Thyroid Cancers: Update

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Vall Hebron Institute of Oncology (VHIO)
Thyroid Cancer: Cell Type and Histology

- Follicular cells (90-95%)
- Papillary
- Follicular
- Hürthle cell
- Medullary thyroid carcinoma (MTC)
- Parafollicular cells (3-5%)
Pembrolizumab for Advanced Papillary or Follicular Thyroid Cancer: Preliminary Results From the Phase 1b KEYNOTE-028 Study

Primary endpoint: Overall objective response rate

Main secondary endpoints:
- Duration of response
- Relationship between PFS and tumor PD-L1 expression and GEP score
- Safety
- Progression free survival
- Overall survival

PD-L1 ≥1% + PTC & FTC
73% pretreated
41% ≥ 2 prior lines

Mehnert ASCO 2016
Pembrolizumab in Thyroid Cancer

- 51 screenings for PD-L1 expression (22C3 moAb Merck)
- 36 (71%) positive ≥1% in tumor and/or stromal cells
- 22 received pembrolizumab

**mPFS: 6.8 months**

Mehnert ASCO 2016
Combination Targeted Therapy with Pembrolizumab and Lenvatinib in Progressive, Radioiodine-resistant Differentiated Thyroid Cancers

Previous VEGFR active multikinase inhibitor (except lenvatinib) – will stratify between both arms of primary study

Patients who have been previously treated with non-VEGFR active kinase inhibitors other than lenvatinib (examples – dabrafenib, vemurafenib, selumetinib) will be eligible for substudy 1.

Patients who have been previously treated with lenvatinib and have RECIST progression will be eligible for substudy 2.

**Primary Outcome:**

**Substudy #1:** Complete Response (CR) as determined by RECIST 1.1 criteria.

**Substudy #2:** Objective Response Rate (CR+PR) as determined by RECIST 1.1 criteria.
NTRK fusions in Thyroid Cancer

First reported clinical response in Trk-fusion patients\textsuperscript{11}

- \textit{NTRK1} fusions in cholangiocarcinoma\textsuperscript{12}
- \textit{NTRK1} fusions in Spitz tumors\textsuperscript{13}
- \textit{ETV6-NTRK3} in radiation-associated thyroid cancer\textsuperscript{14}
- \textit{NTRK1,2,3} fusions in pediatric gliomas\textsuperscript{15}
- \textit{NTRK2} fusions in NSCLC\textsuperscript{16}
- \textit{NTRK3} fusions in CRC and H\&N\textsuperscript{16}
- \textit{NTRK1} fusions in sarcoma\textsuperscript{16}

- \textit{ETV6-NTRK3} in congenital fibrosarcoma\textsuperscript{3} & nephroma\textsuperscript{4}
- \textit{ETV6-NTRK3} in secretory breast cancer\textsuperscript{6}

- \textit{ETV6-NTRK3} in MASC\textsuperscript{7}

- \textit{NTRK1} fusions in PTC\textsuperscript{2}

- \textit{NTRK1} fusions in pediatric PTC\textsuperscript{21}
- \textit{NTRK3} fusions in Spitz tumors\textsuperscript{22}
- \textit{NTRK1} fusions in lipofibromatosis-like neural tumors\textsuperscript{23}

- \textit{LMNA-NTRK1} in congenital infantile fibrosarcoma\textsuperscript{24}

- \textit{LMNA-NTRK1} in CRC\textsuperscript{17}
- \textit{LMNA-NTRK1} in soft tissue sarcoma\textsuperscript{18}
- \textit{SQSTM1-NTRK1} in NSCLC\textsuperscript{19}
- \textit{NTRK3} fusions in inflammatory myofibroblastic tumor\textsuperscript{20}

- \textit{NTRK1} fusions in NSCLC\textsuperscript{8}
- \textit{NTRK2} fusions in astrocytoma\textsuperscript{9}
- \textit{NTRK1} fusions in GBM\textsuperscript{10}

\textit{NTRK1-NTRK3} in cholangiocarcinoma\textsuperscript{12}
NTRK fusions in Thyroid Cancer

Lassen U, et al. ESMO 2018

- ORR (95% CI): 81% (72–88%)
- Best response:
  - PR: 63%
  - CR: 17%

Maximum change in tumor size (%)

- Infantile fibrosarcoma
- Soft tissue sarcoma
- Melanoma
- Colon
- Appendix
- Lung
- Gastrointestinal stromal tumor
- Congenital mesoblastic nephroma
- Pancreas
- Bone sarcoma
- Thyroid
- Salivary gland

* Integrated† (n=109)

# #
Thyroid Cancer:
Cell Type and Histology

- Follicular cells
  - Anaplastic
  - Papillary
  - Follicular
  - Hürthle cell

- Parafollicular cells (3-5%)

- Medullary thyroid carcinoma (MTC)

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SELECTIVE RET INHIBITION

Table 1: Biochemical potency of RET inhibitors and MKIs against RET mutants and VEGFR2

<table>
<thead>
<tr>
<th>Compound</th>
<th>WT RET</th>
<th>RET V804M</th>
<th>RET M918T</th>
<th>VEGFR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOXO-292</td>
<td>0.4</td>
<td>0.8</td>
<td>0.7</td>
<td>100</td>
</tr>
<tr>
<td>BLU-667</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>35</td>
</tr>
<tr>
<td>RXDX-105</td>
<td>3</td>
<td>102</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>11</td>
<td>162</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>4</td>
<td>726</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Seoane J & Capdevila J. *Ann Oncol* 2018
RESEARCH ARTICLE

Precision Targeted Therapy with BLU-667 for RET-Driven Cancers

Vivek Subbiah¹, Justin F. Gainor², Rami Rahal³, Jason D. Bruhaker², Joseph L. Kim³, Michelle Maynard³, Wei Hu³, Qingfang Cao³, Michael P. Sheets³, Douglas Wiltanski¹, Kevin J. Wilson³, Lucian DiPietro³

ORIGINAL ARTICLE

Selective RET kinase inhibition for patients with RET-altered cancers

V. Subbiah¹†, V. Velcherti²†, B. B. Tuch³, K. Ebata³, N. L. Busaidy¹, M. E. Cabanillas¹, L. J. Wirth⁴, S. Stock², S. Smith³, V. Lauriall³, S. Corsi-Travali³, D. Henry³, M. Burkard⁵, R. Hamor⁵, K. Bouhaha⁵, S. Winski⁵, R. D. Wallace⁵, D. Hartley⁵, S. Rhodes⁵, M. Reddy⁵, B. J. Brandhuber³, S. Andrews³, S. M. Rothenberg³* & A. Drilon⁶*
Clinical activity of LOXO-292 in *RET*-altered cancers

<table>
<thead>
<tr>
<th></th>
<th>RET fusion-positive cancers</th>
<th>RET-mutant MTC</th>
<th>No known activating RET alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>NSCLC</td>
<td>Other&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Enrolled</td>
<td>49</td>
<td>38</td>
<td>11</td>
</tr>
<tr>
<td>Eligible for response evaluation&lt;sup&gt;2&lt;/sup&gt;</td>
<td>39</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>77%</td>
<td>77%</td>
<td>76%</td>
</tr>
<tr>
<td>Confirmed Overall Response Rate&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>74%</td>
<td>74%</td>
<td>71%</td>
</tr>
<tr>
<td>CR</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>uCR&lt;sup&gt;5&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>uPR&lt;sup&gt;5&lt;/sup&gt;</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Not evaluable&lt;sup&gt;6&lt;/sup&gt;</td>
<td>3</td>
<td>3</td>
<td>–</td>
</tr>
</tbody>
</table>

1. Patients eligible for response evaluation include thyroid cancer (n=7), pancreatic cancer (n=2). 2. Excludes patients recently enrolled that remain on treatment, but have not had a first post-baseline response assessment. 3. Response status per RECIST 1.1. Overall response rate = CR+uCR+PR+uPR. Overall response rate. Confirmed overall response rate: all RET fusion-positive (30/39, 76.9%), RET fusion-positive, NSCLC (23/30, 76.7%), RET fusion-positive other (7/9, 77.8%), RET-mutant MTC (10/22, 45.5%). 4. Excludes patients with unconfirmed CR/PR pending confirmation at time of data cut-off. 5. Unconfirmed responses in patients that remain on treatment awaiting a confirmatory response assessment. 6. Patients that discontinued treatment prior to a first post-baseline response assessment.

NSCLC = non-small-cell lung cancer; MTC = medullary thyroid cancer; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

April 2, 2018 data cut-off date

Presented By Alexander Drilon at 2018 ASCO Annual Meeting
Efficacy of LOXO-292 in RET-mutant medullary thyroid cancer

Note: Two patients not displayed (one due to treatment discontinuation prior to first post-baseline response assessment; one due to non-measurable disease at baseline (uOR)). T includes cabozantinib, lenvatinib, pazopanib, RXDX-105, sorafenib, sunitinib, and vandetanib; * CR, April 2, 2018 data cut-off date.
Efficacy of LOXO-292 regardless of mutation and starting dose

**RET mutation**
- M918T
- A883F
- E632_L633 del
- C618Y
- D631_L633 del
- D378_G385>E

**Maximum change in tumor size (%)**

**Starting dose**
- 80 mg BD
- 60 mg QD
- 60 mg BD
- 40 mg BD
- 40 mg BD
- 20 mg BD
- 20 mg BD
- 20 mg BD
- 160 mg BD

**BID = twice-daily, QD = once-daily**

**Note:** Two patients not displayed (one due to LOXO-292 discontinuation prior to first post-baseline response assessment, one due to non-measurable disease at baseline [uCR]), *CR*

April 2, 2018 data cut-off date
# LOXO-292 safety profile

<table>
<thead>
<tr>
<th>Treatment-emergent AEs (≥10% overall)</th>
<th>Treatment-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Most treatment-emergent AEs were Grade 1 in severity
- Two treatment-related AEs ≥grade 3: grade 3 tumor lysis syndrome (DLT), grade 3 increased ALT
- MTD not reached

*AE = adverse event, DLT = dose limiting toxicity, ALT = alanine aminotransferase, MTD = maximum tolerated dose. Note: Total %s for any given AE may be different than the sum of the individual grades, due to rounding.*
Thyroid Cancer: Cell Type and Histology

- Follicular cells (90-95%)
- Anaplastic
- Parafollicular cells (3-5%)
- Medullary thyroid carcinoma (MTC)
  - Parafollicular cells
  - Follicular cells
- Differentiated
  - Papillary
  - Follicular
- Hürthle cell
Is there Room for Precision Medicine in ATC?

Efficacy of Dabrafenib and Trametinib in pts with BRAF V600E mutated ATC

**METHODS**

Figure 1. ROAR Trial Design

**BRAF V600 mutation positive**
- Local assessment*

**Dosing**
- Oral dabrafenib 150 mg twice daily plus trametinib 2 mg once daily

**Primary endpoint**
- Overall response rate†

**Secondary endpoints**
- Duration of response
- Progression-free survival
- Overall survival
- Safety

**Expansion Cohorts for Efficacious Histologies**

- Disease assessment every 8 weeks (solid tumors, leukemia) or every 4 weeks (hairy cell leukemia)‡
- Treatment until unacceptable toxicity, disease progression, or death

**Anaplastic thyroid cancer**
- Biliary tract cancer
- Gastrointestinal stromal tumor
- WHO grade 1 or 2 glioma
- WHO grade 3 or 4 glioma
- Nonseminomatous/nongerminomatous germ cell tumors
- Adenocarcinoma of the small intestine
- Hairy cell leukemia
- Multiple myeloma

*Patients could be enrolled based on local *BRAF* V600E mutation results with mutation status confirmed by a central reference laboratory.

†Response determination was based on Response Evaluation Criteria In Solid Tumors v1.1 for the solid tumor cohorts, RANO or modified RANO criteria for the grades I-IV glioma cohorts, International Myeloma Working Group criteria for the multiple myeloma cohort, and protocol-specified consensus criteria for the hairy cell leukemia cohort.

Subbiah V, et al. J Clin Oncol 2018
**RESULTS**

Figure 2. Maximum percent change from baseline in the sum of target lesion diameters in the anaplastic thyroid cancer intent-to-treat population.

Data presented are best investigator-assessed response according to RECIST v1.1 for individual patients in the anaplastic thyroid cancer intent-to-treat population. One patient had progression of disease in the brain at week 1 and thus a percent change could not be calculated.

* An anaplastic thyroid cancer *BRAF V600E* mutation identified locally was not centrally confirmed in this patient.

**RR: 70%**
RESULTS
Figure 4. Treatment duration and time to events.

Overall Survival estimation at 12 months: 80%

Dabrafenib-Trametinib approved by FDA in May/2018 for ATC

Data presented are best investigator-assessed response according to RECIST v1.1 for individual patients in the anaplastic thyroid cancer intent-to-treat population.

Subbiah V, et al. J Clin Oncol 2018
Response and Acquired Resistance to Everolimus in Anaplastic Thyroid Cancer

Remarkable Response to Crizotinib ALK–Rearranged Anaplastic Thyroid Carcinoma


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Phase I/II study of spartalizumab (PDR001), an anti-PD1 mAb, in patients with anaplastic thyroid cancer

Lori Wirth¹, Ekkehard Eigendorff², Jaume Capdevila³, Luis Paz-Ares⁴, Chia-Chi Lin⁵, Matthew Taylor⁶, Rodryg Ramlau⁷, Marcus Butler⁸, Jean-Pierre Delord⁹, Zsolt Horvath¹⁰, Hans Gelderblom¹¹, Paolo A. Ascierto¹², Angelica Fasolo¹³, Dagmar Führer¹⁴, Hongqian Wu¹⁵, Geraldine Bostel¹⁶, Scott Cameron¹⁷, Jason Faris¹⁷, Andreea Varga¹⁸

¹Massachusetts General Hospital, Boston, MA; ²University Hospital Jena, Jena, Germany; ³Vall d’Hebron University Hospital, Barcelona, Spain; ⁴University Hospital 12 de October, Madrid, Spain; ⁵National Taiwan University Hospital, Taipei, Taiwan; ⁶Oregon Health & Science University, Portland, OR; ⁷University of Medical Sciences, Poznan, Poland; ⁸University Health Network, Toronto, Canada; ⁹IUCT Oncopole, Toulouse, France; ¹⁰University of Debrecen, Faculty of Medicine, Institute of Oncology, Debrecen, Hungary; ¹¹Leiden University Medical Center, Leiden, Netherlands; ¹²National Tumour Institute Fondazione G. Pascale, Naples, Italy; ¹³San Raffaele Hospital, Milan, Italy; ¹⁴University Hospital Essen, Essen, Germany; ¹⁵Novartis Pharmaceuticals Corporation, East Hanover, NJ; ¹⁶Novartis Institutes for BioMedical Research, Basel, Switzerland; ¹⁷Novartis Institutes for BioMedical Research, Cambridge, MA; ¹⁸Gustave Roussy Cancer Campus, Paris, France
Results

Figure 5. Percentage change from baseline in sum of longest diameters of target lesions (confirmed, RECIST v1.1)

ORR: 12%
DCR: 26%

PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.
N=28 evaluable; 14 patients were not evaluable due to post-baseline assessment not yet performed, discontinuation prior to first post-baseline assessment, or missing tumor measurements.

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PDR001 (anti-PD-1)

Nov 2016

Jan 2017

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Take Home Messages

➢ Both RAI-R DTC and MTC have two approved MKIs based on phase III data: sorafenib-lenvatinib & vandetanib-cabozantinib

➢ Stronger drug development based on specific molecular aberrations and drug combinations (including immunotherapy) are warranted