Ultrahigh Tumor Mutational Burden (TMB) Is Associated with Improved Survival Outcomes in Patients Treated with Immune Checkpoint Inhibitors

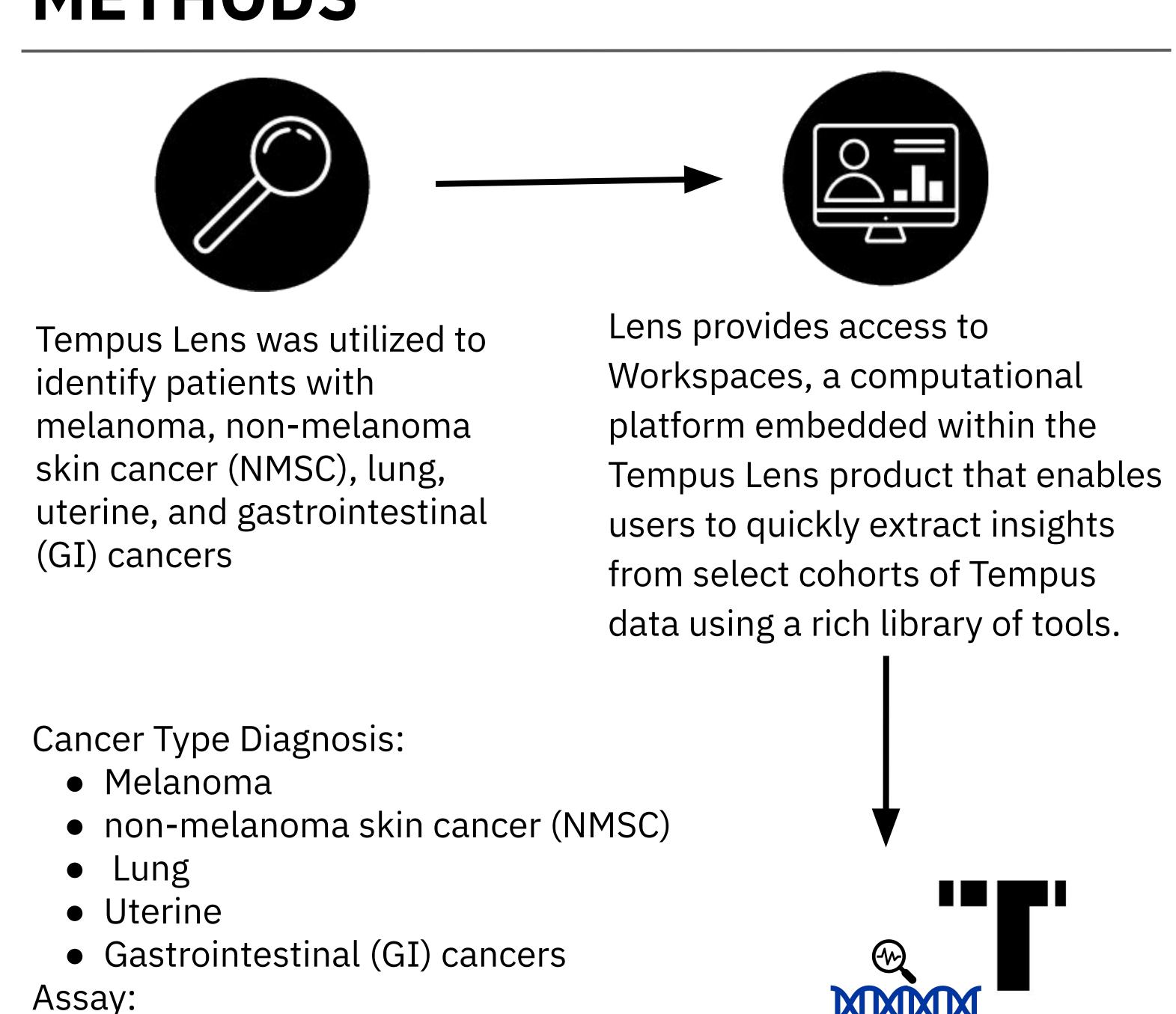Douglas B. Johnson[1], Binyam Yilma[2], Stamatina Fragkogianni[2], Metamia Ciampricotti[2], Tina O'Grady[2], Ben H. Park[1], Justin M. Balko[1]
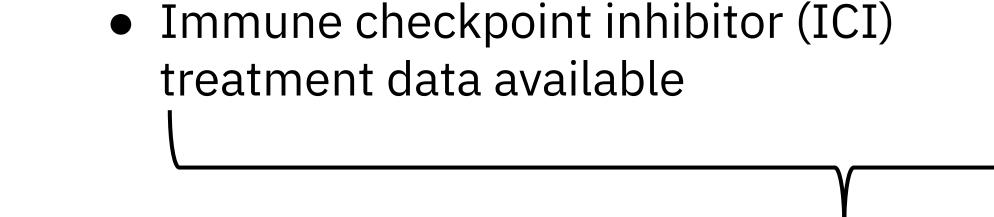[1]Vanderbilt University Medical Center, Nashville TN, USA; [2]Tempus AI, Inc, Chicago, IL, USA

Poster/Abstract #136

INTRODUCTION

- TMB is associated with response to ICI therapy.
- A pan-tumor cutoff of 10 mutations (mt)/MB gained FDA approval of pembrolizumab although optimal cutoffs are not clearly defined.
- Here, we assessed the genomic landscape and clinical outcomes and in pts with higher cutoffs of 40 mt/MB ("ultrahigh TMB").
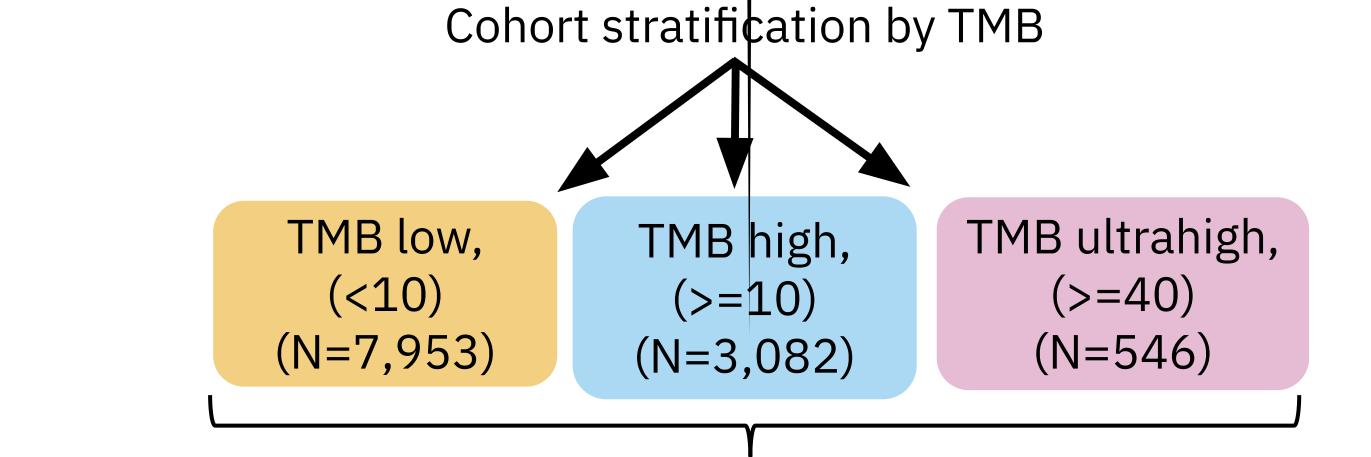
METHODS

Tempus Lens was utilized to identify patients with melanoma, non-melanoma skin cancer (NMSC), lung, uterine, and gastrointestinal (GI) cancers

Lens provides access to Workspaces, a computational platform embedded within the Tempus Lens product that enables users to quickly extract insights from select cohorts of Tempus data using a rich library of tools.

Cancer Type Diagnosis:
- Melanoma
- non-melanoma skin cancer (NMSC)
- Lung
- Uterine
- Gastrointestinal (GI) cancers

Assay:
- Tempus xT (DNA-seq) testing
- Samples obtained within one year before or 15 days after starting ICI therapy

Treatment:
- Immune checkpoint inhibitor (ICI) treatment data available

Selection Criteria
(N=17,449)

Cohort stratification by TMB

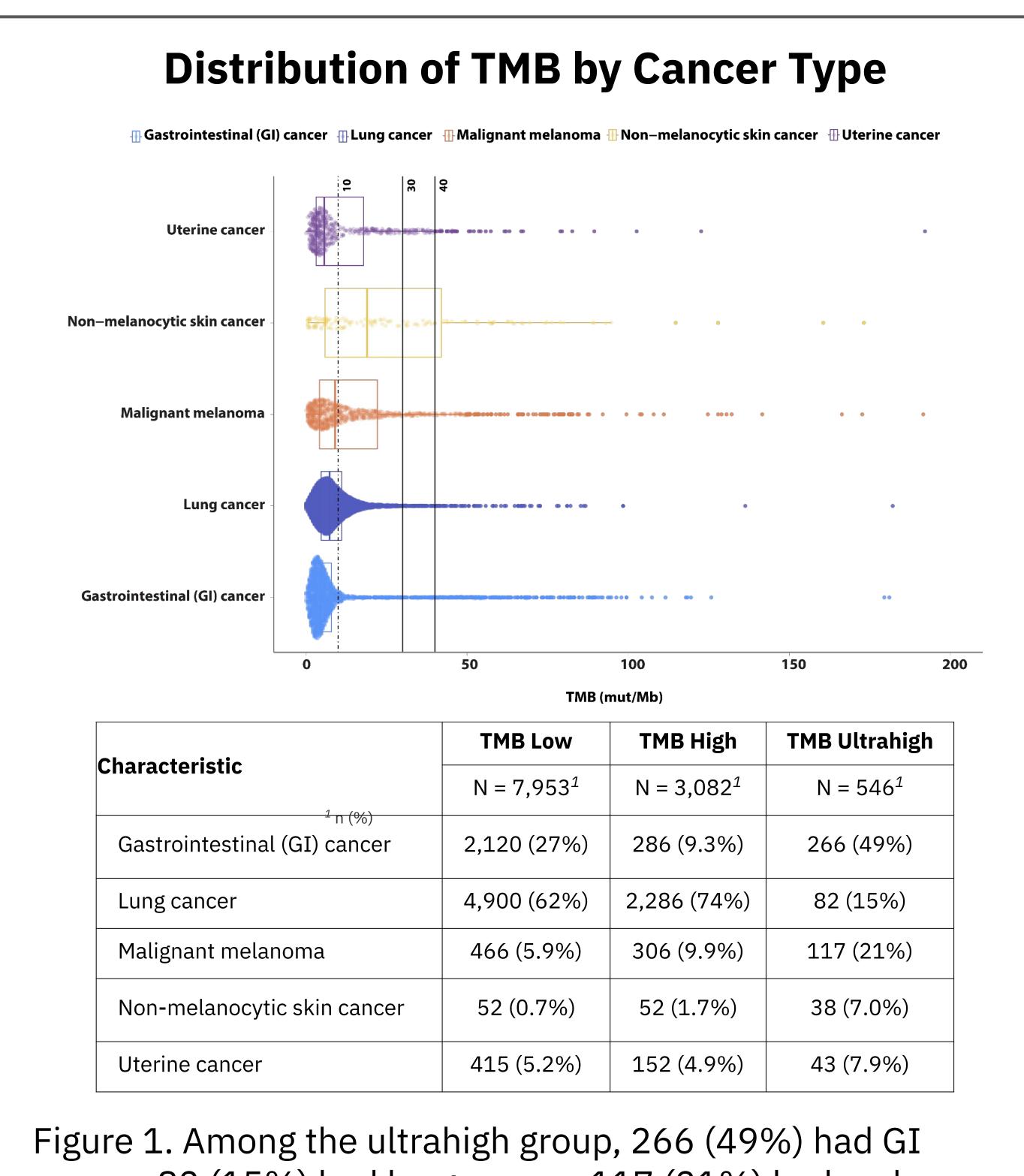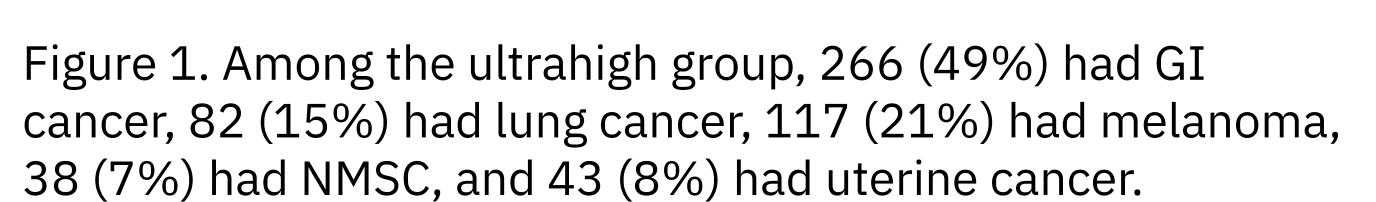| TMB low, (<10) (N=7,953) | TMB high, (>=10) (N=3,082) | TMB ultrahigh, (>=40) (N=546) |

Analysis:
- Immune cell proportions (%) were estimated from RNA using quanTIseq.
- Real-world (rw) objective response rates (rwORR) were assessed at 365-days after ICI tx start, and compared using Pearson's Chi-Squared test.
- RW overall survival (rwOS) was defined as time from ICI start to death, lost to follow-up. Median rwOS was estimated using Kaplan-Meier (KM) and hazard ratios (HR) using Cox proportional hazard models.
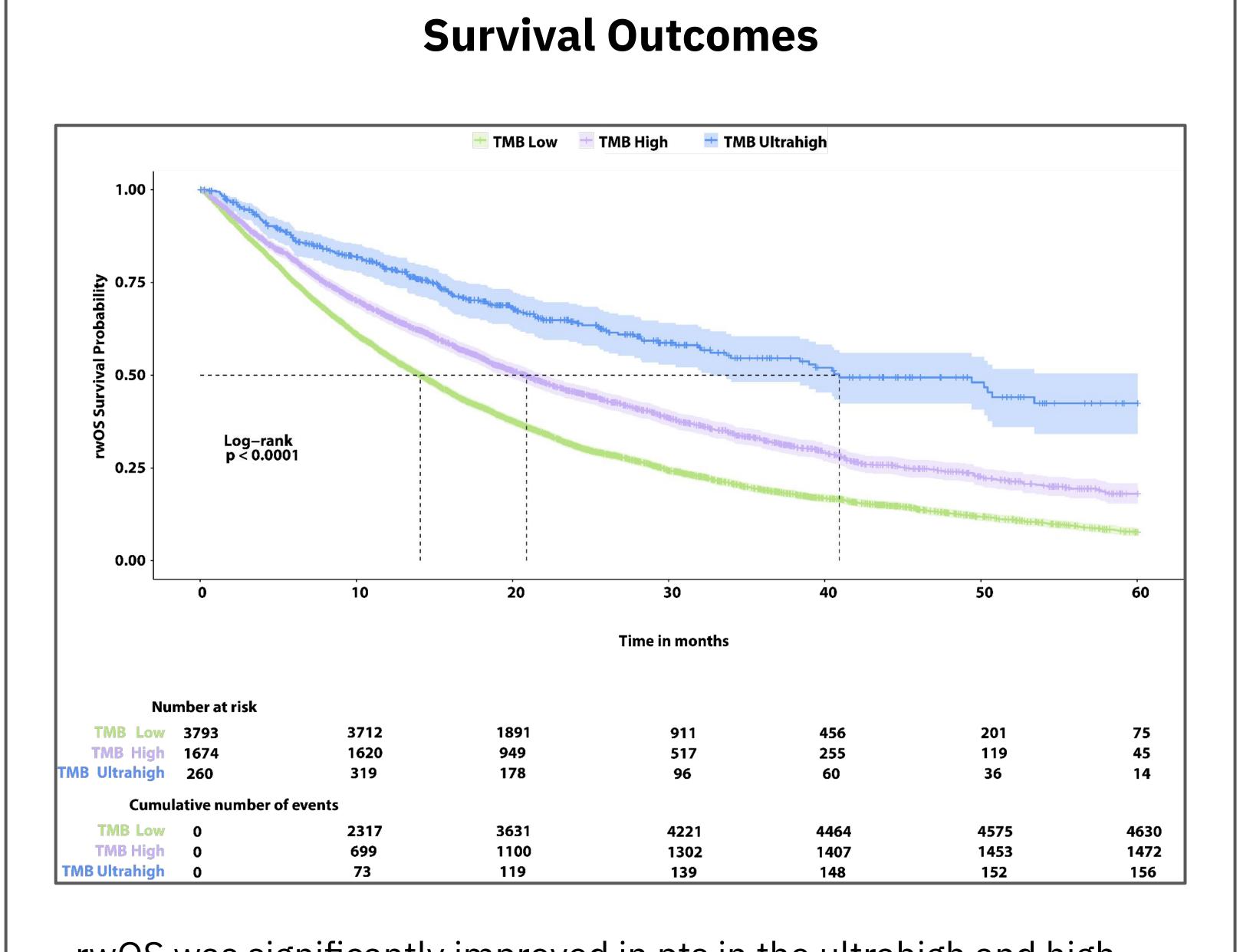
SUMMARY

- Ultrahigh TMB (>=40 mt/MB) comprises a novel marker for ICI response and is associated with improved rwOS independent of other prognostic markers like tumor type and MSI status.
- Ultrahigh TMB is associated with increased transcriptomic evidence of T cell and myeloid cell infiltration.
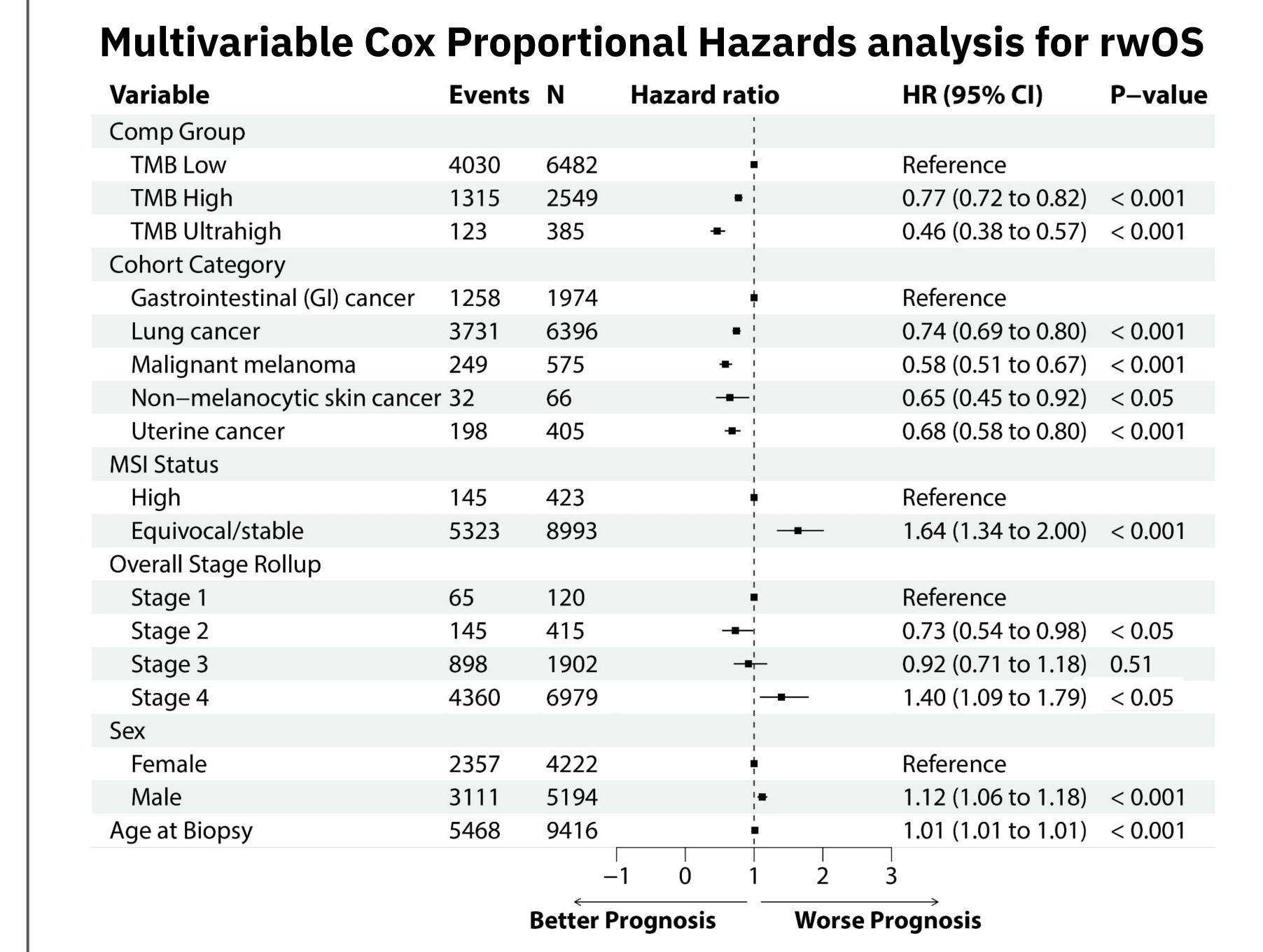
RESULTS

Distribution of TMB by Cancer Type

Characteristic	TMB Low	TMB High	TMB Ultrahigh
	N = 7,953[1]	N = 3,082[1]	N = 546[1]
	[1] n (%)		
Gastrointestinal (GI) cancer	2,120 (27%)	286 (9.3%)	266 (49%)
Lung cancer	4,900 (62%)	2,286 (74%)	82 (15%)
Malignant melanoma	466 (5.9%)	306 (9.9%)	117 (21%)
Non-melanocytic skin cancer	52 (0.7%)	52 (1.7%)	38 (7.0%)
Uterine cancer	415 (5.2%)	152 (4.9%)	43 (7.9%)

Figure 1. Among the ultrahigh group, 266 (49%) had GI cancer, 82 (15%) had lung cancer, 117 (21%) had melanoma, 38 (7%) had NMSC, and 43 (8%) had uterine cancer.
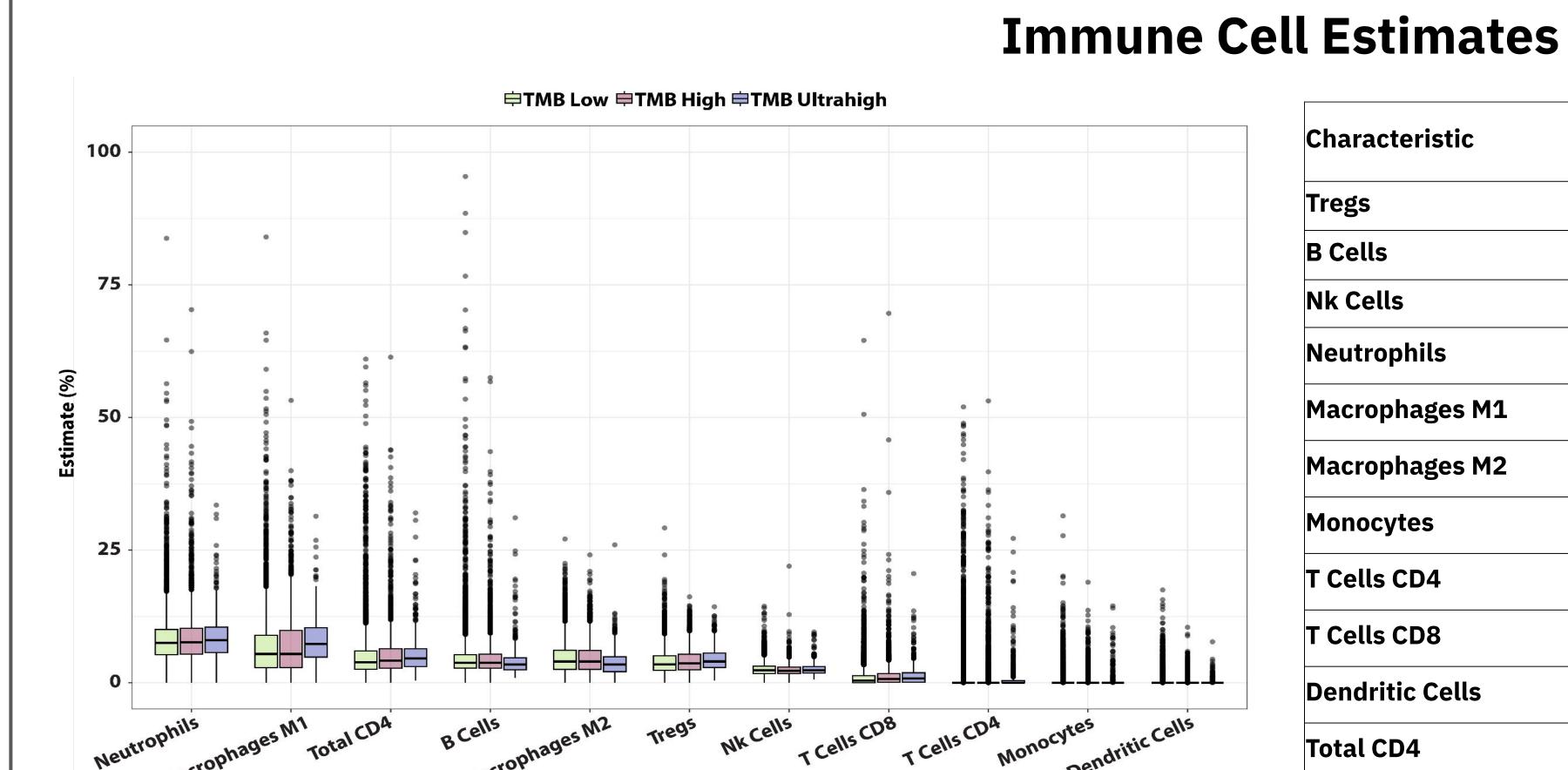
Survival Outcomes

rwOS was significantly improved in pts in the ultrahigh and high TMB groups compared to the low group (HR 0.38, 0.69, p<0.001; median OS x vs. y vs. z). rwPFS was also improved in ultrahigh and high TMB groups (data not shown, HR x, y, p=x).

Multivariable Cox Proportional Hazards analysis for rwOS

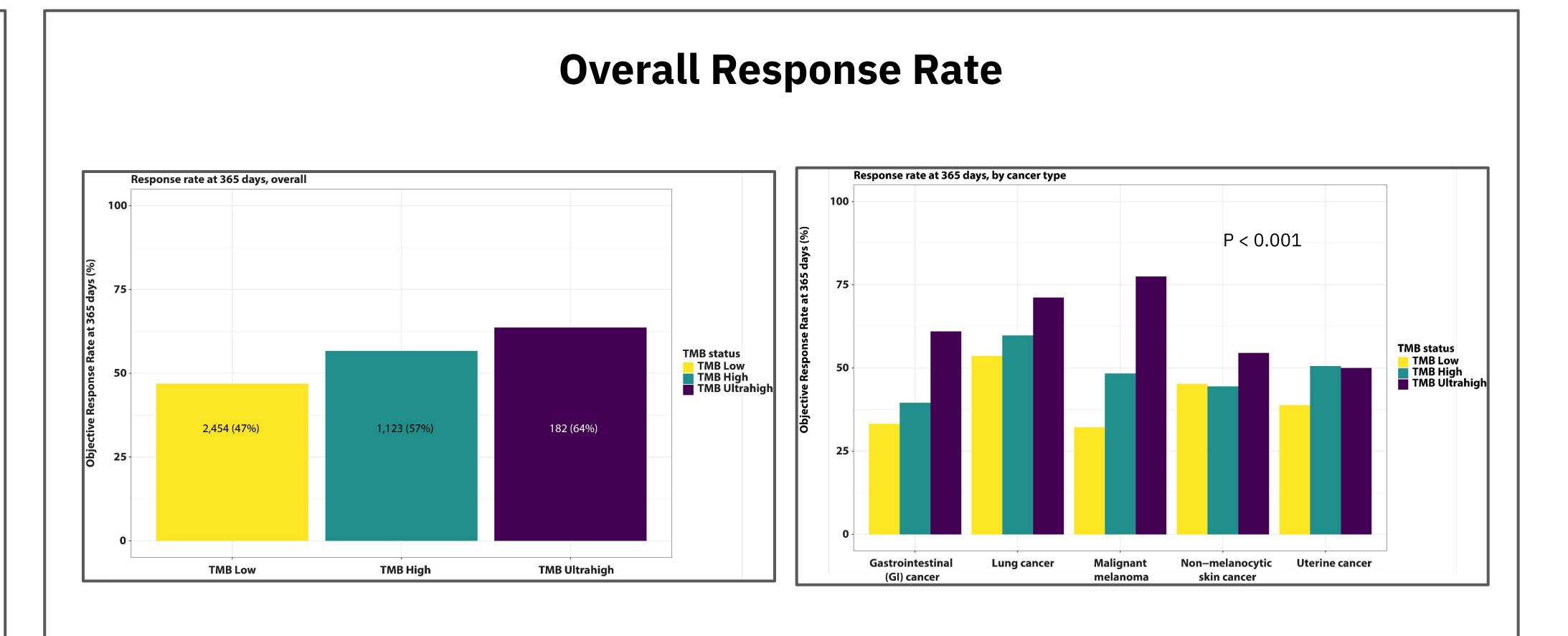| Variable	Events	N	Hazard ratio	HR (95% CI)	P-value
Comp Group					
TMB Low	4030	6482		Reference	
TMB High	1315	2549		0.77 (0.72 to 0.82)	< 0.001
TMB Ultrahigh	123	385		0.46 (0.38 to 0.57)	< 0.001
Cohort Category					
Gastrointestinal (GI) cancer	1258	1974		Reference	
Lung cancer	3731	6396		0.74 (0.69 to 0.80)	< 0.001
Malignant melanoma	249	575		0.58 (0.51 to 0.67)	< 0.001
Non-melanocytic skin cancer	32	66		0.65 (0.45 to 0.92)	< 0.05
Uterine cancer	198	405		0.68 (0.58 to 0.80)	< 0.001
MSI Status					
High	145	423		Reference	
Equivocal/stable	5323	8993		1.64 (1.34 to 2.00)	< 0.001
Overall Stage Rollup					
Stage 1	65	120		Reference	
Stage 2	145	415		0.73 (0.54 to 0.98)	< 0.05
Stage 3	898	1902		0.92 (0.71 to 1.18)	0.51
Stage 4	4360	6979		1.40 (1.09 to 1.79)	< 0.05
Sex					
Female	2357	4222		Reference	
Male	3111	5194		1.12 (1.06 to 1.18)	< 0.001
Age at Biopsy	5468	9416		1.01 (1.01 to 1.01)	< 0.001

Better Prognosis ← → Worse Prognosis

rwOS for patients treated with ICI with various characteristics. Ultrahigh TMB resulted in superior rwOS adjusting for tumor type, MSI status, age, gender, and stage.

Immune Cell Estimates

Characteristic	TMB Low	TMB High	TMB Ultrahigh	p-value[2]
	N = 6,699[1]	N = 2,564[1]	N = 475[1]	
Tregs	3.48 (2.33, 5.09)	3.66 (2.44, 5.37)	4.02 (2.88, 5.62)	<0.001
B Cells	3.75 (2.79, 5.32)	3.79 (2.74, 5.39)	3.44 (2.46, 4.73)	<0.001
Nk Cells	2.37 (1.74, 3.12)	2.26 (1.72, 2.96)	2.36 (1.85, 3.05)	<0.001
Neutrophils	7.50 (5.27, 10.04)	7.66 (5.40, 10.26)	8.03 (5.70, 10.55)	0.002
Macrophages M1	5.44 (2.83, 8.94)	5.44 (2.88, 9.85)	7.31 (4.83, 10.41)	<0.001
Macrophages M2	4.01 (2.52, 6.15)	4.01 (2.52, 6.08)	3.44 (2.09, 4.92)	<0.001
Monocytes	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.067
T Cells CD4	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.45)	0.046
T Cells CD8	0.40 (0.00, 1.35)	0.72 (0.09, 1.74)	0.83 (0.12, 1.89)	<0.001
Dendritic Cells	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.012
Total CD4	3.88 (2.53, 6.00)	4.18 (2.73, 6.40)	4.60 (3.06, 6.43)	<0.001

[1] Median (Q1, Q3)
[2] Kruskal-Wallis rank sum test

Immune cell infiltration was higher in the ultrahigh TMB group for CD8, regulatory T-cells, M1 macrophages, and neutrophils, and lower for B cells and M2 macrophages (p<0.001).

Overall Response Rate

Patients with higher tumor mutational burden (TMB), particularly in the ultrahigh TMB groups, showed favorable objective responses to immune checkpoint inhibitors (ICI) at 365 days. This association was more pronounced in specific cancer types like melanoma and lung cancer.

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