Emerging Targeted Therapies

Thomas E Hutson, DO, PharmD, FACP

Professor of Medicine
Director, GU Oncology Program
Co-Director, GU Center of Excellence
Associate Chair, GU Research

Texas Oncology, PA
Baylor-Sammons Cancer Center
Dallas, Texas
Texas AM HSC College of Medicine
US Oncology
Disclosures

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Emerging Targeted Therapies

- Cabozantanib
  - ESMO 2015
  - FDA approval expected
  - Pending OS results, with attractive HR
- Delantercept + Axitinib (DART)
- Tivozanib
- Lenvatanib + Everolimus
- Nivolumab
- IO + IO, IO + TKI, IO + VEGF
  - Ipi Nivo Phase III
  - MPD + Bev Phase III
Cabozantinib versus everolimus in patients with advanced renal cell carcinoma: results of a randomized phase 3 trial (METEOR)

Cabozantanib

Study Design

Advanced RCC (N=650)
- Clear cell histology
- Measurable disease
- Progression on prior VEGFR TKI within 6 months of enrollment
- No limit to the number of prior therapies
- Antibodies targeting PD-1/PD-L1 allowed
- Brain metastases allowed if treated

Randomization 1:1
- No cross-over allowed
- Cabozantinib 60 mg qd orally
- Everolimus 10 mg qd orally

Stratification:
- MSKCC\textsuperscript{1} risk groups: favorable, intermediate, poor
- Number prior VEGFR-TKIs: 1, 2 or more

\textsuperscript{1} Motzer R. et al., J Clin Oncol. 2004
Cabozantinib

Progression-Free Survival
Independent Central Radiology Review

Median PFS
mo (95% CI)  No. of Events

- Cabozantinib (N=187)  7.4 (5.6-9.1)  121
- Everolimus (N=188)   3.8 (3.7-5.4)  126

Hazard ratio, 0.58 (95% CI 0.45-0.75, P<0.001)

No. at Risk
Cabozantinib  187  152  92  68  20  6  2
Everolimus    188  99  46  29  10  3  0

Months

Progression-free Survival (%)
Kaplan-Meier Estimates of Overall Survival
Interim Analysis (49% Information Fraction)

Hazard ratio, 0.67 (95% CI 0.51-0.89, P=0.005)
(Medians cannot yet be estimated due to frequent early censoring)

No. at Risk
Cabozantinib 330 317 294 189 101 32 6 1 0
Everolimus 328 306 260 156 88 24 5 1 0

The interim boundary to reach significance (P=0.0019) was not reached.
Survival follow up is continuing to the planned final analysis.
# Cabozantinib

## All-causality Adverse Events

<table>
<thead>
<tr>
<th>Preferred Term, %</th>
<th>Cabozantinib (N=331)</th>
<th>Everolimus (N=322)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td><strong>Any adverse event</strong>*</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td><strong>PPE syndrome</strong></td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

### Events of interest

<table>
<thead>
<tr>
<th>Event</th>
<th>Cabozantinib</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GI Perforation</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fistula</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Events reported in at least 25% of patients in either study group; PPE, palmar-plantar erythrodysesthesia.
The DART Study: Part 1 results of dalantercept plus axitinib dose escalation and expansion cohorts in advanced RCC

M. H. Voss, E. Plimack, B. Rini, M. B. Atkins, R. Alter, R. S. Bhatt, J. T. Beck

Memorial Sloan Kettering Cancer Center, New York, NY; Fox Chase Cancer Center, Philadelphia, PA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Georgetown University Medical Center, Washington, DC; John Theurer Cancer Center Hackensack UMC, Hackensack, NJ; Beth Israel Deaconess Medical Center, Boston, MA; Highlands Oncology Group, Fayetteville, AR

Presented at the Genitourinary Cancers Symposium
Dalantercept and ALK1 Signaling

- **BMP9/10**
- **ALK1** (Type I Receptor)
- **BMPRII** (Type II Receptor)
- **Endoglin** (Accessory Receptor)
- **R-SMAD1/5/8**
- **SMAD4**
- **SRE (Smad Responsive Element)**
- **Vascular Maturation**

**Endothelial cell**

Presented by Martin H. Voss, M.D.
Additive Efficacy of Dalantercept plus VEGFR TKI in RCC Xenograft Models

DART: Part 1 Study Schema

Open-Label, Dose Selection (n = 29)
Primary Endpoints: Safety, RP2D, PK
Secondary Endpoints: PFS, ORR, exploratory PD biomarkers in archived tissue and serum

Dose-Escalation
- Axitinib 5 mg BID + Dalantercept (0.6 mg/kg) (n = 6)
- Axitinib 5 mg BID + Dalantercept (0.9 mg/kg) (n = 4)
- Axitinib 5 mg BID + Dalantercept (1.2 mg/kg) (n = 5)

Expansion
- Axitinib 5 mg BID + Dalantercept 0.9 mg/kg (n = 5)
- 1.2 mg/kg (n = 9)

Advanced RCC
> 1 prior VEGFR TKI, ≤ 3 lines of prior therapy

Note: dose titration of axitinib to 7mg and 10mg BID permitted after 4 weeks on study
Key Eligibility Criteria

• Predominantly clear cell advanced RCC
• Progression on at least 1 VEGFR TKI
  – Inclusive of adjuvant therapy
• No more than 3 prior lines of therapy
• Treated, stable CNS disease permitted
• ECOG performance status: 0 – 1
# Clinical Adverse Events of Interest

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.6 mg/kg (N=6)</th>
<th>0.9 mg/kg (N=9)</th>
<th>1.2 mg/kg (N=14)</th>
<th>Overall (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades n (%)</td>
<td>Grade = 3* n (%)</td>
<td>All grades n (%)</td>
<td>Grade = 3* n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>6 (66.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (66.7)</td>
<td>1 (16.7)</td>
<td>6 (66.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (16.7)</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (33.3)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>1 (16.7)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0</td>
<td>0</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (16.7)</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note: there were no grade 4/5 drug-related adverse events*
### Disease Response and Preliminary PFS Analysis

<table>
<thead>
<tr>
<th>Response</th>
<th>0.6 mg/kg (N = 6)</th>
<th>0.9 mg/kg (N = 9)</th>
<th>1.2 mg/kg (N = 13)</th>
<th>Overall N = 28 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>2</td>
<td>6</td>
<td>9</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Disease Control Rate ≥ 8 cycles (~ 6 months)</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>Median PFS in months (95% CI)</td>
<td>5.5</td>
<td>NR</td>
<td>6.9</td>
<td>8.3 (4.1, NR)</td>
</tr>
</tbody>
</table>

Note: 1 patient not evaluable based upon ineligibility.  
NR = not reached; CI: confidence interval
Best Overall Response and Duration of Treatment

Presented by Martin H. Voss, M.D.

* Active on therapy

Duration of Treatment (Months)

2.0 <1 1.3 <1 1.6 1.4 5.0 1.4 2.5 4.4 2.7 17.2 1.6 9.8 6.9 13.1 8.4 10.6 5.6 2.8 16.2 9.3 7.0 10.2 8.1 13.9 19.9
DART: Part 2 Study Schema

Randomized, Double-Blind, Placebo-Controlled (N = 130)
Primary Endpoint: PFS
Secondary Endpoints: ORR, OS, Safety, PK, exploratory PD biomarkers

Advanced RCC
1 prior VEGFR TKI, may have also had
1 mTOR inhibitor and/or any prior
immune therapy

Dalantercept
(0.9 mg/kg)
+ Axitinib 5mg BID
(n = 65)

Placebo
+ Axitinib 5mg BID
(n = 65)

Note: dose titration of axitinib to 7mg and 10mg BID permitted after 4 weeks on study

NCT01727336

Presented at the Genitourinary Cancers Symposium

Presented by Martin H. Voss, M.D.
A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma

AV-951-15-303

AUGUST 2015
Tivozanib Unique Biochemical Properties

**Potency & Dose**

- **IC$_{50}$ (nM)**
  - **tivozanib**: 1.5
  - axitinib: 10
  - Sutent: 50
  - Votrient: 800
  - Nexavar: 800

- **Dose (mg/day)**
  - Less potent
  - More potent

**Selectivity**

- **Fold selectivity (VEGFR/off-target kinase)**
  - **[c-kit] tivozanib**: 9
  - axitinib: 8
  - Sutent: 7
  - Votrient: 6
  - Nexavar: 5

**Half Life**

- **$t_{1/2}$ (h)**
  - **Tivozanib** exhibits a half life of ~4.5 days

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*In vitro data
+ In vivo data

CONFIDENTIAL INFORMATION
Study 902 Antitumor Activity of Tivozanib After PD on Sorafenib

Patients Receiving Tivozanib following Progression on Sorafenib

Next Line PFS as Determined by Investigator Review

<table>
<thead>
<tr>
<th>Status [n (%)]</th>
<th>TIVOZANIB (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects who had progression or Died</td>
<td>113 (69.3)</td>
</tr>
<tr>
<td>Subjects with censored endpoints</td>
<td>50 (30.7)</td>
</tr>
<tr>
<td>Median PFS (months) w/ 95% CI</td>
<td>11.0 (7.4, 12.9)</td>
</tr>
</tbody>
</table>

Next Line Overall Survival

<table>
<thead>
<tr>
<th>Status [n (%)]</th>
<th>TIVOZANIB (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>83 (50.9)</td>
</tr>
<tr>
<td>Alive</td>
<td>80 (49.1)</td>
</tr>
<tr>
<td>Median OS (months) w/ 95% CI</td>
<td>21.6 (17.0, 27.6)</td>
</tr>
</tbody>
</table>
# Significant Activity in Second Line RCC with Tivozanib

<table>
<thead>
<tr>
<th>Study</th>
<th><strong>AXIS:</strong> Phase 3, 2(^{nd}) line RCC \ axitinib vs sorafenib (1:1)(^1)</th>
<th><strong>Dovitinib study:</strong> Phase 3, 3(^{rd}) line RCC dovitinib vs sorafenib (1:1)(^2)</th>
<th><strong>TIVO-1:</strong> Phase 3, 2(^{nd}) line RCC subset crossing over to tivozanib following sorafenib progression(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Size</strong></td>
<td>n=361 (axitinib arm) n=362 (sorafenib arm) (54% sunitinib refractory)</td>
<td>n=280 (dovitinib) n=284 in sorafenib arm (TKI &amp; mTOR refractory)</td>
<td>n=163 (tivozanib)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>sunitinib refractory pts 6.5 mo (axitinib) vs. 4.5 mo (sorafenib)*</td>
<td>TKI &amp; mTOR Refractory 3.7 mo (dovitinib) vs. 3.6 mo (sorafenib)</td>
<td>sorafenib refractory pts 11.0 mo(^\wedge) (tivozanib)</td>
</tr>
<tr>
<td></td>
<td>HR = 0.636, p&lt;0.0002*</td>
<td>HR 0.86, p=0.063</td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>sunitinib refractory pts 15.2 mo (axitinib) vs. 16.5 mo (sorafenib)</td>
<td>TKI &amp; mTOR refractory 11.1 mo (dovitinib) vs. 11.0 mo (sorafenib)</td>
<td>sorafenib refractory pts 21.6 mo(^\wedge) (tivozanib)</td>
</tr>
</tbody>
</table>

* n= 389; investigator assessed PFS; independent PFS = 4.8 mo vs. 3.4 mo, HR = 0.741 (p=0.011)

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1) Motzer et al Lancet Oncol 2013; 14: 552–62
2) Motzer et al Lancet Oncol 2014
3) Hutson et al ASCO 2015
Phase III RCC study

• Third line RCC
  – S/P VEGF TKI and something else
    • Second TKI, mTOR, or PD-1
• Tivozanib vs. Sorafanib
• 15 Months to Enroll Starting in December 2015
• Primary Endpoint is PFS
  – Topline Data in 4Q 2017
• Secondary Endpoint is OS
  – Present available data to show positive trend.
• File NDA in 1H 2018
Potential Phase 3 Confirmatory Study Design in Recurrent/Metastatic RCC

Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma

- N = ~314
  - Recurrent/metastatic RCC
  - Failed at least two prior regimens including VEGFR-TKI (not sorafenib)
  - ECOG PS 0 or 1

Randomize 1:1

- Tivozanib
- Sorafenib

- \(^1\): PFS
- \(^2\): OS, ORR, DoR, Safety and tolerability for ITT & Pre-Specified Biomarkers

Open-label, randomized, controlled, multi-national trial

Subjects will be randomized in a 1:1 ratio (tivozanib:sorafenib) stratified by IMDC (good, intermediate, poor) and prior therapy (prior PD-1(L), two TKIs, neither)
Randomized phase 2 three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC)

There is an unmet need for improved treatment outcome of metastatic RCC patients to standard VEGF-targeted therapies and mTOR inhibitors.

Fibroblast Growth Factor (FGF) pathway activation has been proposed as a mechanism of escape from VEGF-targeted therapies.\(^1\)

Lenvatinib is a highly potent tyrosine kinase inhibitor of VEGFR1–3 and FGFR1–4.\(^2-4\)

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**Kinase inhibitory profile of lenvatinib**

<table>
<thead>
<tr>
<th>Cell-free kinase</th>
<th>IC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR3</td>
<td>2.3</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>3.0</td>
</tr>
<tr>
<td>VEGFR1</td>
<td>4.7</td>
</tr>
<tr>
<td>FGFR2</td>
<td>27</td>
</tr>
<tr>
<td>FGFR4</td>
<td>43</td>
</tr>
<tr>
<td>FGFR3</td>
<td>52</td>
</tr>
<tr>
<td>FGFR1</td>
<td>61</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>29</td>
</tr>
</tbody>
</table>

---

Study Design

Key eligibility criteria:
- Advanced or metastatic RCC
- Measurable disease
- Progression on/after 1 prior VEGF-targeted therapy
- Progression within 9 mos of stopping prior treatment
- ECOG PS ≤1

Patients were treated until:
- Disease progression
- Unacceptable toxicity

Stratification factors:
- Hemoglobin (normal vs low)
- Corrected serum calcium (≥ vs < 10 mg/dL)

Lenvatinib
18 mg PO qd
+ Everolimus
5 mg PO qd

Lenvatinib
24 mg PO qd

Everolimus
10 mg PO qd
Primary Endpoint: Progression-free Survival

Number at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (mos)</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib/Everolimus</td>
<td>51</td>
<td>1</td>
<td>41</td>
<td>27</td>
<td>23</td>
<td>16</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>52</td>
<td>1</td>
<td>41</td>
<td>29</td>
<td>20</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Median, mos (95% CI)

- Lenvatinib/Everolimus: 14.6 (5.9–20.1)
- Lenvatinib: 7.4 (5.6–10.2)
- Everolimus: 5.5 (3.5–7.1)

HR 0.40 (95% CI 0.24–0.68); P < 0.001

HR 0.61 (95% CI 0.38–0.98); P = 0.048
## Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib/Everolimus (n = 51)</th>
<th>Lenvatinib (n = 52)</th>
<th>Everolimus (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, %</strong></td>
<td>43</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>29–58</td>
<td>16–41</td>
<td>1–17</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial</td>
<td>41</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>41</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Progression</td>
<td>4</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>12</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td><strong>Median duration of objective response, (months)</strong></td>
<td>13.0</td>
<td>7.5</td>
<td>8.5</td>
</tr>
</tbody>
</table>

NE, not estimable.
Overall Survival (Updated Analysis)

Median, mos (95% CI)
- Lenvatinib/Everolimus: 25.5 (16.4–NE)
- Lenvatinib: 19.1 (13.6–26.2)
- Everolimus: 15.4 (11.8–19.6)

Lenvatinib/Everolimus vs Everolimus
HR 0.51 (95% CI 0.30–0.88); P = 0.024

Lenvatinib vs Everolimus
HR 0.68 (95% CI 0.41–1.14); P = 0.118

Number at risk:
- Lenvatinib/Everolimus: 51, 48, 46, 44, 38, 35, 29, 21, 14, 6
- Lenvatinib: 52, 50, 45, 42, 37, 31, 26, 16, 7, 4
- Everolimus: 50, 46, 42, 38, 30, 27, 20, 14, 8
**Lenvatinib/Everolimus vs Lenvatinib**

**Progression-free Survival**
- **Lenvatinib/Everolimus**: 14.6 (5.9–20.1) mos
- **Lenvatinib**: 7.4 (5.6–10.2) mos

**Overall Survival (Updated)**
- **Lenvatinib/Everolimus**: 25.5 (16.4–NE) mos
- **Lenvatinib**: 19.1 (13.6–26.2) mos

**Objective response rates:** Lenvatinib/Everolimus vs Lenvatinib: 43% vs 27%; Fisher $P=0.101$

**Median duration of objective response:** Lenvatinib/Everolimus, 13.0 mos; Lenvatinib, 7.5 mos
## Selected Treatment-emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>Lenvatinib/Everolimus (n = 51)</th>
<th>Lenvatinib (n = 52)</th>
<th>Everolimus (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3 (4)</td>
<td>Any grade</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>100</td>
<td>71 (14)</td>
<td>100</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>84</td>
<td>20</td>
<td>71</td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>59</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>31</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>29</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24</td>
<td>0 (2)</td>
<td>21</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>20</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>
## Summary of Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Lenvatinib/Everolimus (n = 51)</th>
<th>Lenvatinib (n = 52)</th>
<th>Everolimus (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate, %</strong></td>
<td>43</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>95% CI</td>
<td>29–58</td>
<td>16–41</td>
<td>1–17</td>
</tr>
<tr>
<td>Benefit vs everolimus</td>
<td>( P &lt; 0.001 )</td>
<td>( P = 0.007 )</td>
<td>NA</td>
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<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
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<tr>
<td>Median (mo)</td>
<td>14.6</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9–20.1</td>
<td>5.6–10.2</td>
<td>3.5–7.1</td>
</tr>
<tr>
<td>Benefit vs everolimus</td>
<td>( P &lt; 0.001 )</td>
<td>( P = 0.048 )</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Overall survival (updated)</strong></td>
<td></td>
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<tr>
<td>Median (mo)</td>
<td>25.5</td>
<td>19.1</td>
<td>15.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>16.4–NE</td>
<td>13.6–26.2</td>
<td>11.8–19.6</td>
</tr>
<tr>
<td>Benefit vs everolimus</td>
<td>( P = 0.024 )</td>
<td>( P = 0.118 )</td>
<td>NA</td>
</tr>
</tbody>
</table>