Beyond ALK and EGFR: Novel molecularly driven targeted therapies in NSCLC

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Oncogenic drivers in NSCLC

- Certain tumours arise as a result of aberrant activation of a single oncogene and become dependent on this activation
- Identification of druggable oncogenic drivers creates the potential for highly active therapeutic interventions
**ROS1 Translocations in NSCLC**

Patients with ROS1 rearrangements share many features in common with ALK-positive patients (adenocarcinoma histology, younger age at diagnosis, never or light smokers)

Mutually exclusive with EGFR, HER2, KRAS, BRAF mutations and with ALK translocation

Prognostic role is not defined
Methods of *ROS1* Detection

- **RT-PCR**
  - Cons: False negatives; 9 variants have been described in a matter of 12 months. Has to be multiplexed, i.e., probes to all known variants. Unknown variants will not be detected.

- **FISH break apart**
  - Cons: if inversion involves a small locus it could be false negative; can not distinguish variants; cut of is 15% of nuclei with split signal; low throughput

- **IHC**
  - Cons: Possibility of false positive: FISH confirmation is required
**ROS1** positive NSCLC are sensitive to pemetrexed

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**A**

Pemetrexed-based chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>PFS (days)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>28</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>2nd line</td>
<td>21</td>
<td>181</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

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**B**

PFS on pemetrexed (days)

- **P = 0.0105**

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Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Preclinical Activity of Crizotinib

B

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One trial many answers: the A8081001 study

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

Part 2: Molecularly enriched cohorts
- Cohort 6 (n=9) 250 mg BID MTD/RP2D

ALK, MET, ROS1

NCT00585195
BID, twice daily; QD, once daily
RP2D, randomized phase 2 dose

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Crizotinib in ROS1+ NSCLC

Shaw A, et al. NEJM 2014

ORR 72%; DCR 90%  
mDOR 17.6 months

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Crizotinib in *ROS1+* NSCLC: PFS

Median PFS: 19.2 months

Shaw A et al, NEJM 2014

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Phase II study of crizotinib in East Asia ROS1+ NSCLC

Response to therapy

Total enrolled: 127
Response Rate: 69.3%
Complete response: 11.0%


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Phase II study of crizotinib in East Asia $ROS1^+$ NSCLC


Median PFS = 13.4 months

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Crizotinib in MET amplified or ROS1 translocated NSCLC: The METROS trial

- NSCLC with tumor tissue available
  - All test negative
    - Not eligible
  - MET amplification
    - Crizotinib until disease progression
  - ROS1 translocation
    - Crizotinib until disease progression

Tumor assessment q 2 months

Landi L et al, AIOM 2016

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
**METROS study overview**

- **Pts Screened**
  - N = 329

- Not evaluable (N=54)
  - Inadequate Tumor Sample

- **275 pts evaluable for ROS1 rearrangement and/or MET amplification/mutation**

- **Cohort A: ROS1+**
  - N = 31
  - Not included (N=7)
    - Not eligible

- **Treated pts**
  - N = 24

- **Cohort B: MET+**
  - N = 25
  - Not included (N=10)
    - Not eligible

- **Treated pts**
  - N = 15

*Landi L et al, AIOM 2016*
METROS: Response in the ROS1+ cohort

- Par$al$ response (PR)
- Stable disease (SD)
- Progressive disease (PD, new lesions)
- Ongoing treatment

* 21 evaluable pts
(3 pts are not evaluated yet)

RR 71 %
Median DOR 9.0 months

Landi L et al, AIOM 2016
METROS PFS in the *ROS1*+ cohort

* ITT Population = 24 pts; NR; not reached

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy

Landi L et al, AION 2016
Response to crizotinib therapy in *ROS1*+ NSCLC

Break-apart FISH analysis shows single green signal pattern (white arrows). Red probes are hybridized to the 5’ region of *ROS1* and green probes to the 3’ region.

Computed tomography scan image showing a partial response after 2 months of crizotinib.

Landi L et al, AIOM 2016
Crizotinib Now Approved for $ROS1^+$ NSCLC

- **EMA indication:**
  - Crizotinib is indicated for the:
    - first-line treatment of adults with $ALK^+$ advanced NSCLC
    - treatment of adults with previously treated $ALK^+$ advanced NSCLC
    - treatment of adults with $ROS1^+$ advanced NSCLC (*new from 25\textsuperscript{th} August 2016*)

- **FDA indication:**
  - Crizotinib is a kinase inhibitor indicated for the treatment of patients with:
    - metastatic NSCLC whose tumours are $ALK^+$ as detected by an FDA-approved test
    - metastatic NSCLC whose tumours are $ROS1^+$
Crizotinib Resistance Can Be Mediated by Secondary ROS1 Resistance Mutations

Awad et al., NEJM 368(25): 2395-2401, 2013;
Drilon et al., CCR 22(10): 2351-8, 2016
Acquired resistance to crizotinib in ROS1 NSCLC

Awad MM, et al. NEJM 2013

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Overcoming Crizotinib Resistance in Advanced *ROS1*+ NSCLC

<table>
<thead>
<tr>
<th></th>
<th><em>WT ROS1</em></th>
<th><em>G2032R</em></th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceritinib1</td>
<td>10.9 nM</td>
<td>277 nM</td>
<td>Phase 2 (SIGNATURE)</td>
</tr>
<tr>
<td>Brigatinib1</td>
<td>2.7 nM</td>
<td>322 nM</td>
<td>Investigator initiated trials</td>
</tr>
<tr>
<td>Lorlatinib2</td>
<td>0.11 nM</td>
<td>186 nM</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>--</td>
<td>--</td>
<td>Phase 2 (CNS relapse only)</td>
</tr>
<tr>
<td>DS-6051b</td>
<td>--</td>
<td>--</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Cabozantinib1</td>
<td>2 nM</td>
<td>13.5 nM</td>
<td>Phase 2 (MSKCC)</td>
</tr>
<tr>
<td>Foretinib3</td>
<td>1.8 nM</td>
<td>50 nM</td>
<td>None</td>
</tr>
</tbody>
</table>

2. Zou et al., AACR-EORTC-NCI, 2013;  

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Phase I design and patient population of an ongoing phase I/II study

ALK/ROS1+ NSCLC:
- Treatment-naïve in advanced setting or PD after at least 1 prior ALK/ROS1 TKI;
- any prior chemotherapy
N=54

Histologically or cytologically confirmed metastatic NSCLC and either:
- ALK rearrangement, by FDA-approved FISH assay or by IHC (Ventana Inc.)
- ROS1 rearrangement, by FISH, RT-PCR, or NGS via a local diagnostic test
≥1 measurable extracranial target lesion per RECIST v1.1
- Patients with asymptomatic CNS metastases (treated or untreated) were eligible

*Treatment until PD or unacceptable toxicity; treatment beyond PD allowed if deriving benefit

ALK, anaplastic lymphoma kinase; BID, twice daily; CNS, central nervous system; DL1, dose level 1; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer; PD, progressive disease; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1; RT-PCR, reverse transcription polymerase chain reaction; TKI, tyrosine kinase inhibitor

Solomon B et al ASCO 2016
Majority of $ROS1^+$ patients had a decrease in target lesion size

*Number of prior TKIs counted by line

ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor
CNS responses in ALK/ROS1+ patients with measurable disease

Best change from baseline (%)

-100 -80 -60 -40 -20 0 20 40 60 80

Ongoing treatment

No prior TKI 1 prior TKI ≥2 prior TKI

R Indicates the patients with ROS1 rearrangements

ALK, anaplastic lymphoma kinase; PD, progressive disease; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor

Solomon B et al ASCO 2016
Ceritinib in *ROS1*-rearranged NSCLC: A Korean nationwide phase II study

As of April 18\textsuperscript{th}, 2016, the efficacy results from this study based on RECIST 1.1 are shown in the table below.

<table>
<thead>
<tr>
<th>Efficacy Parameters</th>
<th>All (N=32)</th>
<th>Crizotinib-naive (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate</td>
<td>67%</td>
<td>62%</td>
</tr>
<tr>
<td>Complete Response, n</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial Response, n</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Duration of Response, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>18.4 (95% CI, 8.0, 18.4)</td>
<td></td>
</tr>
<tr>
<td>PFS, months, median (95% CI)</td>
<td>10.0 (95% CI, 2.5-17.4)</td>
<td>20.7 (95% CI, 4.7, NE)</td>
</tr>
</tbody>
</table>

15 patients are still ongoing response

**Figure 1. Prescreening for *ROS1* rearrangement**

**Table 3. Intracranial Response**

<table>
<thead>
<tr>
<th>Intracranial Response (RECIST 1.1)</th>
<th>Patients with brain metastases at baseline (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (12)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (12)</td>
</tr>
<tr>
<td>SD or Non-CR/Non-PD</td>
<td>3 (37)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>3 (37)</td>
</tr>
<tr>
<td>IDCR (CR + PR + SD/Non-CR/Non-PD), n (%)</td>
<td>5 (61)</td>
</tr>
</tbody>
</table>

Sun Min Lim et al, ESMO 2016
The MET Pathway Can be Activated by Multiple Mechanisms

- HGF overexpression
- MET amplification
- MET mutation

Normal Physiological Function
- CBL degradation

Oncogenic Activities
- CBL degradation

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MET deregulation is a negative prognostic factor

Survival of resected NSCLC according to different methods

*MET* mutation  *MET* amplification  MET overexpression

Analyses conducted in 680 Asiatic NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Type</th>
<th>Development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ligand antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ficlatuzumab (AV-299)</td>
<td>HGF</td>
<td>Monoclonal antibody</td>
<td>I and II</td>
</tr>
<tr>
<td>Rilotumumab (AMG-102)</td>
<td>HGF</td>
<td>Monoclonal antibody</td>
<td>II</td>
</tr>
<tr>
<td>TAK-701</td>
<td>HGF</td>
<td>Monoclonal antibody</td>
<td>I</td>
</tr>
<tr>
<td><strong>Receptor inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onartuzumab (OA5D5)</td>
<td>MET</td>
<td>Monoclonal antibody</td>
<td>III completed</td>
</tr>
<tr>
<td><strong>Receptor TKIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tivantinib (ARQ-197)</td>
<td>MET</td>
<td>Non-ATP competitive TKI</td>
<td>III completed</td>
</tr>
<tr>
<td>Cabozantinib (XL-184)</td>
<td>MET, RET, VEGFR1-3, KIT, FLT3, TIE2</td>
<td>ATP competitive TKI</td>
<td>II</td>
</tr>
<tr>
<td>Foretinib (XL-880)</td>
<td>MET, RON, VEGFR1-3, PDGFR, KIT, FLT3, TIE2</td>
<td>ATP competitive TKI</td>
<td>II</td>
</tr>
<tr>
<td>Crizotinib (PF-02341066)</td>
<td>MET, ALK</td>
<td>ATP competitive TKI</td>
<td>II and III</td>
</tr>
<tr>
<td>MGCD-265</td>
<td>MET, RON, VEGFR1-2, PDGFR, KIT, FLT3, TIE2</td>
<td>ATP competitive TKI</td>
<td>II</td>
</tr>
</tbody>
</table>

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Onartuzumab (MetMAb) Phase III
2L/3L MET-positive NSCLC

Key eligibility criteria:
- Stage IIIB or IV Met diagnostic positive NSCLC
- 1-2 prior lines of tx
- No prior EGFR inhibitor
- ECOG PS 0 or 1

Stratification criteria:
- EGFR mut status
- MET 2+ or 3+ score
- # of prior lines of tx
- Histology

Primary endpoint:
- Overall survival (OS)

Secondary endpoints:
- Progression-free survival (PFS)
- Overall response rate (ORR)
- Quality of life (QoL)
- Safety

*PRE-SCREENING: Patients could submit tumor samples for testing prior to requiring treatment with 2L or 3L therapy

2L and 3L NSCLC pts
(1 prior Pt-based line)

Central testing for*:
- MET status
- EGFR mutation status

N = 490

Randomise 1:1

erlotinib + onartuzumab

Treatments:
- Tarceva 150 mg PO qd
- onartuzumab/placebo 15 mg/kg IV q3wk

Treat until PD

erlotinib + placebo

No crossover tx

Spigel D, et al. JCO 2016

Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Onartuzumab: Overall Survival Results

Median 9.1 months (95% CI 7.7–10.2)

Median 6.8 months (95% CI 6.1 – 7.5)

HR 1.27 (95% CI: 0.98–1.65)  
*p=0.07*

Placebo + erlotinib (n=249)

Onartuzumab + erlotinib (n=250)

Censored

Number of patients at risk

Placebo + erlotinib

Onartuzumab + erlotinib

Spigel D, et al. JCO 2016
MARQUEE phase III study design

Key Eligibility Criteria
- Inoperable, locally advanced or metastatic NSCLC
- Non-squamous histology
- 1-2 prior systemic regimens, including mandatory prior platinum-based doublet therapy
- No prior EGFR TKI
- Tissue for biomarker analysis
- Stable brain metastases were permitted
- ECOG 0 or 1

Randomize

Tivantinib @ 360 mg PO BID + Erlotinib @ 150 mg QD

Placebo PO BID + Erlotinib @ 150 mg QD

1:1

Stratification Factors
- Gender
- Smoking history
- # prior lines of systemic therapies
- EGFR genotype
- KRAS genotype

Primary end-point: OS

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MARQUEE: OS in the study population

- **Tivantinib + Erlotinib**: 526 patients, 300 events, Median = 8.5 months
- **Placebo + Erlotinib**: 522 patients, 314 events, Median = 7.8 months

HR = 0.98 (95% CI: 0.84, 1.15)
Stratified Log Rank Test \( p = 0.81 \)
### Who are MET addicted patients?

**Clinical characteristics of MET amplified or mutated NSCLC**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MET Mutated</th>
<th>MET amplified (ratio (MET/CEP7 \geq 2.2 - &lt;5))</th>
<th>MET amplified (ratio (MET/CEP7 \geq 5))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>3-4%</td>
<td>4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Age (median)</td>
<td>72.5</td>
<td>63</td>
<td>65.5</td>
</tr>
<tr>
<td>Female</td>
<td>70%</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Smokers</td>
<td>65%</td>
<td>94%</td>
<td>88%</td>
</tr>
<tr>
<td>Squamous histology</td>
<td>0%</td>
<td>31%</td>
<td>0%</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>20-30%</td>
<td>15</td>
<td>37%</td>
</tr>
<tr>
<td>Prognostic effect</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Mutually exclusive</td>
<td>yes</td>
<td>No</td>
<td>yes</td>
</tr>
</tbody>
</table>


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Only very high levels of MET gene amplification are mutually exclusive with other drivers.

- **Ratio MET/CEP 7**:
  - 1.8
  - 2.2
  - ≥5

- **Other drivers**:
  - 52%
  - 50%
  - 0%*

* Except MET mutations

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Is MET amplification a driver?
Sensitivity to anti-Met agents only in presence of high levels of MET amplification

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Smolen GA et al., PNAS 2006, Tanizaki J et al., JTO 2011
High levels of $MET$ amplification drive resistance to EGFR-TKIs

**Gefitinib Resistant**

- MET amplification in HCC827 GR6
- Ratio MET/centromere >5

**Gefitinib Sensitive**

- NO MET amplification in HCC827
- Ratio MET/centromere <2

Modified from Cappuzzo F et al., Ann Oncol 2008
Crizotinib in patients with \textit{MET} amplification

- Patients (≥18 years) had histologically confirmed advanced NSCLC, and
  - measurable disease per RECIST v1.0
  - adequate organ function
  - resolution of acute toxic effects of prior therapies or surgical procedures (CTCAE Grade ≤1)
  - received no prior MET- or HGF-targeted therapies

In archival tumor tissue, \textit{MET} amplification was determined by FISH

- \textit{MET} not amplified (not eligible)
  - \textit{MET/CEP7} ratio <1.8

- \textit{MET} amplified (low \textit{MET} level)
  - \textit{MET/CEP7} ratio ≥1.8–≤2.2

- \textit{MET} amplified (intermediate \textit{MET} level)
  - \textit{MET/CEP7} ratio >2.2–<5.0

- \textit{MET} amplified (high \textit{MET} level)
  - \textit{MET/CEP7} ratio ≥5

CEP7, chromosome 7 centromere signal; CTCAE, Common Toxicity Criteria for Adverse Events; FISH, fluorescence in-situ hybridization; RECIST, Response Evaluation Criteria In Solid Tumors

Camidge R, et al. ASCO 2014

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Tumor Shrinkage Seen in Intermediate and High MET Cohorts

Best percent change from baseline in target tumor lesions\textsuperscript{a} by patient

\textsuperscript{a}Confirmed objective responses.

\textsuperscript{b}Based on investigator assessment.

\textsuperscript{c}Two patients in the intermediate MET group had an unconfirmed PR that was not confirmed in a second assessment.

Camidge R, et al. ASCO 2014
Antitumor Activity of crizotinib in MET Exon 14 mutated NSCLC

Maximum Response to Crizotinib in Patients with MET Exon 14-Altered Lung Cancers
(n=16 with measurable disease at baseline and ≥1 response assessment scan)


Department of Oncology-Hematology, AUSL della Romagna, Ravenna, Italy
Activity of crizotinib in MET + cohort

Response*

<table>
<thead>
<tr>
<th>ID Pt</th>
<th>MET amplification</th>
<th>MET Ex.14 mutation</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT-001-016</td>
<td>2.7</td>
<td>WT</td>
<td>SD</td>
</tr>
<tr>
<td>MT-004-286</td>
<td>2.3</td>
<td>Mutated</td>
<td>PR</td>
</tr>
<tr>
<td>MT-006-079</td>
<td>3.4</td>
<td>WT</td>
<td>PD</td>
</tr>
<tr>
<td>MT-006-109</td>
<td>2.5</td>
<td>WT</td>
<td>PR</td>
</tr>
<tr>
<td>MT-010-057</td>
<td>7.3</td>
<td>WT</td>
<td>SD</td>
</tr>
<tr>
<td>MT-010-080</td>
<td>2.8</td>
<td>WT</td>
<td>SD</td>
</tr>
<tr>
<td>MT-010-083</td>
<td>3.3</td>
<td>WT</td>
<td>SD</td>
</tr>
<tr>
<td>MT-012-121</td>
<td>0.9</td>
<td>Mutated</td>
<td>PD</td>
</tr>
<tr>
<td>MT-012-129</td>
<td>0.9</td>
<td>Mutated</td>
<td>PD</td>
</tr>
<tr>
<td>MT-012-182</td>
<td>2.6</td>
<td>WT</td>
<td>PD</td>
</tr>
<tr>
<td>MT-014-042</td>
<td>2.8</td>
<td>WT</td>
<td>PD</td>
</tr>
<tr>
<td>MT-022-197</td>
<td>3.6</td>
<td>WT</td>
<td>PD</td>
</tr>
<tr>
<td>MT-022-203</td>
<td>3.4</td>
<td>WT</td>
<td>SD</td>
</tr>
</tbody>
</table>

WT; wild type

RR 18%; DCR 54%

* 13 pts with measurable disease and >1 assessment scan
1 Pt with pending assessment; 2 pts withdrawn IC before 1st assessment
MAO7.06: Crizotinib in ROS1 rearranged or MET deregulated Non-Small-Cell Lung Cancer (NSCLC): preliminary results of the METROS trial – Landi L.

Progression-free survival and overall survival in ITT population*

* 16 patients

Median FU: 3.5 months
Conclusions

- *ROS1* rearrangement is a rare but relevant target in NSCLC
- Crizotinib is now approved for *ROS1*+ NSCLC
- Patients inevitably develop acquired resistance to crizotinib
- Several new agents including lorlatinib and ceritinib are currently under investigation
- MET is a relevant target driving tumor growth in approximately 3-4% of NSCLC
- Current data support a role as driver event for *MET* mutations and high levels of *MET* amplification (ratio $\text{MET/CEP7} \geq 5$)
- Prospective studies need to define the best cut-off (ratio 2.2 versus 5) and the best agents