2021 ASCO ANNUAL MEETING

PRELIMINARY RESULTS OF A PHASE 2 STUDY OF ALRIZOMADLIN (APG-115), A NOVEL, SMALL-MOLECULE MDM2 INHIBITOR, IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA OR ADVANCED SOLID TUMORS THAT HAVE BEEN RESISTANT TO IMMUNO-ONCOLOGIC (IO) DRUGS

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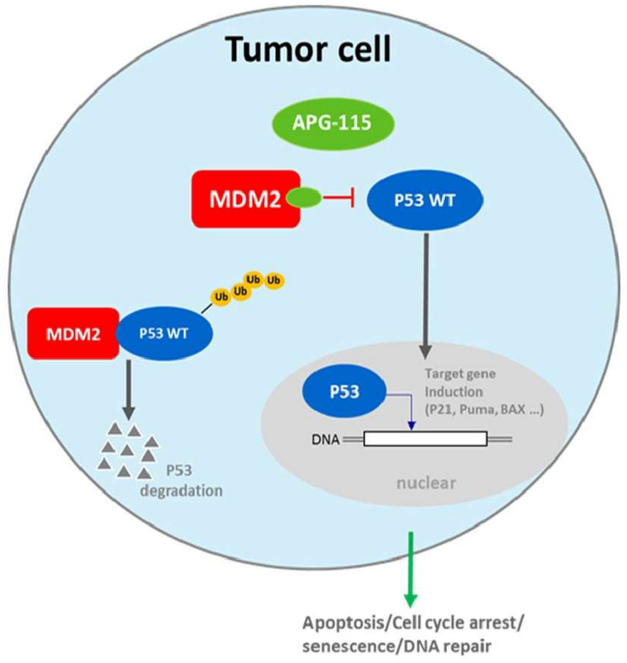
June 7, 2021

Disclosures to come (ASCO to populate)

INTRODUCTION

- **APG-115 is a novel, potent, small-molecule, orally bioavailable MDM2-p53 antagonist.**
  - Blocks MDM2-p53 protein-protein interaction.
  - Restores p53-mediated apoptosis in tumor cells with WT*TP53* or MDM2 amplification.[1-3]
- **APG-115 shows synergy with PD-1 blockade in both WT P53 and MUT P53 syngeneic murine tumor models.[3]**
  - Increases $CD8^+$ T cells and promotes a shift from M2 to M1 macrophages in the tumor microenvironment.
  - Regulates host immunologic responses and tumor immune escape mechanisms.

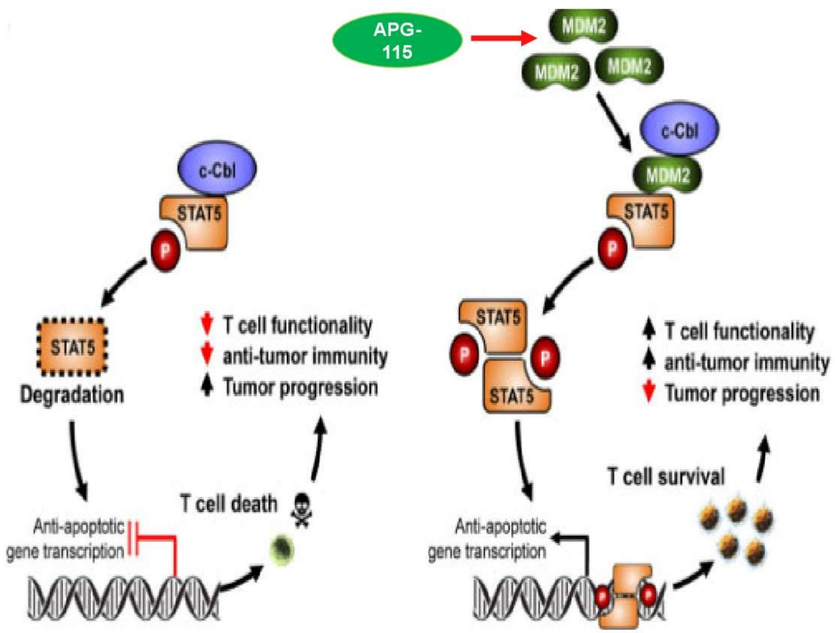


MDM2, mouse double minute homolog (E3 ubiquitin-protein ligase); PD-1, programmed cell death protein 1; P53, p53 protein; WT, wild-type (unmutated); MUT, mutated .

1. Aguilar A et al. J Med Chem 2017;60:2819-2839; 2. Chen H et al. Oncotarget 2017;8:43008-43022; 3. Fang DD et al. J Immunother Cancer 2019;7:327.

APG-115 is a host immunomodulator

- STAT5 activation is important for CD8+ T-cell survival and function.
- MDM2 competes with c-Cbl and prevents c-Cbl-mediated STAT5 degradation.
- APG-115 synergizes with IO and enhances T-cell mediated antitumor immunity.



Zhou J et al. Nat Immunol 2021;22:460-470.

STAT5, signal transducer and activator of transcription 5.

4. Zhou J et al. 2021 Nat Immunol;22:460-470; 5. Tolcher AW et al. Molec Cancer Ther 2019;18:A086.

Study schema

Phase Ib (*completed*)
Dose escalation

APG-115 orally QOD ×
2 consecutive wk and 1 wk off in a 21-day cycle

- **200 mg**
- **150 mg**
- **100 mg**
- **50 mg**

Plus

Pembrolizumab
200 mg IV infusion for 30 min on Day 1 of a 21-day cycle

Determine DLT and RP2D

Phase 2: Dose expansion at APG-115 RP2D (150 mg QOD) plus pembrolizumab (200 mg IV on Day 1 of a 21-day cycle)

- **Cohort A: (n = 34) IO resistant melanoma**
- **Cohort B: (n = 15) IO resistant non-small cell lung cancer (NSCLC); (n = 10) STK-11-mutant lung adenocarcinoma**
- **Cohort C: (n = 20) solid tumors with ATM mutation and WT P53**
- **Cohort D: (n = 15) liposarcoma with MDM2 amplification and WT P53**
- **Cohort E: (n = 15) IO resistant urothelial carcinoma**
- **Cohort F: (n = 10) Malignant peripheral nerve sheathe tumor (MPNST)**

Primary endpoint: Safety and Efficacy: ORR (% with best overall confirmed CR or PR) per RECIST v1.1 and iRECIST

Treat until disease progression, unacceptable toxicity, or another discontinuation criterion. Pembrolizumab administered for up to 35 cycles.

RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

NCT# 03611868

Key inclusion/exclusion criteria

Inclusion:

- Male or female, age ≥ 18 yr
- Histologically confirmed, unresectable or metastatic solid tumors
- Refractory/relapsed after PD-1/PD-L1 inhibitor for melanoma, NSCLC, and urothelial carcinoma
- Refractory to standard-of-care therapies
- ECOG PS 0-2
- Measurable disease according to RECIST 1.1

Exclusion:

- Prior MDM2-p53 inhibitor
- CNS metastases
- Concurrent anticancer therapies or uncontrolled illness
- Active infection requiring systemic medication
- Corticosteroids discontinued ≤ 13 days before first dose of APG-115
- Autoimmune disease warranting systemic steroids or immunosuppressive agents

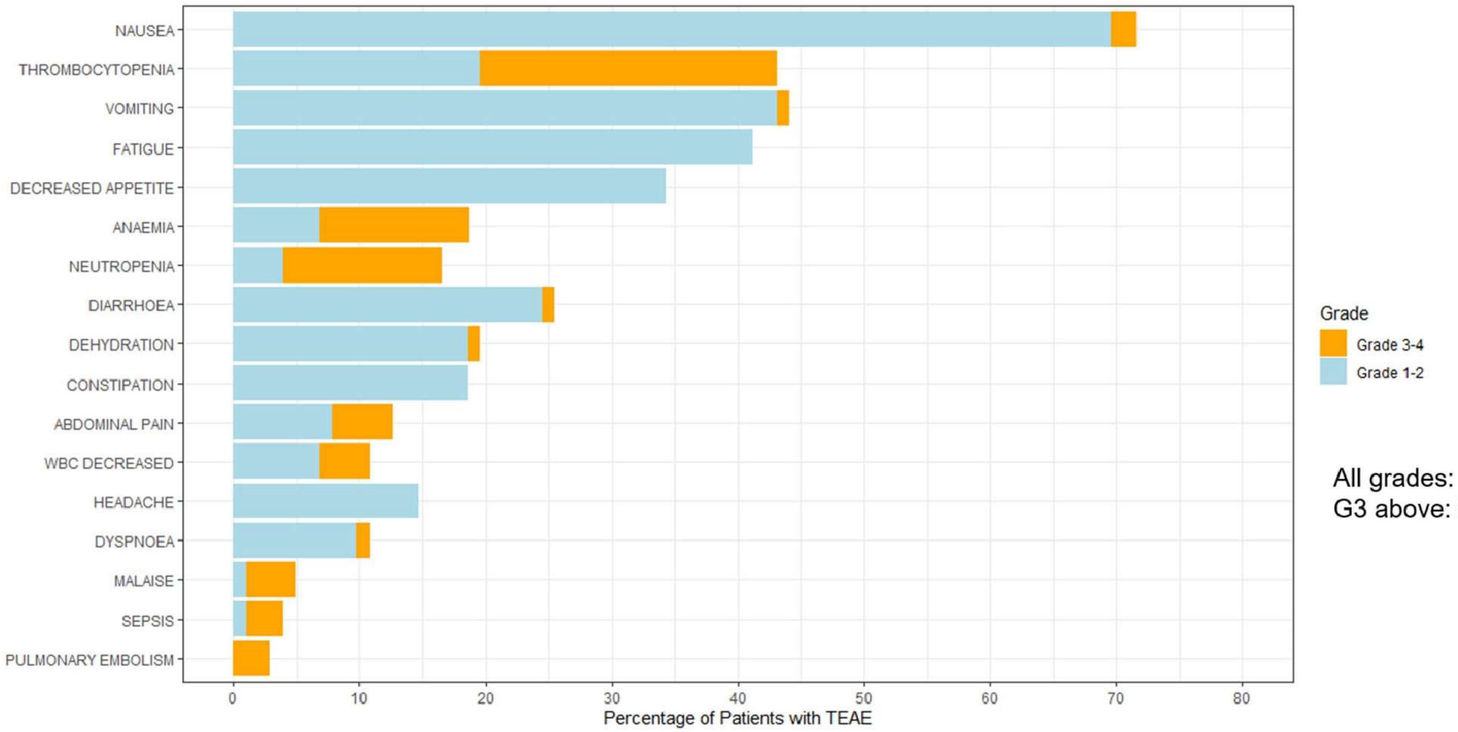
ECOG PS, Eastern Cooperative Oncology Group performance status.

Patient characteristics and disposition[a]

	N = 102			N = 102
Median (range) age, yr	64 (23–89)		**Type of cancer, no. (%)[b]**	
			Melanoma	32 (31.4)
Gender, no. (%)			NSCLC	19 (18.6)
Male	63 (61.8)		STK11-mutant lung adenocarcinoma	5 (4.9)
Female	39 (38.2)		ATM-mutant solid tumor	11 (10.8)
			Liposarcoma	17 (16.7)
ECOG PS, no. (%)			Urothelial carcinoma (UC)	12 (11.8)
0	45 (44.1)		MPNST	6 (5.9)
1	51 (50.0)			
2	5 (4.9)		**Median (range) number of cycles received**	2.0 (1-22)
Missing	1 (1.0)			
			Treatment discontinuation, no. (%)[b]	76 (74.5)
No. of prior therapies, no. (%)[b]			Adverse event (AE)[c]	14 (18.4)
0	10 (9.8)		Progressive disease	47 (61.8)
1	28 (27.5)		Consent withdrawal	8 (10.5)
2	27 (26.5)		Physician decision	3 (4.0)
≥ 3	37 (36.3)		Other	4 (5.3)

[a]Data presented are from the phase 2 study; data cutoff: April 15, 2021.
[b]Certain percentages do not sum to 100 because of rounding.
[c]Drug-related AEs include: grade 2 vomiting (n = 1), grade 2 fatigue (n = 1), grade 2 posterior reversible encephalopathy syndrome (PRES; n = 1), and ≥grade 3 thrombocytopenia (n = 2); Non-drug related AEs include: grade 1 (n = 1), grade 3 (n = 3), and grade 5 (n = 5).

Safety: Treatment Emergent AEs (TEAEs)



All grades: ≥ 10%
G3 above: ≥2%

Efficacy in all Cohorts

Response	Melanoma (n = 32)	NSCLC (n = 19)	STK-11 (n = 5)	ATM (n = 11)	Liposarcoma (n = 17)	UC (n = 12)	MPNST (n = 6)
ORR (CR + PR)	24.1% (7/29)	6.7% (1/15)	0	0	6.2% (1/16)	12.5% (1/8)	16.7% (1/6)
DCR (CR + PR + SD)	55.2% (16/29)	46.7% (7/15)	25% (1/4)	44.4% (4/9)	81.2% (13/16)	12.5% (1/8)	66.7% (4/6)
Best overall RECIST or iRECIST response							
CR	1	0	0	0	0	0	0
PR	6 (2 unconfirmed)	1	0	0	1 (unconfirmed)	1	1 (unconfirmed)
SD	9	6	1	4	12	0	3

ORR and DCR are based on efficacy evaluable population; stable disease (SD) requires a minimum duration of 2 cycles.
CR, complete response; DCR disease control rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma.

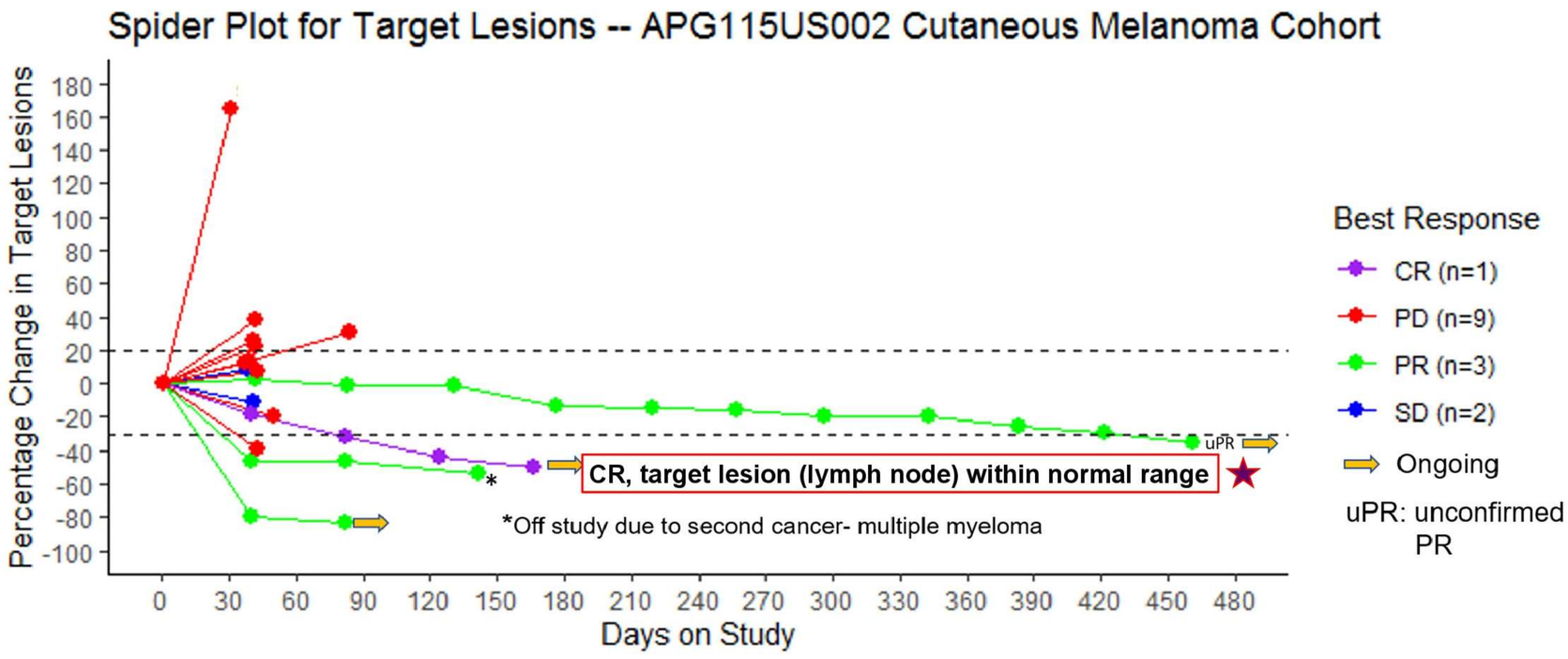
Efficacy in Patients with IO Resistant Melanoma

Response	Uveal (n = 8)	Mucosal (n = 5)	Cutaneous (n = 16)	Unknown primary (n = 3)	Total (N = 32)
ORR (CR + PR)	14.3% (1/7)	40% (2/5)	26.7% (4/15)	0	**24.1%** (7/29*)
DCR (CR+ PR+ SD)	71.4% (5/7)	40% (2/5)	46.7% (7/15)	100% (2/2)	**55.2%** (16/29)
Best overall RECIST or iRECIST response					
CR	0	0	1	0	**1**
PR	1	2 (1 unconfirmed)	3 (1 unconfirmed)	0	**6**
SD	4	0	3	2	**9**

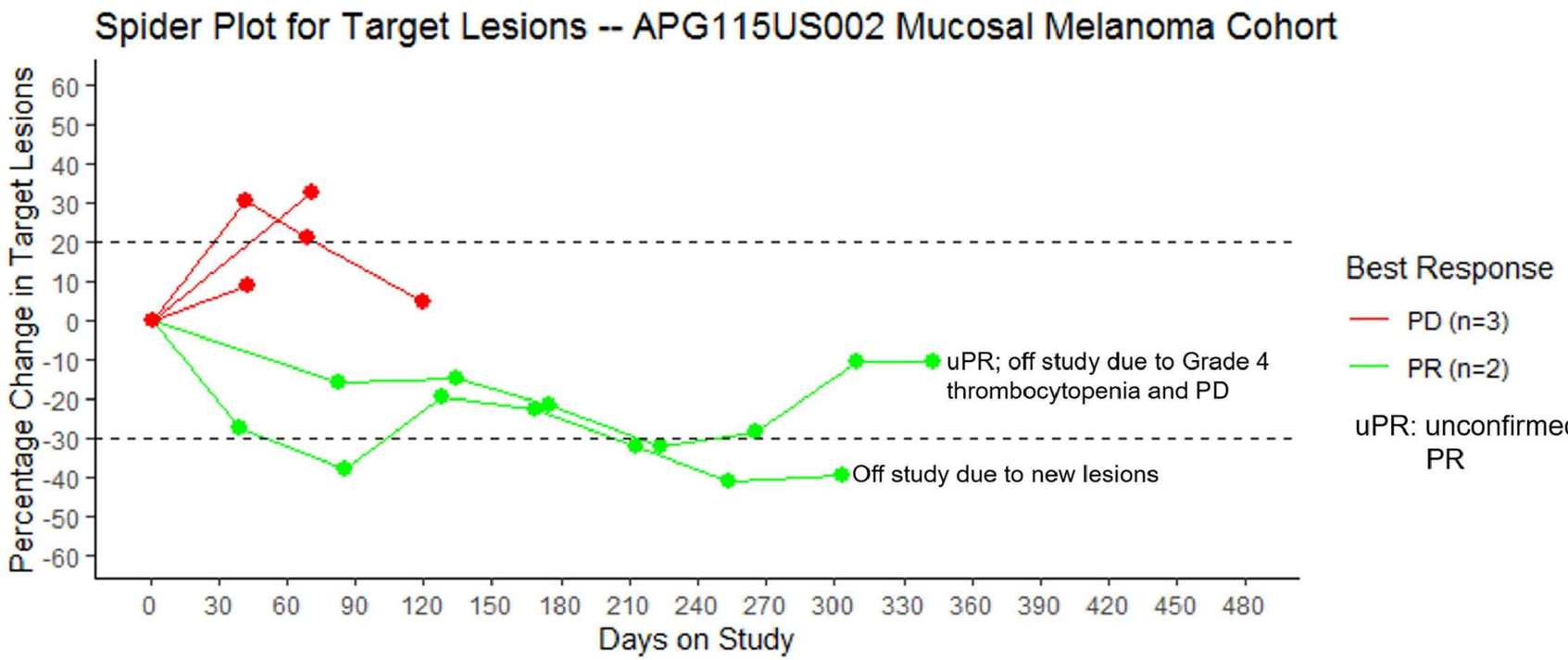
Data cutoff: April 15, 2021.

* Total evaluable patient N: 29

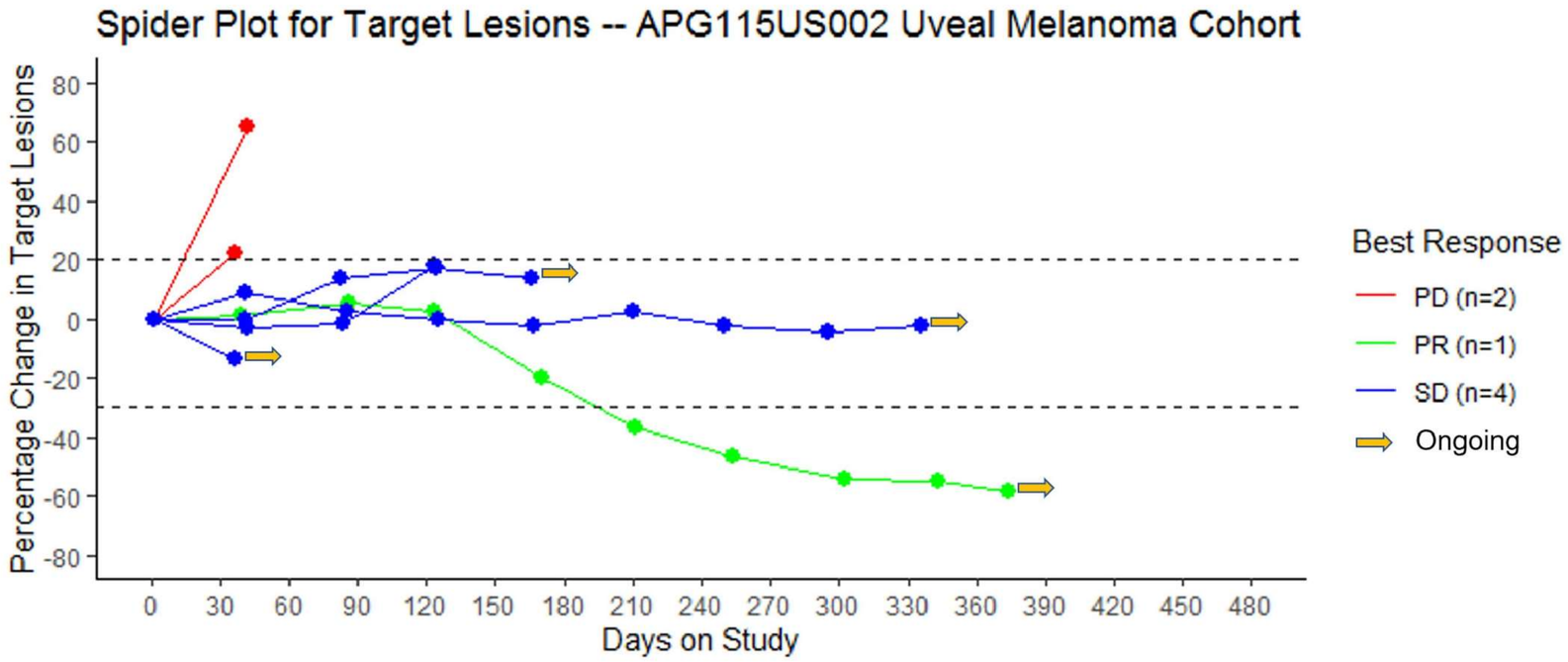
Efficacy in Patients with IO Resistant Cutaneous Melanoma Treated with APG-115 Plus Pembrolizumab



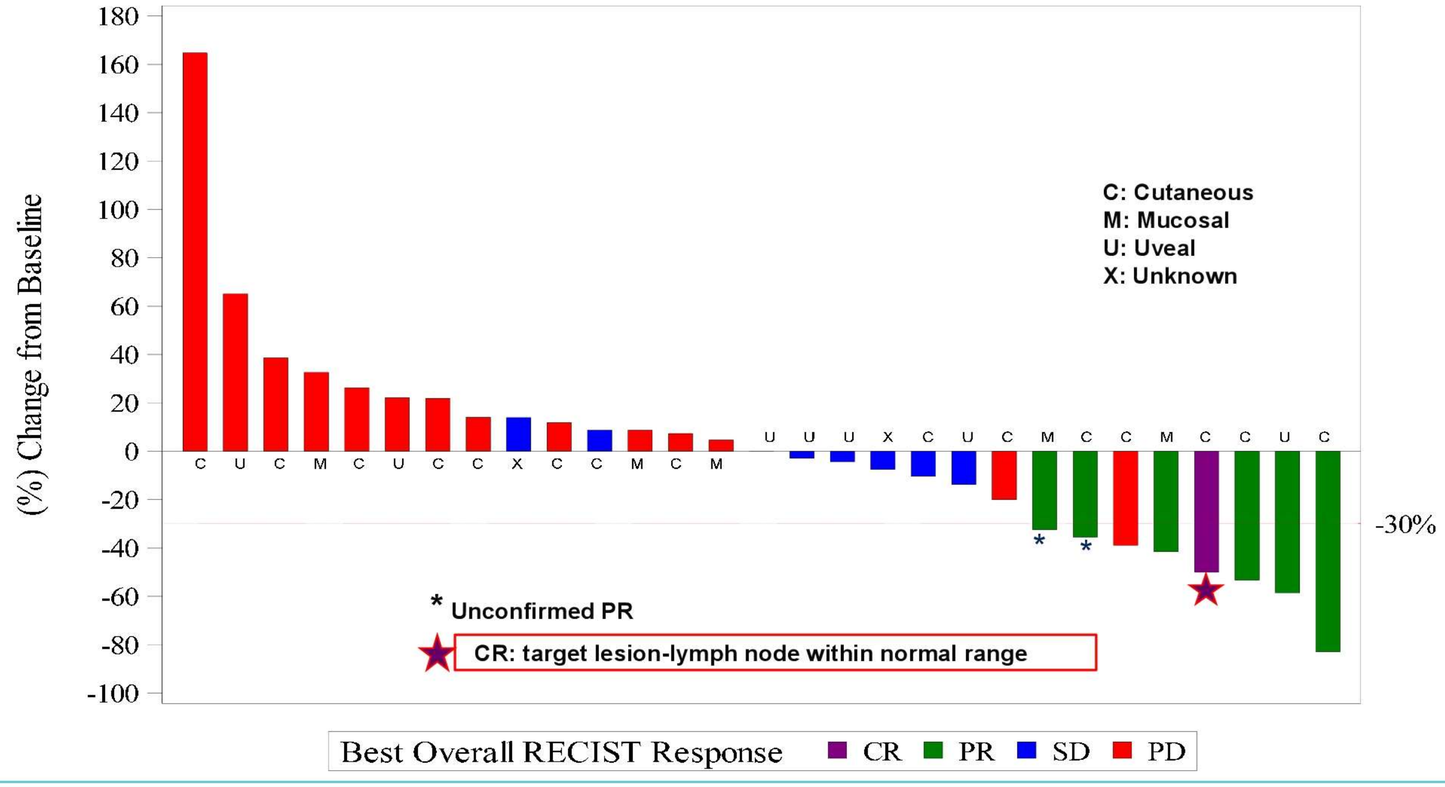
Efficacy in Patients with IO Resistant Mucosal Melanoma Treated with APG-115 Plus Pembrolizumab



Efficacy in Patients with IO Resistant Uveal Melanoma Treated with APG-115 Plus Pembrolizumab



Waterfall Plot: Best Overall Response for all Melanoma Subtypes



CONCLUSIONS

- In this Phase 2 study, APG-115 in combination with pembrolizumab is well tolerated, with no overlapping adverse effects between the two agents.

- The preliminary results have established proof of concept clinically that APG-115 in combination with pembrolizumab is efficacious in patients with IO relapsed/refractory metastatic melanoma, including uveal, mucosal and cutaneous melanoma, with 24% ORR and 55% DCR in 29 evaluable patients.
  - Study showed promising antitumor activity in patients with MPNST and liposarcoma which pembrolizumab has no approved indications

ACKNOWLEDGMENTS

The authors thank the co-investigators of the clinical trials and the patients, their families, and caregivers who are participating.

This study was conducted in collaboration with Merck & Co., Inc., Kenilworth, NJ, USA

BACK-UP SLIDES

Safety: Treatment Related AEs (TRAEs)

Any grade (≥ 5%)	No. (%)
All patients	N = 102
Any TRAE	88 (86.3)
Nausea	68 (66.7)
Decreased platelet count	44 (43.2)
Vomiting	40 (39.2)
Fatigue	36 (35.3)
Decreased appetite	29 (28.4)
Diarrhea	22 (21.6)
Decreased neutrophil count	17 (16.7)
Anemia	11 (10.8)
Decreased leukocyte count	9 (8.8)
Dehydration	7 (6.9)
Headache	7 (6.9)
Decreased weight	6 (5.9)

≥ Grade 3 (≥ 2%)	No. (%)
All patients	N = 102
Any ≥ grade 3 TRAE	32 (31.4)
Decreased platelet count	23 (22.6)
Decreased neutrophil count	13 (12.8)
Anemia	8 (7.8)
Malaise	4 (3.9)
Decreased leukocyte count	3 (2.9)
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Drug-related SAE	No. (%)
All patients	N = 102
Any treatment-related SAE	4 (3.9)
Asthenia	1 (1.0)
Hypophysitis	1 (1.0)
Posterior reversible encephalopathy syndrome	1 (1.0)
Pyrexia	1 (1.0)
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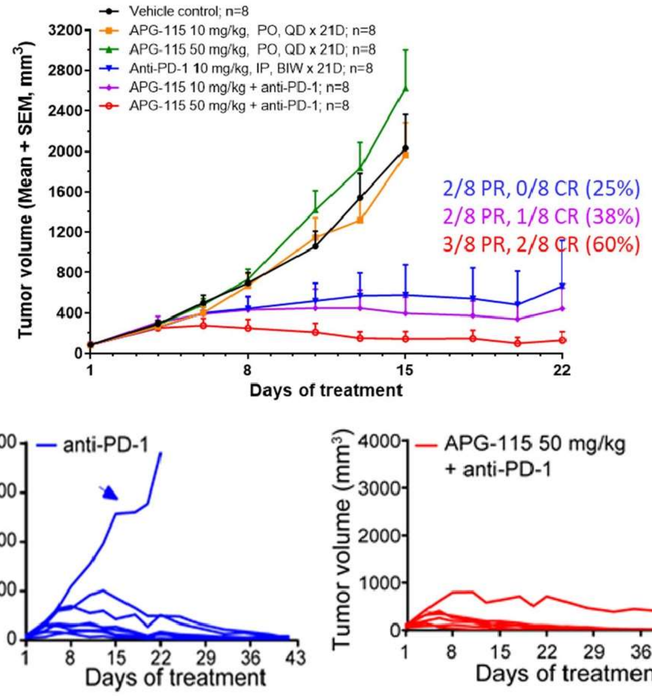
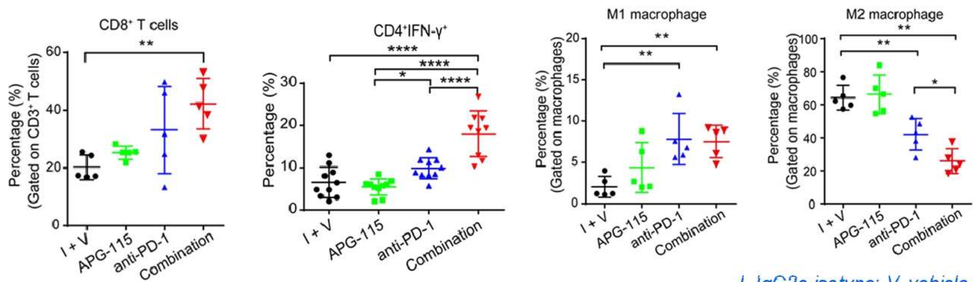
TEAEs related to either APG-115 or pembrolizumab are included.

APG-115 demonstrates synergy with anti-PD-1 blockade[3]

Trp53^{WT} MH-22A hepatoma model



Increases in CD8⁺ T, activated CD4⁺ T cells, a shift of M2 to M1 macrophages in the TME



I, IgG2a isotype; V, vehicle

3. Fang DD et al. J Immunother Cancer 2019;7:327