Abstract #1552

Targeting HPV E6/E7 Upregulation of the Transmembrane Receptor Tyrosine Kinase ROR2 with the ADC Ozuriftamab Vedotin in Patients with Advanced HPV+ Oropharyngeal Squamous Cell Carcinoma

Jacob Thomas,[1] Winston Wong,[2] Douglas Adkins,[3] Jamal Misleh,[4] Jochen Lorch,[5] Jaspreet Grewal,[6] Kathleen C. Kerrigan,[7] Jeffery Russell,[7] Jeremy Cetnar,[8] Kartik Aysola,[9] Bill Boyle,[9] Judith Llorin-Sangalang,[9] Eric Sievers,[9] Alan Ho[2]

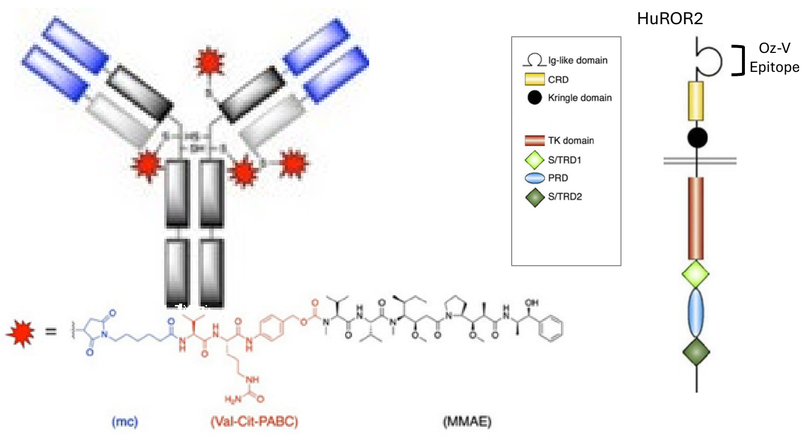
[1]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]Christiana Hospital, Newark, DE, USA; [5]Northwestern University, Chicago, IL, USA; [6]Norton Cancer Institute, Louisville, KY, USA; [7]Huntsman Cancer Institute, Salt Lake City, UT, USA; [8]Oregon Health & Science University, Portland, OR, USA; [9]BioAtla, Inc., San Diego, CA, USA

BACKGROUND

- Ozuriftamab vedotin (Oz-V, BA3021) is a Conditionally Active Biologic or CAB anti-ROR2 antibody–drug conjugate (CAB-ROR2-ADC) employing an MMAE payload (DAR 4) and protease–cleavable linker **(Figure 1).**
- Preclinical results indicate that CAB anti-ROR2 ADC is efficacious and well tolerated and may be a promising treatment for cancer patients with ROR2-expressing tumors[1].
- A Phase 1 study of all comers with solid tumors revealed that HNSCC was a potential indication due to the expression of ROR2 and the response to Oz-V treatments.
- Oz-V was granted FDA Fast Track Designation for treatment of pts with R/M SCCHN who have experienced disease progression following platinum-based chemotherapy and anti-PD-(L)1 antibody therapy.

Figure 1. Ozuriftamab Vedotin (Oz-V)

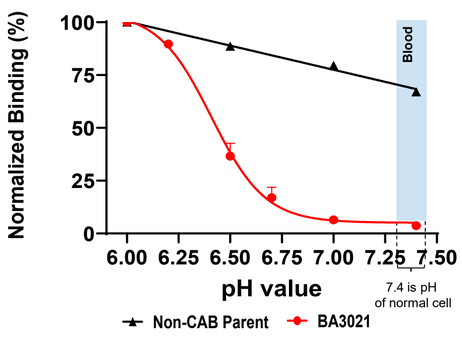
- CAB humanized IgG1 antibody directed to ROR2 N-terminal region.
- MMAE-containing ADC (DAR4) with cleavable linker.



Oz-V, is an ADC targeting ROR2 that delivers auristatin to malignant cells causing immunogenic cell death.

- Oz-V is a Conditionally Active Biologic or CAB anti-ROR2 antibody–drug conjugate (CAB-ROR2-ADC) employing an MMAE payload (DAR 4) and protease–cleavable linker.
- Oz-V conditionally and reversibly binds to the ROR2 target under the low–pH conditions (pH 5.3 to 6.7) of the tumor microenvironment, thus sparing normal cells **(Figure 2)**.

Figure 2. Oz-V pH binding inflection point designed for TME selectivity.

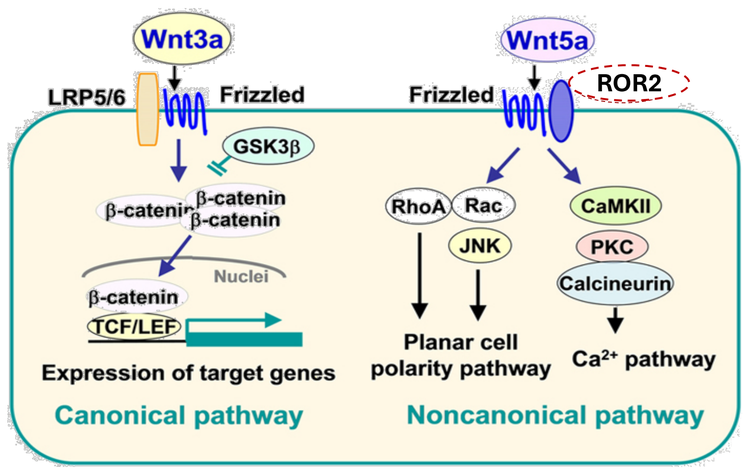


- The antibody binding is designed to reduce off-tumor toxicity utilizing a novel mechanism that avoids tissue–mediated drug disposition.

Physiologic and Pathologic role of ROR2 Tyrosine Kinase

- **A signaling receptor:** Receptor tyrosine kinase-like orphan receptor 2 (ROR2) is a human transmembrane protein that acts as a non-canonical receptor for Wnt ligands[2,3] **(Figure 3).**
- **Oncofetal Protein**: Expressed in developing tissues and is involved in planer cell polarity formation during limb bud formation and elongation; chondrogenesis of calcenous bones, melanocyte stem cell migration and differentiation.
- **Linked to cancer progression:** ROR2 has been identified as a highly relevant tumor-associated antigen in a variety of cancer indications of high unmet need, including TNBC, NSCLC, melanoma, colorectal carcinoma, renal cell carcinoma, sarcomas/GIST, osteosarcoma, and ovarian cancer.
- Overexpression of ROR2 is associated with poor prognosis of multiple solid tumor types including lung, pancreatic colon and breast. Increased ROR2 expression has been associated with acquired resistance to chemotherapy, PD-(L)1 inhibitors, molecular targeted therapy, and radiation therapy.[5,6]

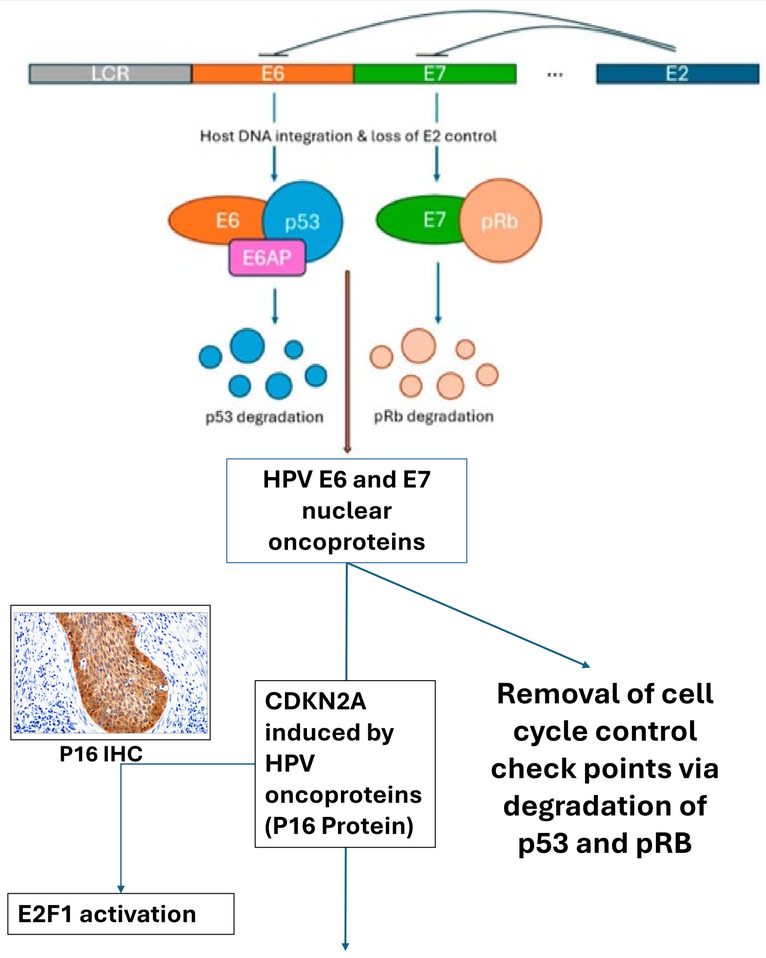
Figure 3. ROR2 is a Noncanonical WNT5a Receptor



Relationship Between ROR2, HPV and OPSCC

- **Linked to cancer progression:** Studies show that ROR2 is highly expressed in SCCHN that is positive for HPV[4].
- **Oncoprotein driven:** Research has provided strong evidence that the HPV oncogenes E6 and E7 drive the increased expression of ROR2 in HPV-positive cancer cells **(Figure 4)**.
- **Promotes tumor growth:** Once upregulated, ROR2 helps promote the proliferation and invasive migration of the cancer cells, contributing to the tumor's progression.

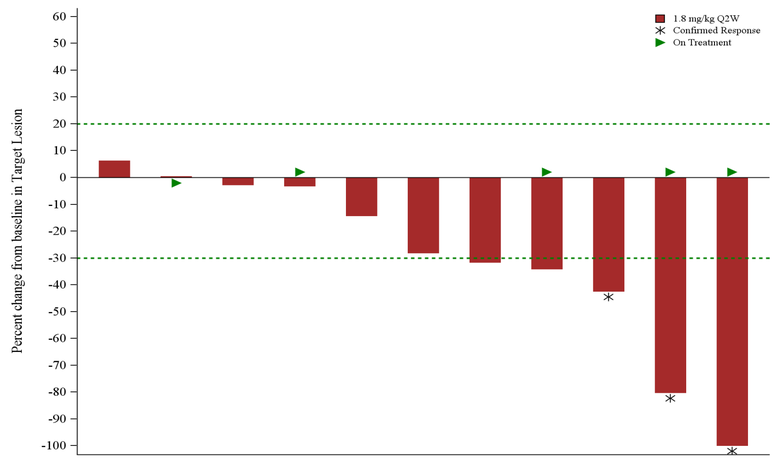
Figure 4. HPV infection drives ROR2 overexpression[4]



- HPV associated expression of E6 and/or E7 oncoproteins drives progression by upregulating ROR2 expression.[1, 4]
- ROR2 acts as a non-canonical receptor for Wnt family of ligands involved in cell migration in normal tissue formation[3], which:
  - Can influence cell proliferation and survival by regulating downstream signaling pathways, such as the PI3K/Akt pathway.
  - Can promote or inhibit metastasis potentially by modulating cell migration, invasion, and angiogenesis.
  - Increased ROR2 expression has been associated with acquired resistance to chemotherapy, PD-(L)1 inhibitors, molecular targeted therapy, and radiation therapy.[5,6]

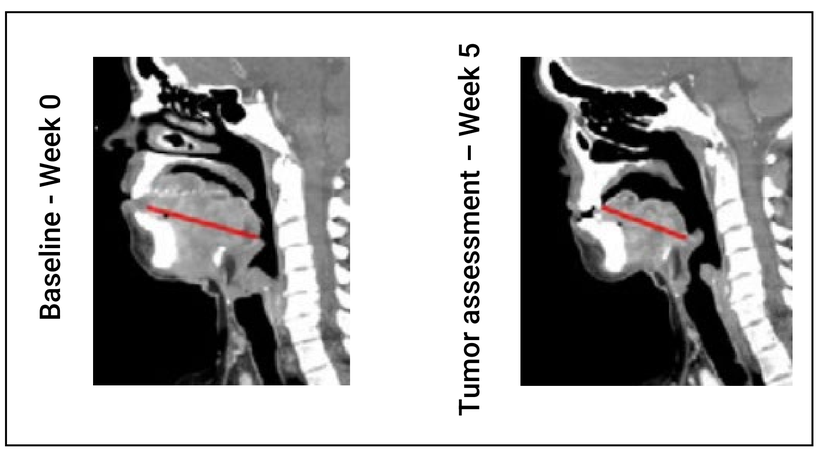
1.8 mg/kg Q2W selected: Promising anti-tumor activity & better tolerated

Figure 5. Q2W Oz-V in HPV+ OPSCC (n=11 evaluable).



100% DCR in patients with heavily pre-treated HPV+ OPSCC receiving Q2W

Figure 6. Confirmed partial response (42% tumor reduction) from Oz-V at 1.8 mg/kg Q2W in HPV+ OPSCC.



51-year-old female with stage IV SCCHN post-radiotherapy. Previous treatments included pembrolizumab, platinum, and arenavirus-based experimental therapy.

Conclusions

- **Oz-V, a conditionally binding ADC targeting ROR2, achieved promising antitumor activity among heavily pretreated patients with SCCHN.**
- **Oz-V delivered at 1.8 mg/kg Q2W achieved 100% disease control among pts with HPV+ OPSCC and was particularly well-tolerated.**
- **Oz-V has the potential to address the marked unmet need among the recurrent/metastatic HPV+ OPSCC population.**
- **These encouraging findings provide compelling rationale to investigate Oz-V in additional high unmet need HPV-associated cancers.**

Abbreviations

CAB = Conditionally Active Biologic, **GIST** = gastrointestinal stromal tumor, **HPV** = Human Papilloma Virus, **IHC** = Immunohistochemistry, **IV** = intravenous (weight-based dosing), **MTD** = maximum tolerated dose, **NSCLC** = Non-Small Cell Lung Cancer, **OPSCC** = oropharyngeal squamous cell carcinoma, **PAD** = pharmacologically active dose, **PD** = pharmacodynamics, **PK** = pharmacokinetics, **ROR2** = Receptor tyrosine kinase-like orphan receptor 2, **SAE** = serious adverse event, **SC** = subcutaneous, **SCCHN** = squamous cell carcinoma of the head and neck, **TCE** = T-cell engager, **TCR** = T-cell receptor, **TME** = tumor microenvironment, **TNBC** = triple-negative breast cancer.

References

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Disclosures

BB: Employee of BioAtla, Inc.

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Correspondence: Kartik Aysola, MD - medicalaffairs@bioatla.com
Presenting Author: William Boyle, PhD – bboyle@bioatla.com

Clinical Trial Identifier

A Phase 2 Open Label Study of BA3021 in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck.
Clinical Trial Registry Number: NCT05271604

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