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(Abstract 795) A multicenter phase II trial (SWOG S1609, Cohort 51) of Ipilimumab and Nivolumab in metastatic or unresectable angiosarcoma: a sub-study of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART)

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Angiosarcoma

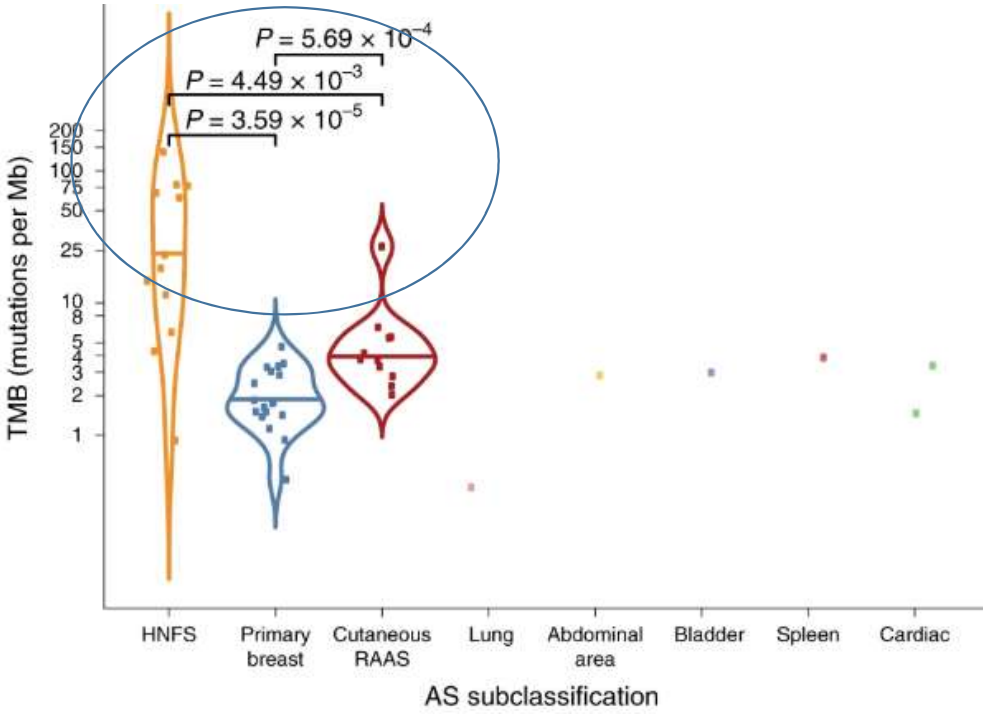
- **Epidemiology**
  - **Account for <3% of all soft tissue sarcomas**
  - **Arise in any part of body**
  - **Long-term survival is poor for patients who develop metastases**
- **Primary or Secondary (associated with prior radiation or chronic lymphedema)**

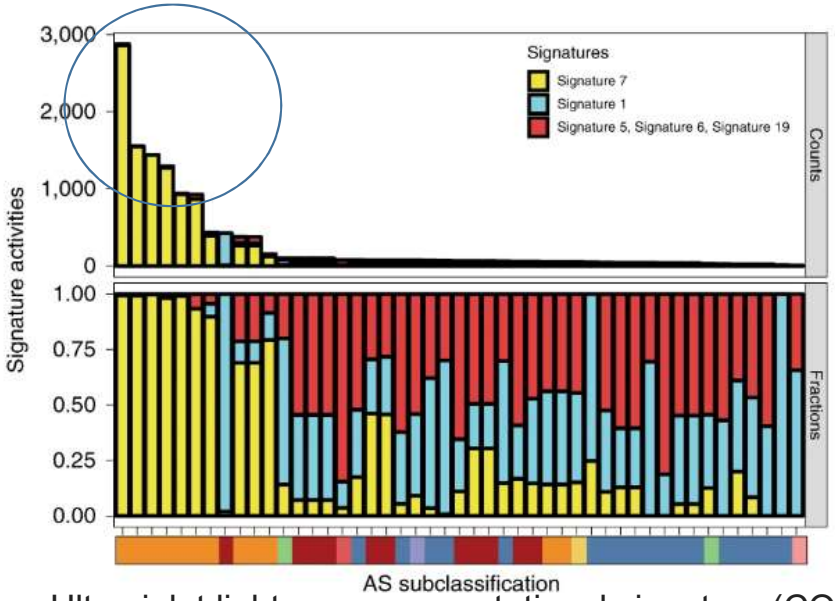
	Number (%)
Head and neck	144 (27·0%)
Breast	105 (19·7%)
Extremities	82 (15·3%)
Trunk	51 (9·5%)
Liver	32 (6·0%)
Heart	25 (4·7%)
Bone	19 (3·6%)
Spleen	14 (2·6%)
Other or unknown	62 (11·6%)

Table 1: Distribution of angiosarcoma with pooled data from 534 patients[1,6-9]

Young et al., Lancet Oncology 2010

Subsets of Angiosarcoma Identified With NGS



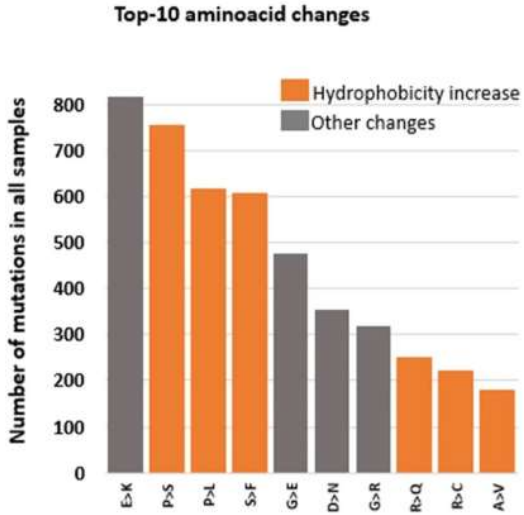


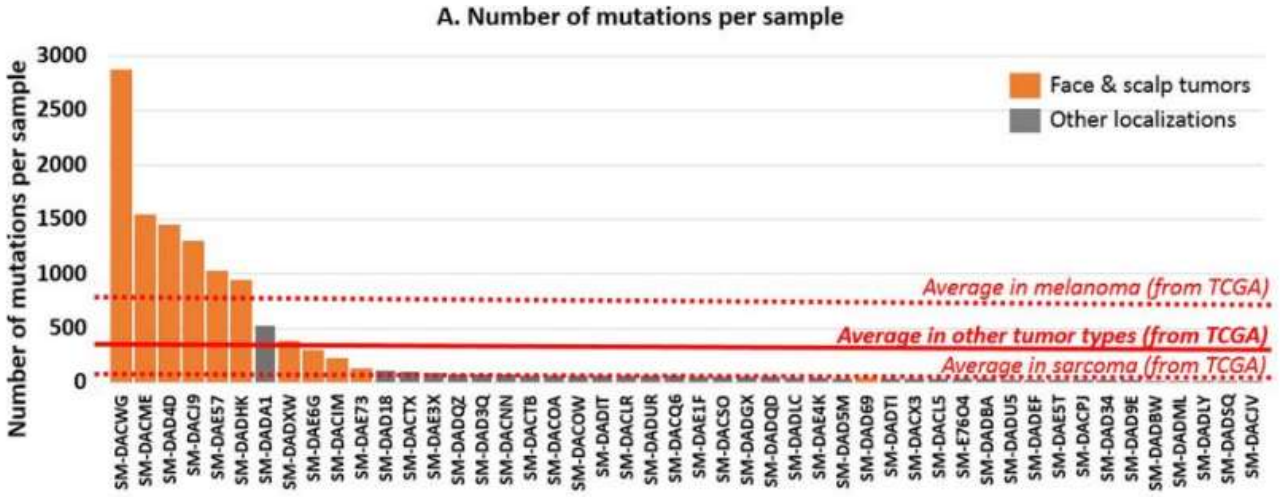
Ultraviolet light exposure mutational signature (COSMIC Signature 7, indicated in yellow)

- **Subset of AS patients have high TMB and UV mutation signature**

Painter et al, Nature Med, 2020

Angiosarcoma mutation pattern suggests increased immunogenicity





- **Common mutations increase hydrophobicity, suggesting greater immunogenicity**
- **High TMB angiosarcomas are comparable to other cancer types that are responsive to ICI**

Boichard, Wagner, Kurzrock, Genome Med 2020

Clinical Responses to Immune Checkpoint Inhibition: a retrospective cohort

Patient	Demographics	Pathology	Disease state	Prior therapies	Immunotherapy	Number of ICI doses	Response at 12 weeks
1	32-year-old female	Primary breast AS	MetastaticSoft tissue, Bones	Gemcitabine/ Docetaxel	Axitinib + Pembrolizumab (NCT02636725)	4	Progression of disease
2	71-year-old female	Breast RAS	Metastatic Mediastinal lymph nodes, Lung	Doxorubicin/ Olaratumab, Gemcitabine/ Docetaxel, Pazopanib	Pembrolizumab	5	Partial response
3	62-year-old female	cAS	Locally advanced-face	Doxorubicin, Gemcitabine/ Docetaxel, Pazopanib, Ifosfamide, Notch Inhibitor (NCT01695005), Temozolamide/ Bevacizumab	Anti-CTLA-4 (NCT02694822)	14	Partial response
4	68-year-old female	cAS	Metastatic Lymph nodes, Bones	IL-2/ Cyclophosphamide/ Methotrexate, Paclitaxel, Bevacizumab	Pembrolizumab	6	Partial response[b]
					Ipilimumab/ Nivolumab	8	Partial response[b]
5	89-year-old female	cAS	Multifocal-scalp	Gemcitabine, Paclitaxel, Pazopanib	Pembrolizumab	5	Partial response[a]
6	76-year-old male	cAS	Multifocal-scalp	Pazopanib/TRC105 (NCT02979899), Doxorubicin/ Cyclophosphamide/ Olaratumab, Gemcitabine/ Docetaxel	Pembrolizumab	5	Partial response[a]
7	65-year-old male	cAS	Multifocal-nose	Doxorubicin/ Ifosfamide, Doxorubicin/ Cyclophosphamide, Gemcitabine/ Docetaxel	Anti-CTLA-4 (NCT02694822)	7	Progression of disease

RAS, Radiation associated angiosarcoma; cAS, cutaneous angiosarcoma

- **Prospective data are needed**

Florou et al, JITC 2019

Dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors: DART

- **Multi-cohort prospective Phase II trial for patients with rare cancers run through SWOG Early Therapeutics and Rare Cancers Committee**
- **> 50 cohorts of rare cancer subtypes (NCT02834013)**
- **Ipilimumab 1mg/kg q6 weeks + Nivolumab 240 mg q2 weeks**

Statistical Design of S1609: DART

- Single-arm Phase II Trial
- Primary Endpoint: RECIST v1.1 Response; assessments every 8 weeks
- Secondary Endpoints: PFS, OS, stable disease at six months, and toxicity
- Alpha (one sided) 0.13, Power 87%
- Ho = 5%; Ha = 30%
- First stage: 6 patients, ≥1 response to continue to second stage
- Second Stage: 10 additional patients (n=16 in total cohort), ≥2 responses in cohort warrant further study in angiosarcoma

Baseline Patient and Tumor Characteristics

	Summary [Median (min, max) or N (%) reported]
Age	68 (25, 81)
Gender	
Female	6 (38)
Male	10 (62)
Performance status	
0	7 (44)
1	9 (56)
Ethnicity	
Hispanic	2 (12)
Not Hispanic	14 (88)
Race	
White	13 (81)
Black	2 (12)
Unknown race	1 (6)

Primary site	Summary [Median (min, max) or N (%) reported]
Breast	4 (25)
Extremity	2 (12)
Face/Scalp	5 (31)
Heart	1 (6)
Liver	2 (12)
Spleen	1 (6)
Stomach	1 (6)
Cutaneous Primary	
No	7 (44)
Yes	9 (56)
Radiation Associated	
No	13 (81)
Yes	3 (19)
Number Prior Therapies	2 (0, 5)

Toxicity

	Any Grade	Grade 3-5
Any	12 (75.0%)	4 (25.0%)
Serious	3 (18.8%)	2 (12.5%)
Led to Discontinuation	2 (12.5%)	2 (12.5%)
Lead to Death	0 (0.0%)	0 (0.0%)

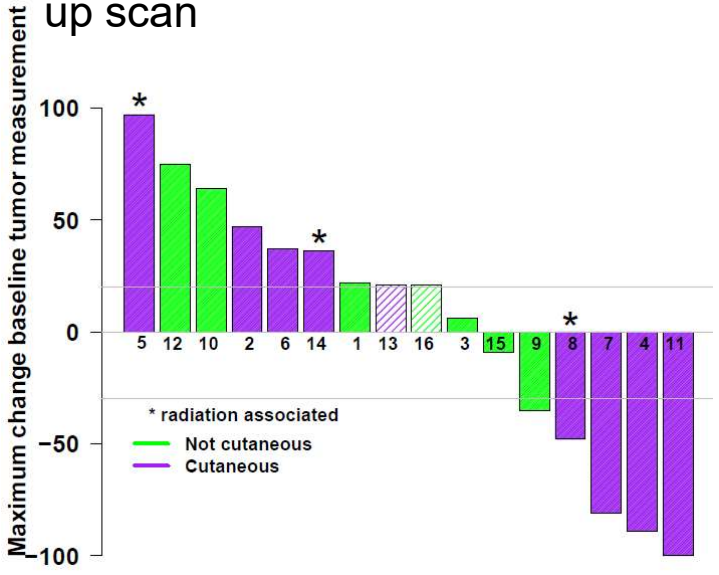
- Most common (each occurred in 3 patients, *1/3 instance of grade 3):
  - ALT/AST increase*
  - Anemia*
  - Diarrhea*
  - Fatigue
  - Hypothyroidism
  - Pneumonitis
  - Pruritis
  - Rash

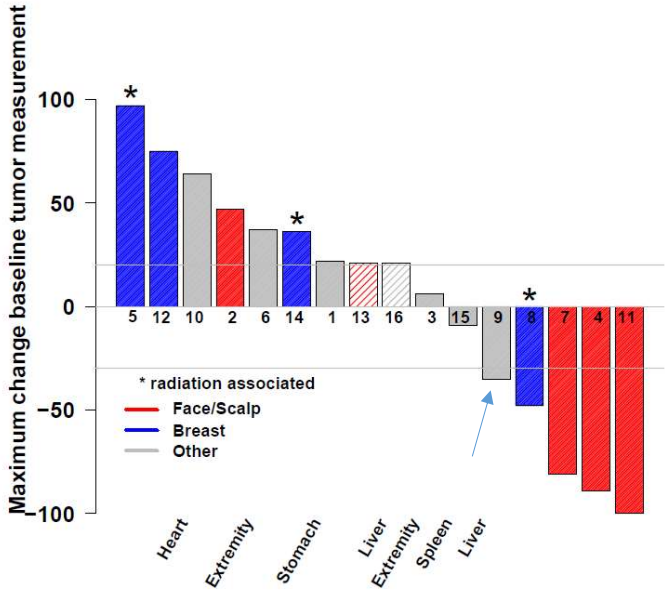
Immune Related Toxicity

	Any Grade	Grade 3-5
Immune-mediated	11 (68.8%)	2 (12.5%)
Alanine aminotransferase increased	3 (18.8%)	1 (6.3%)
Aspartate aminotransferase increased	3 (18.8%)	1 (6.3%)
Diarrhea	3 (18.8%)	1 (6.3%)
Hypothyroidism	3 (18.8%)	0 (0%)
Pneumonitis	3 (18.8%)	0 (0%)
Pruritus	3 (18.8%)	0 (0%)
Rash maculo-papular	3 (18.8%)	0 (0%)
Infusion related reaction	2 (12.5%)	0 (0%)
Lipase increased	2 (12.5%)	0 (0%)
Arthralgia	1 (6.3%)	0 (0%)
Hyperthyroidism	1 (6.3%)	0 (0%)
Serum amylase increased	1 (6.3%)	0 (0%)

Waterfall Plots by Location and Cutaneous vs Non-cutaneous

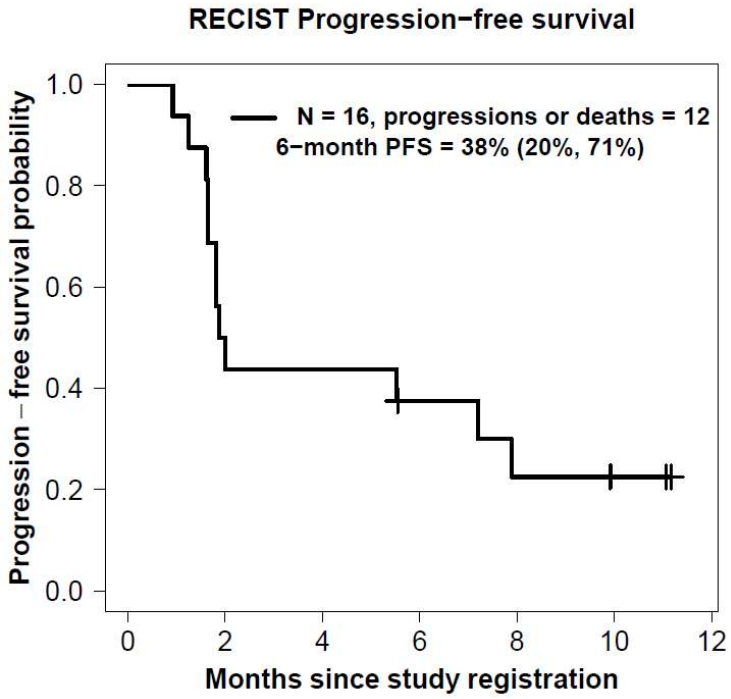
- Overall Response Rate 25% (4/16)
  - Responses seen in patients with cutaneous disease of the scalp/face (3/5) and radiation associated breast angiosarcoma (1/3)
  - Additional patient with liver primary had reduction >30% but progressed on confirmatory follow up scan

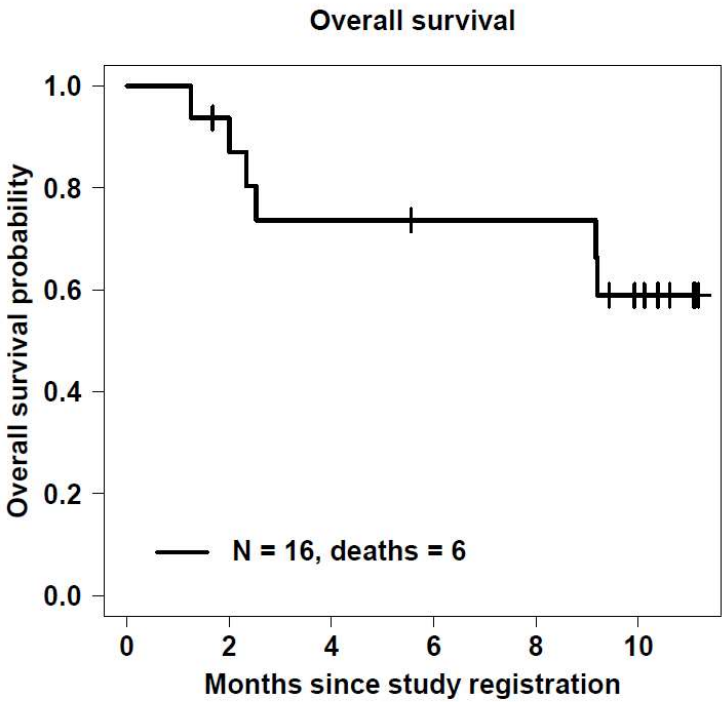




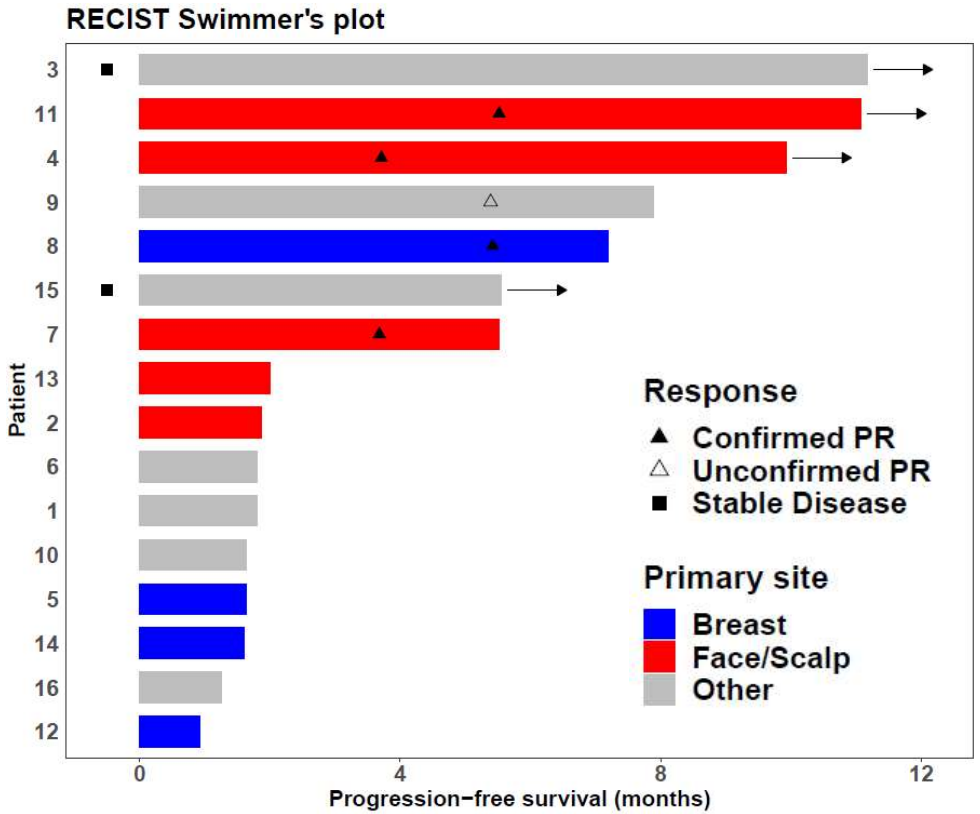
Examples of Cutaneous Responses

Kaplan Meier Analysis





Swimmer's Plot



Clinical NGS Results for Enrolled Patients (N = 8)

Primary Tumor Site	Assay	TMB (mut/mb) [interpretation in report)	PDL1 status (Antibody)	NGS Findings (characterized alterations; no VUSs)	Best Response
Right atrium	Tissue NGS (FoundationOne Heme Panel, 405 genes) genes)	3	Not done	BRAF G469R, MLL2 Q52* and W2818*	PD
Scalp	Tissue NGS (FoundationOne Heme Panel, 406 genes)	8 [Intermediate]	TPS 50% (Ventana SP263 antibody)	HRAS and HGF amplification, ATRX splice site mutation, TP53 A159V mutation	Died prior to first response assessment
Breast- XRT	Guardant 360 liquid biopsy (74 genes)	Not done	Not done	PEAR1-NTRK1 Fusion, ATM R337C, TP53 T140fs, MYC amplification	PR
Breast	Tissue NGS (FoundationOne Heme Panel, 406 genes)	0 [low]	Not done	PIK3CA P471L, HRAS G13D, ASXL Q623fs*8, PRDM1 G585fs*48	PD
Skin of face	Tissue NGS (Tempus 1714 genes)	8.4 [Intermediate]	TPS 30% (22C3 antibody)	CDKN2A copy number loss, POT1 p.Y122_E128delins*(LOF), SPEN p.R653* (LOF CDKN2B copy number loss	PR
Scalp	Tissue NGS (Local institutional panel, 170 genes)	24 [High]	Not done	KIT amplification, TP53 A347V and E286K	PR
Spleen	Tissue NGS (Local Institutional Panel, 523 genes)	5 [low]	Not done	ATM R337H, NOTCH1 c.2882delC:p.Thr961ArgfsTer218	SD (6+ months and ongoing)
Skin of arm	Tissue NGS (FoundationOne Heme Panel, 406 genes)	5 [low]	TPS 0% (Ventana SP263 antibody)	BRCA1 N1355fs*10, CDKN2A/B loss, NOTCH1 V1575L	PD

Clinical Molecular Characterization of Enrolled Patients (N = 8)

- 7 patients had TMB available, 2 patients with PR had TMB available
  - 1/7 patients had high TMB
  - Responders were intermediate and high TMB
- All eight patients had ≥2 deleterious genomic alterations
  - Each patient had distinct molecular profile
- One patient had a fusion involving *NTRK1*, one patient had an atypical *BRAF* mutation and one patient had a *BRCA1* alteration
- 2/3 patients with PDL1 IHC available had high staining (TPS of 30 and 50%)

Conclusions

- **Ipilimumab and Nivolumab is well tolerated and safe in patients with angiosarcoma**
- **ORR in all patients was 25% (4/16); cutaneous scalp/face and radiation associated breast tumors responded**
- **A larger study of ipilimumab and nivolumab is warranted for angiosarcoma**

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