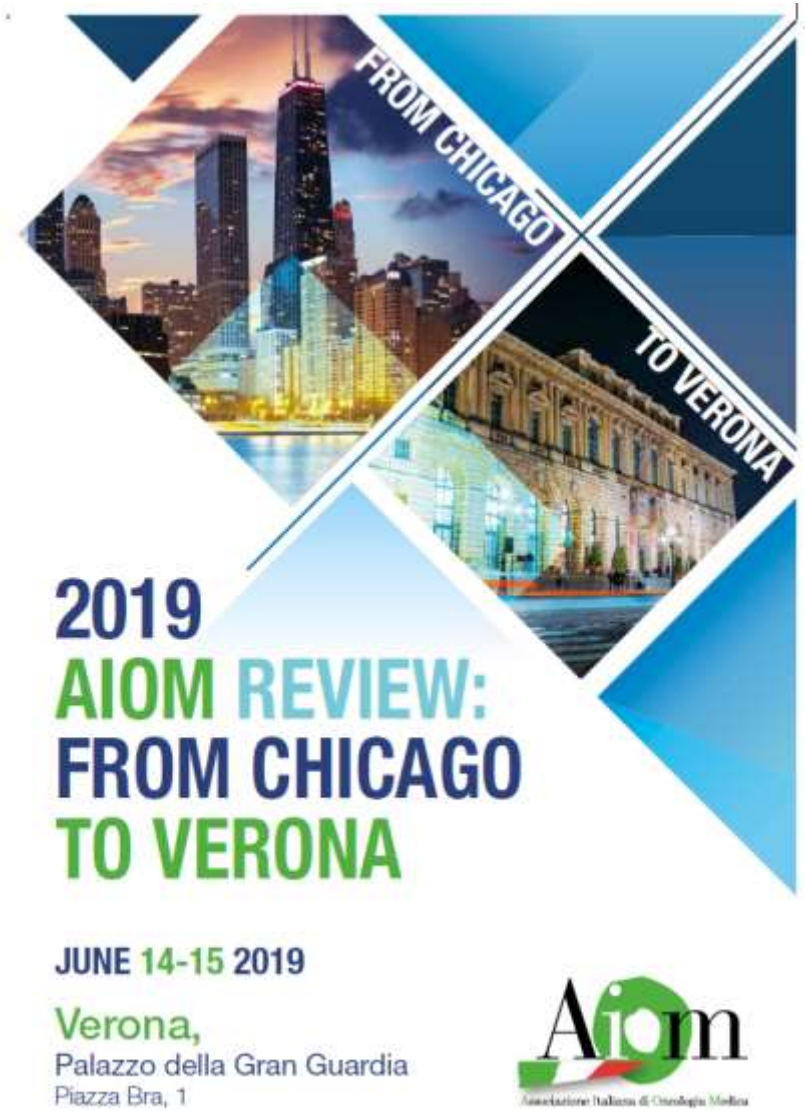
POST ASCO. MELANOMA CRITICAL REVIEW



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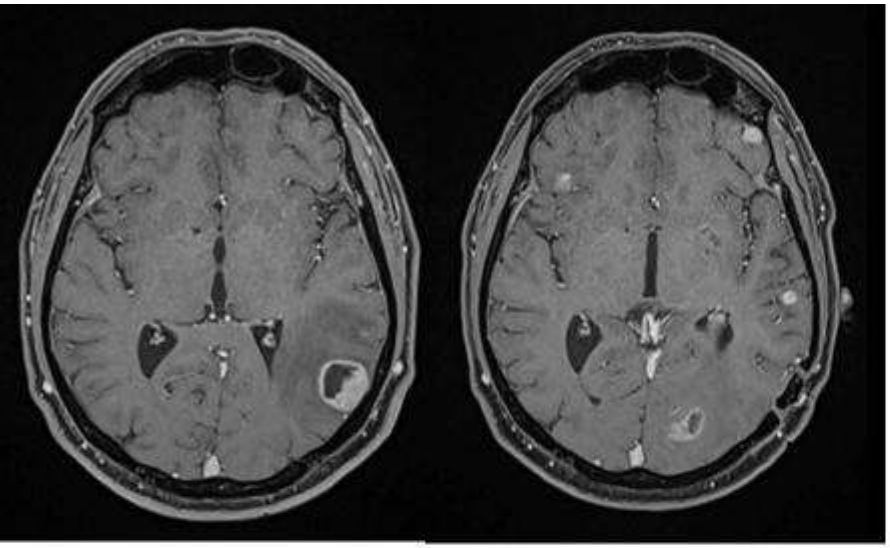
Verona 14.6.2019

OUTLINE

- THE ROLE OF WBRT
- SALVAGE AFTER ANTI PD-1 IN ADJUVANT SETTING
- LONG TERM OUTCOME WITH DABRAFENIB AND TRAMETINIB
- DEPTH RESPONSE AND ITS ROLE IN DRUG DEVELOPMENT



Stage 4: 25% 1 year, 30-40% 2 years

Surgery and stereotactic radiosurgery: highly effective for small number of mets

High risk of further intracranial disease: 50% within first 12 months

All previous adjuvant whole brain RT trials: mixed cancer histologies, 5% melanoma

- Better intracranial control
- No survival benefit
- Neurocognitive decline

Role of adjuvant WBRT in melanoma: controversial, lack high level evidence

1-3 brain mets on MRI
Surgery and/or SRS
LDH <2x normal
ECOG 0-2

Stratified by
- Age (<65 vs ≥65)
- Sex
- 1 vs 2-3 brain mets
- Presence or absence extracranial disease
- Planned RT dose (30Gy/10# or higher)

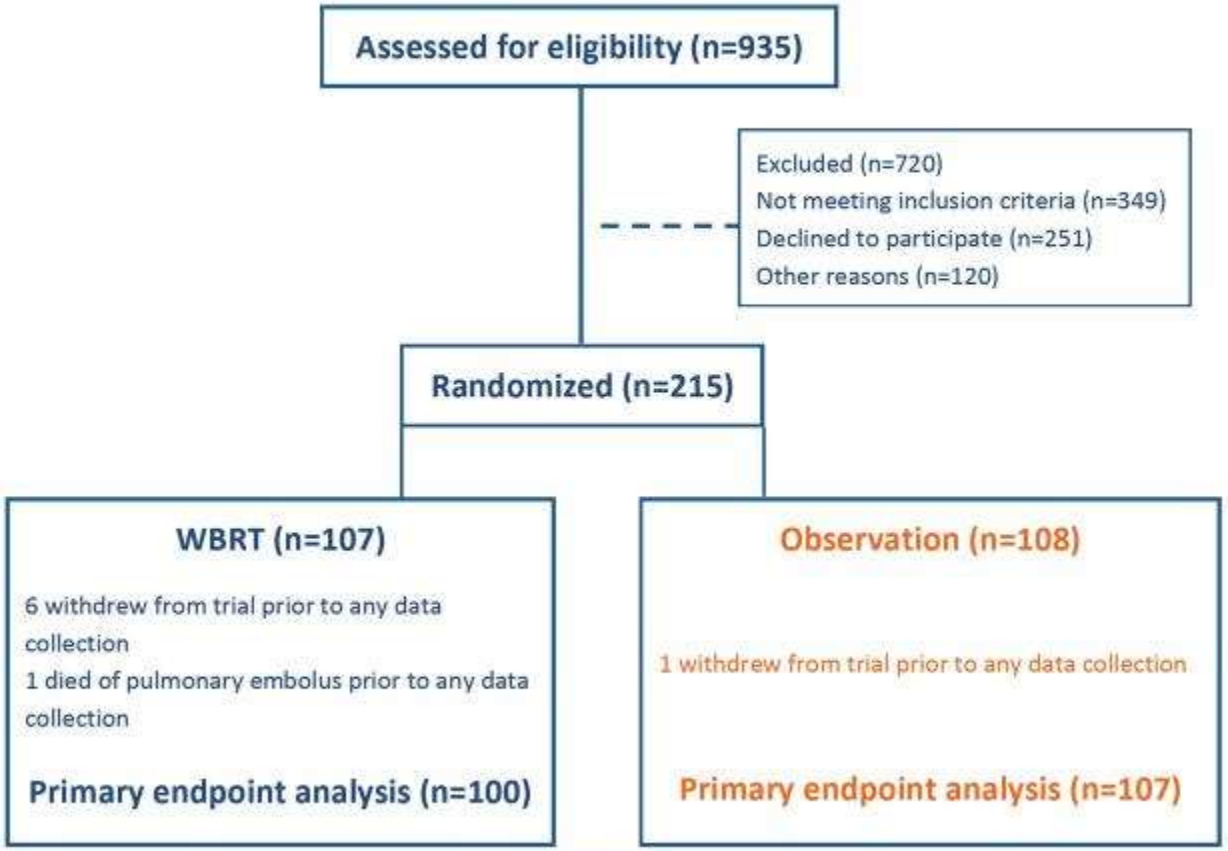
WBRT

Observation

Follow Up and Outcome Assessment (continued until withdrawal or death)
- 3 monthly MRI

Any systemic therapy was permitted
Central radiology review
WBRT quality assurance

April 2009-Sept 2017: 24 sites (Australia, Norway, UK)



Primary endpoint: Distant intracranial control at 12 months

distant failure= new lesion >1cm away from initial mets

Sample size: 220, 84% power to detect a reduction from 55% to 33%

Secondary endpoints

Local intracranial failure

Overall survival

Time to deterioration in ECOG performance status

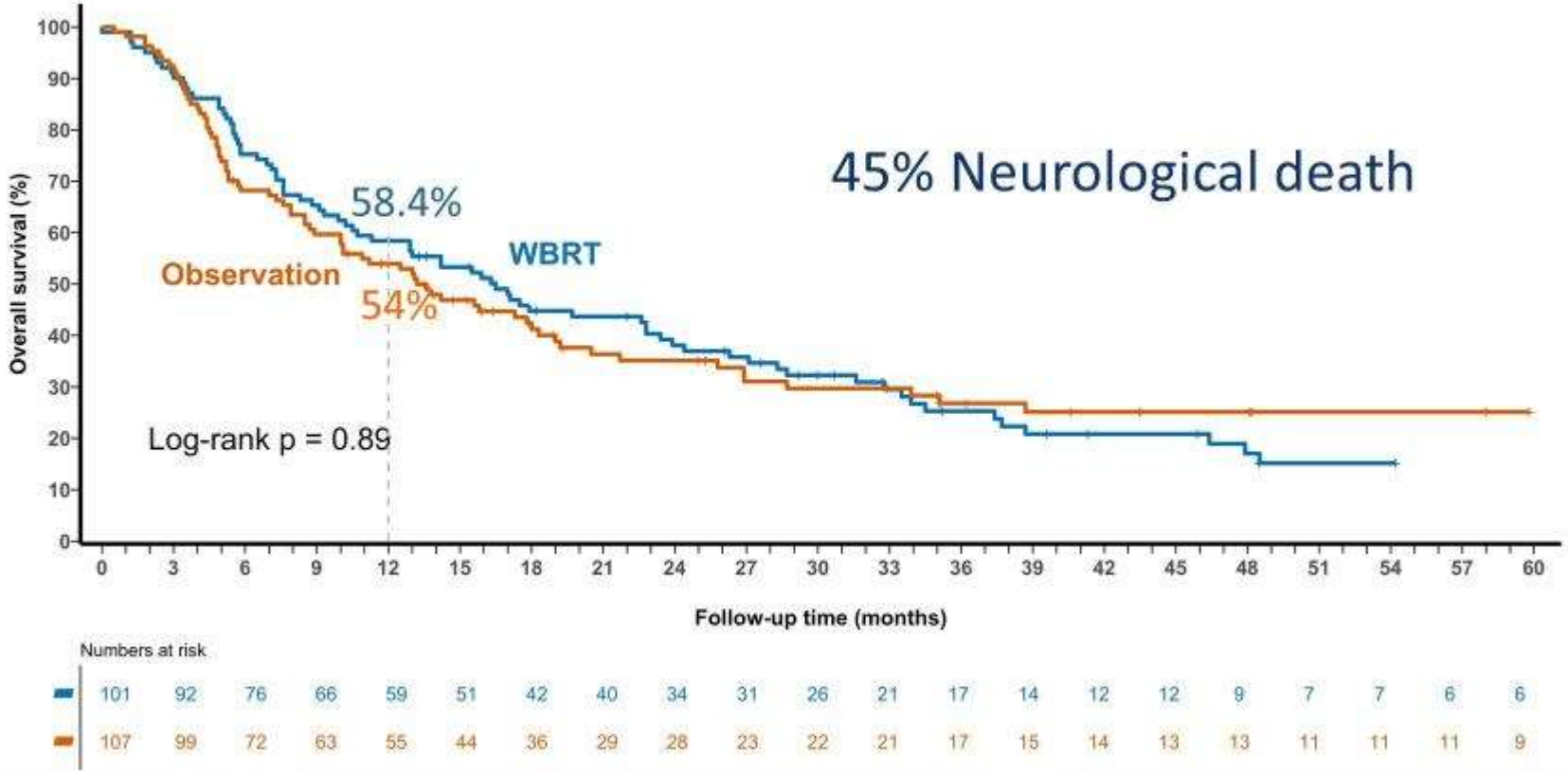
Quality of Life

Neurocognitive function

Health economics

Distant intracranial failure

Overall Survival



45% Neurological death

BRAIN MET: MY POINT OF VIEW

Asymptomatic patients	**Combo immuno: RST for residual disease**
“Reversible Symptomatic”	**Combo with previous RST**
Patients with extensive BRAF mutated symptomatic disease	**Target**
Resected solitary metastasis	**RST? Nivolumab**

Mandalà et al. Meta-analysis Cancer in press

CHALLENGING

PS 2

LEPTOMENINGEAL INVOLVEMENT

SYMPTOMATIC PATIENTS (Tawbi et al. ASCO 2019)

RADIONECROSIS: HOW TO DIAGNOSE?

ALL PATIENTS NEED TO BE TREATED WITH SYSTEMIC THERAPY?

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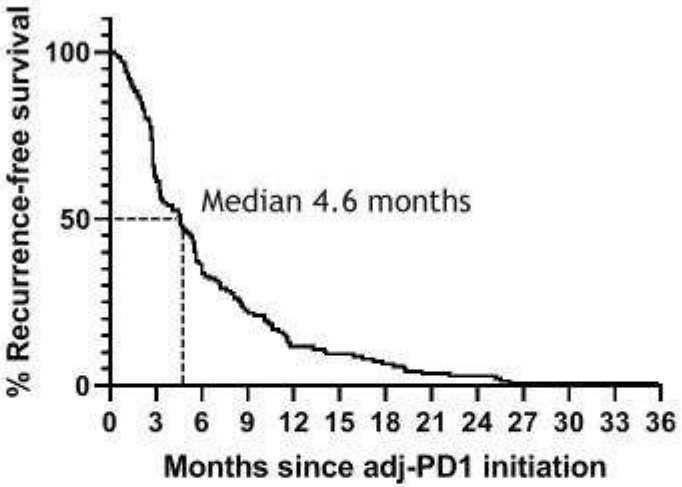
- 147 pts recurred
  - **136 cutaneous melanoma (including 14 acral)**
  - 11 mucosal melanoma
- **~17%** of total treated with adj-PD1

Adjuvant therapy*	N (%)
Nivolumab	58 (43%)
Pembrolizumab	39 (29%)
Nivolumab + ipilimumab	20 (15%)
Nivolumab +/- ipilimumab	19 (14%)

*75% treated on a clinical trial

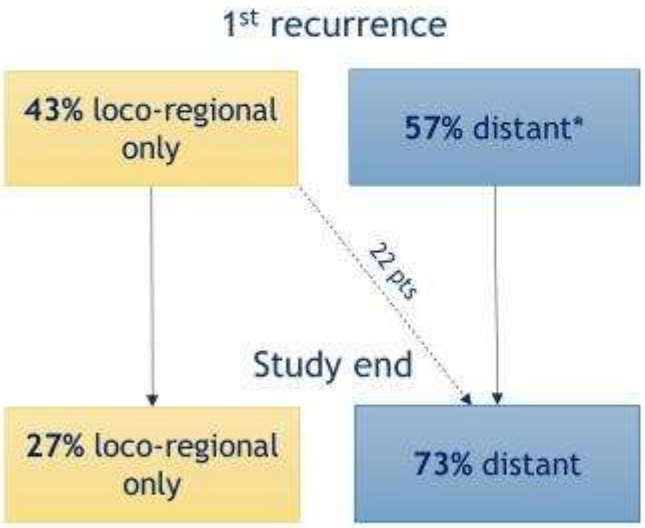
Timing of initial recurrence in relation to adj-PD1



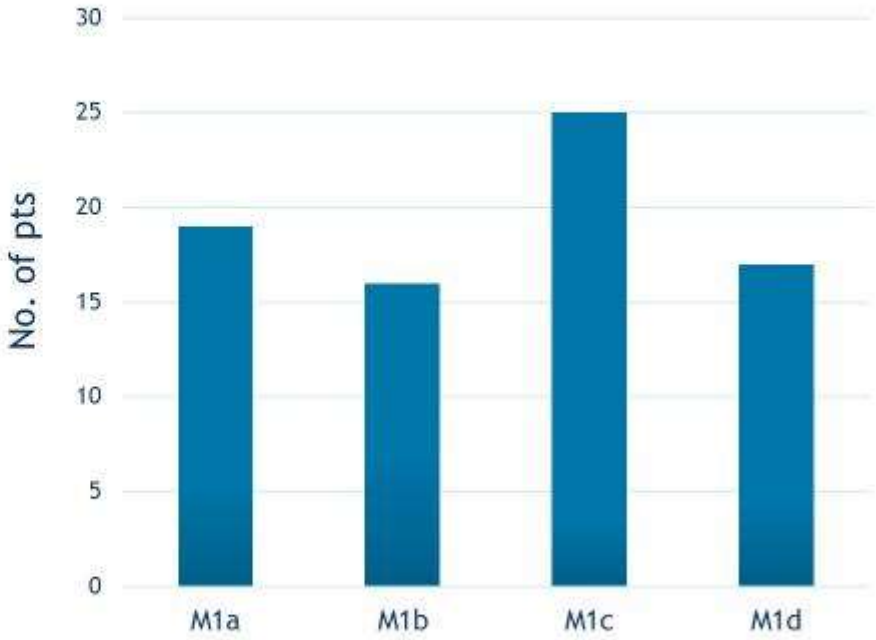
*1 withdrew consent at 1m

Pattern of initial recurrence

- Loco-regional vs distant



- Distant; substage



*22 pts had concurrent distant and loco-regional mets at 1st recurrence

Systemic therapy; Responses to first-line and subsequent therapy in evaluable patients (n=92 of 109)

Timing of initial recurrence	Systemic treatment	Best response				ORR
		N	CR/PR	SD	PD	
ON adj-PD1	Ipilimumab +/-anti-PD1	33	8	5	20	24%
	BRAF/MEKi	23	18	5	0	78%
	Anti-PD1 + novel agent	9	1	1	7	11%
	Anti-PD1	6	0	1	5	0%
OFF adj-PD1	Ipilimumab +/-anti-PD1	5	2	0	3	40%
	BRAF/MEKi	10	9	0	1	90%
	Anti-PD1 + novel agent	1	0	0	1	0%
	Anti-PD1	5	2	1	2	40%

KEY MESSAGES

TAILORED FOLLOW-UP

POST PROGRESSION TO BE TAILORED

SYSTEMIC RECURRENCE IS PREDOMINANT

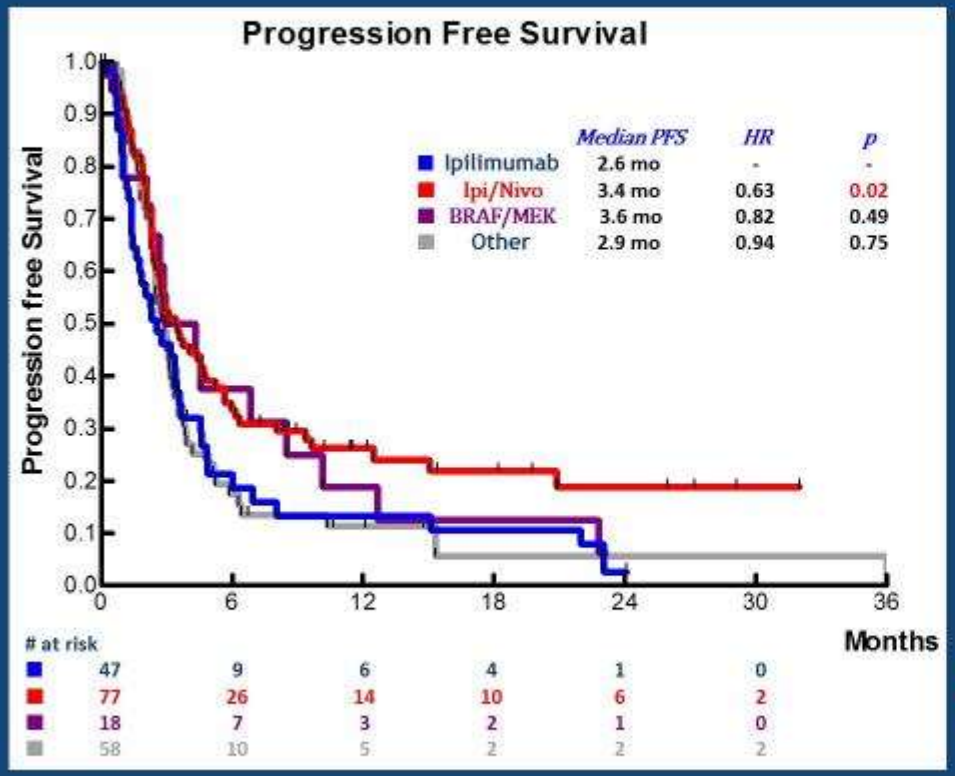
ANY IMPACT BY MSLT-2 AND DECOG ?

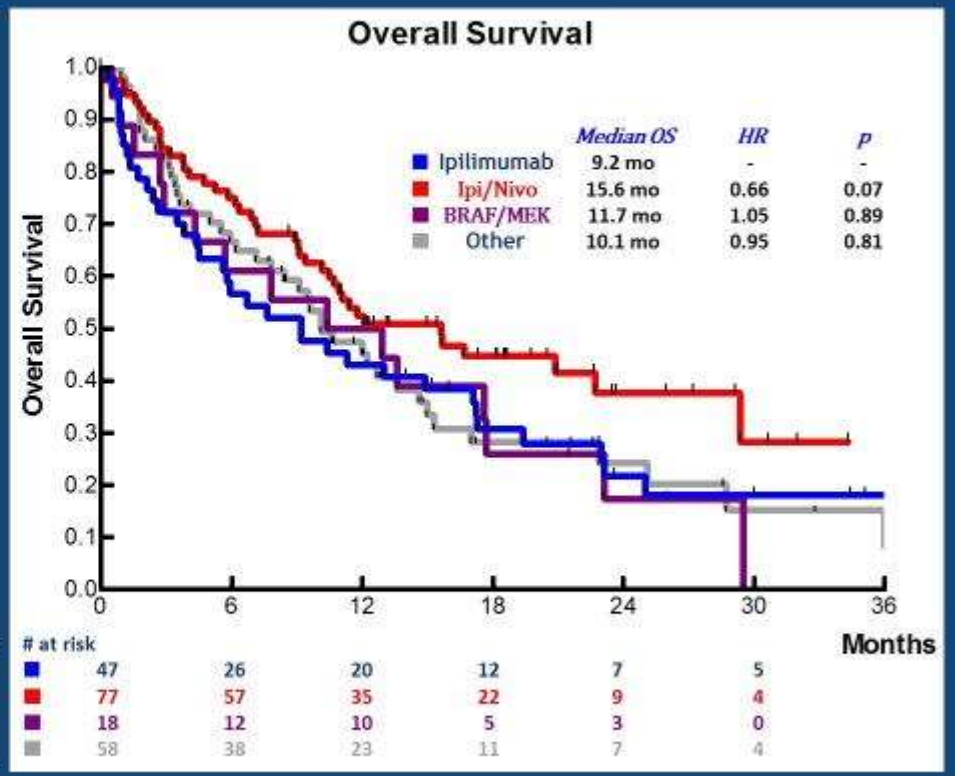
Treatment Outcome

	Ipilimumab (n=47)	Ipilimumab /Nivolumab (n=77)	BRAF-i/Mek-i re-Challenge (n=18)	Other: Chemo, TVEC etc. (n=58)
Median Follow-up	30 months	19 months	26 months	22 months
Objective Remissions	2 (4.2 %)	15 (19.5 %)*	4 (22.2 %)*	7 (12.1 %)
Disease Control Rate	9 (17.0 %)	34 (44.2 %)**	9 (50.0 %)*	14 (24.2 %)
Toxicity °III/IV or Tx Discontinuation	17 (36.2 %)	26 (33.8 %)	3 (16.7 %)	6 (10.4 %)
Median PFS	2.6 months	3.4 months	3.6 months	2.9 months
12 Month PFS Rate	13.3 %	26.2 %	18.8 %	11.3 %
Median OS	9.2 months	15.6 months	11.7 months	10.1 months
12 Months OS rate	43.0 %	52.3 %	50.0 %	45.2 %
18 Months OS rate	30.7 %	44.7 %	25.9 %	28.2 %

* $p<0.05$ ** $p<0.01$ (as compared to Ipilimumab)

Treatment Outcome





ORIGINAL ARTICLE

Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long

POOLED ANALYSIS COMBI-D/COMBI-V
563 PATIENTS

	4-YEAR	5-YEAR	<LDH	>LDH	<LDH < 3 ORGAN SITES	RC
PFS	21%	19%	25%	8%	31%	49%
OS	37%	34%	43%	16%	55%	71%

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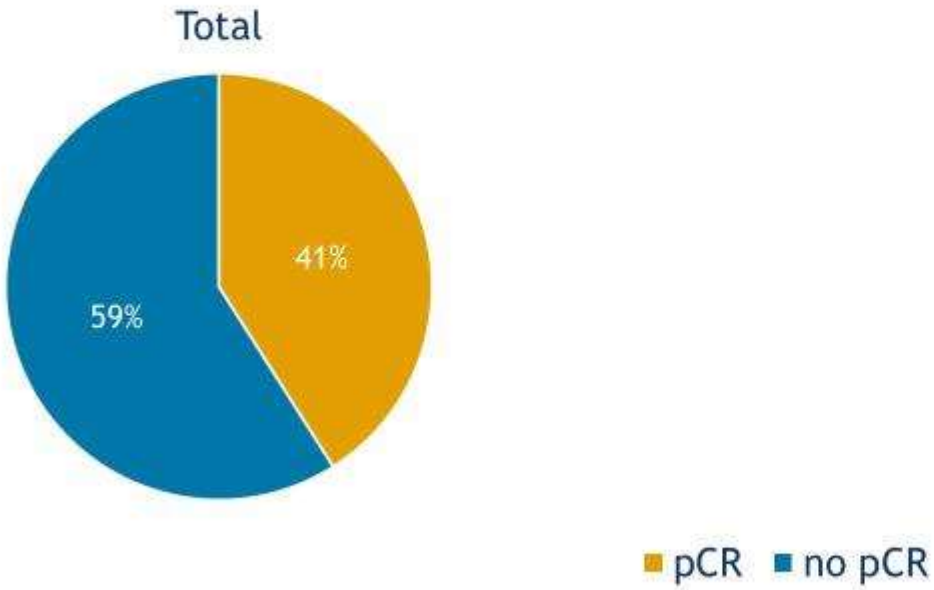
Modern melanoma NST trials

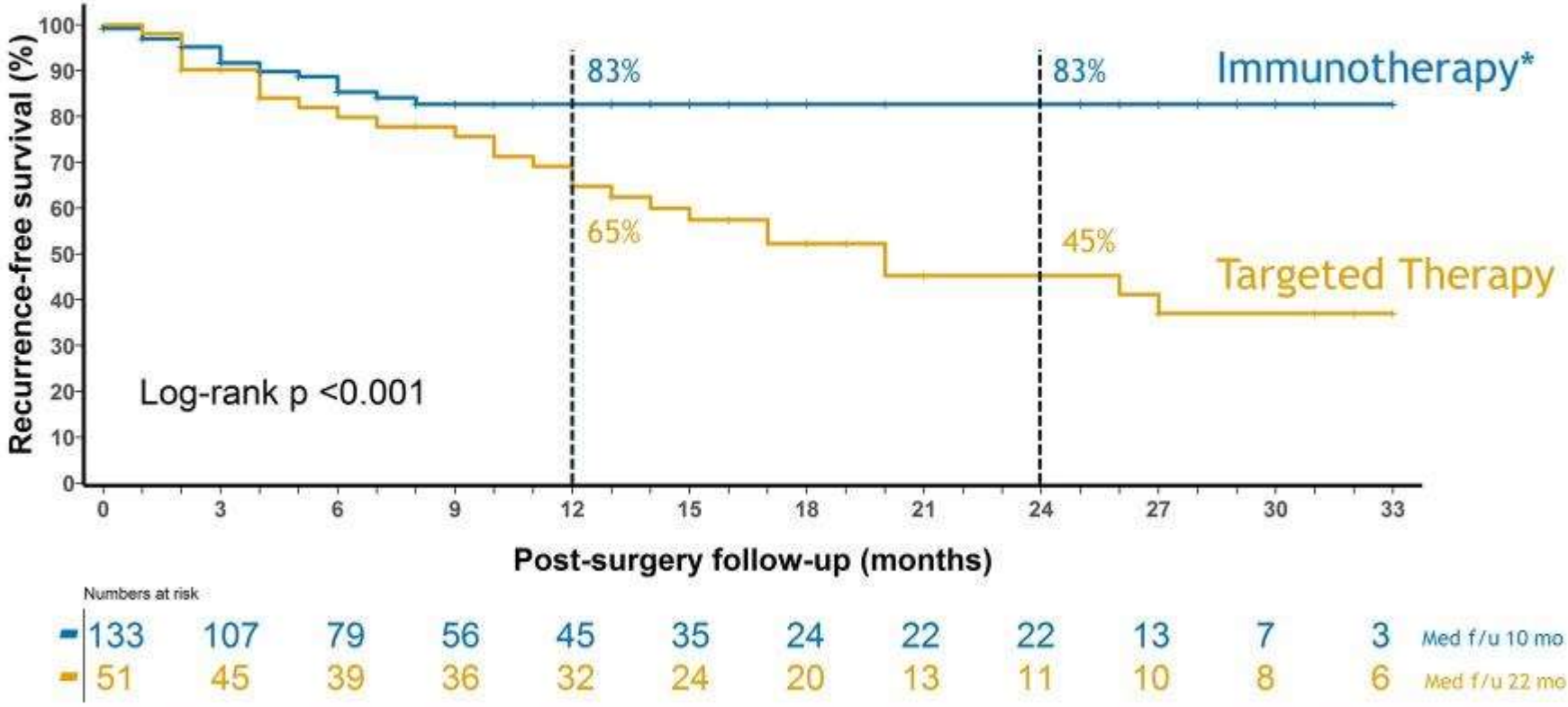
Trial	Population	Regimen	N
NCT02231775 Amaria et al Lancet Oncol 2018	Clincial stage III, resectable IV BRAF V600E/K	Dab/Tram x8w – surgery – Dab/Tram x44w	21
NCT01972347 Long et al Lancet Oncol 2019*	Clinical stage III BRAF V600 E/K	Dab/Tram x12w – surgery – Dab/Tram x40w	35
NCT02437279 Blank et al Nat Med 2018	Clinical stage III	I3N1 x2 – surgery – I3N1 x2	10
NCT02519322 Amaria et al Nat Med 2018	Clinical stage III, resectable IV	A: Nivo x4 – surgery – Nivo x13 B: I3N1 x3 – surgery – Nivo x13	A: 12 B: 11
NCT02434354 Huang et al Nat Med 2019	Clinical stage III, resectable IV	Pembro x1 – surgery – Pembro x17	30
NCT02977052 Rozeman et al Lancet Oncol 2019*	Clinical stage III	A: I3N1 x2 – surgery B: I1N3 x2 – surgery C: Ipi x2 – Nivo x2 – surgery	A: 30 B: 30 C: 26

* In press

Results – pCR rates



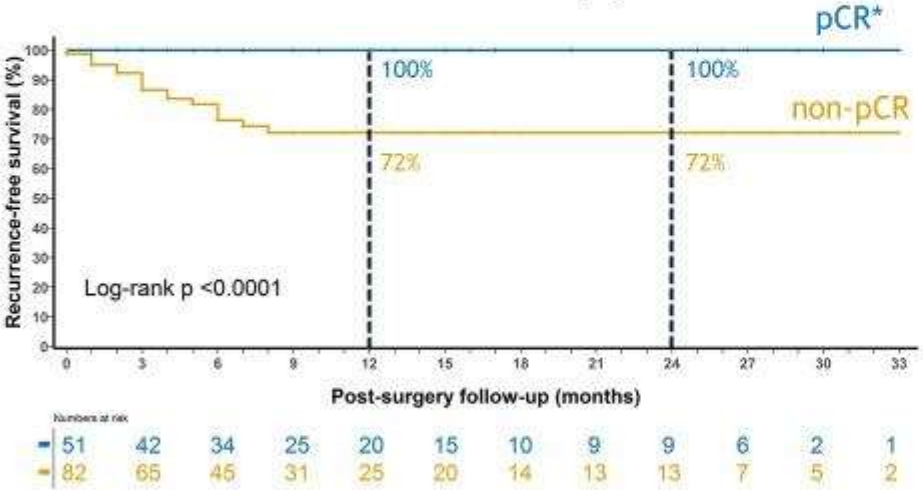
RFS by drug class



* 1 pt died from toxicity without recurrence, censored at time of death

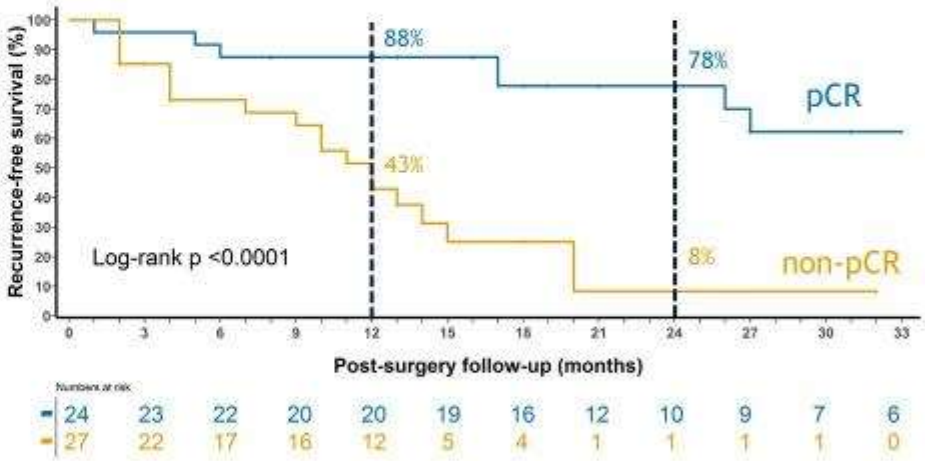
RFS by pathological response and drug

Immunotherapy



Med f/u 10 mo

Targeted Therapy



Med f/u 22 mo

* 1 pt died from toxicity without recurrence, censored at time of death

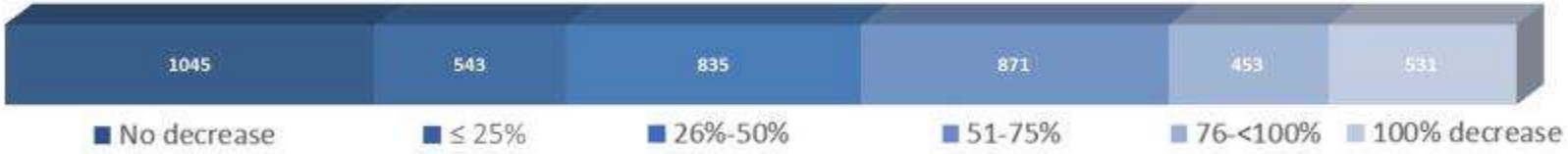
My considerations for neoadjuvant studies/approach

- It'a a biologically sound approach
- In preclinical models better than adjuvant*
- Preliminary clinical data promising
- Of paramount importance for translational studies
- Need to be tested in appropriate clinical studies

Liu Canc Discovery 2016*

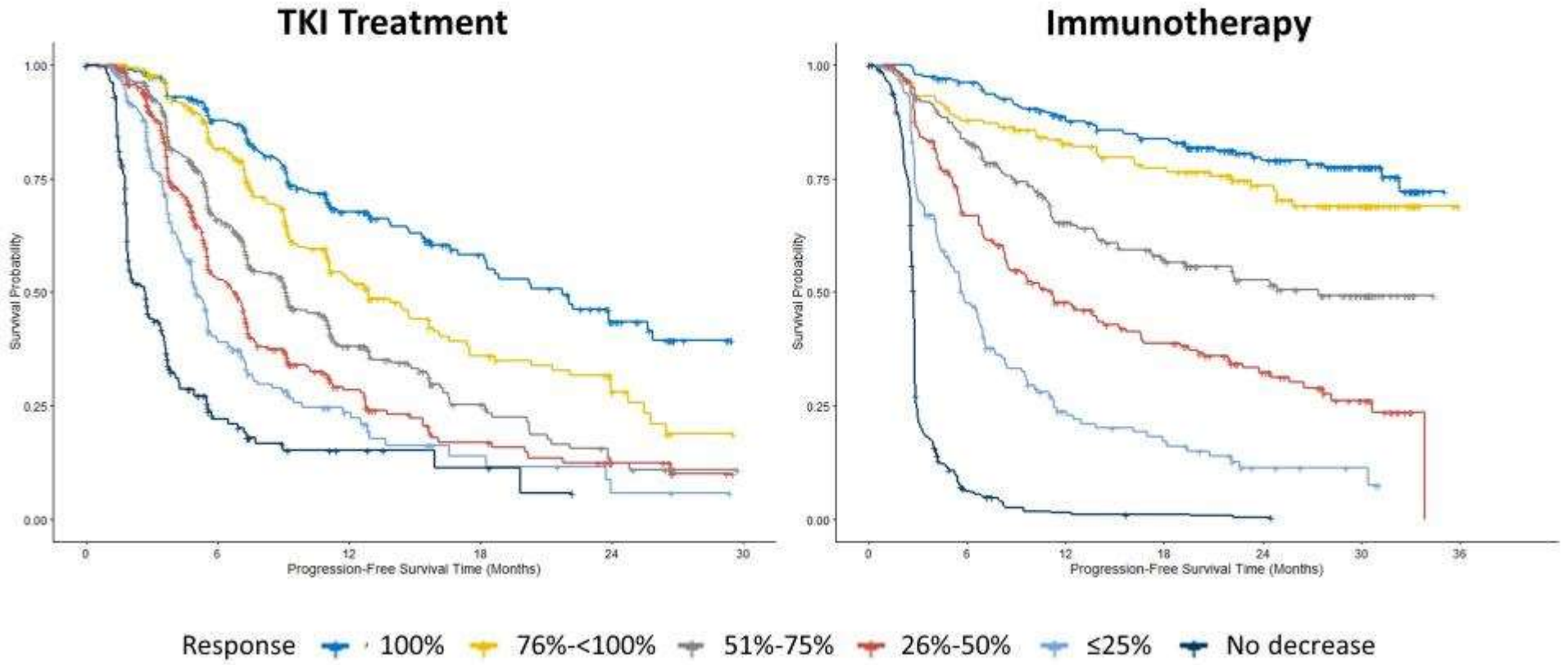
Methods - Statistical

- Depth of Response grouped by maximal tumor reduction

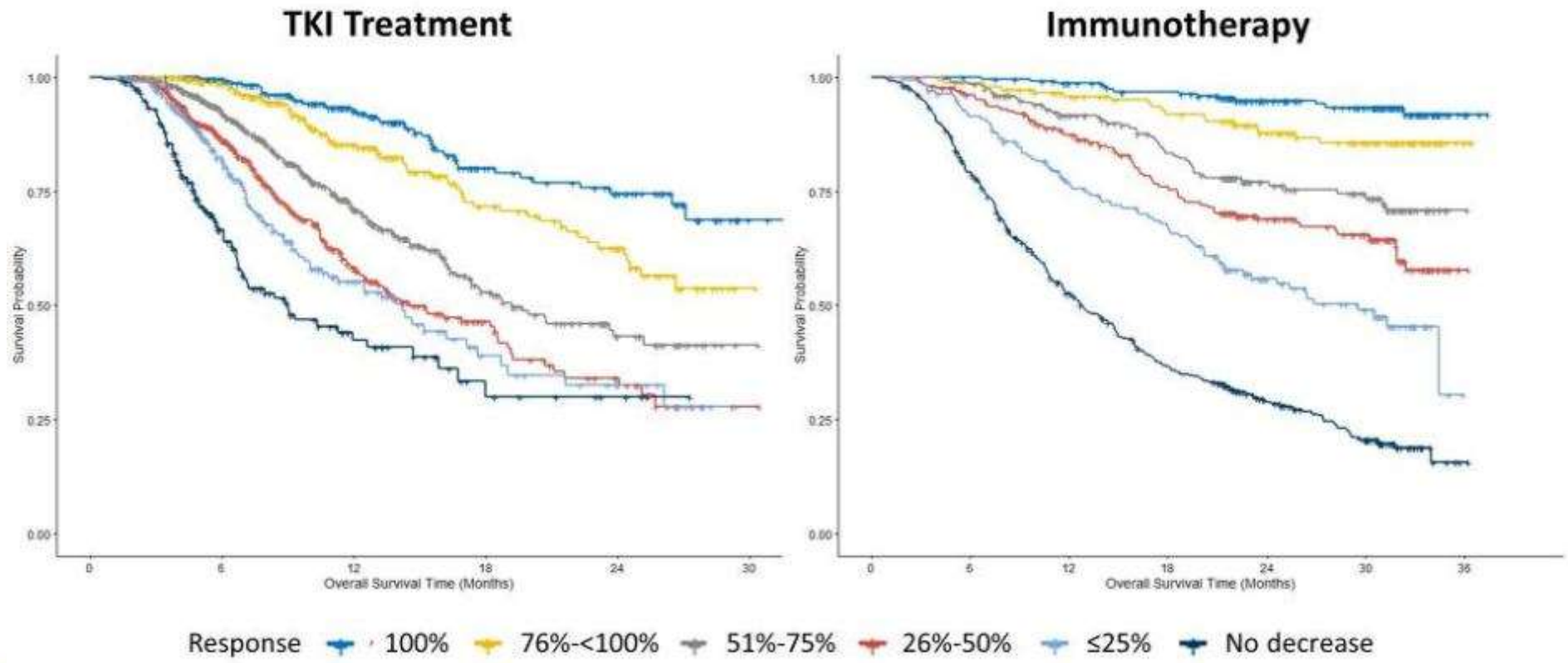


- Cox proportional hazards model generated hazard ratios
  - Tumor reduction category included as a time varying covariate
- Patient's best depth of response category used to fit Kaplan-Meier PFS and OS curves

Progression Free Survival by Reduction Category



Overall Survival by Reduction Category



CONCLUSIONS

WBRT IS NOT AN EFFECTIVE STRATEGY IN MELANOMA

TAILORED STRATEGY AFTER RECURRENCE UPON ANTI PD-1 THERAPY

TARGETED THERAPY IS AN «ORAL IMMUNOTHERAPY»

DEPTH OF RESPONSE IS A SURROGATE OF OUTCOME AND MAY DESERVE CONSIDERATION BY REGULATORY AGENCIES

NEOADJUVANT IMMUNOTHERAPY NEEDS FURTHER INVESTIGATION