Oltre l’immunoterapia: nuovi bersagli terapeutici

Dr Roberto Iacovelli
Agenda

• The angiogenesis

• New conjugates antibodies

• The FGFR
The end of angiogenesis-era in UCs

Docetaxel + Ramucirumab

mUCs previously treated with platinum

Median PFS:
D+Ramucirumab 4.07 months
D+Placebo 2.76 months

Primary endpoint: PFS
Secondary endpoints: OS, ORR, safety

The end of angiogenesis-era in UCs

Overall Survival, ITT population

Censored observations
- Ramucirumab+Docetaxel (n=263); median = 9.40 months
- Placebo+Docetaxel (n=267); median = 7.85 months

Log-rank P = .2461
HR = 0.887 (95% CI, 0.724 to 1.096)

Petrylak DP, et al. Presented at ESMO 218, abst 865PD.
Conjugated Antibody: Enfortumab Vedotin

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Roberto Iacovelli
Nectin-4

The encoded protein contains two immunoglobulin-like (Ig-like) C2-type domains and one Ig-like V-type domain. It is involved in cell adhesion through trans-homophilic and -heterophilic interactions. It is a single-pass type I membrane protein.

Mutations in this gene are the cause of ectodermal dysplasia-syndactyly syndrome type 1, an autosomal recessive disorder.

Conjugated Antibody: Enfortumab Vedotin

Change in Tumor Burden From Baseline in All Patients (N = 112)

Conigated Antibody: Enfortumab Vedotin

<table>
<thead>
<tr>
<th>Survival Endpoint</th>
<th>EV 1.25 mg/kg</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All (N = 112)</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>5.4 (5.1-6.2)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
</tr>
<tr>
<td>Median, mos (95% CI)</td>
<td>13.6 (11.0-15.4)</td>
</tr>
<tr>
<td>Estimated 6-mo rate, %</td>
<td>74.4</td>
</tr>
<tr>
<td>Estimated 12-mo rate, %</td>
<td>56.3</td>
</tr>
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Ongoing Trials

Enfortumab Vedotin

Best Chemo (vin, pacl, doc)

Enfortumab Vedotin

Pebrolizumab or Atezolizumab

Adv/metast. disease, Previous cisplatin and CPI.

Phases:
- Phase: III
  - Primary endpoint: OS
  - Patients: 550

Enfortumab Vedotin

Adv/metast. disease, Previous Tx

Phases:
- Phase: Ib
  - Primary endpoint: Safety
  - Patients: 85

Enfortumab Vedotin

Adv/metast. disease, Previous cisplatin and CPI.

Phases:
- Phase: II
  - Primary endpoint: Safety
  - Patients: 85

Clinicaltrial.gov

Enfortumab Vedotin

Adv/metast. disease, Prev CPI, platinum-naïve and cisplatin-ineligible

Phases:
- Phase: II
  - Primary endpoint: ORR
  - Patients: 100 (Cohort 1)

Clinicaltrial.gov

Enfortumab Vedotin

Adv/metast. disease, Previous cisplatin and CPI.

Phases:
- Phase: II
  - Primary endpoint: ORR
  - Patients: 100 (Cohort 2)
The inhibition of the FGFR

4 distinct receptors in the FGFR family

Serve as receptors for 22 proteins that comprise the FGF family and control growth, differentiation, survival, angiogenesis, and invasion

Driver events in various malignancies include

- Point mutations
- Gene fusions
- Gene amplification
- Protein overexpression

Driver events may play a role in acquired resistance to other targeted therapies

Slide credit: clinicaloptions.com
## The inhibition of the FGFR

<table>
<thead>
<tr>
<th>Gene</th>
<th>Molecular Alterations</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGFR1</strong></td>
<td>Amplification</td>
<td>Squamous NSCLC (20%)&lt;br&gt;Breast cancer (10%)&lt;br&gt;Ovarian cancer (~5%)&lt;br&gt;Bladder cancer (3%)&lt;br&gt;Others: oral SCC, esophageal SCC</td>
</tr>
<tr>
<td></td>
<td>Mutations</td>
<td>Melanoma (rare)&lt;br&gt;Glioblastoma&lt;br&gt;Pilocytic astrocytoma (5% to 8%)</td>
</tr>
<tr>
<td></td>
<td>Translocations</td>
<td>8p11 myeloproliferative syndrome&lt;br&gt;Chronic myeloid leukemia (rare)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Gene</th>
<th>Molecular Alterations</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGFR2</strong></td>
<td>Mutations</td>
<td>Squamous NSCLC (3%)&lt;br&gt;Melanoma (loss of function?)&lt;br&gt;Endometrial cancer (12%)</td>
</tr>
<tr>
<td></td>
<td>Germline SNP</td>
<td>Second intron SNP: BC susceptibility</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>Bladder cancer&lt;br&gt;Salivary adenoid cystic cancer</td>
</tr>
</tbody>
</table>

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<tr>
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<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGFR3</strong></td>
<td>Mutations</td>
<td>Bladder cancer (50% to 60% NMIBC)&lt;br&gt;Cervical cancer (5%)&lt;br&gt;Myeloma (5%)&lt;br&gt;Spermatocytic seminoma (7%)</td>
</tr>
<tr>
<td></td>
<td>Translocations</td>
<td>Myeloma (15% to 20%)</td>
</tr>
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<tr>
<th>Gene</th>
<th>Molecular Alterations</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGFR4</strong></td>
<td>Amplification/mutations</td>
<td>Rhabdomyosarcoma (7% to 8%)</td>
</tr>
<tr>
<td></td>
<td>Germline SNP</td>
<td>Coding SNP; poor prognosis</td>
</tr>
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The inhibition of the FGFR

“Multi” TKIs often hit FGFR, but at a lower potency than primary targets

- Dovitinib (TKI258)
- Cediranib (AZD 2171)
- Brivanib (BMS-58266)
- Nintedanib (BIBF-1120)

Numerous selective FGFR TKIs are in development

- AZD4547
- BAY 1163877 (rogaratinib)
- BGJ398 (infgratinib)
- JNJ-42756493 (erdaftinib)
- LY2874455
- PRN1371
The inhibition of the FGFR

**BLC2001: Study Design**

- **International, open-label phase II trial**
  
  Patients with metastatic or un-resectable locally advanced UC; PD on ≥ 1 line prior systemic CT or within 12 mos (neo) adjuvant CT, or cisplatin ineligible* and CT naive; prior IO therapy permitted (N = 99)

*Defined as peripheral neuropathy or impaired renal function. 'Titration up to 9 mg QD if target not reached for serum phosphate (≥ 5.5 mg/dL) by Day 14 and no TRAEs.

- **Primary endpoint: ORR**
  
  - Study has 85% power with 1-sided α = 0.025 to test primary hypothesis that ORR > 25% in Regimen 3


- **Secondary endpoints: PFS, OS, safety, DoR, PK, predictive biomarker evaluation**
The inhibition of the FGFR

BLC2001: Antitumor Activity

- Tumor shrinkage observed in 76% of evaluable patients receiving erdafitinib 8 mg QD
- Responses were durable

<table>
<thead>
<tr>
<th>Response, ** n (%)</th>
<th>Patients (N = 99)</th>
</tr>
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<tbody>
<tr>
<td>ORR</td>
<td>40 (40.4)</td>
</tr>
<tr>
<td>• CR</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>• PR</td>
<td>37 (37.4)</td>
</tr>
<tr>
<td>SD</td>
<td>39 (39.4)</td>
</tr>
<tr>
<td>PD</td>
<td>18 (18.2)</td>
</tr>
<tr>
<td>Median TTR, mos</td>
<td>1.4</td>
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<tr>
<td>Median DoR, mos</td>
<td>5.6</td>
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<table>
<thead>
<tr>
<th>Response, %</th>
<th>Patient Subgroups</th>
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<tbody>
<tr>
<td></td>
<td>CT Naive (n = 12)</td>
</tr>
<tr>
<td>ORR to erdafitinib</td>
<td>41.7</td>
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<tr>
<td>ORR to prior IO</td>
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Slide credit: clinicaloptions.com
The inhibition of the FGFR

**BLC2001: Most Common TRAEs**

<table>
<thead>
<tr>
<th>TRAEs in &gt; 20% of Patients, n (%)</th>
<th>Erdafitinib 8 mg QD (N = 99)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
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<tr>
<td>Hyperphosphatemia</td>
<td>72 (73)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>54 (55)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (37)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35 (35)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>32 (32)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (21)</td>
</tr>
</tbody>
</table>

- Most TRAEs were grade 1/2
  - No grade 4/5 TRAEs observed
- Serious TRAEs observed in 9 patients (9%)
  - No serious TRAE observed in \( \geq 1 \) patient
Ongoing Trials

**Rogaratinib**
- Adv/metast. disease, Previous cisplatin, FGFR mut/ampl
- Phase: II/III
- Primary endpoint: OS
- Patients: 400

**Best Chemo (vin, pacl, doc)**

**Atezolizumab**
- Adv/metast. disease, Previous cisplatin, FGFR mut/ampl
- Phase: I/II
- Primary endpoint: PFS, safety
- Patients: 190

**Erdaftinib**
- Adv/metast. disease, Previous cisplatin, FGFR mut/ampl
- Phase: III
- Primary endpoint: OS
- Patients: 631

**Best Chemo (vin, doc)**

**Pembrolizumab**

**JNJ-63723283**
- Adv/metast. disease, Previous cisplatin, FGFR mut/ampl
- Phase: I/II
- Primary endpoint: Safety, ORR
- Patients: 102