

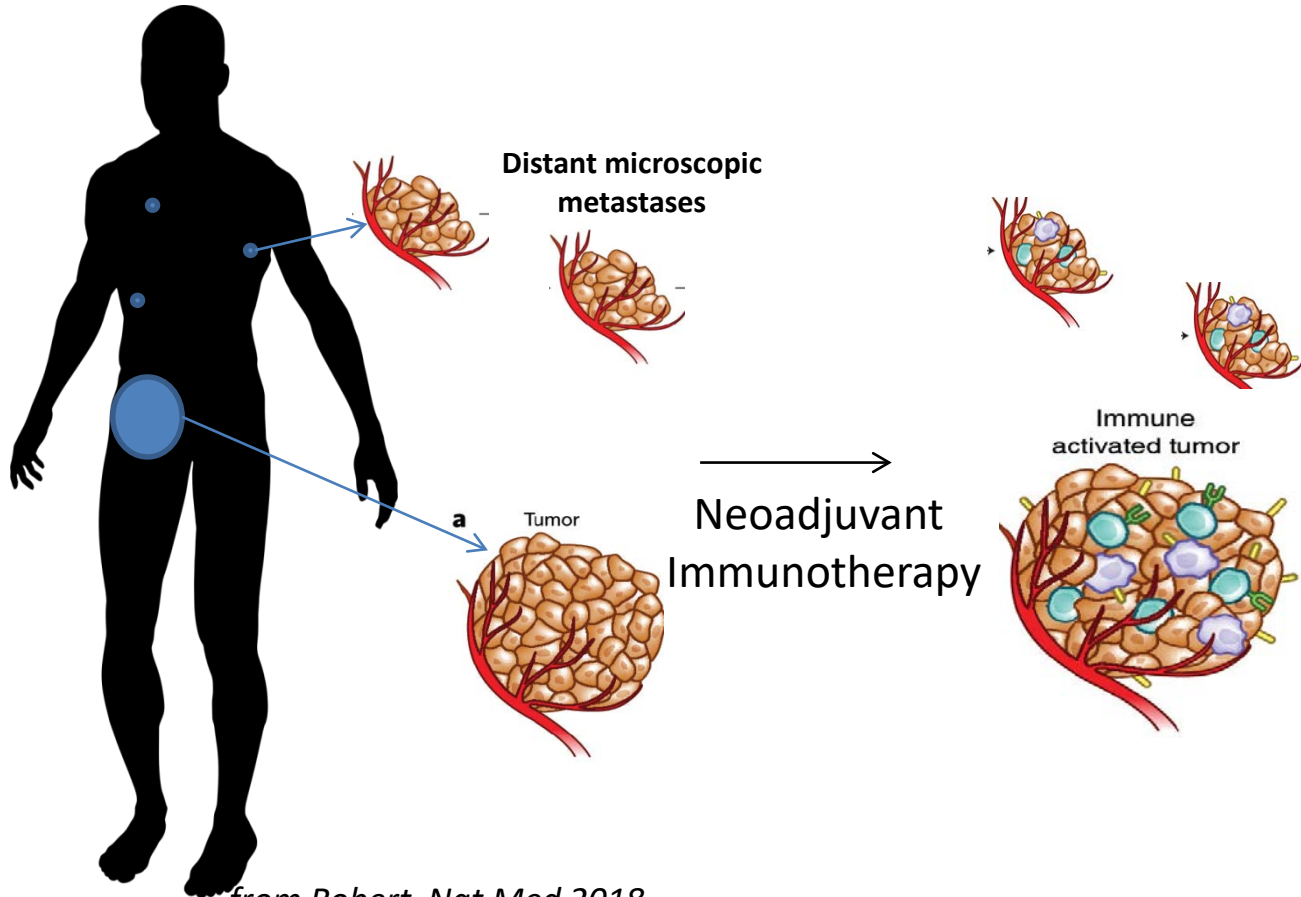
Melanoma Neoadjuvant Clinical Trials with Immunotherapy

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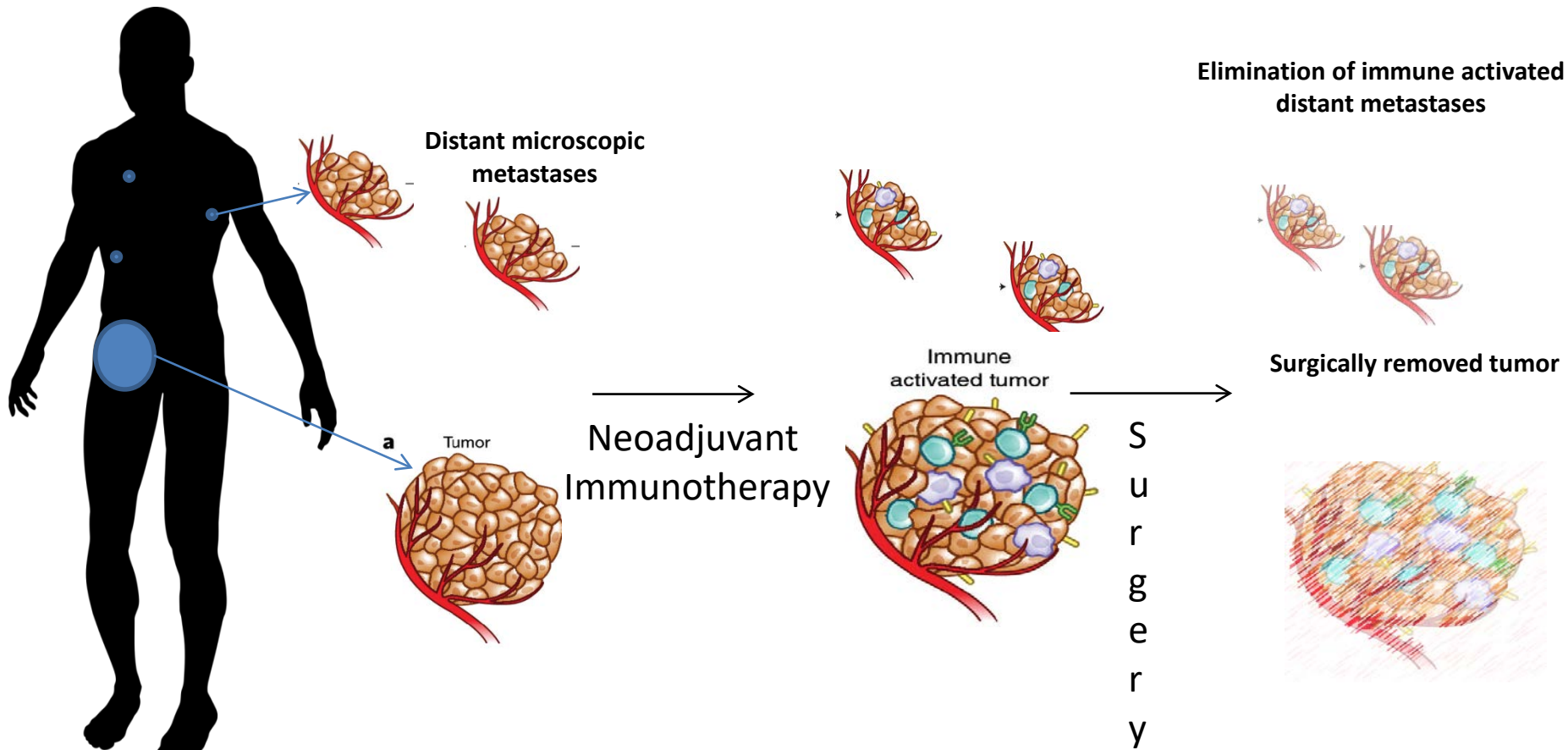


COI

- Consultant with personal fees for BMS, MSD, Amgen, Sanofi, Roche, Novartis, Pierre Fabre



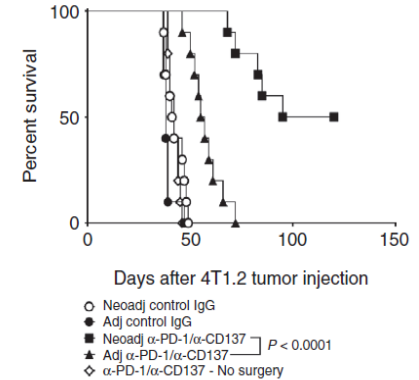
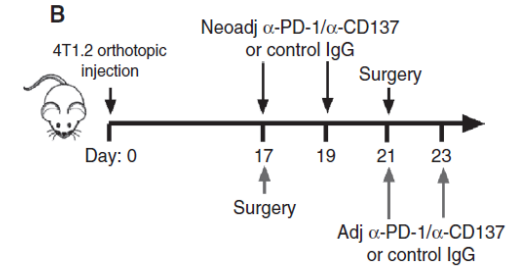
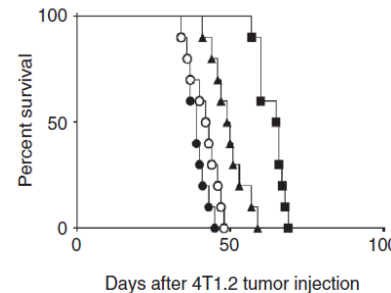
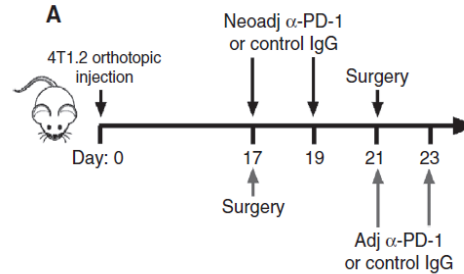
from Robert Nat Med 2018



from Robert Nat 2018s

PRECLINICAL NEOADJUVANT IMMUNOTHERAPY MODEL

- Metastatic breast cancer models (4T1.2 and E0771)
- Neoadjuvant immunotherapy :
 - Treg depletion or anti-PD1 + agonist anti-CD137
 - Depends on CD8⁺ T cells and INF- γ
- Neoadjuvant treatment increases tumor specific CD8⁺T cells in the blood and organ



NEOADJUVANT TRIALS IN MELANOMA

- 58 neo-adjuvant trials on Clinical Trial.gov
 - 10 active not recruiting
 - 12 recruiting
 - 6 trial that are not yet recruiting

ACTIVE, NON RECRUITING TRIALS

Study phase	N	Drug(s)	Disease stage	1 st End point	
2	35	dabra+ trame	IIIB	Path R	
2	24	vemu + cobl	IIIB-C	Feasibility	
2	7	nivo + HF-10	IIIB-C, M1a	Path R	
2	150	T-vec vs surgery alone	IIIB-C, M1a	RFS	
2	90	vemu + combi+ Atezo	IIIC-IV	RFS	
3	259	imiquimod vs placebo	IA	Margins	
1	30	pembro + HDI	III-IV	Biomarkers	
2	11	axitinib	III	Radio R	

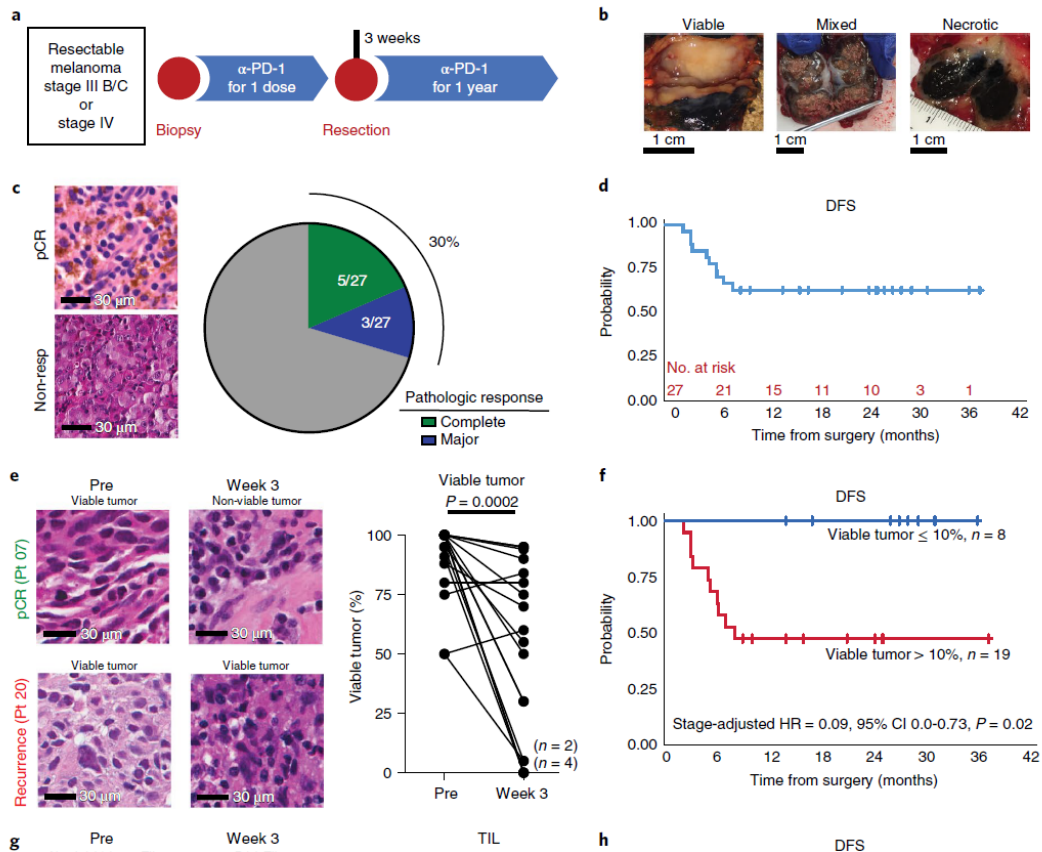
Study phase	N	Drug(s)	stage	1 st End point
	20	GM-CSF	I-III	Biomarker in SN
2	63	pembro	IIB-C	Rate of + SN
2	50 mucosal melanoma	pembro		RFS
2	248	daromun vs sugery alone	IIIB-C	RFS
2	30	atezo + cobo + vemu (BRAfV600) Atezo + cobo (BRAf WT)	III	Path R and RFS
2	60	dabra + trame then pembro Dabra + trame + pembro pembro	III	Path R
2	20	dabra + trame + T-Vec	III	RFS
2	110	ipi+ nivo various regimen	III	Safety; Path R; RFS
2	526	pembro adj+/- pembro neoaj	III-IV	RFS
2	53	nivo vs nivo + ipi vs nivo + relatlimab	III-IV	Path R
2	32	nivo + CMP-001	IIIB-C-D	Path R
2	78	dabra + trame	III	RFS according to path R

NOT YET RECRUITING

Study phase	N	Drug(s)	Disease stage	1 st endpoint
1	20	atezo x 2	I-II (residual disease)	Path R
1b	40	domatinostat (HDAC-I)+ nivo vs nivo domatinostat + nivo + ipi vs domatinostat + nivo	III (INF- γ signature high or low)	Safety; feasibility
2	28	pembro + T-vec for 6 months	III	Path R
2	45	nivo vs nivo + ipi vs nivo + IDO-I	III-IV	Path R
2	56	dostarlimab+/-TIM3-i	IIIB to IV	Path R
2	60	1 nivo dose	IIIB-C-D	Path response will impact adjuvant regimen

ANTI-PD1 MONOTHERAPY

A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma



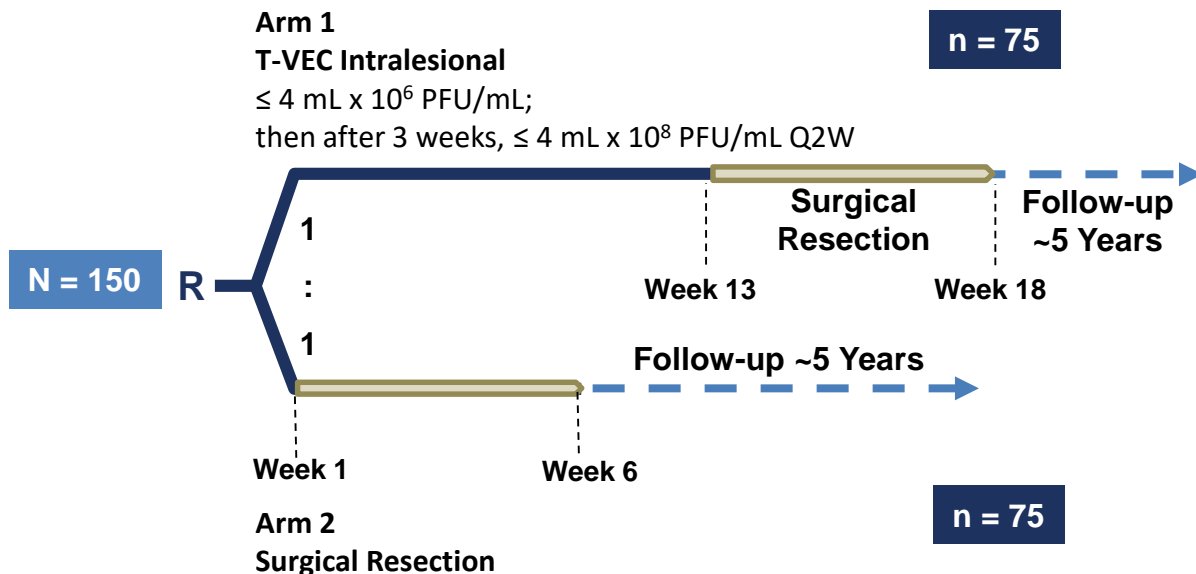
PHASE 2 T-VEC NEOADJUVANT TREATMENT + SURGERY VS SURGERY

Resectable Stage IIIB–IVM1a⁶ Melanoma

- ◆ Injectable and measurable
- ◆ LDH ≤ 1.5 x ULN for IIIB/C and ≤ 1 x ULN for IVM1a
- ◆ ECOG PS 0 or 1
- ◆ Prior treatment completed ≥ 3 months prior

Stratification:

- ◆ Disease stage
- ◆ Planned adjuvant therapy



Primary Endpoint:

RFS

Key Secondary Endpoints:

RFS,* overall survival (OS),* overall tumor response (in Arm 1 only), pathological complete response (in Arm 1 only), rates of histopathological tumor-free (R0) surgical resection, local RFS, regional RFS, distant metastases-free survival, safety

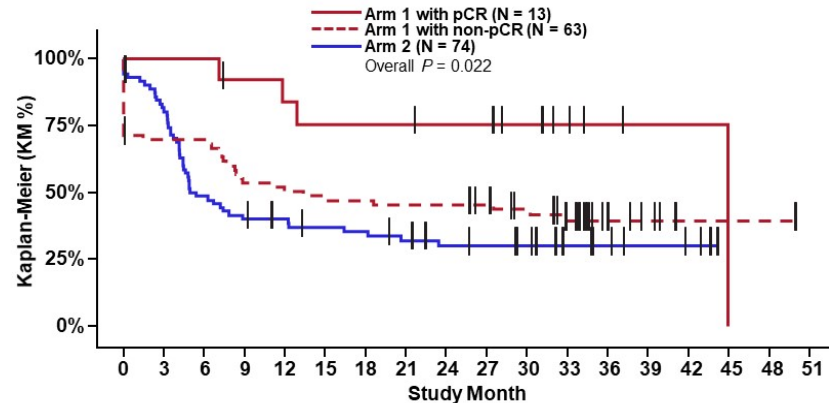
Exploratory Endpoints:

Analyses of tumor tissue biomarkers and correlations with clinical outcomes for T-VEC

PHASE 2 T-VEC NEOADJUVANT TREATMENT + SURGERY VS SURGERY

	Arm 1: T-VEC + Surgery	
	Efficacy Analysis Set (n = 57)	ITT Analysis Set (n = 76)
pCR ^a – n(%)	13 (22.8)	13 (17.1)

RFS (Sensitivity Analysis) by Arm & pCR (Intent to Treat Analysis Set)



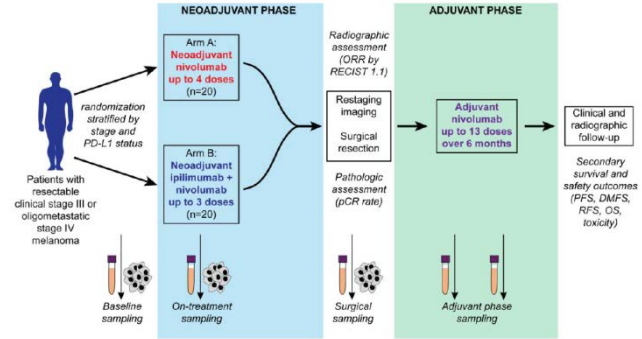
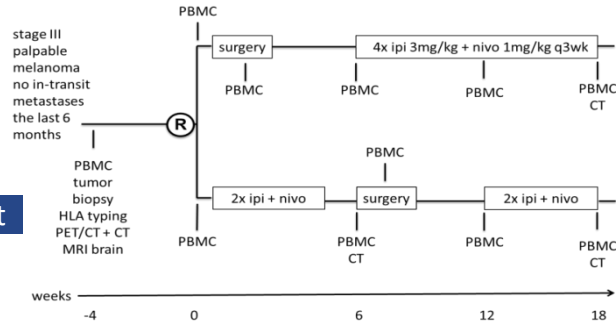
Number of Patients at Risk:

Arm 1 pCR:	13	13	13	11	10	9	9	9	8	8	6	4	2	1	1	0	
Arm 1 non-pCR:	63	43	43	33	31	29	29	28	28	26	22	16	7	5	1	1	0
Arm 2:	74	56	34	28	26	23	22	19	16	15	13	9	6	4	3	0	

NEOADJUVANT IPILIMUMAB + NIVOLUMAB

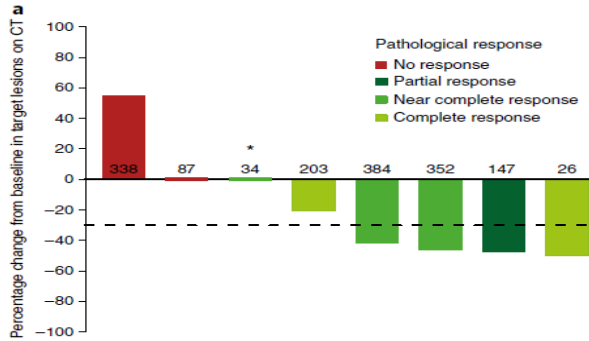
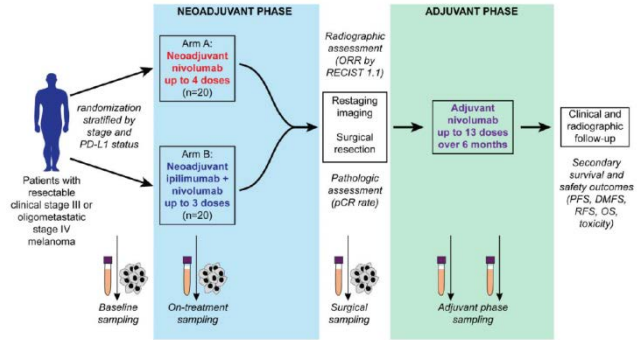
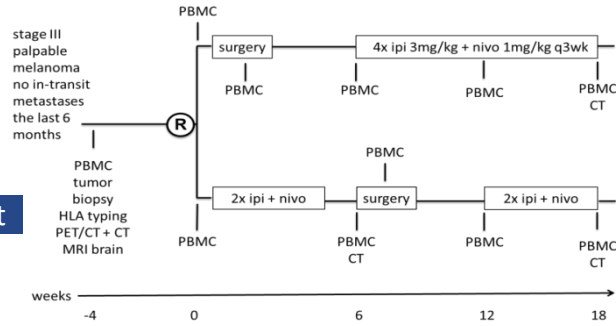
Adjuvant

Neo-adjuvant

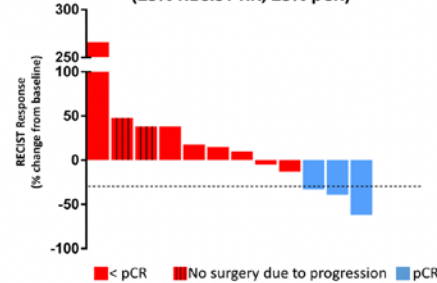


NEOADJUVANT IPILIMUMAB + NIVOLUMAB

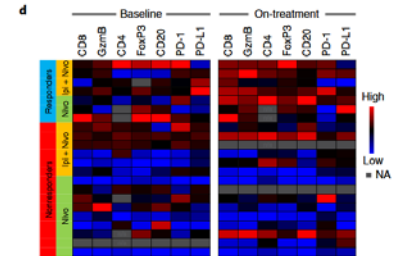
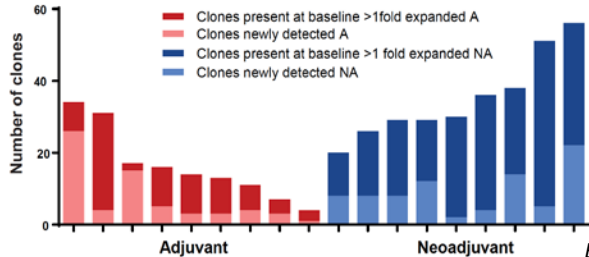
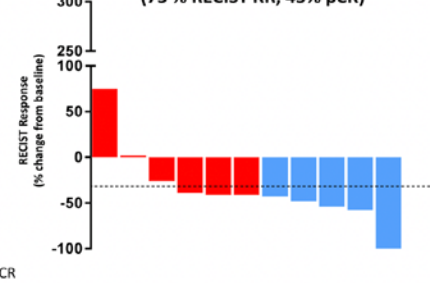
Adjuvant



(25% RECIST RR, 25% pCR)



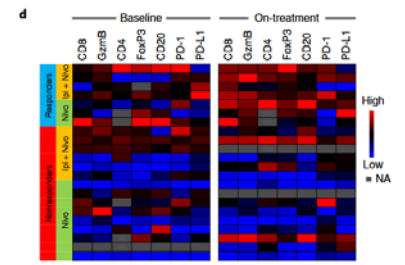
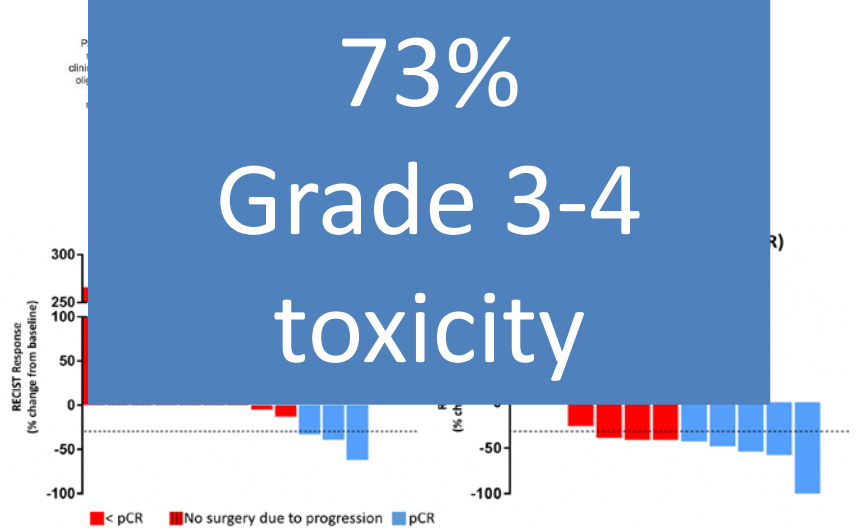
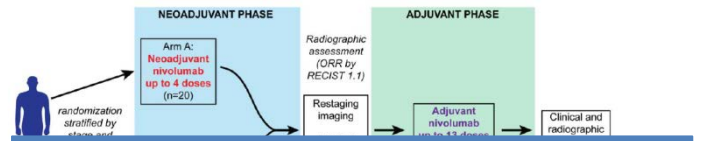
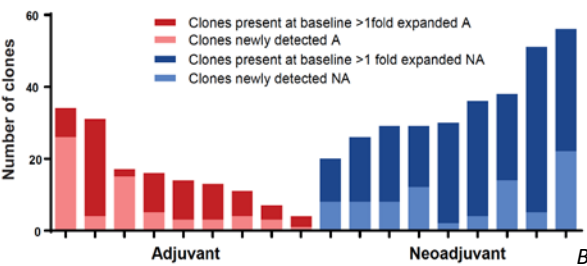
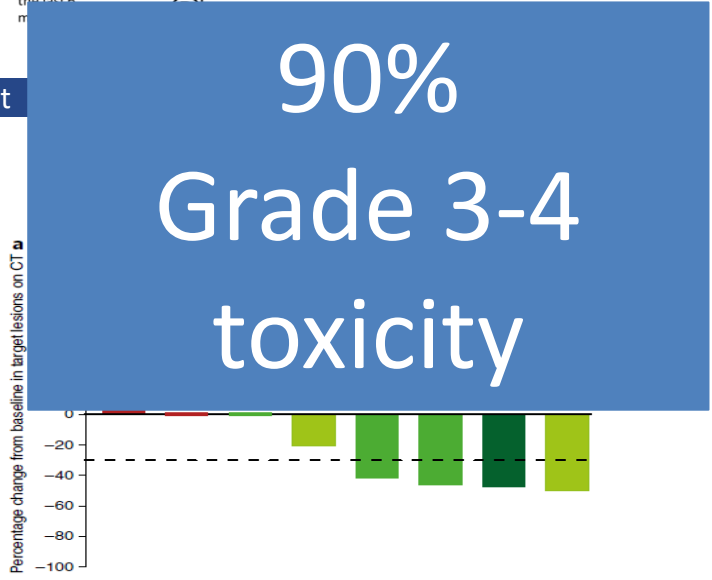
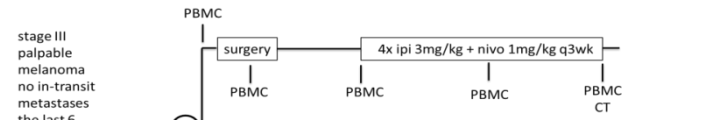
(73% RECIST RR, 45% pCR)



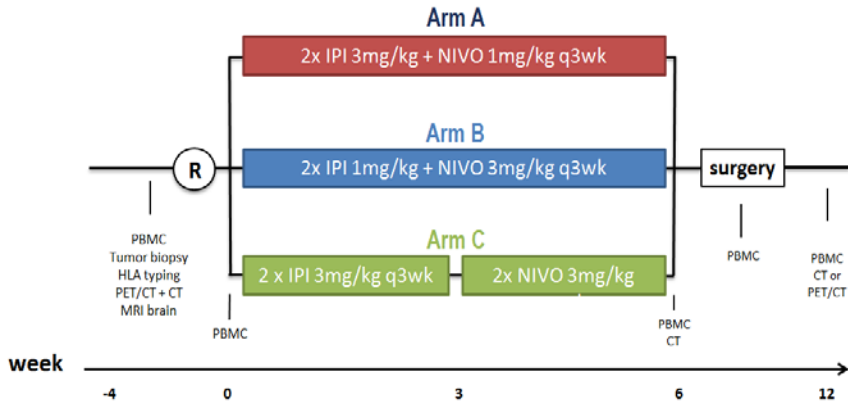
HIGHLY TOXIC BUT PROMISING RESULTS

Adjuvant

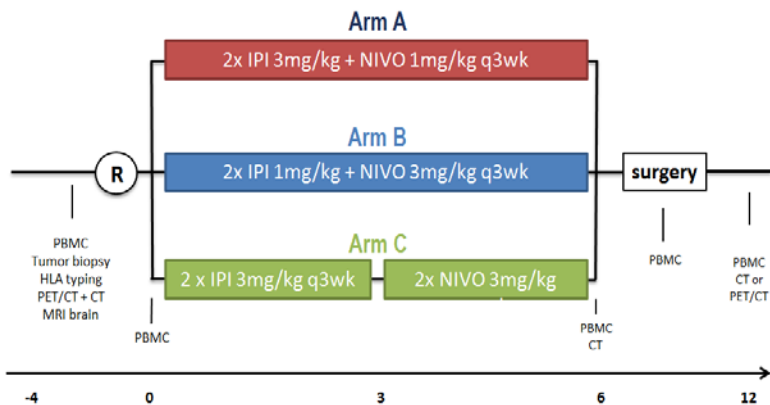
Neo-adjuvant



In search for the optimal neoadjuvant regimen Opacin-Neo trial



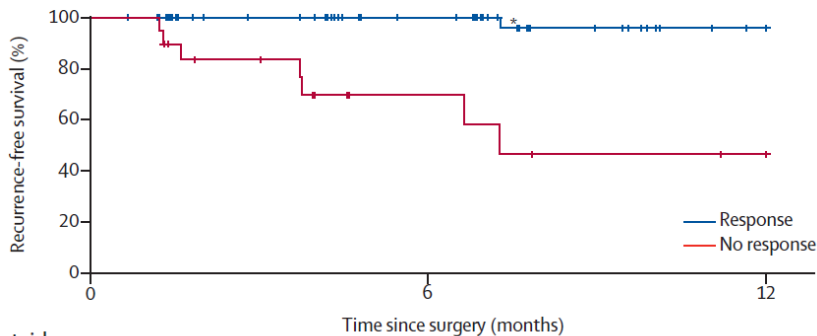
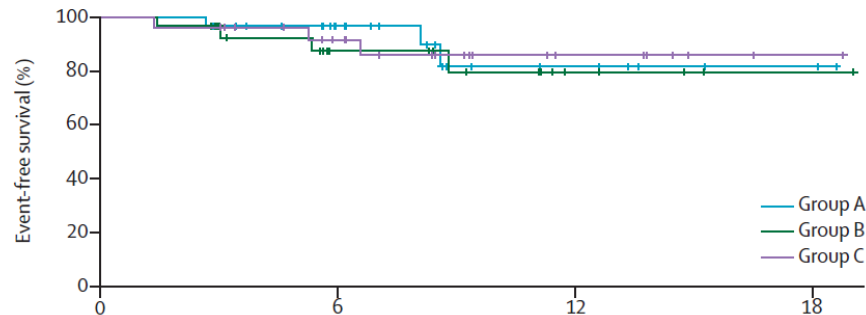
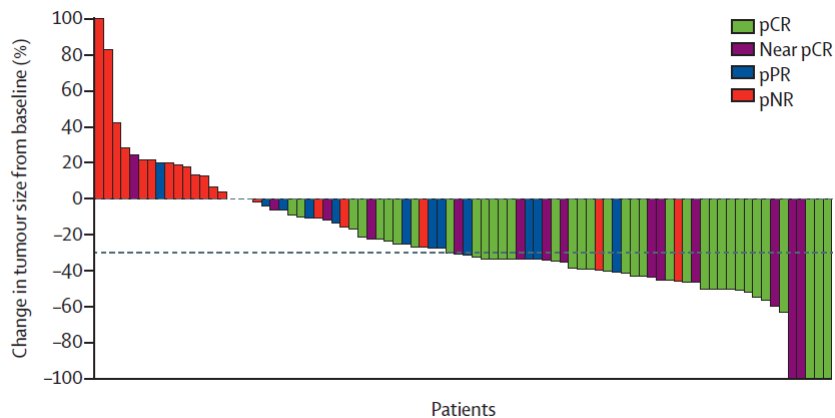
In search for the optimal neoadjuvant regimen Opacin-Neo trial



All gr AE	Gr 3-4 AE
29 (97)	12 (40)
29 (97)	6 (20)
26 (100)	13 (50)

(IPI 1 + NIVO3 x 3) appears as the optimal regimen

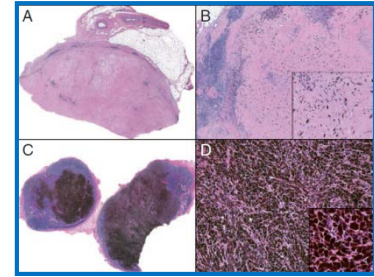
Pathological response quality is associated with long term benefit



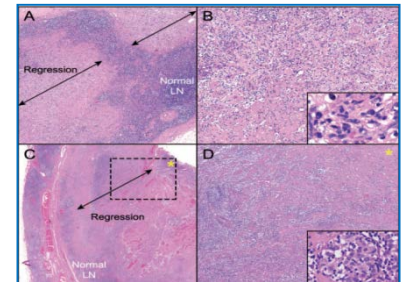
	0	6	12
Response	64 (0)	34 (30)	10 (53)
No response	19 (0)	6 (8)	2 (10)

Pathological Complete Response

- Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma
- Is pathological complete response accurately predict long term survival?
- Not for neoadjuvant chemotherapy for breast or pancreatic cancers
- Significance of pathological response varies upon the type of treatment



Targeted therapy : hyalinized fibrosis and melanosis (melanophages)



Checkpoint inhibitor : immune-mediated tumor regression, immune infiltrate, features of wound healing/repair

CONCLUSIONS

- The concept of neoadjuvant immunotherapy for melanoma with high risk of relapse is convincing and highly promising even to be considered for early stages (stages IIB-C)
- Mostly anti-PD1 mAb-based
- Place of intratumor neoadjuvant immunotherapy remains TBD
- Pathological response and relapse free survival interval seem reasonable endpoints