitinib</td>
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<td>Ponatinib</td>
<td>VEGFR2, FLT3 PDGFRα, FGFR1-2-3-4, BCR-ABL</td>
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<td>FGF trap</td>
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DDR2 in SCC

- In 290 SCC tissue samples, frequency of DDR2 mutations, 3.8% (Hammerman Cancer Disc 2011)
  - DDR2 mutations drive molecular alterations whose activation has been inhibited by dasatinib
  - SCC p harboring a DDR2 kinase domain mutation who responded to dasatinib and erlotinib treatment

- Trial of dasatinib in subjects with advanced cancers harboring DDR2 mutation or inactivating B-RAF mutation
  - Study terminated (lack of efficacy and slow accrual)
New targets relevant after the era of EGFR and ALK

- What is the optimal treatment for patients with ROS1, RET, BRAF or HER2 genomic alterations after standard treatment?
  - 2nd ESMO Consensus Conference on Lung Cancer (B Besse and Panel members, Ann Oncol 14):

  - **Recommendation:** Specific targeted treatments should be discussed with the patient and may be considered in individual patients based on expected risk-benefit, biological plausibility, preclinical data, and limited clinical efficacy data for authorised therapies in different indications.
New targets relevant after the era of EGFR and ALK

<table>
<thead>
<tr>
<th>Genetic Alteration (ie, Driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
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</table>
| **BRAF** V600E mutation*             | vemurafenib\(^1\)  
dabrafenib\(^2\)                                                            |
| **MET** amplification                | crizotinib\(^3,4\)                                                        |
| **ROS1** rearrangements              | crizotinib\(^5\)                                                          |
| **HER2** mutations                   | trastuzumab\(^6\) (category 2B)  
afatinib\(^7\) (category 2B)                                                 |
| **RET** rearrangements               | cabozantinib\(^8\) (category 2B)                                          |

\(^*\)Non-V600E mutations have variable kinase activity and response to these agents.
New targets relevant after the era of EGFR and ALK

- NSCLC is divided in subsets by the presence of targetable molecular alterations (EGFR, ALK, KRAS, ROS1, RET, HER2, BRAF, NTRK1, FGFR, among others)

- At present, EGFR, ALK and ROS1 should be tested in non-SCC

- Challenges
  - Genotyping
  - Some molecularly defined subsets are infrequent; a clear effort required to identify these patients
  - Few trials in these uncommon molecular alterations
  - International collaboration
Thanks!!!
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