University of Iowa Holden Comprehensive Cancer Center

Clinical Activity of Combined Telomerase Vaccination and Pembrolizumab in Unresectable Melanoma

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Disclosures over 5 years:

- Advisory Board: **Ultimovacs**, Bristol Myers Squibb, Amgen, Roche Diagnostics, Novartis, Janssen, Eisai, Exelixis, Castle Bioscience, Genzyme Corporation, Astrazeneca, Array, Bayer, Pfizer, Clovis, EMD serono, Myovant.
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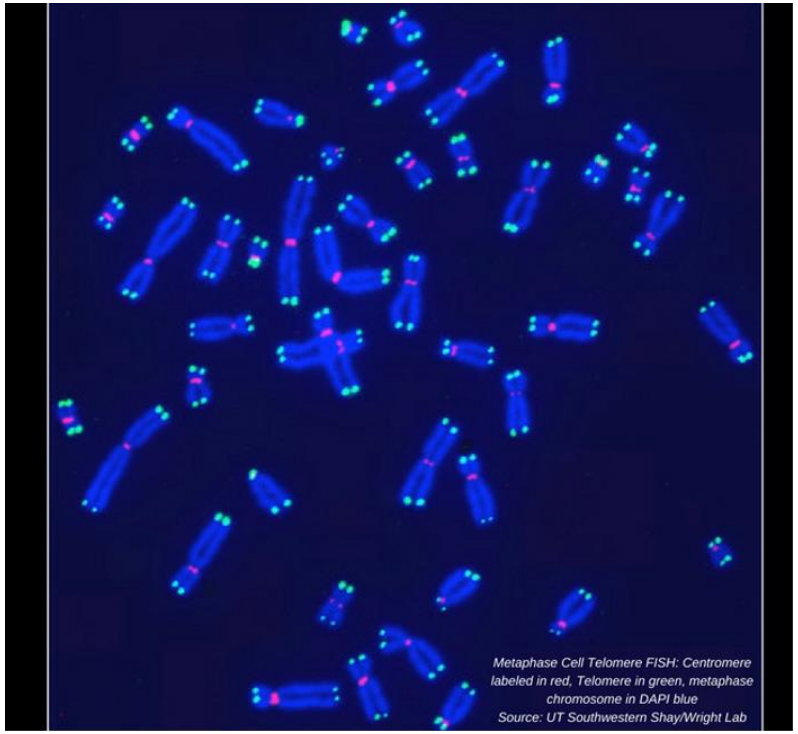
- Travel support: **Ultimovacs**.

Telomerase (TERT) Activation in Cancer

- Telomerase is activated in >90% of all cancers to enable replicative immortality[1]
- High telomerase activity level correlates with poor prognosis[2,3]
- Persistent antigen presence[4]
- Relevant antigen in otherwise heterogenous and TMB-low tumors[4]
- Spontaneous anti-TERT immune response predictive of CPI response and survival[3]



1: Shay JW. Eur J Cancer. 1997
2: Hugdahl E. Br J Cancer. 2018
3: Nardin C. J Invest Dermatol. 2021
4: Ellingsen EB. Front Immunol. 2021

UV1 – Peptide-Based Cancer Vaccine Targeting Telomerase

- Composed of 3 synthetic long peptides covering the active site of telomerase reverse transcriptase (TERT)
- Peptides selected based on immunogenicity screeening – immune response against UV1-region associated with long-term survival
- Designed to promote inflammatory TME through induction of tumor-associated antigen (TAA)-specific CD4+ T cell responses
- GM-CSF used as vaccine adjuvant to attract DCs to vaccination site

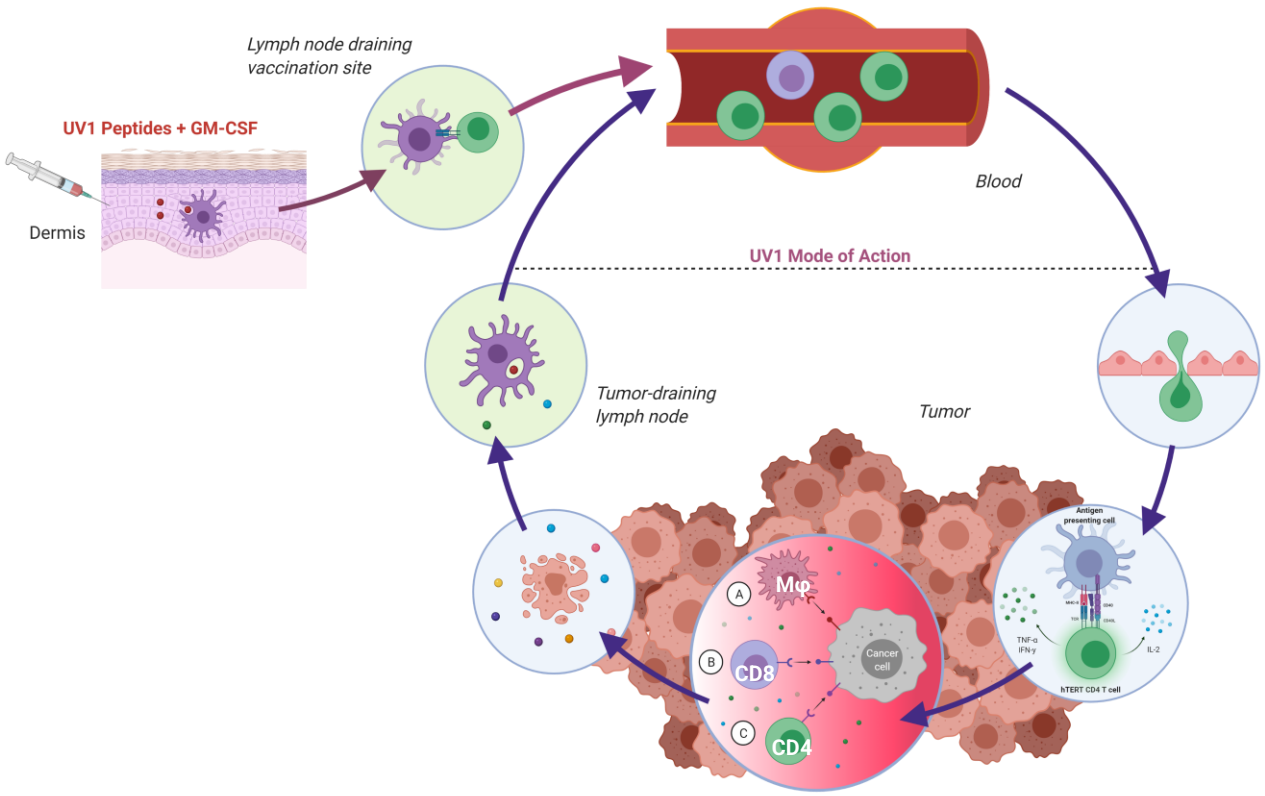


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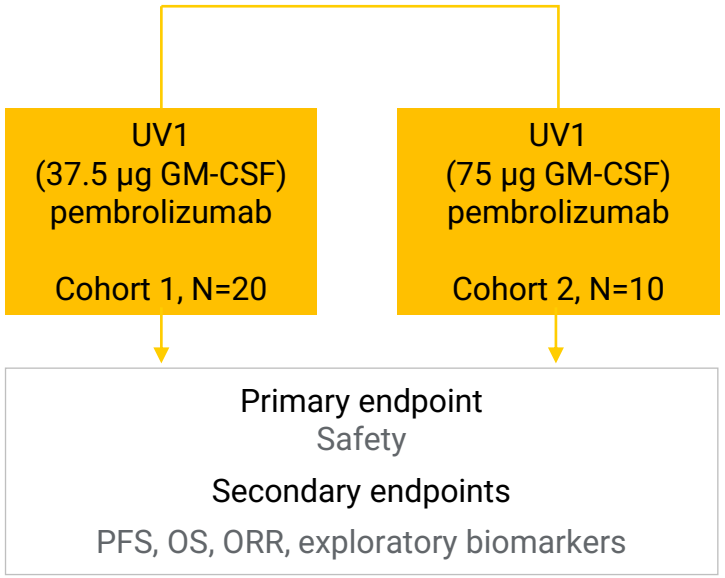
Figure adapted from: Ellingsen EB et al. Front Immunol. 2021

Study Design

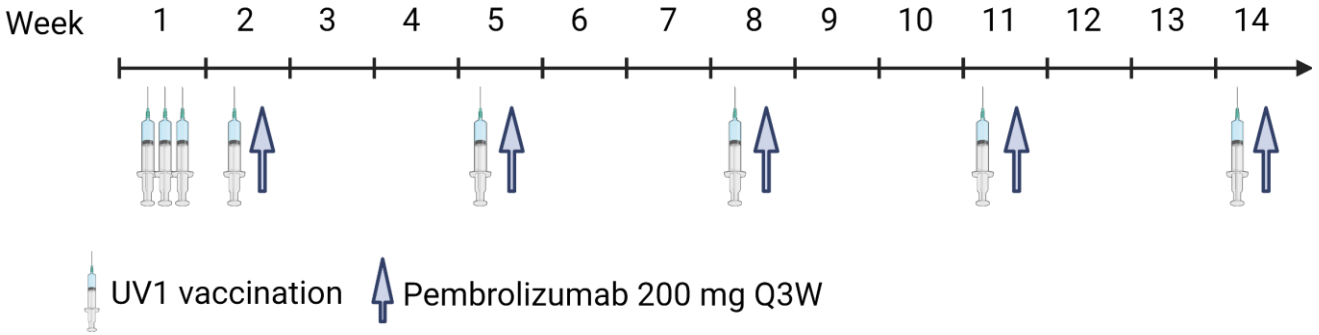
Phase I Trial Design



Key Eligibility Criteria

- Advanced histologically confirmed malignant melanoma (stage IIIB-C, IV)
- Measurable and evaluable disease according to iRECIST
- Previously untreated and eligible for pembrolizumab (prior BRAF and MEK inhibitors permitted)
- ECOG 0-1
- Active brain metastases, and uveal or ocular melanoma not permitted

Treatment Schedule



Followed by pembro monotherapy per label

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Patients Demographics

Characteristic		N= 30 (%)
Age (years)		
Median, range		70,5 (30-87)
Sex		
	female	9 (30%)
	male	21 (70%)
ECOG status		
	0	19 (63%)
	1	11 (37%)
Stage		
	IIIB	2 (7%)
	IIIC	9 (30%)
	IV M1a	5 (17%)
	IV M1b	5 (17%)
	IV M1c	8 (27%)
	IV M1d	1 (3%)
Liver metastases		
	Yes	4 (13%)
	No	26 (87%)

Characteristic		N=30 (%)
BRAF V600E*		
	Mut	10 (33%)
	Wild-type	17 (57%)
LDH^		
	above ULN	9 (31%)
	below ULN	20 (69%)
Prior lines of systemic therapy		
	0	30 (100%)
	≥1	0 (0%)
PD-L1 status		
	Positive (≥1%)	8 (36%)
	Negative	14 (64%)
	Missing	8
Tumor mutational burden		
	High (≥20 mut/Mb)	3 (18%)
	Intermediate (6-19 mut/Mb)	6 (35%)
	Low (0-5 mut/Mb)	8 (47%)
	Missing	13

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* Unknown BRAF status in 3 patients. ^ LDH = Lactate dehydrogenase, ULN = upper limit of normal. Unknown in one patient.
PD-L1 staining with 22C3 pharmDx for Autostainer Link 48. PD-L1 positive defined as ≥1% of tumor cells

Adverse Events

- Combination of UV1 and pembrolizumab was well tolerated with safety profile similar to pembrolizumab monotherapy*
- No difference in safety profile between cohort 1 and cohort 2
- 4 patients*** discontinued any treatment due to AEs. None were related to UV1 vaccination

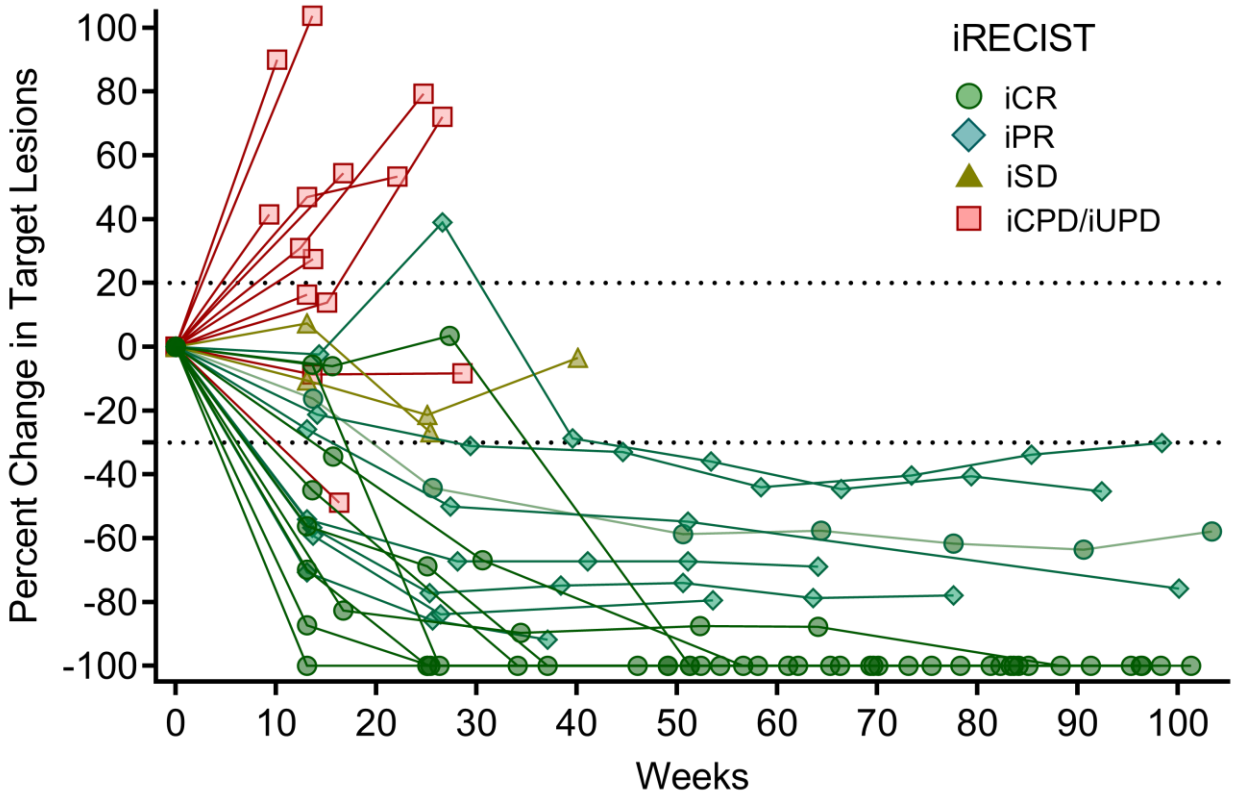
Event	UV1/GM-CSF + pembrolizumab (N=30)	
	Number of patients with events (%)	
	Any Grade	Grade 3 or 4
Any Treatment-emergent adverse event (TEAE)	28 (93.3)	17 (56.7)
Any drug *related* TEAE**	21 (70.0)	6 (20.0)
Fatigue	10 (30.0)	0
Hypothyriodism	6 (20.0)	0
Injection site reaction	6 (20.0)	0
Colitis	5 (16.7)	2 (6.7)
Diarrhea	5 (16.7)	0
Hyperthyriodism	4 (13.3)	1 (3.3)
Pruritus	4 (13.3)	0
Rash	3 (10.0)	0
Arthritis	2 (6.7)	2 (6.7)
Dyspnea	2 (6.7)	0
Chorioretinitis	1 (3.3)	1 (3.3)
Diabetes mellitus	1 (3.3)	1 (3.3)

** Drug related TEAEs listed here were reported in more than one patient or grade 3 or 4. None of the drug related TEAE were grade 4. Patients with same AE/grade counted only once.
*** 2 patients discontinued treatment late in the study treatment period due to dyspnea and chorioretinits, 2 patients discontinued pembrolizumab between week 19-25 due to colitis, diarrhea, hyper-and hypothyroidism

*Robert C et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. New England Journal of Medicine. 2015

Efficacy

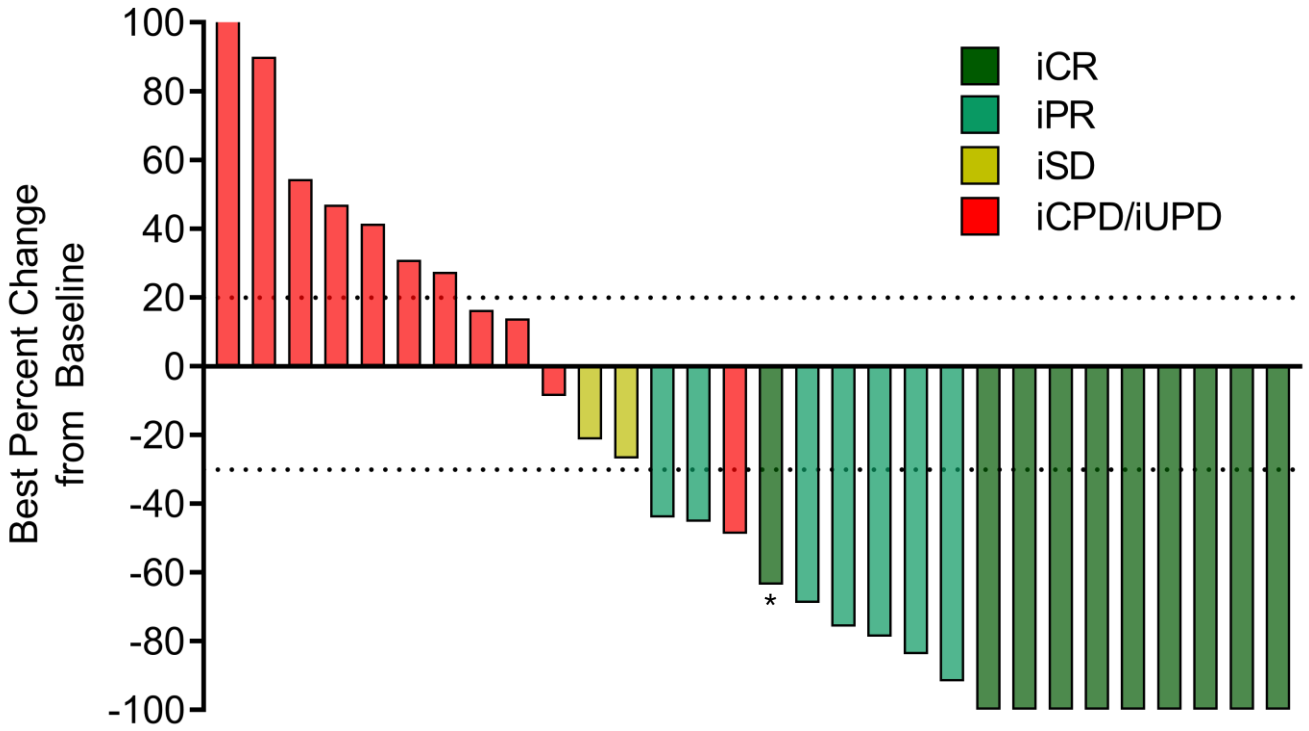
Durable Objective Responses



Best Overall Response (iRECIST)	n	%
Objective Response Rate	17	56.7
Complete Response	10	33.3
Partial Response	7	23.3
Stable Disease	2	6.7
Confirmed/Unconfirmed Progressive Disease	11	36.7

Efficacy

Objective Responses Regardless of PD-L1 Status



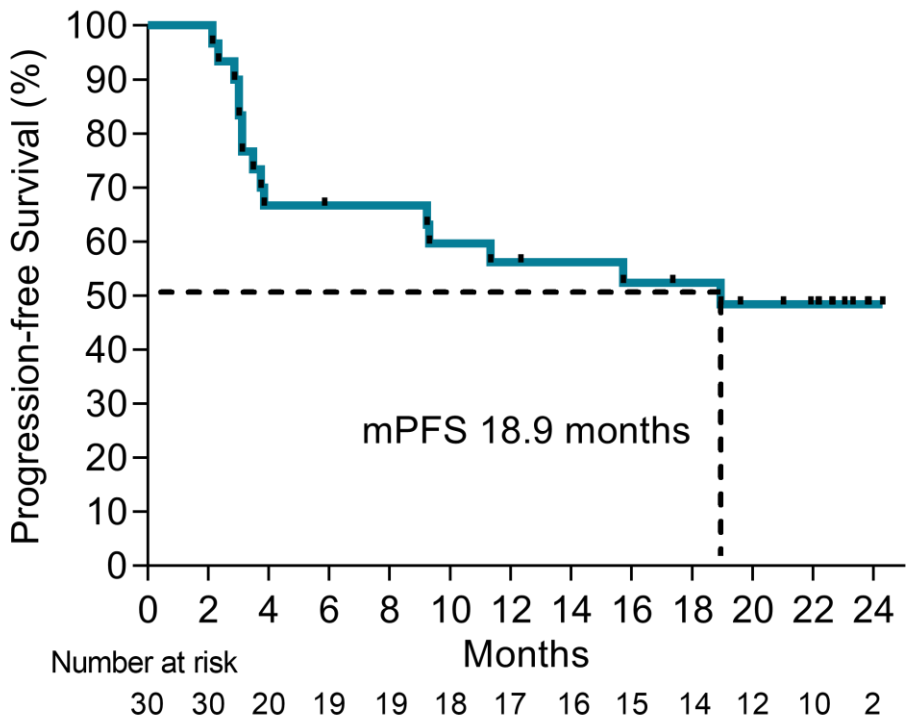
Population	ORR (%)	iCR (%)	iPR (%)
PD-L1 (≥1%) (n=8)	4 (50.0%)	3 (37.5%)	1 (12.5%)
PD-L1 (<1%) (n=14)	8 (57.1%)	5 (35.7%)	3 (21.4%)

* Lymph node target lesion was reduced from 17.2 mm to 6.3 mm (-63% change). A lymph node size of <10 mm is considered normal, and a PET/CT-scan later confirmed no malignant activity. The patient is therefore considered an iCR according to iRECIST

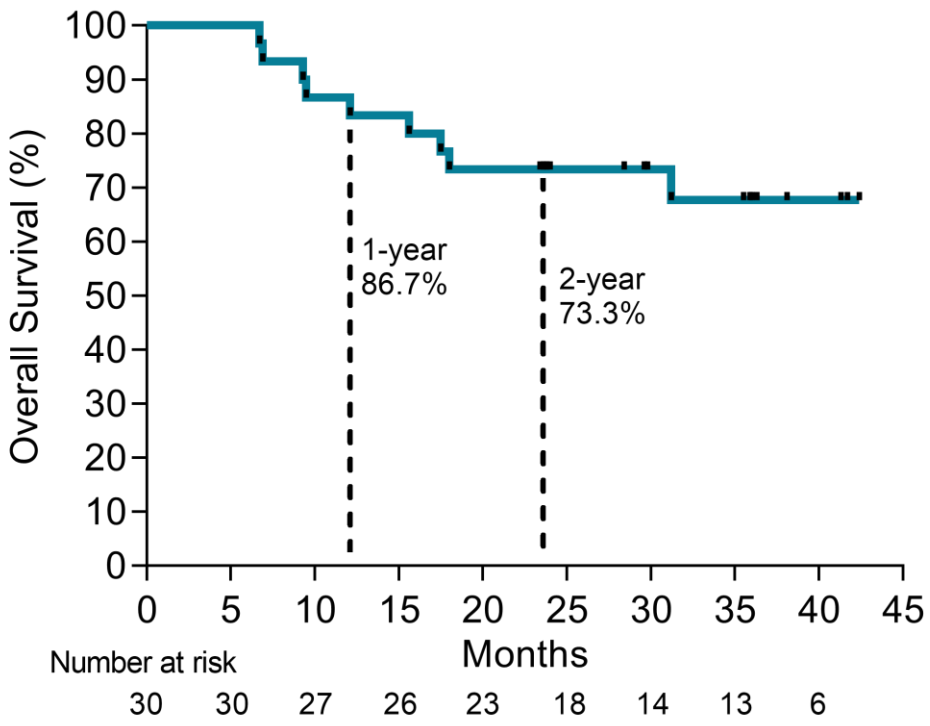
Efficacy

Progression-free and Overall Survival

Progression-free Survival (n=30)



Overall Survival (n=30)



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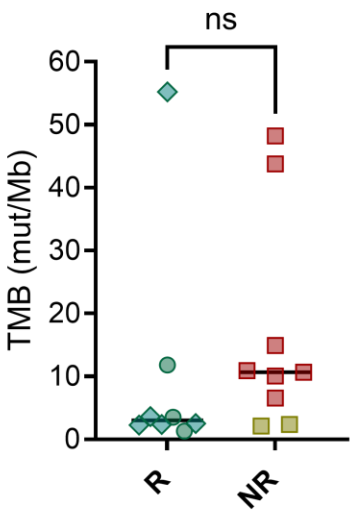
Baseline TMB, Neoantigens, and IFN-γ Signature

Objective responses in TMB-low and neoantigen-low tumors not enriched for IFN-γ

TMB



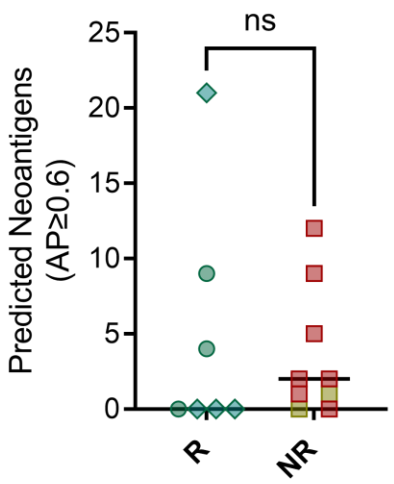
Responders (R)

- iCR (n=3)
- iPR (n=5)

Non-Responders (NR)

- iCPD/iUPD (n=7)
- iSD (n=2)

Neoantigens



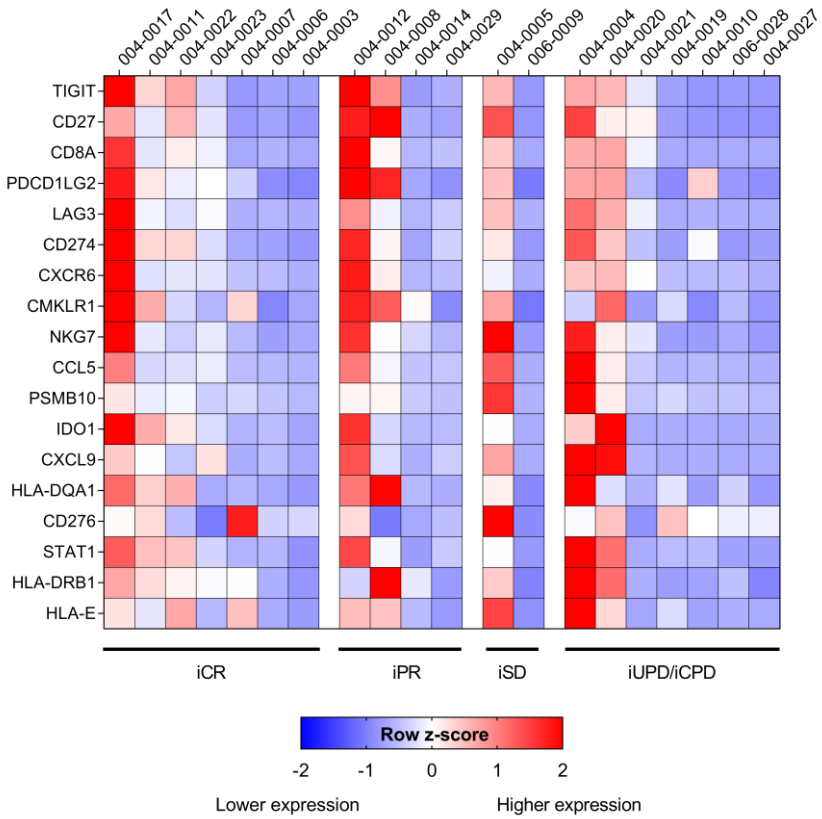
Responders (R)

- iCR (n=3)
- iPR (n=4)

Non-Responders (NR)

- iCPD/iUPD (n=7)
- iSD (n=2)

IFN-γ Gene Signature[1]



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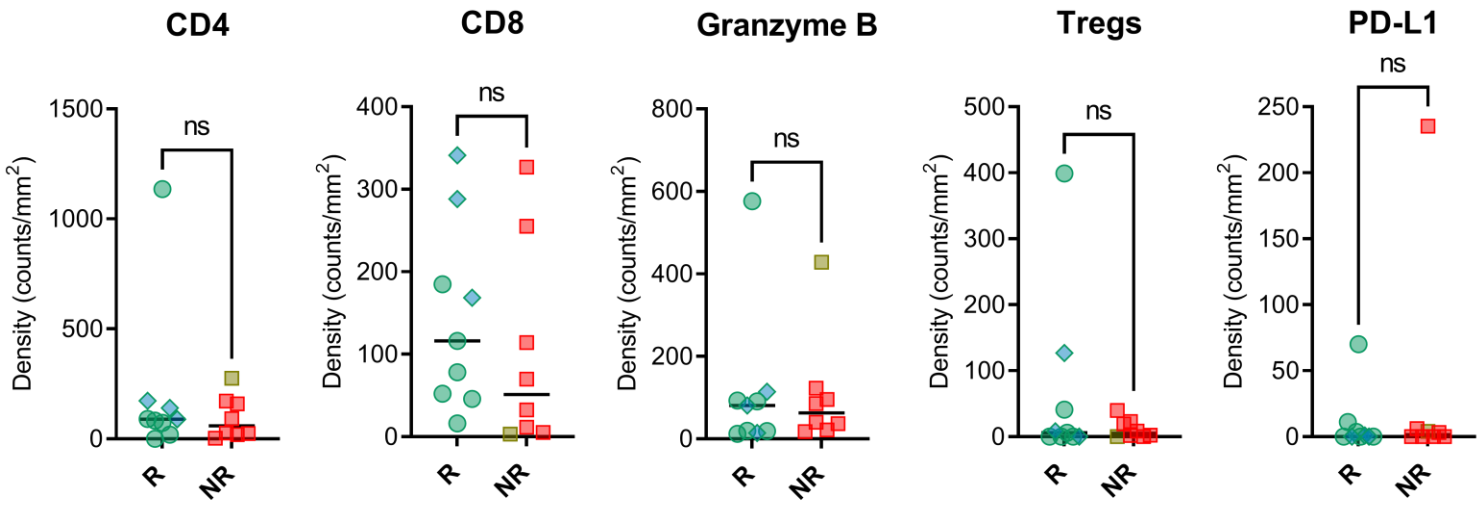
1: **Ayers M** et al. IFN-γ–related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest. 2017

Immunofluorescence Staining

No difference in TILs at baseline - Increased in responders at week 14

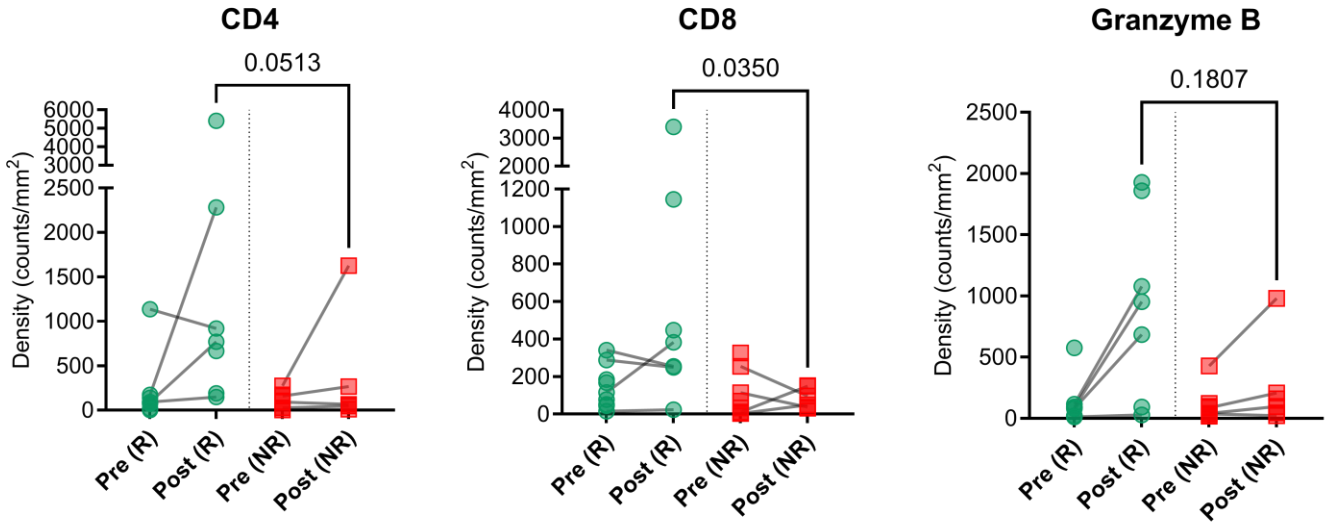
Baseline



Responders (R)
- iCR (n=6)
- iPR (n=3)

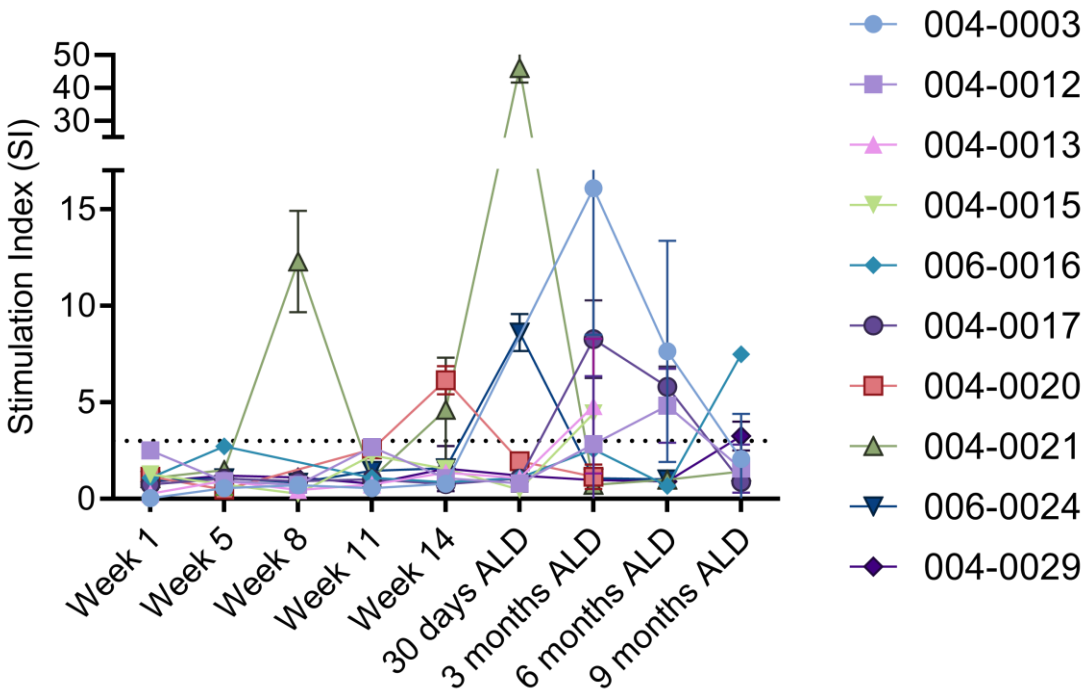
Non-Responders (NR)
- iSD (n=1)
- iCPD/iUPD (n=7)

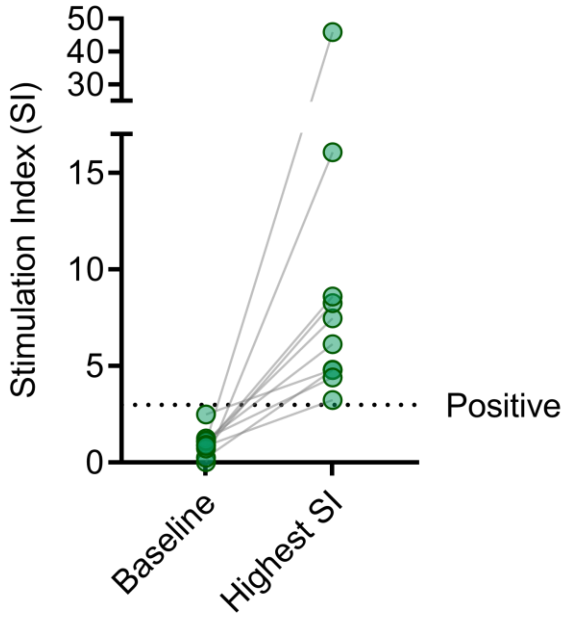
Baseline vs End of Treament



UV1-induced Immune Responses in PBMC*

Development of TERT specific T cell response.





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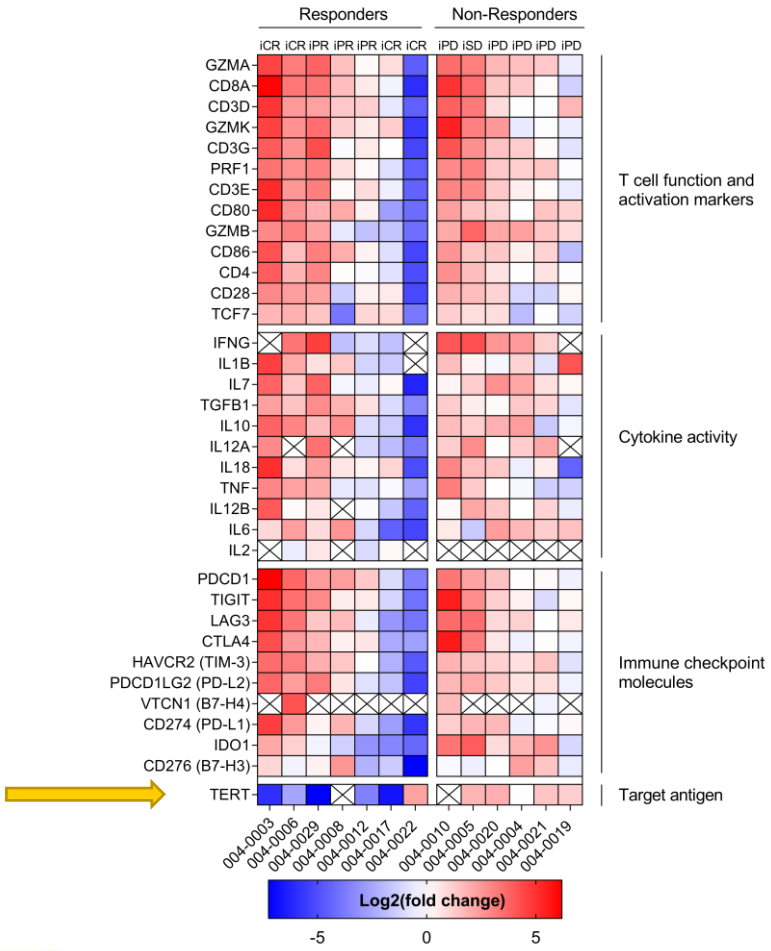
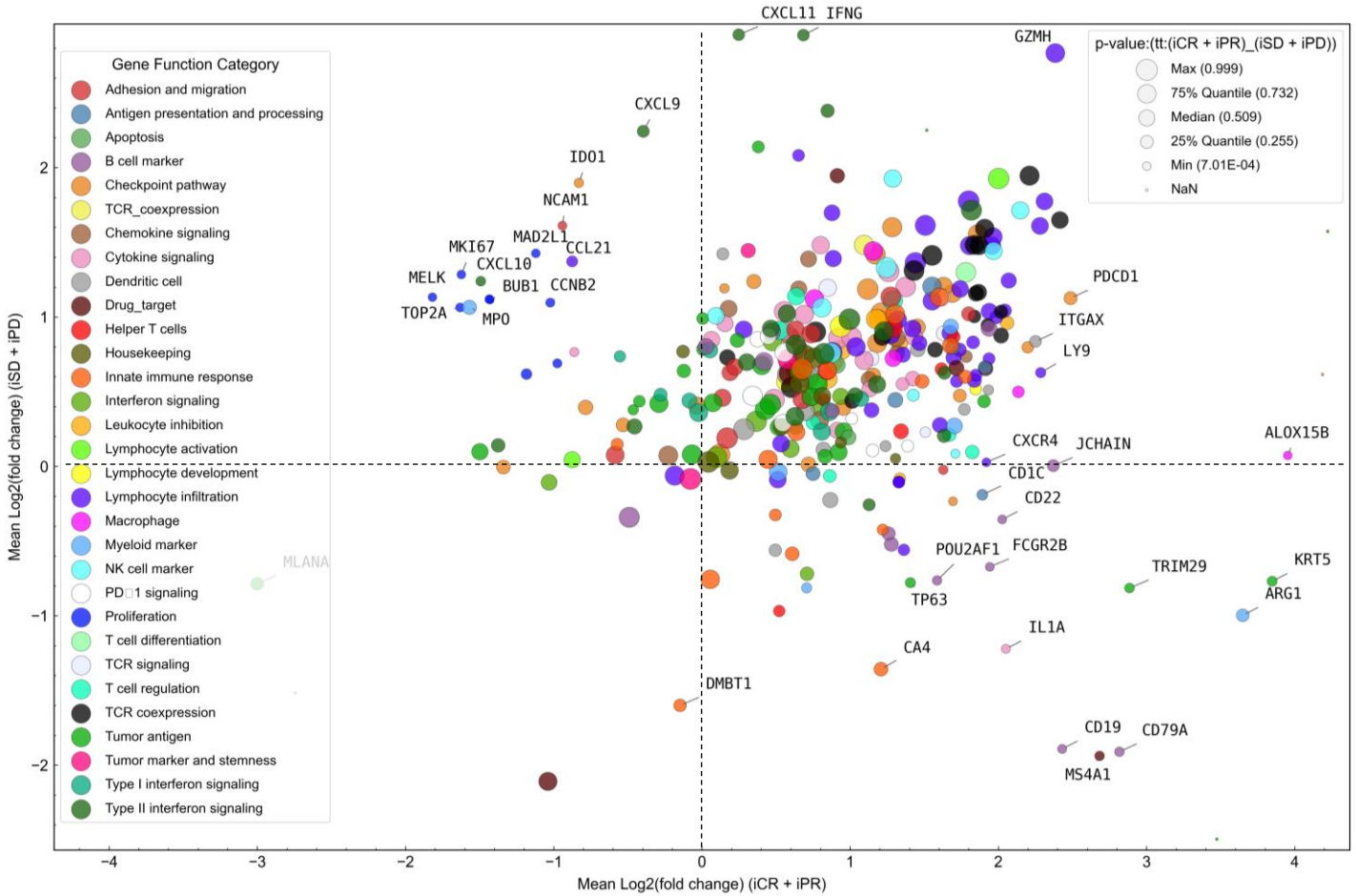
*Due to poor sample quality, very few samples were evaluable for anti-hTERT immune responses. Patients with a positive immune response (SI≥3) are shown in the figures.
ALD: After last dose

Increase in Inflammatory Gene Signatures at Week 14

Both responders and non-responders exhibited relative increase in expression of IO-related genes





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Conclusion

- No new safety signals – profile similar to pembrolizumab monotherapy
- Encouraging efficacy
  - Objective responses in patients with biomarker levels expected less responsive to monotherapy checkpoint inhibition
- Phase II randomized trial with ipi/nivo recruitment completed (n=156)
  - Topline results 1H23

Acknowledge

- Patients and families
- Collaborators, Regulatory Teams, Coordinators
- Ultimovacs for sponsoring

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