TARGETING EGFR AND ALK DRIVEN TUMOURS

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DISCLOSURES SLIDE

Advisory Boards: Eli Lilly, Roche, Genentech, Boehringer-Ingelheim, Astra-Zeneca, Pfizer, MSD, Clovis, Pierre Fabre, Bristol-Myers-Squibb, Novartis

Symposia: Eli Lilly, Roche, Pfizer, Astra-Zeneca, Boehringer-Ingelheim, Novartis
Whole Body and Intracranial Efficacy of Ceritinib in Patients With Crizotinib-pretreated, ALK+ NSCLC and Baseline Brain Metastases: Results From ASCEND-1 And ASCEND-2 Trials

E. Felip et al.

141PD
Current Treatment Strategy for ALK+ Patients

- **Crizotinib**
  - PD
  - **Isolated CNS PD**
  - Biopsy? cfDNA?
  - CT

- Ceritinib
  - PD
  - CT

**Hazard ratio for progression or death in the crizotinib group:**
- HR = 0.45 (95% CI, 0.35–0.60)
- P<0.001 (two-sided stratified log-rank test)

**No. at Risk**
- Crizotinib: 172, 120, 65, 38, 19, 7, 1, 0
- Chemotherapy: 171, 105, 36, 12, 2, 1, 0

**ALK mutations**
- ~22–33%
  - L1196M
  - G1202R
  - S1206Y
  - G1269A
  - 1151Tins
  - Others

**ALK amplification**
- ~6–16%

**Increased EGFR signalling**
- ~30–35%

**Change in driver mutations**
- ~5%

**KIT amplification**
- ~10%

**No identification of AR mechanism**
- ~25%

**Solomon, NEJM 2014; Camidge, Nat Rev Clin Oncol 2014**
ASCEND-1: Activity of Ceritinib (750 mg/day) in ALK+ NSCLC Patients
Impact of the Sequential Crizotinib-Ceritinib Strategy on ALK+ Patients Survival

OS for patients treated with sequential crizotinib and ceritinib

Survival probability (%)

Time (mo)

Number at risk

0 20 40 60 80 100 120 140

100 90 80 70 60 50 40 30 20 10 0

Overall survival 49.4

0.0 10.0 20.0 30.0 40.0 50.0 60.0

Crizotinib PFS
Post-progression crizotinib
Crizotinib-ceritinib interval
Ceritinib PFS

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Gainor, CCR 2015
# ALK Inhibitors after Crizotinib Failure
Systemic Efficacy and Tolerance

<table>
<thead>
<tr>
<th></th>
<th>Alectinib NP28673</th>
<th>Alectinib NP28761</th>
<th>Brigatinib</th>
<th>Ceritinib ASCEND-1 (prior ALKi)</th>
<th>Ceritinib ASCEND-2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>n=122</td>
<td>n=69</td>
<td>n=70</td>
<td>n=163</td>
<td>n=140</td>
</tr>
<tr>
<td>ORR, %</td>
<td>50</td>
<td>51</td>
<td>71</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>DCR, %</td>
<td>79</td>
<td>80</td>
<td>87</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>mDoR, mos</td>
<td>11.2</td>
<td>13.5</td>
<td>9.3</td>
<td>8.3</td>
<td>9.7</td>
</tr>
<tr>
<td>mPFS, mos</td>
<td>8.9</td>
<td>8.1</td>
<td>13.4</td>
<td>6.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Toxicity issues</td>
<td>Very few</td>
<td>Dyspnea</td>
<td>GI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR: objective response rate; DCR: disease control rate; mDoR: median duration of response; mPFS: median progression-free survival

*By IRC; **By investigator

Ou, JCO 2016; Shaw, Lancet Oncol 2016; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015
**Profile 1005 + 1007: Crizotinib Antitumour Activity In Pts With Or Without Brain Metastasis At Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Previously untreated for BM (n=109)</th>
<th>Previously treated for BM (n=166)</th>
<th>No BM detected (n=613)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Outcome</td>
<td>n</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>109</td>
<td>7 (3−14)</td>
<td>166</td>
</tr>
<tr>
<td>Target-lesion BM</td>
<td>22</td>
<td>18 (5−40)</td>
<td>18</td>
</tr>
<tr>
<td>Systemic</td>
<td>109</td>
<td>53 (43−63)</td>
<td>166</td>
</tr>
<tr>
<td>Median duration of response (range), weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>8</td>
<td>26.4 (6.1−59.3)</td>
<td>12</td>
</tr>
<tr>
<td>Systemic</td>
<td>58</td>
<td>47.9 (5.3−55.0)</td>
<td>77</td>
</tr>
</tbody>
</table>

- For patients with brain metastases at baseline: CNS is the first site of disease progression in 72% patients
- For patients without brain mets at baseline: CNS is the first site of disease progression in 20% patients
Ceritinib in ALK+ Crizotinib-Pretreated Pts with "Stable" Brain Metastases

- Pts treated with ceritinib 750 mg/d in ASCEND-1 and ASCEND-2 trials
- Prospective assessment of systemic response by investigators and IRC
  - N=98 in ASCEND-1
  - N=100 in ASCEND-2
  - 71% had previous brain RT
- Retrospective, centrally reviewed, evaluation of intra-cranial response for patients with measurable disease
  - Measurable lesions: longest diameter $\geq$10 mm, time from possible previous brain RT not specified
  - N=61 in ASCEND-1+2
  - 80% had previous brain RT without specification about SBRT or WBRT
### Systemic Response: Baseline Brain Metastases Do Not Affect Response Rate and Duration of Response

<table>
<thead>
<tr>
<th></th>
<th>ASCEND-1 (N=98)</th>
<th>ASCEND-1 (N=163)</th>
<th>ASCEND-2 (N=100)</th>
<th>ASCEND-2 (N=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brain mets</td>
<td>All patients</td>
<td>Brain mets</td>
<td>All patients</td>
</tr>
<tr>
<td>ORR, n (%) [95 % CI]</td>
<td>50 (51.0) [40.7-61.3]</td>
<td>56</td>
<td>33 (33.0) [23.9, 43.1]</td>
<td>39</td>
</tr>
<tr>
<td>DCR, n (%) [95 % CI]</td>
<td>72 (73.5) [63.6, 81.9]</td>
<td>74</td>
<td>74 (74.0) [64.3, 82.3]</td>
<td>77</td>
</tr>
<tr>
<td>Median DOR, months [95% CI]</td>
<td>6.9 [5.4–8.3]</td>
<td>8.3</td>
<td>9.2 [5.5, 11.1]</td>
<td>9.7</td>
</tr>
<tr>
<td>Median PFS, months [95% CI]</td>
<td>6.9 [4.9–8.4]</td>
<td>6.9</td>
<td>5.4 [4.7, 7.2]</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Similar safety profile of ceritinib in crizotinib-pretreated patients with ALK+ NSCLC and baseline brain metastases to that seen in the full ALK+ NSCLC population.
## Intracranial Tumor Activity of Ceritinib

<table>
<thead>
<tr>
<th></th>
<th>Pooled ASCEND-1 and ASCEND-2</th>
<th>Measurable lesions N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % [95 % CI]</td>
<td>37.7 [25.6, 51.0]</td>
<td></td>
</tr>
<tr>
<td>CR, %</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>DCR, % [95 % CI]</td>
<td>73.8 [60.9, 84.2]</td>
<td></td>
</tr>
<tr>
<td>Median intracranial DOR, months [95 % CI]</td>
<td>12.8 [6.9, NE]</td>
<td></td>
</tr>
</tbody>
</table>
CNS Penetration and P-gp Transporter

- **ABC=ATP-Binding Cassette Transporters:** ABCB1 (MDR-1/P-gp), ABCG2 (BCRP) …
- BBB is reinforced by a high concentration of P-gp, drug-efflux-transporter protein
- Crizotinib and ceritinib are substrates of P-gp and BCRP but not alectinib nor lorlatinib

**Drug** | **IC$_{50}$ (nM)**
---|---
Ceritinib | 180.4
Ceritinib + Verapamil | 18.51
Ceritinib + MS209 | 18.63
Ceritinib + FTC | 163.8
Plasma/CSF Level of ALK TKIs

Alectinib

Alectinib $C_{\text{through}}$ in CSF = 2.69 nM
similar to the unbound systemic $C_{\text{trough}}$ (3.12 nM)
exceeding in vitro $IC_{50}$ (1.9 nM) for ALK inhibition

Ceritinib

In a rat model, brain-to-blood exposure ratio of about 15%

Crizotinib

$[\text{CSF}] < 0.3\% \text{ [plasma]}$
Ceritinib demonstrated a similar level of systemic activity in patients with brain metastases to that in all crizotinib pretreated patients.

- No unexpected safety signal

- Intracranial activity was meaningful and durable but
  - Possible impact of previous WBRT not assessed
  - Lower response and disease control rates than for alectinib but with a similar duration of response
  - Ceritinib CSF/plasma ratio is likely lower than that of alectinib as ceritinib is a substrate of active drugs exporters in blood-brain barrier
The Impacts on Work Productivity from Ceritinib Compared with Chemotherapy for Crizotinib-experienced Alk+ Non-small Cell Lung Cancer

J. Zhang et al.

142PD
Drug Development and Market Access

1. Safety
2. Quality
3. Efficacy
4. Cost-effectiveness
“The drug itself has no side effects - but the price may cause dizziness and fainting”
Value = Outcomes/Cost

OS (months)

$ per year

Year 2000: Carboplatin, Paclitaxel
Year 2015: Carboplatin, Pemetrexed, Bevacizumab
Pharmaco-Economy: Cost-Effectiveness

- QALYs = quality-adjusted life-years: assessment of both quantity and quality of life lived

- ICER (Incremental Cost-Effectiveness Ratio)
  - Basis of cost-effectiveness analysis
  - ICER = ratio (€/QUALYs) = incremental cost / QUALY

  Cost Treatment A – Cost Treatment B

  Benefit difference A - B (QUALYs)

- Acceptable threshold for ICER
  - Depending on country and healthcare systems
  - Varying from 30,000 to 100,000 €/QUALY
ASCO Framework to Assess the Value of Cancer Treatment Options: EURTAC as an Example

NHB: net health benefit
Cost Calculation

Costs

Direct costs (DC)
- Medical
  - Hospitalization.
  - Medical and paramedical procedures...
- Non medical
  - Transports.
  - Home care.
  - Social supports...

Indirect costs (IC)
- Out of work
  - Recurrent adverse events

Intangible costs
- Human and psychological costs
  - Prevention.
  - Rehabilitation.
  - Equipments.
  - Drugs
Impact of Work Productivity and Cost-savings of Ceritinib vs Chemotherapy in ALK+ Patients

- Benefit of a targeted therapy from the societal perspective
  - ALK+ patients are younger than NSCLC patients and often still working
  - What is the social impact due to productivity gains for patients and their informal caregivers in 5 European countries with ceritinib?
- Methods
  - Partitioned survival model to estimate the proportion of patients at each of the three mutually exclusive health states: stable disease, progressive disease, and death over a 5-year period
  - Probabilities to return to work based on the distribution of patients PS in clinical trial
  - Efficacy endpoints: PFS, OS
    - ASCEND-1 and -2 trials
    - Control arm of crizotinib trials for chemotherapy (docetaxel or pemetrexed)
Results

- Over a 5-year period, ceritinib treatment was associated with societal savings due to productivity gains.

**Per-patient societal impacts on productivity over 5 years**

<table>
<thead>
<tr>
<th>Country</th>
<th>Society Savings (2014 Euro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>€ 12,420</td>
</tr>
<tr>
<td>France</td>
<td>€ 18,641</td>
</tr>
<tr>
<td>Germany</td>
<td>€ 17,150</td>
</tr>
<tr>
<td>Italy</td>
<td>€ 14,656</td>
</tr>
<tr>
<td>Spain</td>
<td>€ 11,058</td>
</tr>
</tbody>
</table>

**Total societal impacts on productivity of ceritinib vs chemotherapy over 5 years**

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Societal Savings (2014 Euro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>€ 6,0 M</td>
</tr>
<tr>
<td>France</td>
<td>€ 8,9 M</td>
</tr>
<tr>
<td>Germany</td>
<td>€ 10,2 M</td>
</tr>
<tr>
<td>Italy</td>
<td>€ 6,7 M</td>
</tr>
<tr>
<td>Spain</td>
<td>€ 3,5 M</td>
</tr>
</tbody>
</table>

Additional equivalent working days:

- UK: 70
- France: 67
- Germany: 68
- Italy: 65
- Spain: 65

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Limitations

- Data do not come from a randomized trial, generating potential biases
  - No attempt to match ceritinib and chemotherapy patients
- ASCEND-1 included both crizolonaive and crizotinib-pretreated patients with a different impact of ceritinib in terms of response, PFS and OS
- Proportion of ALK+ patients treated with crizotinib is probably > 56% today
- Side-effects were not taken into account; some AEs can preclude patients to return to work
- Model based on an assumption of a 50%/50% distribution between docetaxel and pemetrexed
- Direct medical cost-savings associated with reduced resource use were not captured
Impact of Work Productivity and Cost-savings of Ceritinib vs Chemotherapy in ALK+ Patients

- Ceritinib treatment for crizotinib-pretreated ALK+ pts was associated with greater work productivity for patients and their informal caregivers compared to chemotherapy
- This economic benefit of ceritinib should be added to clinical and QoL benefits
- Using targeted therapies in oncogene driven tumors can lead to important cost-savings in addition to PFS and QoL benefits
- Usual cost-effectiveness studies do not capture these savings that are important from a societal perspective