News Briefing: Highlights from the 2018 Multidisciplinary Head and Neck Cancers Symposium

Tuesday, February 13, 2018
**News Briefing: Highlights from the 2018 Multidisciplinary Head and Neck Cancers Symposium**

**Moderator: Danielle Margalit, MD, Dana-Farber Cancer Institute**

- **A Randomized, Open-Label, Multicenter, Global Phase 2 Study of Durvalumab (D), Tremelimumab (T), or D Plus T in Patients With PD-L1 Low/Negative Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC): CONDOR**  
  Lillian Siu, MD, Princess Margaret Cancer Centre

- **Safety evaluation of nivolumab (Nivo) concomitant with platinum-based chemoradiotherapy (CRT) for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG Foundation 3504**  
  Maura Gillison, MD, PhD, University of Texas MD Anderson Cancer Center

- **A Phase II Trial of Cabozantinib for the Treatment of Radioiodine (RAI)-refractory Differentiated Thyroid Carcinoma (DTC) in the First-line Setting**  
  Marcia S. Brose, MD, PhD, Perelman School of Medicine, University of Pennsylvania

- **OPTIMA—A Phase II Trial of Induction Chemotherapy Response-Stratified RT Dose and Volume De-escalation for HPV+ Oropharynx Cancer: Efficacy, Toxicity, and HPV Subtype Analysis**  
  Tanguy Seiwert, MD, University of Chicago Medicine
A Randomized, Open-Label, Multicenter, Global Phase 2 Study of Durvalumab (D), Tremelimumab (T), or D Plus T in Patients With PD-L1 Low/Negative Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC): CONDOR


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Disclosure

• Consultant for AstraZeneca/MedImmune, Boehringer Ingelheim, Celgene, Merck, and Pfizer

• Grant/research support from AstraZeneca/MedImmune, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Genentech/Roche, GlaxoSmithKline, Merck, Novartis, and Pfizer
Background

- Durvalumab, a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80, showed encouraging antitumor activity in many tumor types, including R/M HNSCC\textsuperscript{1,2}
- Tremelimumab is a selective human IgG2 mAb inhibitor of CTLA-4 that promotes T-cell activity, but does not deplete regulatory T cells\textsuperscript{3,4}
- Combining anti-PD-L1 and anti-CTLA-4 mAbs has shown enhanced preclinical antitumor activity over either agent alone, indicating that the 2 pathways are not redundant\textsuperscript{5}
- There is an unmet need for effective treatment options for patients with PD-L1 low/negative-expressing tumors, due to the serious and life-threatening nature of the disease

CONDOR Study Design
Randomized phase 2 trial in R/M HNSCC in the second-line setting (NCT02319044)

**PATIENTS**
- R/M HNSCC (oral cavity, oropharynx, hypopharynx, larynx)
- ≥1 measurable lesion per RECIST v1.1
- Failure of 1 platinum-based chemotherapy in the R/M setting
- PD-L1 low/negative (<25% TC)
- Stratified by HPV status and smoking status

**PRIMARY ENDPOINTS**
- **ORR** by RECIST v1.1 by BICR assessment (durvalumab + tremelimumab)

**SECONDARY ENDPOINTS**
- DoR, DCR, BOR, PFS, OS (durvalumab/tremelimumab)
- ORR, PFS, and OS for combination vs monotherapies
- Safety and tolerability
- Quality of Life: EORTC QLQ-HN35 and QLQ-C30

**TREATMENT ARM**

1. Durvalumab (10 mg/kg Q2W) for up to 12 months

2. Durvalumab + tremelimumab (D 20 mg/kg Q4W + T 1 mg/kg Q4W) for 4 cycles then durvalumab 10 mg/kg Q2W for up to 12 months

**PATIENTS**
- R/M HNSCC (oral cavity, oropharynx, hypopharynx, larynx)
- ≥1 measurable lesion per RECIST v1.1
- Failure of 1 platinum-based chemotherapy in the R/M setting
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- Stratified by HPV status and smoking status

BICR, blinded independent central review; BOR, best overall response; DCR, disease control rate; DoR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; HPV, human papilloma virus; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell.
# Treatment-Related AEs

<table>
<thead>
<tr>
<th>All grade AEs, %</th>
<th>Durvalumab + tremelimumab (n=133)</th>
<th>Durvalumab (n=65)</th>
<th>Tremelimumab (n=65)</th>
<th>Total (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAE, n (%)</td>
<td>77 (58)</td>
<td>41 (63)</td>
<td>36 (55)</td>
<td>154 (59)</td>
</tr>
<tr>
<td>Diarrhea, %</td>
<td>14.3</td>
<td>10.8</td>
<td>15.4</td>
<td>13.7</td>
</tr>
<tr>
<td>Asthenia, %</td>
<td>9.8</td>
<td>7.7</td>
<td>6.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Hypothyroidism, %</td>
<td>8.3</td>
<td>10.8</td>
<td>1.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Decreased appetite, %</td>
<td>8.3</td>
<td>3.1</td>
<td>4.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Rash, %</td>
<td>6.8</td>
<td>1.5</td>
<td>7.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Fatigue, %</td>
<td>6.0</td>
<td>18.5</td>
<td>6.2</td>
<td>9.1</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>6.0</td>
<td>1.5</td>
<td>0.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>5.3</td>
<td>1.5</td>
<td>7.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Pyrexia, %</td>
<td>4.5</td>
<td>0</td>
<td>6.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Pruritus, %</td>
<td>3.8</td>
<td>7.7</td>
<td>4.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Vomiting, %</td>
<td>1.5</td>
<td>1.5</td>
<td>7.7</td>
<td>3.0</td>
</tr>
</tbody>
</table>

AEs with an incidence ≥5% in any treatment arm are reported.
TRAE, treatment-related adverse events.
## Grade 3/4 Treatment-Related AEs

<table>
<thead>
<tr>
<th>Grade 3/4 AEs, %</th>
<th>Durvalumab + tremelimumab (n=133)</th>
<th>Durvalumab (n=65)</th>
<th>Tremelimumab (n=65)</th>
<th>Total (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3/4 TRAE, n (%)</td>
<td>21 (16)</td>
<td>8 (12)</td>
<td>11 (17)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>Diarrhea, %</td>
<td>3.0</td>
<td>0</td>
<td>4.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Anemia, %</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Asthenia, %</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Fatigue, %</td>
<td>0.8</td>
<td>3.1</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

TRAE, treatment-related adverse events.

- Treatment-related discontinuations per arm:
  - 7 patients (5%) in the combination arm
  - No patients in the durvalumab arm
  - 5 patients (8%) in the tremelimumab arm

- One patient in the combination arm died after experiencing treatment-related grade 3 acute respiratory failure
**Objective Response Rate***

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + tremelimumab (n=129)</th>
<th>Durvalumab (n=65)</th>
<th>Tremelimumab (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, % (n)</strong> [95% CI]</td>
<td>7.8 (10) [3.8–13.8]</td>
<td>9.2 (6) [3.5–19.0]</td>
<td>1.6 (1) [0.04–8.5]</td>
</tr>
<tr>
<td>Odds ratio (95% CI), P-value</td>
<td>Reference</td>
<td>0.83 (0.29–2.53), $P=0.728$</td>
<td>5.21 (0.96–96.70), $P=0.056$</td>
</tr>
<tr>
<td>Complete response, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n</td>
<td>10</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease ≥6 months, † n (%)</td>
<td>7 (5.4)</td>
<td>4 (6.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Disease control rate at 6 months, ‡ n (%)</td>
<td>17 (13.2)</td>
<td>14 (21.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Median duration of response, months</td>
<td>9.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ongoing response at data cutoff, n</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*ORR at 12 months of treatment based on BICR assessments using RECIST 1.1.
Odds ratio is comparison between groups (combination vs monotherapy); an odds ratio >1 favors the combination.
†Based on best objective response.
‡Patients who have a best objective response of complete response or partial response in the first 24 weeks or have demonstrated stable disease for a minimum interval of 24 weeks following randomization. CI, confidence interval; NA, not applicable.
### Progression-Free Survival

<table>
<thead>
<tr>
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<th>Durvalumab + tremelimumab (n=133)</th>
<th>Durvalumab (n=67)</th>
<th>Tremelimumab (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>2.0 (1.9–2.1)</td>
<td>1.9 (1.8–2.8)</td>
<td>1.9 (1.8–2.0)</td>
</tr>
<tr>
<td>HR (95% CI)* for PFS, <em>P</em> value</td>
<td>Reference</td>
<td>1.13 (0.82–1.56), <em>P</em>=0.466</td>
<td>0.73 (0.53–1.01), <em>P</em>=0.050</td>
</tr>
</tbody>
</table>

*Stratified log rank test.

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**Table:**

- **DURVA+TREME:** 133 patients, with 39 patients still at risk at 18 months.
- **DURVA:** 67 patients, with 24 patients still at risk at 18 months.
- **TREME:** 67 patients, with 12 patients still at risk at 18 months.

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**Graph:**

- The graph shows the progression-free survival (PFS) over time for patients receiving durvalumab + tremelimumab (cyan line), durvalumab (blue line), and tremelimumab (green line).

- The x-axis represents the time from randomization in months, ranging from 0 to 18 months.

- The y-axis represents the probability of progression-free survival, ranging from 0.0 to 1.0.

- The legend includes a plot symbol for censored data (+) and lines for each treatment group.

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**Notes:**

- The hazard ratio (HR) for PFS is 1.13 (0.82–1.56) for durvalumab + tremelimumab compared to the reference group, with a *p*-value of 0.466.
- For durvalumab alone, the HR is 0.73 (0.53–1.01) compared to the reference group, with a *p*-value of 0.050.
**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab + tremelimumab (n=133)</th>
<th>Durvalumab (n=67)</th>
<th>Tremelimumab (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months</td>
<td>6.5</td>
<td>6.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>7.6 (4.9-10.6)</td>
<td>6.0 (4.0-11.3)</td>
<td>5.5 (3.9-7.0)</td>
</tr>
<tr>
<td>HR (95% CI)* for OS, P value</td>
<td>Reference</td>
<td>0.99 (0.69-1.43), P=0.8928</td>
<td>0.72 (0.51-1.03), P=0.0608</td>
</tr>
</tbody>
</table>

*Stratified log rank test.

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Number of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>DURVA+TREME (133)</th>
<th>DURVA (67)</th>
<th>TREME (67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from randomization (months)</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Probability of overall survival</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>

+ CENSORED
DURVA+TREME
DURVA
TREME

#HNC518

**MULTIDISCIPLINARY HEAD AND NECK CANCERS SYMPOSIUM | THE WESTIN KIERLAND RESORT AND SPA | SCOTTSDALE, ARIZONA**
Conclusions

In this population of pretreated patients with PD-L1 low/negative R/M HNSCC:

- Durvalumab monotherapy showed an overall response rate of 9.2%, consistent with that of single agent PD-1 inhibitors in second-line settings\(^1,2\)
- The durvalumab + tremelimumab combination resulted in an ORR of 7.8% (95% CI: 3.78%, 13.79%)
- Durvalumab monotherapy and durvalumab + tremelimumab showed clinically relevant OS, but with no observed difference in efficacy measure between the 2 arms
- Both the durvalumab + tremelimumab combination and the monotherapies exhibited manageable safety profiles in a patient population with few treatment options
  - Durvalumab monotherapy safety profile is consistent with prior data,\(^3-5\) and no new safety signals were seen with the combination therapy

This CONDOR study is part of a broader comprehensive clinical program; the ongoing phase 3 EAGLE trial (NCT02369874) will assess the combination of durvalumab + tremelimumab and durvalumab monotherapy compared to standard of care as second-line treatment in patients with PD-L1 high or PD-L1 low/negative expressing R/M HNSCC

Acknowledgments

This study was supported by AstraZeneca.

The authors would like to thank the global study investigators, and the patients and their families, without whom this clinical trial would not have been possible.
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1MD Anderson Cancer Center, Houston, TX, 2Department of Otolaryngology, Eye & Ear Institute, University of Pittsburgh Medical Center, Pittsburgh, PA, 3NRG oncology, Philadelphia, PA, 4Stanford, Palo Alto, CA, 5UC San Diego, Moores Cancer Center, Dept of Radiation Oncology, La Jolla, CA, 6Northwell Health, New York, NY, 7University of California, San Diego, La Jolla, CA, 8Boston Medical Center, Boston, MA, 9Department of Pathology, Stanford University, Stanford, CA, 10UCSF, San Francisco, CA, 11Department of Radiation Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, 12Department of Medical Oncology, UPMC Hillman Cancer Center, Pittsburgh, PA, 13Ohio State University, Columbus, OH, 14Inova Comprehensive Cancer & Research Institute, Falls Church, VA, 15Radiation Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH, 16Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA, 17Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA
Disclosure

• Please list your employer along with any potential conflicts of interest.

• Speakers are also required to disclose the following, if applicable, to the audience at the beginning of your presentation and in accordance with ACCME standards and Food and Drug Administration requirements
  • Any vested interest or intention to discuss off-label and/or investigational use of pharmaceuticals or devices.
  • The existence of any financial or other relationship you have with the manufacturer(s) or any commercial product(s) or provider(s) of any commercial services discussed in an educational presentation IF your disclosure that is displayed on the disclosure slide is not current.

• If you have none, please enter the following statement: “I have no conflicts of interest to disclose.”
Background

• Patients diagnosed with mouth and throat cancer ("head and neck cancer") often present with advanced disease and relapse within two years.

• An antibody to the PD-1 checkpoint receptor (nivolumab) improves survival of patients whose cancer has progressed after platinum chemotherapy.

• Incorporating these drugs into initial therapy of head and neck cancer has the potential to improve survival.

• This study was designed to evaluate the safety of nivolumab when added to four standard of care chemotherapy and radiation platforms.

• Here we present data on the two platforms that include cisplatin.
RTOG Foundation 3504

High-Risk SCC
- OC, Larynx,
- Hypopharynx,
- p16 negative OP
- AJCC 7
- T1-2N2a-N3
- T3-4N0-3

Intermediate-risk
- p16-positive OP
  - >10 pack-years
    - T1-2N2b, T3-4N0-3
  - ≤10 pack-years
    - T4N0-N3, T1-3N3

SEQUENTIALLY ENROLL

Arm 1:
- Nivolumab 240 mgs Q14D X 10
- Cisplatin 40 mg/m²/wk X 7
- 70 Gy/35 Fx/7 weeks

Arm 2:
- Nivolumab 240 mgs Q14D X 1 then 360 mgs Q21D X 6
- Cisplatin 100 mg/m² Q21D X 3
- 70 Gy/35 Fx/7 weeks

Adjuvant:
- Nivolumab 480 mgs Q28D X 7
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 Cisplatin 40 mg/m2/wk n=10</th>
<th>Arm 2 Cisplatin 100 mg/m2 Q21D n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median, min-max</td>
<td>56, 48-66</td>
<td>58, 35-76</td>
</tr>
<tr>
<td>Male Gender, n</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Caucasian Race, n</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Zubrod PS 1, n</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Risk category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate, n</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>High, n</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Positive HPV status, n</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>T3-4 stage, n</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>N2c-3 stage, n</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Smoking &gt; 10 PY, n</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>
Treatment Summary

- The addition of nivolumab to standard therapy raised no safety concerns.
- All evaluable patients completed radiation therapy.
- 15 of 17 patients received a cisplatin does at or above the effective dose.
- 3 of 18 patients had treatment discontinued due to known side effects of nivolumab (blurred vision, diarrhea and joint pain).
- 6 of 8 patients completed a year of nivolumab therapy.
Conclusions

• The addition of nivolumab to standard of care cisplatin and radiation therapy was feasible and no new safety concerns were identified.

• Standard of care therapy was not compromised.

• A total of one year of nivolumab therapy was feasible and tolerable.

• Safety evaluation of nivolumab addition to other platforms is ongoing.

• Phase 3 evaluations of the clinical benefit are ongoing.
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M. S. Brose1, S. Shenoy1, N. Bhat1, A. K. Harlacker1, R. K. Yurtal1, Z. A. Posey1, D. M. Torrente1, C. Grande1, C. M. Squillante2, A. B. Troxel3, and M. Yarchoan4

1University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, 2MD Anderson Cancer Center at Cooper, Camden, NJ, 3NYU School of Medicine, New York, NY, 4Johns Hopkins University, Baltimore, MD
Disclosure

• I am employed by the Perelman School of Medicine at the University of Pennsylvania

• I have grant funding from Loxo, Exelixis, Bayer, Eisai, Genzyme/Sanofi, AstraZeneca

• I have received honoraria or consulting fees in the past two years from Eisai, Loxo, Bayer, Genzyme/Sanofi and Blueprint pharmaceuticals
Background

- It is estimated that in the USA in 2017 there were:
  - >56,000 new cases of thyroid cancer, and
  - 2010 deaths due to thyroid cancer
- In approximately 5–15% of patients with thyroid cancer, the disease becomes refractory to radioactive iodine (RAI)
- Median survival for patients with RAI-refractory DTC and distant metastases without additional treatment is estimated to be 2.5–3.5 years
- Patients often suffer multiple complications associated with disease progression
- Two FDA approved agents in the past five years, sorafenib and lenvatinib have shown activity in increasing progression free survival. However, the responses are not durable and toxicities may limit efficacy.
- Additional treatment options are needed for these patients
Background

• Cabozantinib is a multi-tyrosine kinase inhibitor targeting VEGF receptor kinase, RET, MET and AXL
• Cabozantinib is approved for patients with advanced medullary thyroid cancer and renal cell cancer
• Prior data from a phase I study suggested activity in the RAI-refractory DTC patients that had previously been treated with one or more VEGF receptor inhibitors or other therapy in the salvage setting¹
• In order to further understand the activity of this agent in RAI-refractory DTC, we conducted a single-arm open-label phase II study of cabozantinib in patients in the first-line setting (clinicaltrials.gov: NCT02041260)

¹Cabanillas et al., Thyroid 2014
UPCC 28313: Cabozantinib for patients with progressive RAI-refractory DTC in the first line setting

Eligibility criteria:
- Metastatic, RAI-refractory thyroid cancer
- No prior treatment with VEGFR inhibitor
- Life expectancy > 3 months
- ECOG PS 0-2
- Good organ and bone marrow function

Primary endpoint:
- Overall Response by RECIST 1.1

Secondary endpoints:
- PFS
- Clinical Benefit Rate
- Safety

n = 35
cabozantinib
60mg daily
Methods

• Between March 2014 and August 2017, 35 patients with metastatic, RAI-refractory, unresectable or locally-advanced thyroid cancer were enrolled on study.

• Patients had not received any prior kinase inhibitor therapy.

• Starting dose was 60mg PO daily. Dose reductions to 40mg PO daily, then 20mg PO daily and then 20mg PO QOD were allowed.

• The agent under study will be deemed of further interest if the response rate is approximately 15% or at least 5 responses out of 35 (CR + PR).
## Patient Characteristics

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>65 years (45-84)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>17 (49%)</td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>23 (66%)</td>
</tr>
<tr>
<td>Follicular (Hürthle Cell)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Poorly Differentiated</td>
<td>9 (26%)</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Best Response (by RECIST 1.1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>19 (54%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>15 (43%)</td>
</tr>
<tr>
<td>Stable Disease &gt; 6 Months</td>
<td>9 (26%)</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate (CR+PR+SD&gt;6months)</strong></td>
<td>28 (80%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Progression Free Survival (PFS)</td>
<td>Not reached (only 6 PDs thus far)</td>
</tr>
<tr>
<td>Median Time on Drug</td>
<td>35 weeks (3-198)</td>
</tr>
<tr>
<td>Patients still on Drug as of 2/6/2018</td>
<td>16</td>
</tr>
</tbody>
</table>
Results

Best Response per RECIST 1.1
Most Common Treatment Emergent Adverse Events (all grades) as of 2/6/2018

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>28 (80%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (77%)</td>
</tr>
<tr>
<td>Malaise/Fatigue</td>
<td>26 (74%)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>25 (71%)</td>
</tr>
</tbody>
</table>
Grade 3-5 Adverse Events (occurring in more than one patient) as of 2/6/2018

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Increased Lipase</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>
Conclusions

• This single site phase II study showed that cabozantinib is an active agent for RAI-refractory DTC in the first line setting
  • Treatment with cabozantinib resulted in a 54% response rate and an 80% clinical benefit rate meeting the primary endpoint of the study (PR+CR >15%)
  • Two kinase inhibitors are currently FDA approved and are used sequentially to improve the progression free interval for these patients, but patients ultimately progress and need more treatment options
  • Cabozantinib was well tolerated with mostly grade 1 and 2 adverse events. No unexpected toxicities were identified
  • Cabozantinib is an active agent in these patients and merits additional study in a large multicenter phase III trial to determine its efficacy in patients with RAI-refractory DTC
News Briefing: Highlights from the 2018 Multidisciplinary Head and Neck Cancers Symposium

Moderator: Danielle Margalit, MD, Dana-Farber Cancer Institute

A Randomized, Open-Label, Multicenter, Global Phase 2 Study of Durvalumab (D), Tremelimumab (T), or D Plus T in Patients With PD-L1 Low/Negative Recurrent or Metastatic (R/M) Head and Neck Squamous Cell Carcinoma (HNSCC): CONDOR

Lillian Siu, MD, Princess Margaret Cancer Centre

Safety evaluation of nivolumab (Nivo) concomitant with platinum-based chemoradiotherapy (CRT) for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG Foundation 3504

Maura Gillison, MD, PhD, University of Texas MD Anderson Cancer Center

A Phase II Trial of Cabozantinib for the Treatment of Radioiodine (RAI)-refractory Differentiated Thyroid Carcinoma (DTC) in the First-line Setting

Marcia S. Brose, MD, PhD, Perelman School of Medicine, University of Pennsylvania

OPTIMA—A Phase II Trial of Induction Chemotherapy Response-Stratified RT Dose and Volume De-escalation for HPV+ Oropharynx Cancer: Efficacy, Toxicity, and HPV Subtype Analysis

Tanguy Seiwert, MD, University of Chicago Medicine
OPTIMA—A Phase II Trial of Induction Chemotherapy Response-Stratified RT Dose and Volume De-escalation for HPV+ Oropharynx Cancer: Efficacy, Toxicity, and HPV Subtype Analysis

T. Seiwert¹, J. M. Melotek¹, C. C. Foster¹, E. A. Blair¹, T. G. Karrison¹, N. Agrawal¹, L. Portugal¹, Z. Gooi¹, K. M. Stenson², R. J. Brisson¹, S. Arshad¹, A. Dekker¹, S. Kochanny¹, V. Saloura¹, M. T. Spiotto¹, V. M. Villaflor³, D. J. Haraf¹, and E. E. Vokes¹;

¹University of Chicago, Chicago, IL, ²Rush University Medical Center, Chicago, IL, ³Northwestern University, Chicago, IL
Disclosure

• I work for the University of Chicago

• Honoraria: AstraZeneca, Bristol-Myers Squibb, Innate, Oncolys, Merck, Nanobiotix

• Research Funding: Bristol-Myers Squibb, Jounce, Merck
Background

• HPV+ head and neck cancer:
  • Improved outcomes with curative intent radiation therapy
  • De-escalation approaches are feasible & efficacious
    • e.g. ECOG 1308, RAVD volume de-escalation
    • GOAL is to reduce long-term side effects
  • Despite good prognosis, some HPV+ tumors behave aggressively and are unlikely to be de-escalation candidates
  • Predominant pattern of failure is distant failure
The University of Chicago De-Escalation Approach

• Induction chemotherapy
  • Lower risk of distant failure
  • Identify adverse tumor biology
    ➔ Stratify treatment by response (e.g. RAVD, RADD)

1. Reduce concurrent chemotherapy
2. Reduce RT dose and volume (or ongoing employ TORS selectively)
Methods

**Low Risk**
- \( \leq T3 \) & \( \leq N2B \) & \( \leq 10 \text{ PYH} \)

**High Risk**
- T4 or \( \geq N2C \) or >10 PYH

**Induction Chemotherapy** x 3 Cycles
1. Carboplatin 
   AUC=6, d1
2. Nab-paclitaxel
   100 mg/m\(^2\)
   d1/d18/d15

**Radiologic Assessment of Response**
- \( \geq 50\% \)
  - Low-dose CRT
    PTV1: 45 Gy
    PTV2: 30 Gy
- < 50\%
  - Standard CRT
    PTV1: 75 Gy
    PTV2: 45 Gy

**Enrolled on Protocol** (\( N = 62 \))
- Low Risk (\( N = 28 \))
- High Risk (\( N = 34 \))
Methods

Low Risk

≤T3 & ≤N2B & ≤10 PYH

Radiologic Assessment of Response

> 50%

Low-dose RT
PTV1: 50 Gy

< 50%

Low-dose CRT
PTV1: 45 Gy
PTV2: 30 Gy

High Risk

T4 or ≥N2C or >10 PYH

Induction Chemotherapy x 3 Cycles

1) Carboplatin
   AUC=6, d1
2) Nab-paclitaxel
   100 mg/m²
d1/d18/d15

Enrolled on Protocol (N = 62)

Low Risk
(N = 28)

High Risk
(N = 34)

Standard CRT
PTV1: 75 Gy
PTV2: 45 Gy
Methods

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Risk (N = 28)</th>
<th>High Risk (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-Stage – No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>23 (82.1)</td>
<td>19 (55.9)</td>
</tr>
<tr>
<td>3</td>
<td>5 (17.9)</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>4</td>
<td>--</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td><strong>N-Stage – No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2a</td>
<td>3 (10.7)</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>2b</td>
<td>25 (89.3)</td>
<td>18 (52.9)</td>
</tr>
<tr>
<td>2c-3</td>
<td>--</td>
<td>12 (35.3)</td>
</tr>
</tbody>
</table>
Results

Overall Survival

- 2.5-year OS: 85.7%
- 2.5-year OS: 97.0%

Progression-Free Survival

- 2.5-year PFS: 91.0%
- 2.5-year PFS: 93.8%

Follow-Up

- Mean 22.8 months
- Range 9.1–39.4 months
Results

Pathologic CR Rates:

- Low-dose RT: 94.7% (18/19)
- Low-dose CRT: 89.3% (25/28)
  - Low risk pts: 100% (6/6)
  - High risk pts: 86.4% (19/22)
## Results

### Treatment Arm

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Grade ≥3 Mucositis</th>
<th>P-Value</th>
<th>Grade ≥3 Dermatitis</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose RT</td>
<td>15.0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low dose CRT</td>
<td>46.7</td>
<td>0.01</td>
<td>10.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Standard CRT</td>
<td>63.6</td>
<td></td>
<td>45.5</td>
<td></td>
</tr>
</tbody>
</table>

### Acute Toxicity (%)

- **Grade ≥3 Mucositis**
  - Low dose RT: 15.0
  - Low dose CRT: 46.7
  - Standard CRT: 63.6

- **Grade ≥3 Dermatitis**
  - Low dose RT: 0
  - Low dose CRT: 10.0
  - Standard CRT: 45.5

### PEG-Dependency (%)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>6 Mos.</th>
<th>12 Mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose RT</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low dose CRT</td>
<td>6.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Standard CRT</td>
<td>18.2</td>
<td>9.1</td>
</tr>
</tbody>
</table>

*P < .001*
Conclusion

• OPTIMA approach is feasible and efficacious

• Majority of patients received de-escalated treatment with limited-field 50Gy RT or 45Gy CRT including patients with high-risk nodal stages of disease
  • Excellent pCR and survival outcomes
  • No failures in omitted elective coverage

• Toxicity improved with de-escalation
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Expert Perspective

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On-site Press Office in Scottsdale
Parke Room, Westin Kierland
February 15-16, 8am-4pm MT

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