



ABS 221: Phase I/II Study of a Novel MDM-2 inhibitor (APG-115/Alrizomadlin) in TP53 Wild Type Salivary Gland Cancers

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BACKGROUND

- Malignant salivary gland cancers (SGC) are rare tumors of the head and neck with no approved therapeutics
 - TP53 mutations seen in approx. 20-30%
- The most common histology is adenoid cystic carcinoma (ACC) and the median progression free survival (mPFS) in patients with untreated disease is 2.8 months.
 - Commonly used VEGFR TKIs demonstrate an ORR of 0-15% and mPFS 10.8-17.5 months
- MDM2 gene amplifications are a common event, particularly prevalent in ACC. Overexpression occurs by several other epigenetic mechanisms in other histologies
- MDM2 inhibition has demonstrated significant preclinical activity in TP53 wt ACC models without suggestion of systemic toxicity
 - Significant synergy demonstrated when combined with platinum agent
- APG-115 is a potent oral small-molecule MDM2 inhibitor (IC50= 3.8 +/- 1.1 nM) increasing p53 and p21 overexpression and activating p53 mediated apoptosis in p53 retaining tumor cells
 - Previously evaluated alone and in combination with pembrolizumab (NCT03611868)
- Our hypothesis is that APG-115 +/- chemotherapy would have significant antitumor activity and improve patient outcomes in TP53 wt SGC
- Primary Objective:** Determine the safety (DLT, MTD) and efficacy (ORR) for APG-115 +/- Carboplatin
- Secondary Objectives:** Progression Free Survival, Duration of Response, Overall Survival

METHODS

- Phase I/II Study
- Major Eligibility Criteria:**
 - Malignant high grade salivary gland cancers non amenable to curative treatment
 - TP53 wild type by sequencing
 - ≥20% increase in tumor burden in the preceding 12 months
- Doses assigned using time to event continual reassessment method (TITE-CRM)
 - Started at highest dose DL and de-escalated
 - APG-115: 150 mg orally, Every other day D1-14. Cycle Length- 21D
 - Carboplatin: AUC= 5. D1, Cycle Length- 21D
- Initially consisted of two parallel trials evaluating APG-115 +/- Carboplatin
- Combination arm was closed early due to concerns regarding tolerability
- The trial design was modified to a single arm study of APG-115 monotherapy (n= 34)
- Planned interim analysis after enrollment of 14 patients to monotherapy
 - ≥ 2 responses merited full enrollment

RESULTS

Table 1: Patient Characteristics

	Arm A: APG-115 N= 18	Arm B: APG-115 + Carboplatin N= 4
Age	63.5 (33-75)	44.5 (36-50)
Sex		
Male	9 (50%)	0
Female	9 (50%)	4 (100%)
Adenoid Cystic Ca (ACC)	12 (67%)	4 (100%)
Non-ACC	6 (33%)	0
Salivary Ductal Carcinoma	3	-
Acinic Cell Carcinoma	1	-
Mucoepidermoid Carcinoma	1	-
Myoepithelial Carcinoma	1	-
Prior Systemic Therapy		
No	8 (44%)	4 (100%)
Yes	10 (56%)	0
Number of Lines	2.7 (1-7)	-
VEGF TKI	4 (22%)	-

- As of 6/21/22, 18 pts enrolled to Arm A (APG-115) and 4 pts enrolled to Arm B (APG-115 + Carboplatin)
 - Data cut-off: 9/30/22
- All patients assigned to highest dose level by TITE-CRM
- 2 DLTs, one in each arm
 - Arm A: Grade 3 Dizziness
 - Arm B: Grade 3 Neutropenic Fever

Figure 1: Progression Free Survival

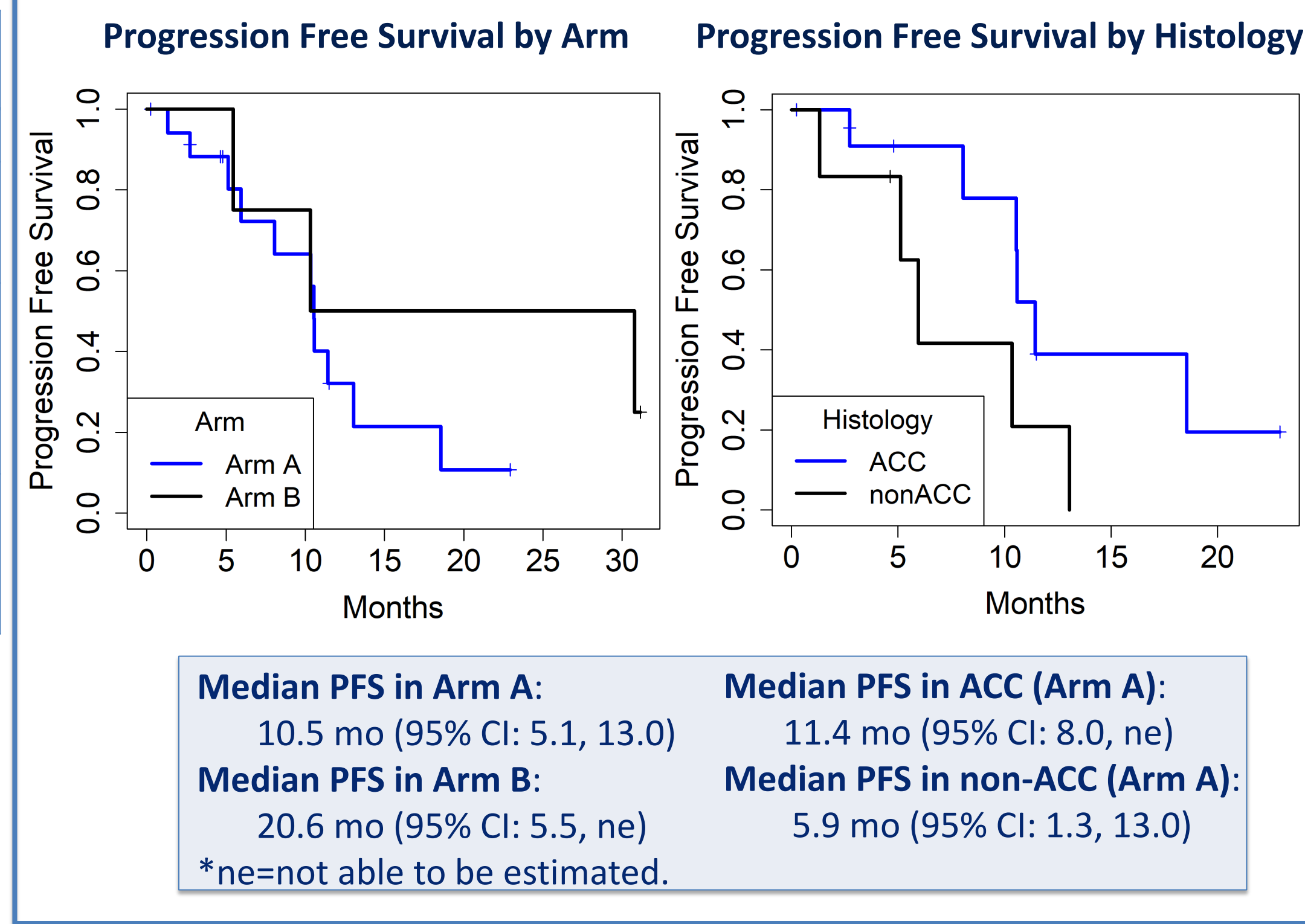


Figure 2: Duration of Response

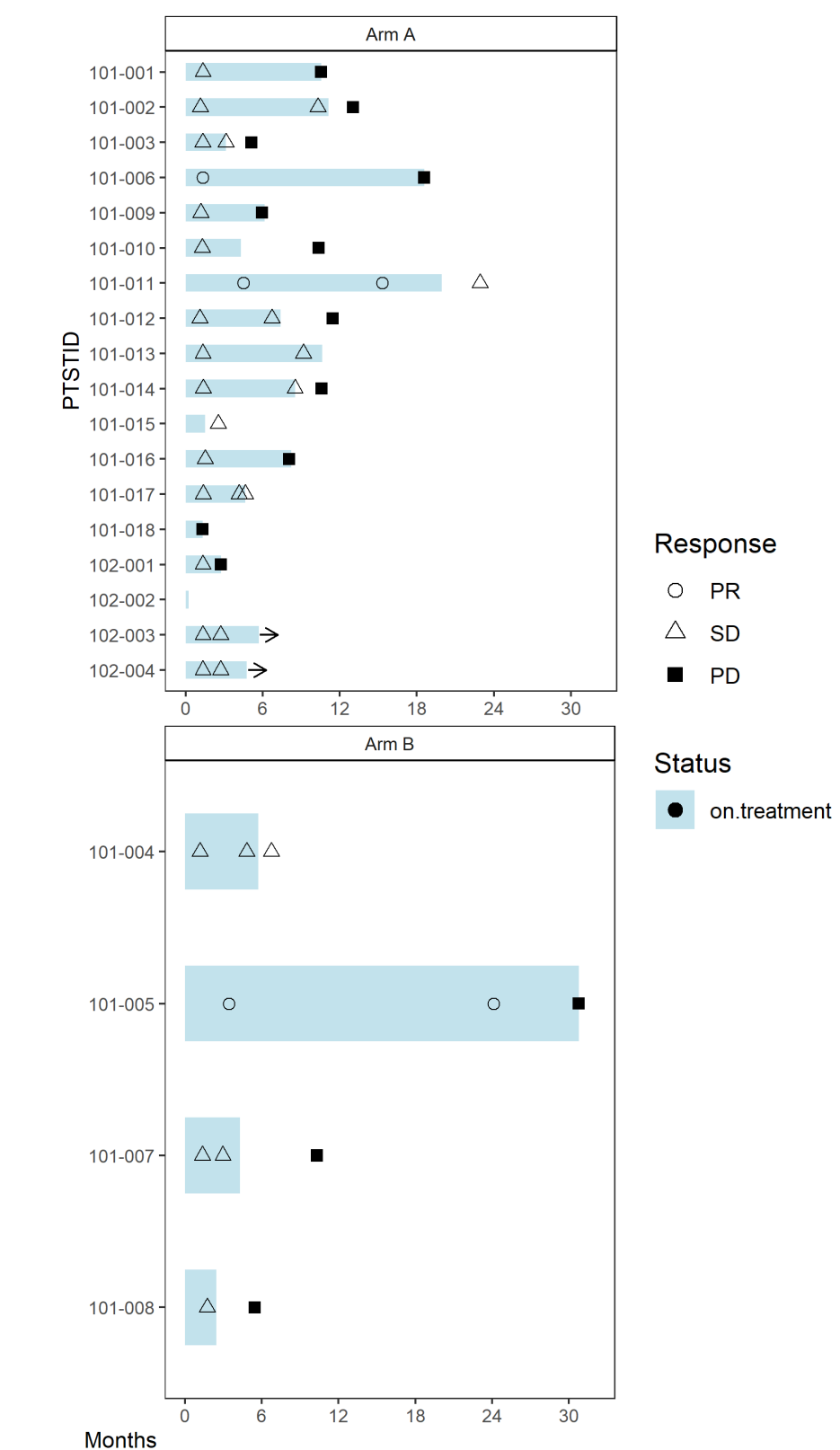


Table 2: Treatment Related Adverse Effects

	Arm A: APG-115 Monotherapy			
	G1	G2	G3	G4
Neutropenia	2 (11%)	0	3 (17%)	2 (11%)
Thrombocytopenia	4 (22%)	2 (11%)	2 (11%)	2 (11%)
Fatigue	5 (28%)	5 (28%)	6 (33%)	0
Nausea	7 (39%)	4 (22%)	4 (22%)	0
Vomiting	4 (22%)	1 (6%)	3 (17%)	0
Anemia	3 (17%)	2 (11%)	1 (6%)	0
Anorexia	2 (11%)	2 (11%)	1 (6%)	0
Lymphocyte Count Decreased	3 (17%)	1 (6%)	1 (6%)	0
Dysgeusia	5 (28%)	0	0	0

	Arm B: APG-115 + Carboplatin			
	G1	G2	G3	G4
Neutropenia	0	1 (25%)	0	2 (50%)
Thrombocytopenia	0	1 (25%)	2 (50%)	1 (25%)
Anemia	0	2 (50%)	2 (50%)	0
Neutropenic Fever	0	0	1 (25%)	0
Lymphocyte Count Decreased	1 (25%)	0	1 (25%)	0
Nausea	1 (25%)	2 (50%)	0	0
Vomiting	2 (50%)	0	0	0
Fatigue	2 (50%)	1 (25%)	0	0
Epistaxis	0	1 (25%)	0	0

Table 3: Treatment Efficacy

		Arm A: APG-115 ACC Only (n=12)	Arm A: APG-115 Non-ACC Only (n=6)	Arm B: APG-115 + Carboplatin (n=4)
Best Response	PR	2 (16%)	0	1 (25%)
	Duration of response	19.3 mo (18.6, 19.9 mo)	-	30.8 mo
	SD	9 (75%)	5 (83%)	3 (75%)
	Duration of response	5.9 mo (1.5, 10.6)	4.6 mo (3.2, 11.1)	4.3 mo (2.4, 5.7)
	PD	1 (8%)	1 (17%)	-
	No Scans Available	1*	-	-
6-month PFS		91% (51%, 99%)	42% (6%, 77%)	75% (13%, 96%)
6-month OS		91% (51%, 99%)	83% (27%, 97%)	100% (ne, ne)

*Patient elected to come off study on Cycle 1, Day 1. For PFS analysis, the patient is censored at time of drop off, however is still followed for survival.

CONCLUSIONS

- This is the first study to evaluate the activity of MDM2 inhibition in patients with salivary gland cancers
- APG-115 monotherapy demonstrates promising antitumor activity among patients with progressive high grade TP53wt salivary gland cancer with an acceptable safety profile
 - mPFS significantly longer than historical cohort treated with placebo
 - On par with outcomes from patients treated with VEGFR TKIs
 - Stability of disease in patients with prior documented progression
- Although the sample size is limited, greatest signal was seen in adenoid cystic carcinoma
- Correlative analysis are in process to investigate potential predictive biomarkers
- Accrual is ongoing in patients with TP53wt ACC for precise assessment of survival characteristics

ACKNOWLEDGEMENTS

This work was supported by the University of Michigan Head and Neck Specialized Program of Research Excellence NIH/NCI P50CA097248 and NIH/NIDCD T32 DC005356, as well as University of Michigan Cancer Center Core Grant NIH/NCI P30 CA046592. Research funding and drug supply was provided to the University of Michigan from Ascentage Pharma. The study team would like to thank the patients and families who made this study possible. Furthermore, they would like to recognize the Adenoid Cystic Carcinoma Research Foundation for their insight, advocacy, and support.

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