Neoadjuvant Melanoma Trials
Data Collection and Endpoint Selection

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Melanoma Research Alliance

FDA

Disclosures

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- Stockownership: Uniti Cars, Neon Therapeutics, Forty Seven

International Neoadjuvant Melanoma Consortium

Advancing treatment for patients with melanoma by facilitating collaborations in neoadjuvant clinical and translational research.

Policy Review

Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium

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Advances in the treatment of metastatic melanoma have improved responses and survival. However, many patients

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1861–1868, 2018
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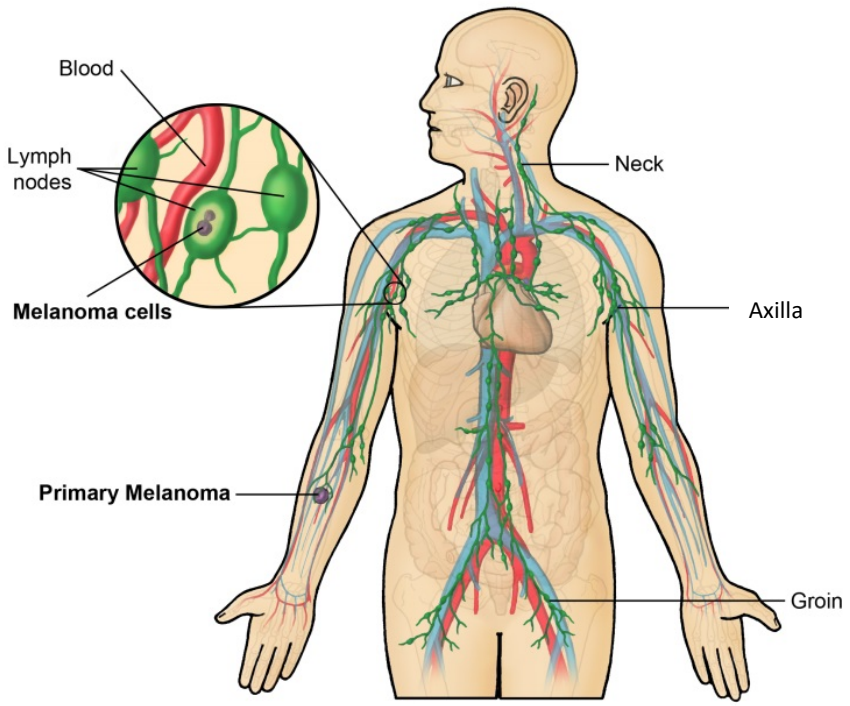
ORIGINAL ARTICLE

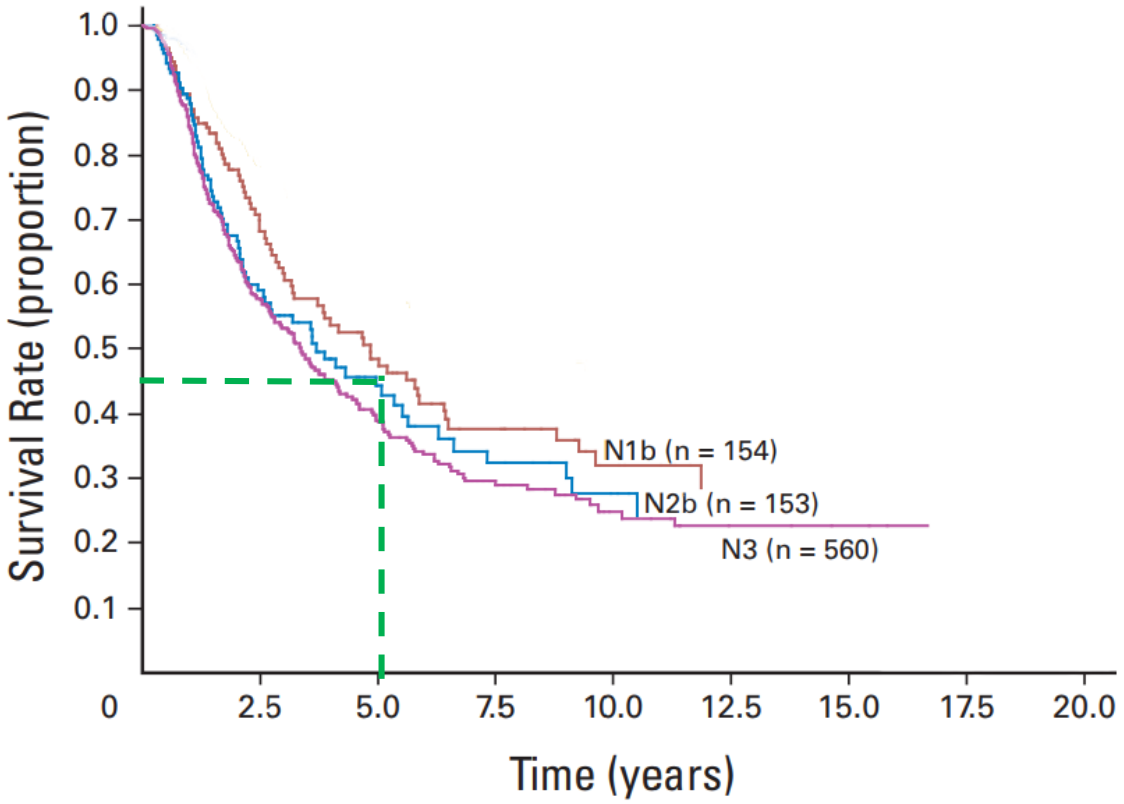
Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma

M. T. Tetzlaff[1,2*], J. L. Messina[3], J. E. Stein[4], X. Xu[5], R. N. Amaria[6], C. U. Blank[7], B. A. van de Wiel[7], P. M. Ferguson[8], R. V. Rawson[8], M. I. Ross[9], A. J. Spillane[10], J. E. Gershenwald[9,11], R. P. M. Saw[8], A. C. J. van Akkooi[7], W. J. van Houdt[7], T. C. Mitchell[12], A. M. Menzies[10], G. V. Long[13], J. A. Wargo[9,14], M. A. Davies[2,6,15], V. G. Prieto[1,16], J. M. Taube[4†] & R. A. Scolyer[8†]

The outcome of high risk stage III melanoma patients is poor

After surgery +/- RT the 5 year OS is only 30-60% [1-3]

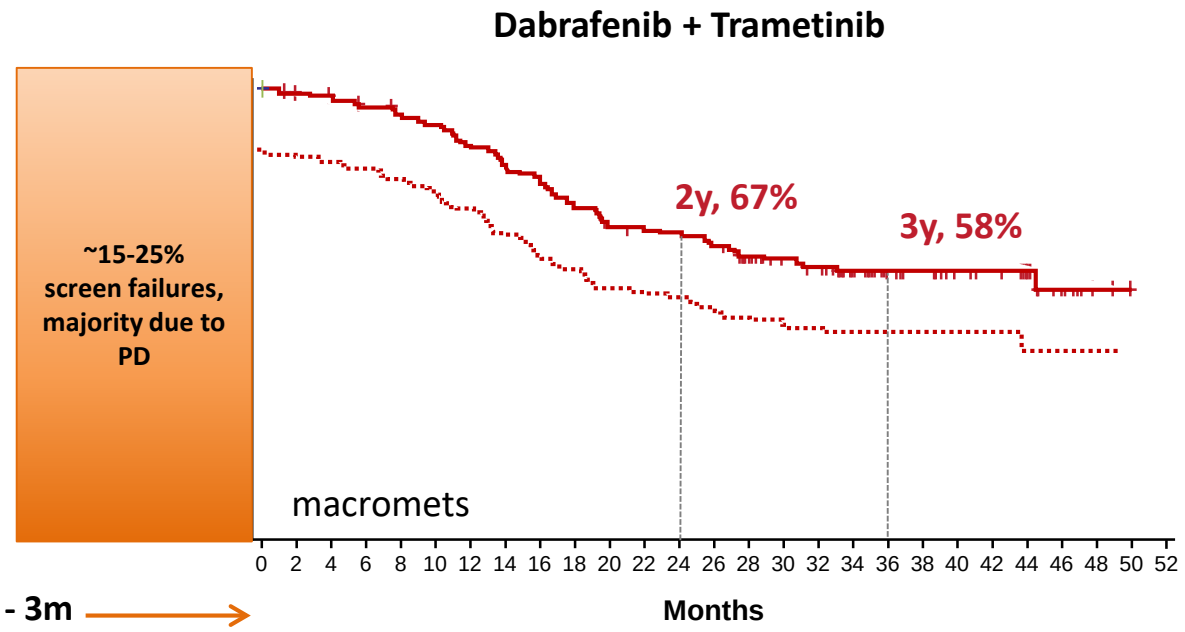


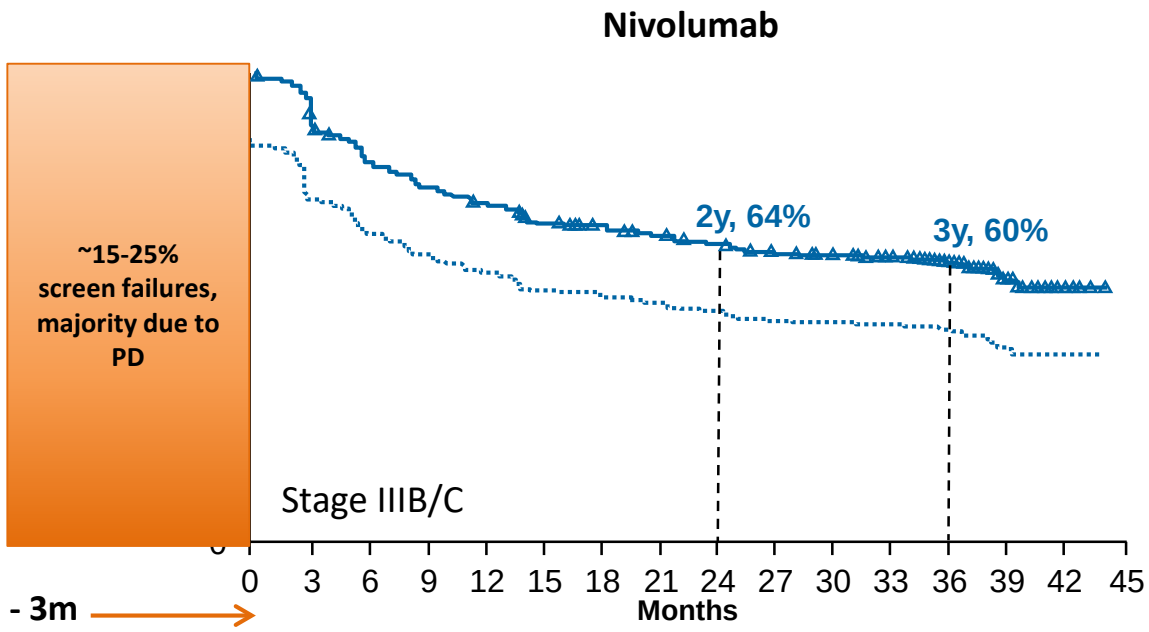


[1]Balch, et al., J Clin Oncol, 2009; [2]van Akkooi, et al., Eur J Surg Oncol, 2007; [3]van der Ploeg, et al., Ann Surg Oncol, 2011,

The EFS outcome of high risk stage III melanoma patients is poor

- Adjuvant therapy improved the RFS, but EFS remains poor [4,5]

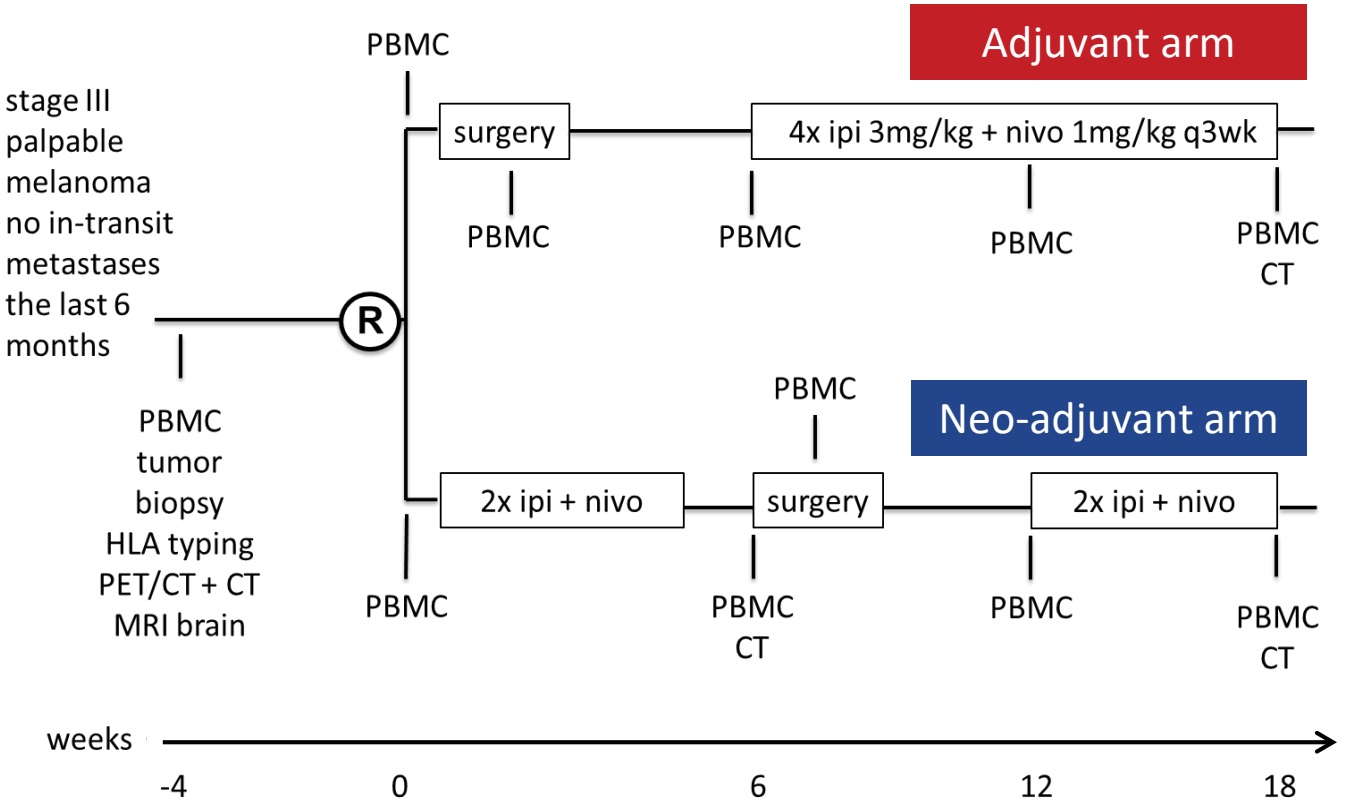




Adapted from Menzies et al ASCO 2019

[1]Balch, et al., J Clin Oncol, 2009; [2]van Akkooi, et al., Eur J Surg Oncol, 2007; [3]van der Ploeg, et al., Ann Surg Oncol, 2011; [4]Combi-AD - Long SMR 2017; [5]Checkmate-238 - Weber ESMO 2019

Neoadjuvant versus adjuvant checkpoint inhibition (IPI+NIVO) in macroscopic stage III melanoma – OpACIN

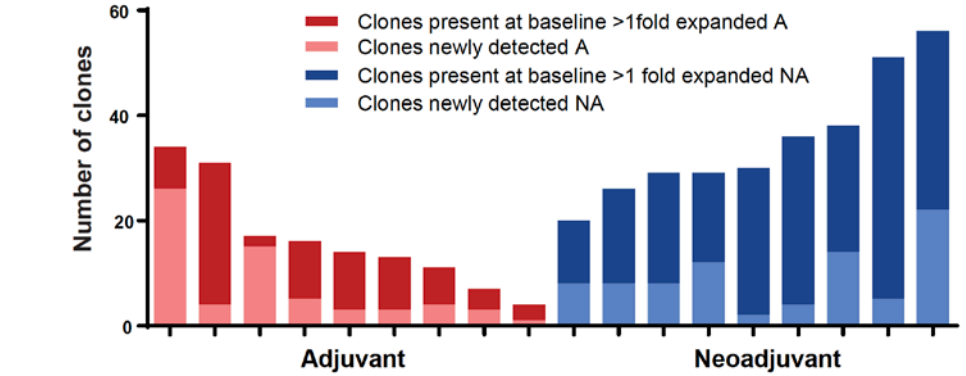


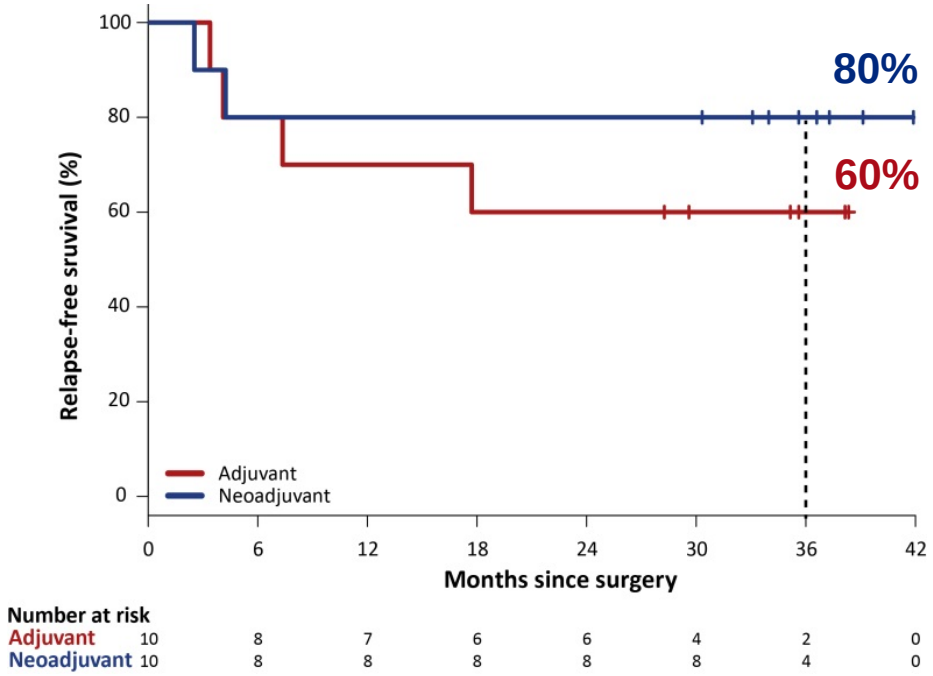
designed by TN Schumacher and CU Blank in 2014

What did we learn from OpACIN?

Neoadjuvant IPI + NIVO:

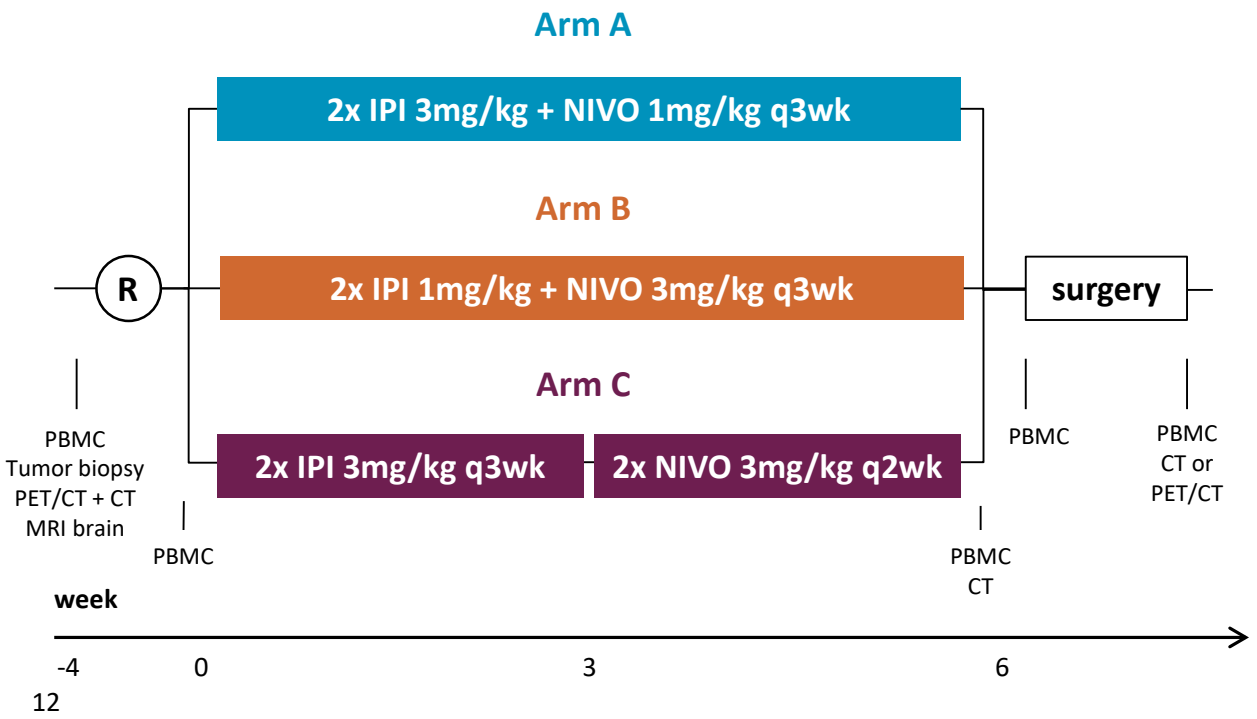
- Did not delay surgery
- Was superior compared to adjuvant therapy in expanding tumor-resident TCR clones
- The pathologic response rate was high (**78%**)
- None of the patients with pathologic response have relapsed
- highly toxic with **90%** grade III/IV adverse events





Blank et al., Nat Med, 2018; Blank et al., ESMO 2019

Multicenter Phase 2 Study to Identify the Optimal neo-Adjuvant Combination Scheme of Ipilimumab and Nivolumab – OpACIN-neo

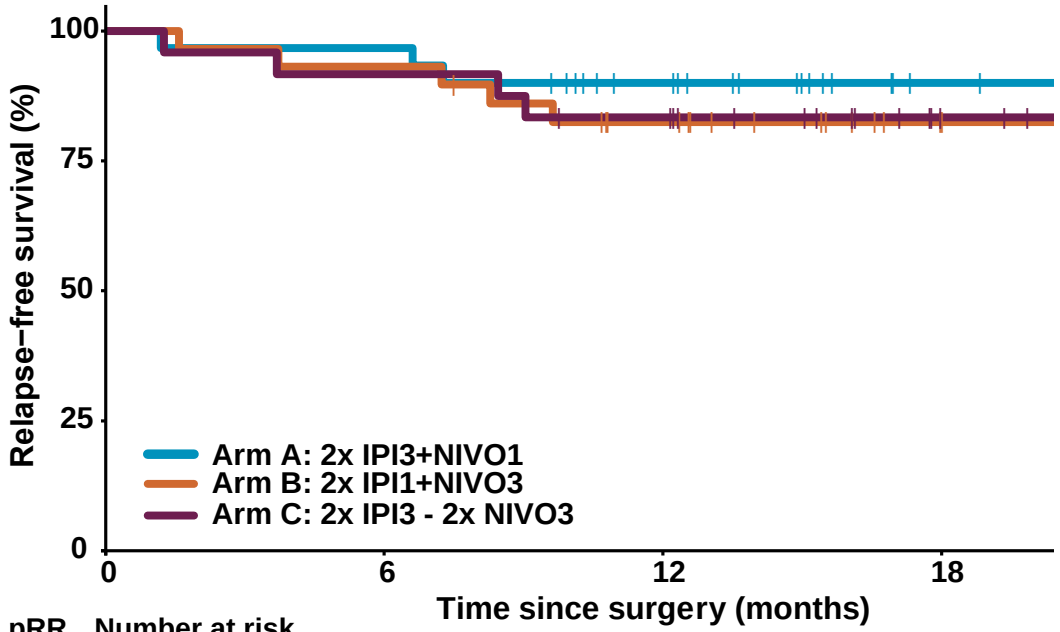


	Grade 3-4 toxicity	Pathologic Response
Arm A	40%	80%
Arm B	20%	77%
Arm C	50%	65%

Dosing in Arm A, B, and C based on data from Blank, Rozeman, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink, Rozeman, et al. Ann Oncol 2017

18-months Relapse-free survival – OpACIN-neo

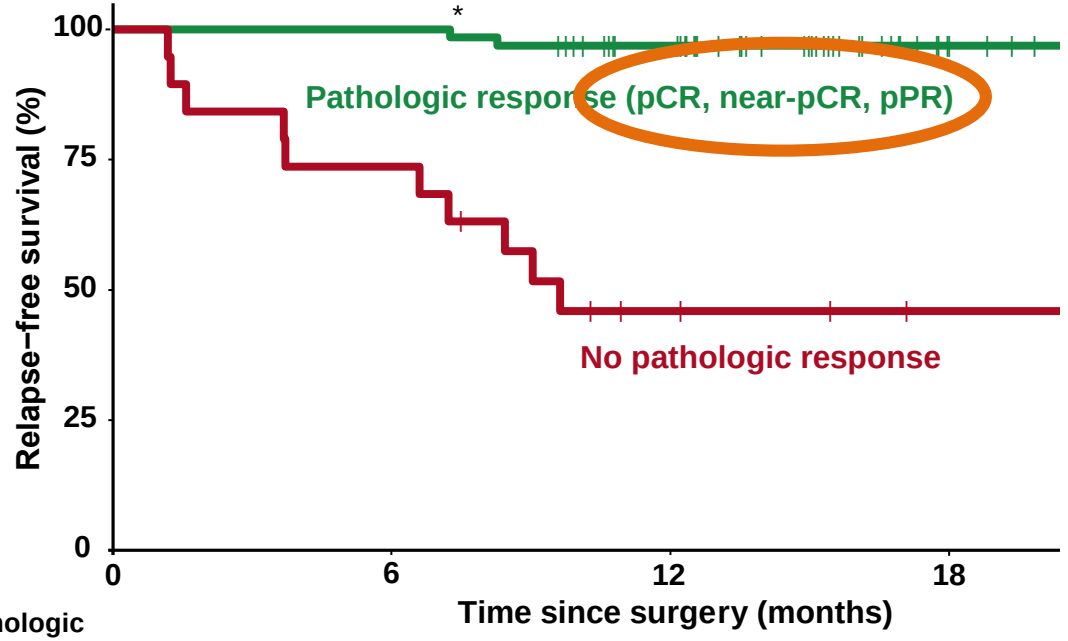
According to treatment arm



Arm	pRR	Number at risk			
A	80%	30	29	21	8
B	77%	29	27	20	9
C	65%	24	22	19	7

pRR = pathologic response rate

According to pathologic response



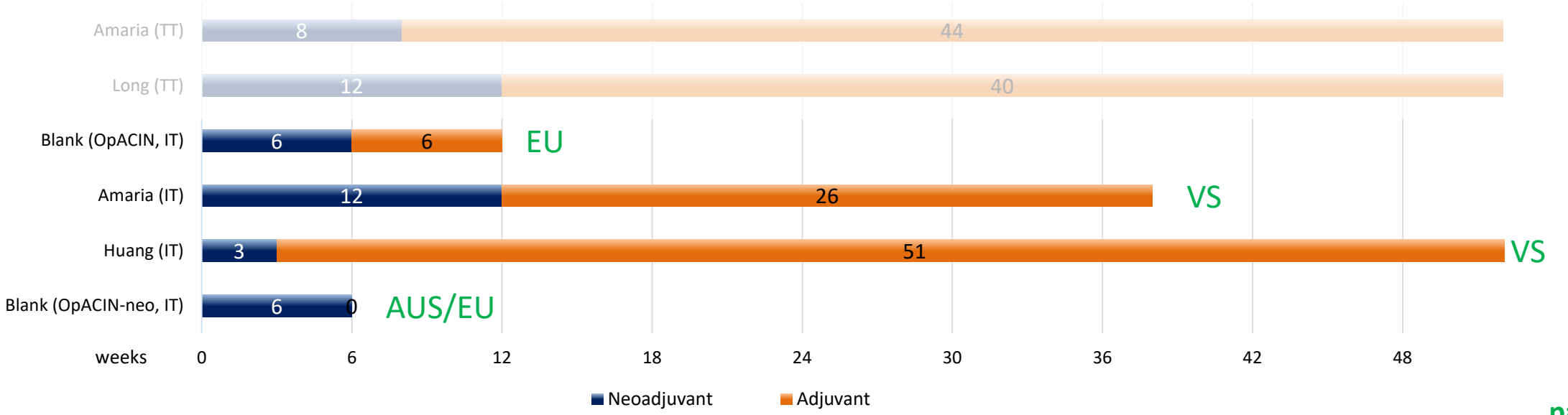
Pathologic response	Number at risk			
Yes	64	64	54	21
No	19	14	6	3

* patient died due to toxicity without signs of melanoma relapse

Pathologic response correlates with outcome!

INMC pooled analysis

- Pooled data from 6 modern NST clinical trials conducted across the INMC.
- Pts with RECIST measurable, surgically resectable, clinical stage III melanoma with nodal metastases ***who underwent surgery*** were included.
- Baseline disease characteristics, treatment regimen, pathologic response and RFS were examined.

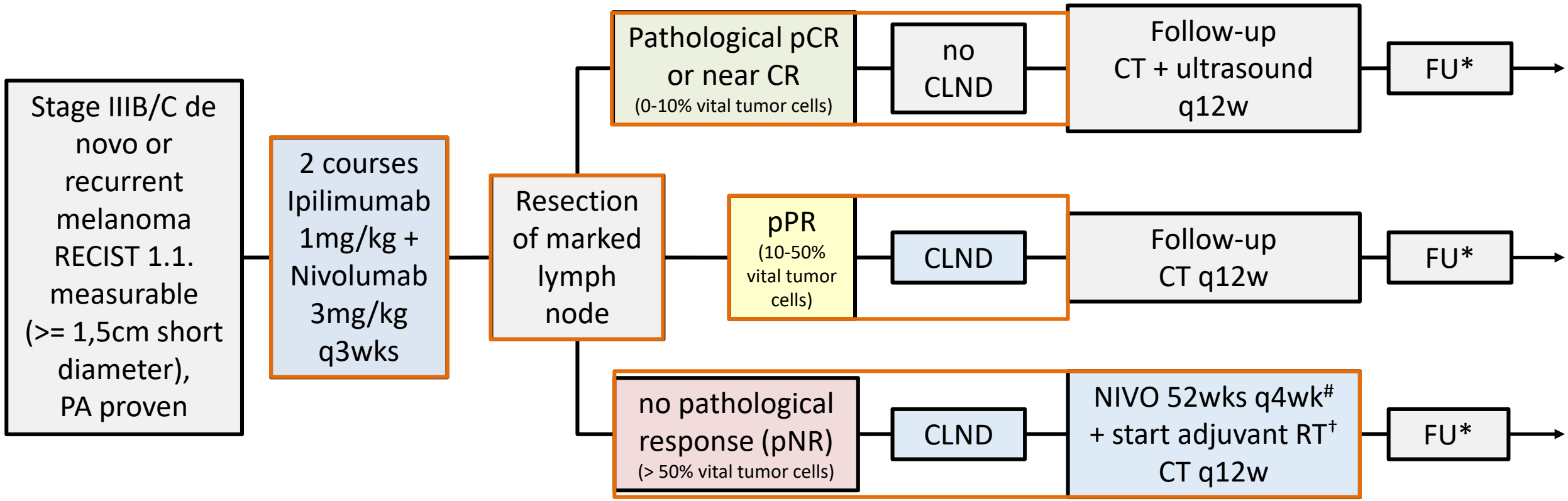


IPI + NIVO (N=107)
N=10
N=11
N= 0
N =86

80% of all patients treated with IT

Adapted from Menzies et al. Presented at ASCO 2019

Personalized Response-driven Adjuvant therapy after Combination of neoadjuvant Ipilimumab and Nivolumab in stage IIIB/C melanoma - PRADO



PET/CT
CT neck thorax abdomen
MRI brain
Lab + PBMC
Feces collection
Tumor biopsy
Lymph node marker placement

Excision marked lymph node
CT
Lab + PBMC
Feces collection

CLND = Complete Lymph node dissection

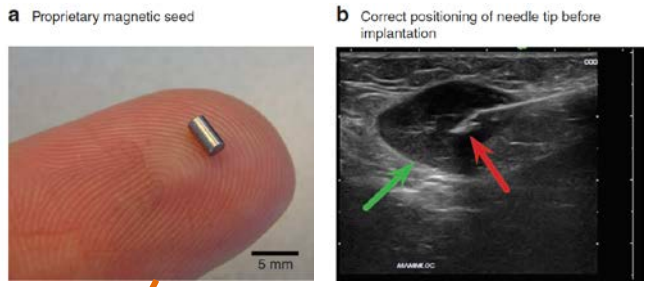
CT
Lab + PBMC

* According to institutes standard
# BRAF+MEK inhibition in BRAF V600E/K patient is allowed according to patient's and treating physician's decision when available
† Adjuvant radiotherapy according to patient's and physician's decision

-4 — 0 — 6 — 12 — 64

The pathologic response in the largest lymph node is representing the whole lymph node bed

(MeMaLoc substudy of OpACIN-neo)



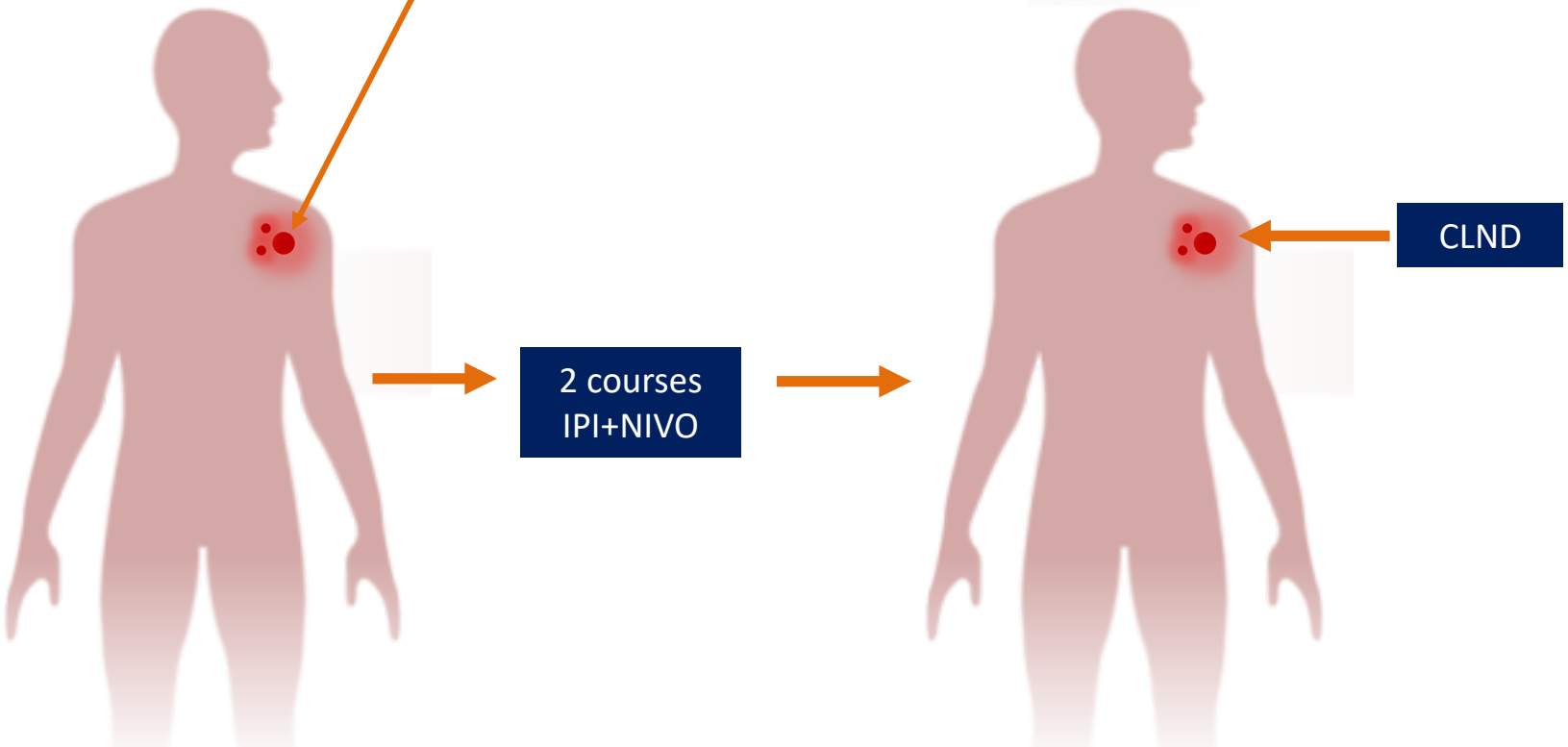
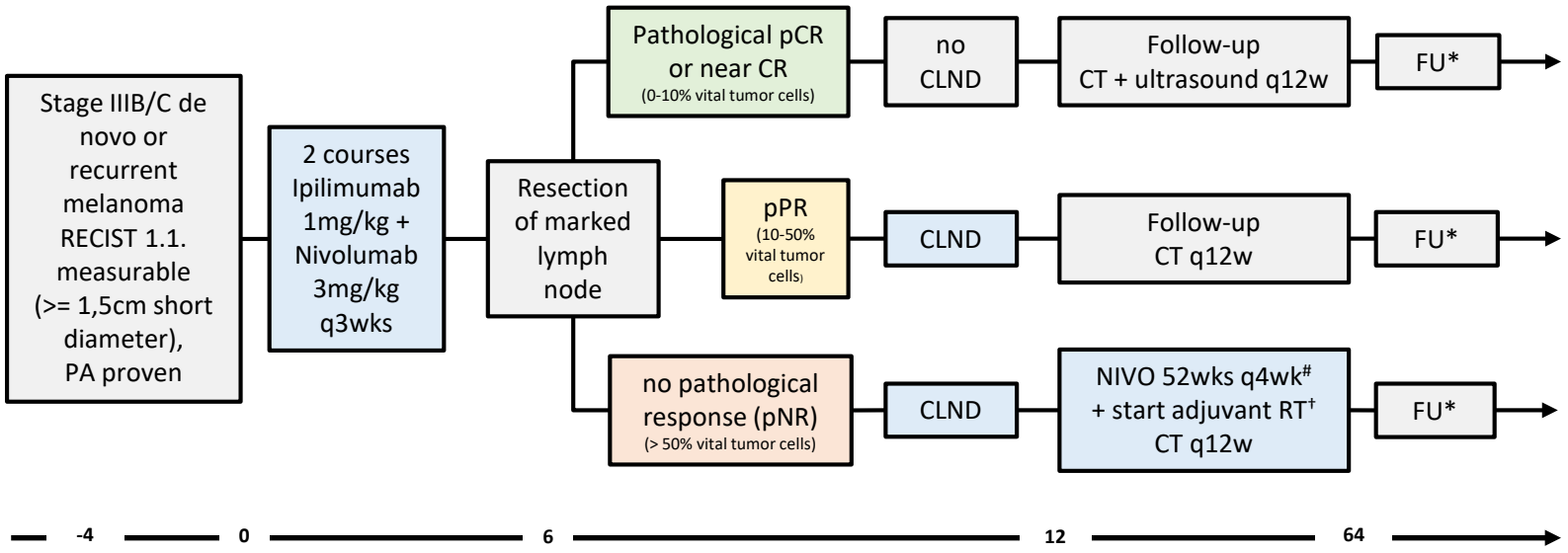


Table 1 Overall results

	No. of patients* ($n = 12$)
Seed *in situ* (days)†	23 (21–27)
Skin to seed distance on ultrasound imaging (mm)†	10 (5–15)
Surgery	
Transcutaneous detection	12
Retrieval rate	12
System Usability Scale score†	98 (90–100)
Pathology	
Total node count per patient†	24 (16–34)
Node count with evidence of viable or treated tumour†	2 (1–3)
Response	
Index node	
pCR	7
Near-pCR	3
pPR	1
pNR	1
Total basin	
pCR	7
Near-pCR	3
pPR	1
pNR	1
Index node congruent with total basin	12

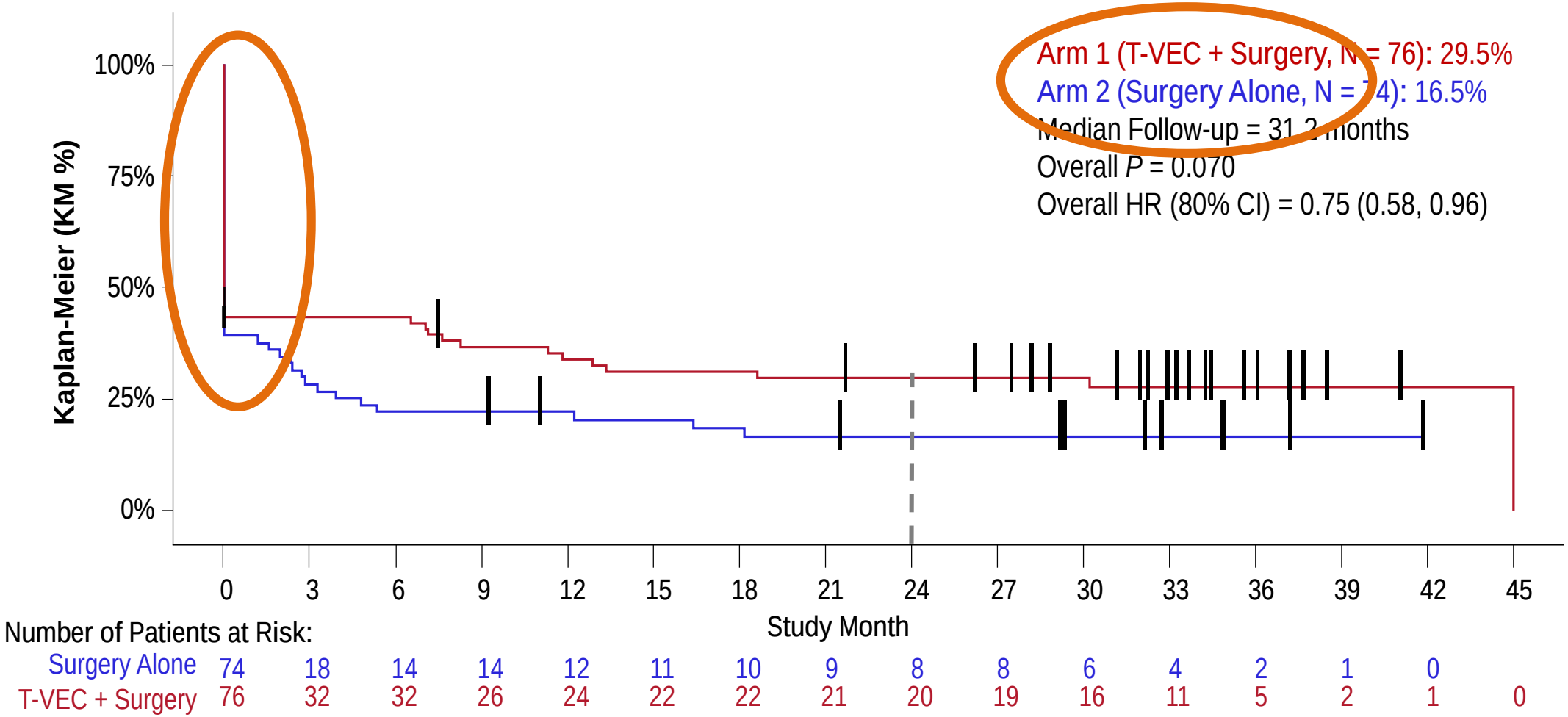
Schermers et al., BJS 2019

What have we learned from **PRADO** so far?



- IPI1+NIVO3 scheme is again well tolerated
- Pre-treatment application of marker in index LN is feasible
- Fast pathologic evaluation of marked LN is feasible
- Timing of CLND within 3 weeks post marked LN resection and start adjuvant therapy (if needed) at week 12 is feasible (NKI & MIA experience)
- Parallel RT to NIVO or DAB+TRAM is feasible

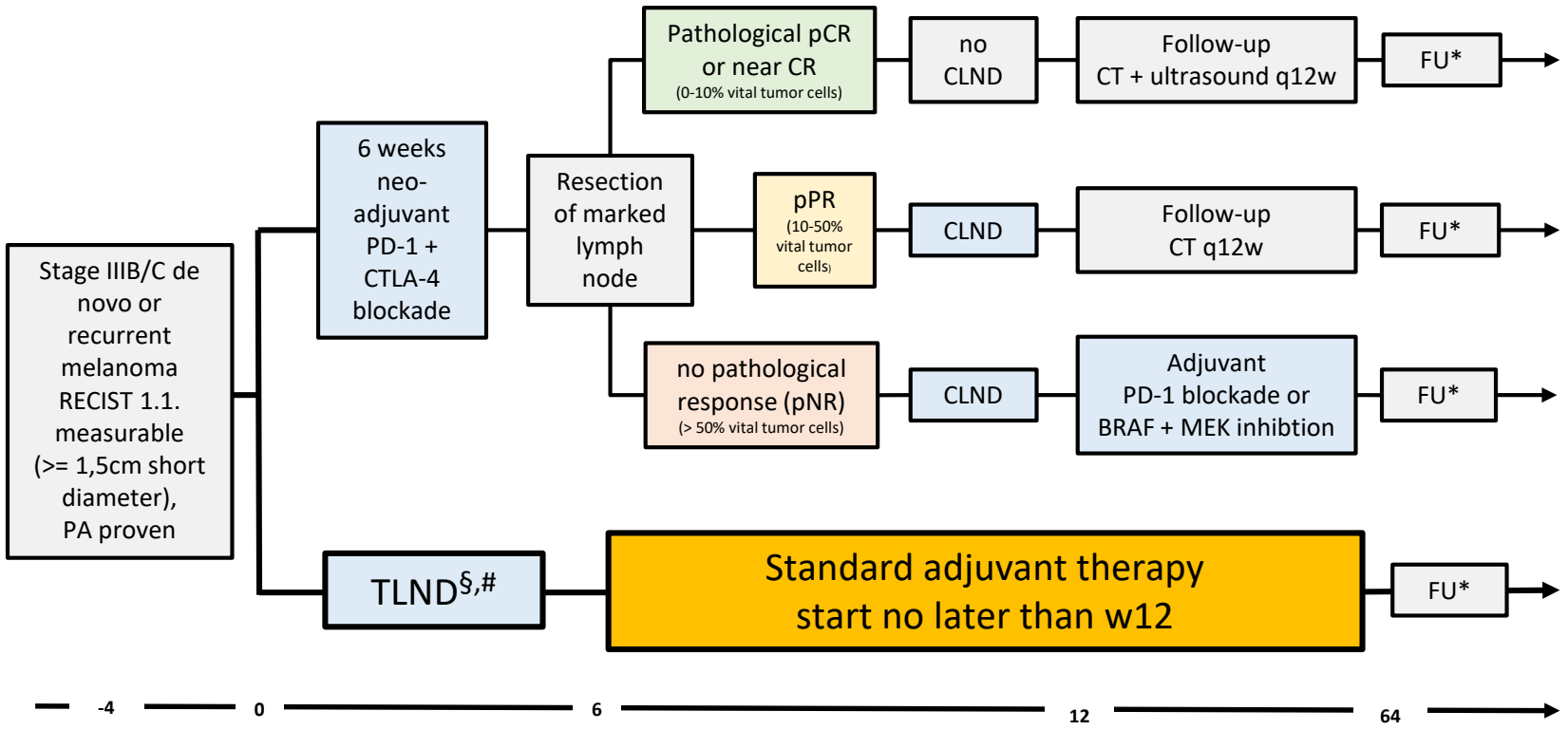
RFS is not advisable in neoadjuvant randomized trials: T-VEC neoadjuvant versus upfront surgery



ITT Analysis Set: 150 patients enrolled and randomized

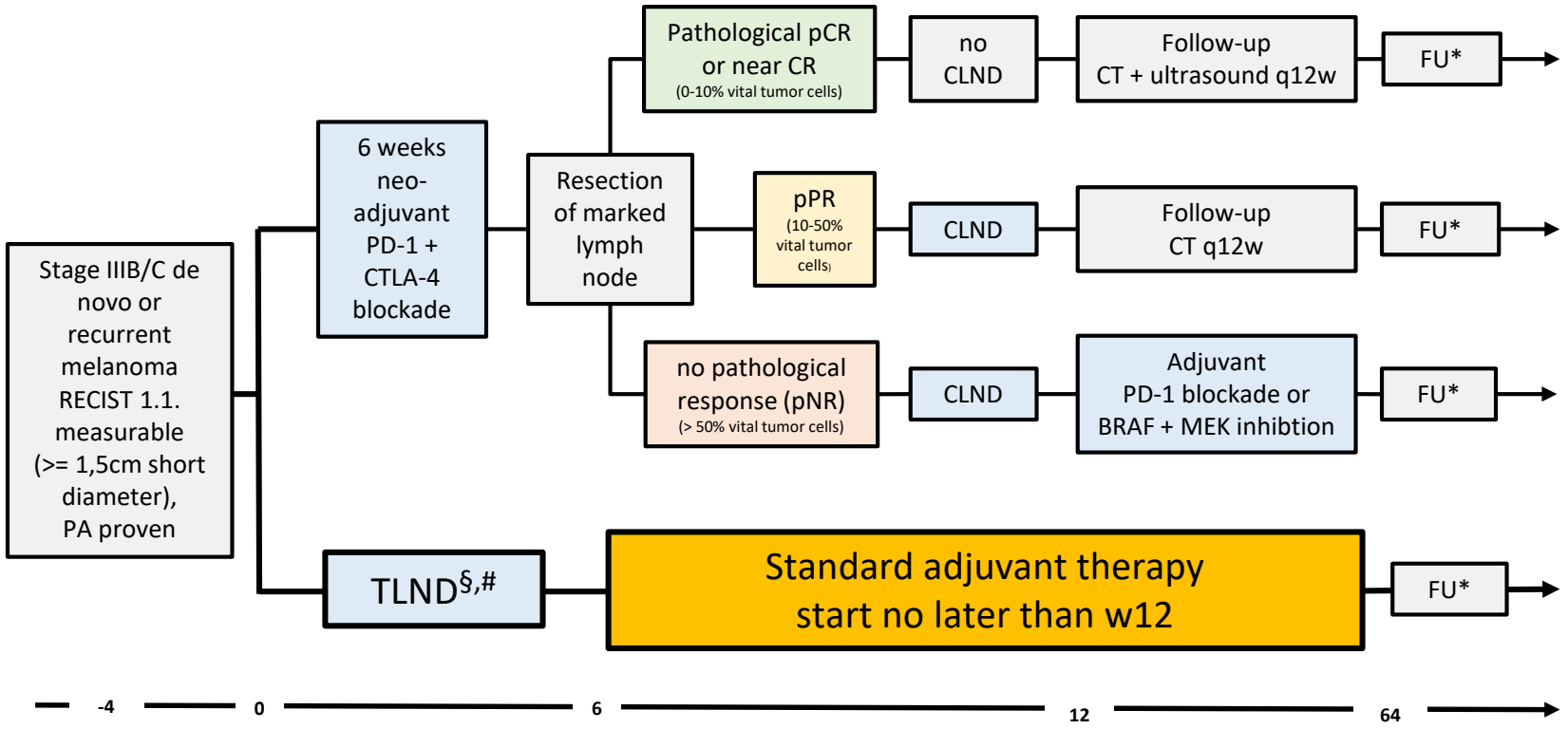
Dummer, et al.

Remaining questions for a phase 3 trial



- Response-driven scheme? Adjuvant versus only FU in MPR patients?
- Primary endpoint EFS ?
- Event also non-melanoma death? Elderly populations!
- Index LN approach versus TLND?
- Stratify for BRAF status? How fast BRAF status available
- Stratify continents?

Remaining questions for a phase 3 trial



- Timing of CLND within 3 weeks post marked LN resection feasible?
- Start adjuvant therapy (if needed) at week 12 broadly feasible?
- Pathology fast enough? pRR or MPR as surrogate markers?
- Adjuvant RT parallel NIVO or DAB+TRAM in NR patients?
- How to deal with change to other adjuvant therapy in non-MPR which will be reality

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