Renal Cell Carcinoma (RCC): KOL Insight (2017)
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RESEARCH OBJECTIVES

The goal of this FirstWord Therapy Trends report is to present a comprehensive qualitative review of targeted therapies in the RCC market, with an emphasis on current and future treatment pathways. In order to achieve this goal, FirstWord analysts conduct detailed secondary research into current and late-stage pipeline therapies. This research focuses on the development of commercial and clinical profiles for each product; the identification of key clinical data; the isolation of key ongoing clinical trials; and the classification of the current treatment algorithm based on patient segment, line of therapy and patient characteristics.

Following this research, FirstWord conducted 60-minute telephone interviews with 12 KOLs from the US and Europe, between 3 and 20 April 2017, to provide expert views on the current treatment landscape and how it is expected to change in the future. In order to ensure the quality of the interviews, the KOLs were carefully selected based on their clinical experience, scientific publications, involvement in clinical trials, participation in treatment guideline development and record of presenting at high-profile international conferences. Moderators with detailed knowledge of the market dynamics and a track record of obtaining valuable insights from KOLs conducted the interviews, with the objective of obtaining answers to the following questions:

- Which drugs constitute the first- and subsequent-line therapies of choice for advanced and metastatic RCC? Which product attributes contribute to this preference?

- How are the marketed products perceived by the medical community in terms of efficacy, tolerability, ease of administration and other product attributes, and how do they compare with other treatment options?

- Which recently completed or ongoing clinical trials have the greatest potential to impact prescribing trends, and how will the results affect the future treatment of RCC?

- What do pipeline targeted therapies for RCC need to show in order to become the treatment of choice in a specific patient segment and line of therapy, and is it likely the current late-stage development products will meet these requirements?
How will the use of each current and pipeline product change in the future in terms of patient segments, line of therapy and preference?

What will pipeline products need to show in terms of efficacy and tolerability endpoints to effectively compete with current therapies, and what is the likelihood they will achieve those endpoints?

Which pipeline products are the most promising, and how will they impact current players in the market?

How will the treatment landscape for RCC evolve in the future?

The insights obtained from the primary and secondary research are organised by product class and detailed for each current and pipeline product. At the end of the report, the current and future treatment algorithms are summarised, allowing rapid identification of key players and expected future developments.
VEGF INHIBITORS

Overview

Vascular endothelial growth factor (VEGF) inhibitors are the main class of agents approved for the treatment of advanced/mRCC. Their success in treating RCC lies in the fact that VEGF is over-expressed in RCC and is a potent mediator of angiogenesis. To date, VEGF inhibitors belong to two main classes: anti-VEGF monoclonal antibodies and VEGF tyrosine kinase inhibitors (TKIs). Roche’s Avastin belongs to the former group, whilst all other approved VEGF inhibitors (Pfizer’s Sutent, Novartis’ Votrient, Bayer’s Nexavar, Pfizer’s Inlyta, Exelixis’ Cabometyx and Eisai’s Lenvima/Kisplyx) fall into the latter category. Some of the second-generation VEGF TKIs target additional receptors (e.g., MET and ALT in the case of Cabometyx and FGF in the case of Lenvima/Kisplyx), which may confer certain efficacy advantages over other VEGF TKIs, although this has not yet been demonstrated conclusively in clinical trials. AVEO Oncology is developing the VEGF TKI Tivopath for the treatment of advanced RCC.
Nexavar (sorafenib; Amgen/Bayer)

Key insights summary

Figure 3: Key insights for Nexavar (sorafenib; Amgen/Bayer)

Key insights for Nexavar (sorafenib; Amgen/Bayer)

- Nexavar’s current use is reserved for later lines of therapy
- Most KOLs are sceptical about the potential for Nexavar as adjuvant therapy and do not expect the Phase III adjuvant trial to yield positive results
- Overall use of Nexavar expected to remain limited and could potentially decline

Source: FirstWord

Drug summary

Table 7: Nexavar (sorafenib; Amgen/Bayer) Commercial Profile

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Nexavar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>sorafenib</td>
</tr>
<tr>
<td>Approval dates</td>
<td>US: December 2005; EU: July 2006</td>
</tr>
<tr>
<td>Approved indications</td>
<td>US: Advanced RCC</td>
</tr>
<tr>
<td></td>
<td>EU: Patients with advanced RCC who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy</td>
</tr>
<tr>
<td>Marketing company</td>
<td>Amgen/Bayer</td>
</tr>
</tbody>
</table>

Source: Adis R&D Insight, (c) 2017 Springer Science+Business Media, used with permission; See footnotes

Drug summary

Table 13: Cabometyx (cabozantinib; Exelixis) Commercial Profile

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Cabometyx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>cabozantinib</td>
</tr>
<tr>
<td>Approval dates</td>
<td>US: April 2016; EU: September 2016</td>
</tr>
<tr>
<td>Approved indications</td>
<td>US: The treatment of patients with advanced RCC who have received prior anti-angiogenic therapy; EU: The treatment of advanced RCC in adults following prior VEGF-targeted therapy</td>
</tr>
<tr>
<td>Marketing company</td>
<td>Exelixis (US); Ipsen (EU)</td>
</tr>
<tr>
<td>Notes</td>
<td>VEGF=vascular endothelial growth factor</td>
</tr>
</tbody>
</table>

Source: Adis R&D Insight, (c) 2017 Springer Science+Business Media, used with permission; See footnotes

Table 14: Cabometyx (cabozantinib; Exelixis) Clinical Profile

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Inhibits multiple tyrosine kinases, including MET, RET, AXL and VEGFR-1, -2 and -3.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Oral, once daily</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Patients with advanced RCC (n=658) who had received at least one prior anti-angiogenic therapy were randomised to receive Cabometyx 60mg daily (n=330) or everolimus 10mg daily (n=328). The main efficacy outcome measure was PFS; other efficacy endpoints were ORR and OS. Patients received treatment until disease progression or they experienced unacceptable toxicity. Median PFS: 7.4 months (Cabometyx) vs 3.8 months (everolimus); HR: 0.58 (p&lt;0.0001) Median OS: 21.4 months (Cabometyx) vs 16.5 months (everolimus); HR: 0.66 (p=0.0003) Confirmed ORR: 17% (Cabometyx) vs 3% (everolimus); p&lt;0.0001</td>
</tr>
<tr>
<td>Tolerability</td>
<td>According to the US prescribing information, the most frequent adverse reactions (≥20%) are: diarrhoea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decrease and constipation.</td>
</tr>
<tr>
<td>Safety</td>
<td>The US prescribing information warns of a potential risk of haemorrhage, GI perforations and fistulas, thrombotic events, hypertension, diarrhoea, PPES, reversible posterior leukoencephalopathy syndrome (RPLS) and embryofoetal toxicity.</td>
</tr>
</tbody>
</table>

Notes: VEGF=vascular endothelial growth factor; MET=hepatocyte growth factor receptor protein; PRS=progression-free survival; OS=overall survival; ORR=overall response rate

Source: Adis R&D Insight, (c) 2017 Springer Science+Business Media, used with permission; See footnotes

Despite being regarded as extremely effective, Cabometyx’s toxicity profile dampens KOLs’ enthusiasm for the agent

KOLs consider that Cabometyx’s greatest advantage is its efficacy, in particular its ability to achieve rapid tumour shrinkage and impact bone metastases – advantages that have also been shown in subanalyses of the METEOR trial. A minority of oncologists state that since Cabometyx is an oral drug, they may select it over intravenous Opdivo for working and active patients.

At the same time, KOLs concur that cabozantinib requires careful adverse event monitoring and appropriate dose reductions because of its side-effect profile. The most frequent grade 3–4 adverse events with Cabometytx recorded in the METEOR trial were: hypertension (15 percent), diarrhoea (11 percent), fatigue (nine percent) and hand-foot syndrome (eight percent). Apart from concerns about its toxicity profile, a few KOLs note that Cabometyx is not easy to titrate.

“We use this drug and recommend it in the patients in whom you want to see a rapid decrease in tumour size and rapid control of their disease.”

US Key Opinion Leader

“It seems to be interesting particularly for patients having bone metastases, a huge tumour burden and papillary tumours. But it’s not an easy drug to use because it has side effects, probably equivalent to Sutent in many respects.”

EU Key Opinion Leader

“For patients who have a high tumour burden where there is a need to reduce the tumour mass, in these patients cabozantinib might be preferred. However, also for these patients we have the alternative with everolimus and lenvatinib, which has a higher rate of tumour shrinkage, although these data are based not on a Phase III but on a Phase II trial.”

EU Key Opinion Leader

“There is no doubt it is an efficacious drug, but it also can be very toxic and difficult to dose; like Sutent it is hard to titrate the dose.”

US Key Opinion Leader

**Drug summary**

Table 22: Tivopath (tivozanib; AVEO Oncology) Clinical Profile

<table>
<thead>
<tr>
<th><strong>Brand name</strong></th>
<th>Tivopath</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic name</strong></td>
<td>tivozanib</td>
</tr>
<tr>
<td><strong>Company</strong></td>
<td>AVEO Oncology (EUSA Pharma is a sublicensee in the EU)</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>VEGF-TKI (inhibits VEGFR-1, 2 and 3)</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral, once daily</td>
</tr>
<tr>
<td><strong>Study populations</strong></td>
<td>Patients with mRCC who were either treatment naïve or had been pre-treated (although pre-treatment with a VEGF or mTOR inhibitor was not permitted)</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Phase III TIVO-1 trial</td>
</tr>
<tr>
<td></td>
<td>Patients (n=517) with metastatic RCC were randomly assigned to Tivopath (n=260) or sorafenib (n=257). The primary endpoint was PFS by independent review. Patients who progressed on sorafenib (n=156) crossed over to receive Tivopath.</td>
</tr>
<tr>
<td></td>
<td>PFS: 11.9 months (Tivopath) vs 9.1 months (sorafenib); HR=0.797; p=0.042</td>
</tr>
<tr>
<td></td>
<td>OS: 28.8 months (Tivopath) vs 29.3 months (sorafenib); HR=1.245; p=0.105</td>
</tr>
<tr>
<td><strong>Tolerability</strong></td>
<td>Adverse events more common with Tivopath than with sorafenib were hypertension (44% vs 34%) and dysphonia (21% vs 5%). Adverse events more common with sorafenib than with Tivopath were hand-foot skin reactions (54% vs 14%) and diarrhoea (33% vs 23%).</td>
</tr>
</tbody>
</table>

Notes: VEGFR=vascular endothelial growth factor receptor; TKI=tyrosine kinase inhibitor; PFS=progression-free survival; OS=overall survival; HR=hazard ratio

**Source:** Adis R&D Insight, (c) 2017 Springer Science+Business Media, used with permission; See footnotes

Table 23: Tivopath (tivozanib; AVEO Oncology) Key Trials to Watch

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Trial Acronym</th>
<th>Title</th>
<th>Phase</th>
<th>Primary completion date</th>
<th>Expected completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02627963</td>
<td>TIVO-3</td>
<td>A Phase III, Randomized, Controlled, Multi-Centre, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma</td>
<td>III</td>
<td>Aug 2018</td>
<td>Oct 2018</td>
</tr>
</tbody>
</table>

**Source:** [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

APPENDIX

KOL details

KOLs from North America

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Robert Motzer, Professor of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Brian Rini, Professor of Medicine, Lerner College of Medicine, The Cleveland Clinic Taussig Cancer Center, Cleveland, OH
KOLs from Europe

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Giuseppe Procopio, Professor of Medicine, Fondazione IRCCS – Istituto Nazionale dei Tumori, Milan

Anonymous KOL, Professor of Haematology and Oncology, major university medical centre, Germany

Anonymous KOL, Professor of Haematology and Oncology, major university hospital, Germany

Anonymous KOL, Professor and Chairman of the Department of Urology, major university hospital, Germany