Systemic Neoadjuvant Therapy for Regional Metastasis of Melanoma

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Conflict of Interest

Clinical Research: **Roche, MSD, BMS, Novartis, Pfizer**

Speaker: **Roche, MSD, BMS, Novartis, Pfizer, United Medical, AstraZeneca**

Advisory Board: **Roche, MSD, BMS, Novartis, Pfizer, United Medical, AstraZeneca, Blau**

Neoadjuvant Chemo and Biochemo
The beginning

Neoadjuvant CVD Chemotherapy

Pilot Study of Preoperative Chemotherapy with Cisplatin, Vinblastine, and Dacarbazine in Patients with Local-Regional Recurrence of Melanoma

Antonio C. Buzaid, M.D., Sewa S. Legha, M.D.,* Charles M. Balch, M.D.,† Merrick Ross, M.D.,† Sigrid Ring, R.N.,* Carl Plager, M.D.,* Nicholas E. Papadopoulos, M.D.,* Adel K. El-Naggar, M.D., Ph.D.,‡ and Robert S. Benjamin, M.D.**

Background. Because the prognosis of patients with local-regional recurrence of melanoma treated with surgery alone usually is poor, the authors conducted a study designed to determine the efficacy of preoperative chemotherapy using cisplatin, vinblastine, and dacarbazine (CVD) in this patient population.

Methods. Eligibility included biopsy-proven, measurable, and potentially resectable local-regional disease in the form of lymph node metastases, satellite/in-transit has significant activity in local-regional recurrences of melanoma, resulting in pathologic complete response in 10% of the patients. Because its impact on survival remains unclear, this treatment strategy should currently remain investigational. Preoperative chemotherapy, however, could be offered to certain patients with bulky, borderline resectable, regional disease for whom cytoreduction may make surgery easier or less mutilating. *Cancer* 1994;74:2476–82.

Neoadjuvant Biochemotherapy

Melanoma Research 1998, **8**, pp. 549–556

Phase II study of neoadjuvant concurrent biochemotherapy in melanoma patients with local-regional metastases

A. C. Buzaid*, M. Colome, A. Bedikian, O. Eton, S. S. Legha, N. Papadopoulos, C. Plager, M. Ross, J. E. Lee, P. Mansfield, J. Rice, S. Ring, J. J. Lee, E. Strom and R. Benjamin

Oncology Center, Hospital Sírio-Libanês, Rua Adma Jafet 91, São Paulo, SP 01308-050, Brazil. Tel: (+55) 11 234 8810; Fax: (+55) 11 234 8808; Email: buzaid@ibm.net (A. C. Buzaid). Department of Melanoma/Sarcoma and Surgical Oncology (M. Colome, A. Bedikian, O. Eton, S. S. Legha, N. Papadopoulos, C. Plager, M. Ross, J. E. Lee, P. Mansfield, J. Rice, S. Ring, J. J. Lee, R. Benjamin) and Division of Radiation Oncology (E. Strom), The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA.

Very first neoadjuvant studies in melanoma – pCR rates

Author	Regimen	N	pCR	Reference
Buzaid et al	CVD	52	10%	Cancer 74:2476, 1994
Buzaid et al	Biochemo	62	6,5%	Mel Res 8:549, 1998
Gibbs et al	Biochemo	48	11%	Cancer 94:470, 2002

Neoadjuvant Checkpoint Inhibitor Therapy

Inibidor de Checkpoint Neoadjuvante. MDACC

nature medicine

LETTERS

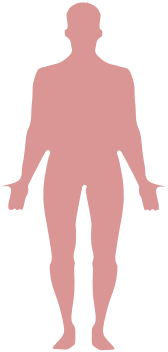
https://doi.org/10.1038/s41591-018-0197-1

Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

Rodabe N. Amaria[1,12], Sangeetha M. Reddy[2,12], Hussein A. Tawbi[1], Michael A. Davies[1], Merrick I. Ross[3], Isabella C. Glitza[1], Janice N. Cormier[3], Carol Lewis[4], Wen-Jen Hwu[1], Ehab Hanna[4], Adi Diab[1], Michael K. Wong[1], Richard Royal[3], Neil Gross[4], Randal Weber[4], Stephen Y. Lai[4], Richard Ehlers[3], Jorge Blando[5], Denái R. Milton[6], Scott Woodman[1], Robin Kageyama[7], Danny K. Wells[7], Patrick Hwu[1], Sapna P. Patel[1], Anthony Lucci[3], Amy Hessel[4], Jeffrey E. Lee[3], Jeffrey Gershenwald[3], Lauren Simpson[1], Elizabeth M. Burton[3], Liberty Posada[1], Lauren Haydu[3], Linghua Wang[8], Shaojun Zhang[8], Alexander J. Lazar[9], Courtney W. Hudgens[9], Vancheswaran Gopalakrishnan[3], Alexandre Reuben[3], Miles C. Andrews[3], Christine N. Spencer[8], Victor Prieto[9], Padmanee Sharma[5,10], James Allison[5], Michael T. Tetzlaff[9,11,13] and Jennifer A. Wargo[3,8,13]*

Amaria et al Nature Medicine, 2018

Phase II trial to test the hypothesis that treatment with neoadjuvant (+ adjuvant) checkpoint blockade would enhance responses in this subset of patients



Patients with resectable stage IIIB/IIIC melanoma, no brain mets or prior ICB

Stratify by Stage

Ipi 3mg/kg + Nivo 1 mg/kg q 3 wks x 3 doses (n=20)

Nivo 3mg/kg q 2 wks x 4 doses (n=20)

RECIST restaging (if no PD)

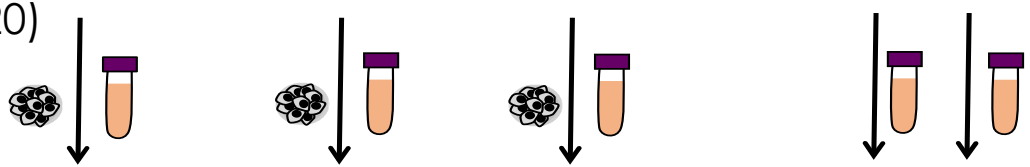
Nivo 3 mg/kg

months

Trial was stopped early given some signals on efficacy and toxicity

Primary Endpoint:
Path response
Secondary endpdoints:

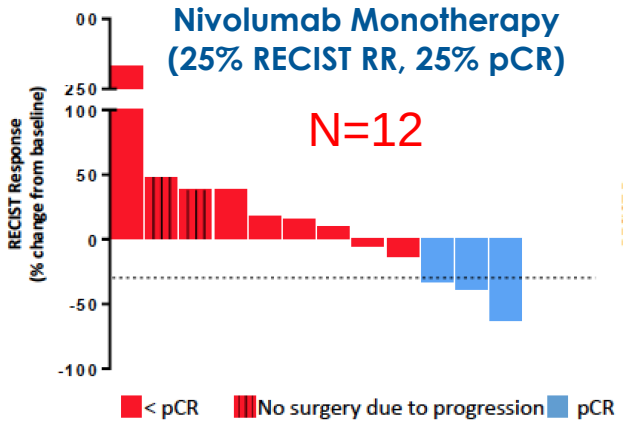
-DMFS
-OS
-Toxicity
- correlatives

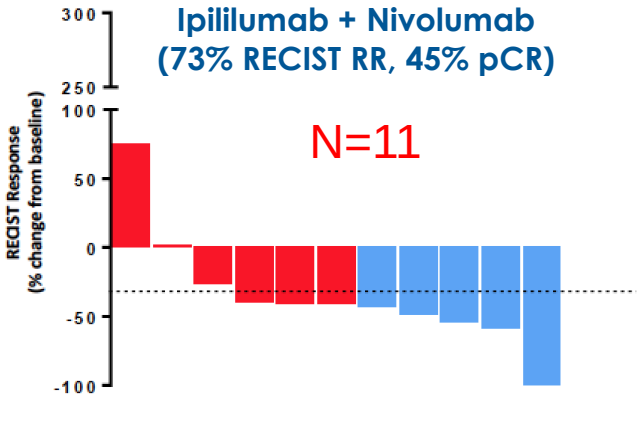


Baseline On-treatment Surgery Adjuvant

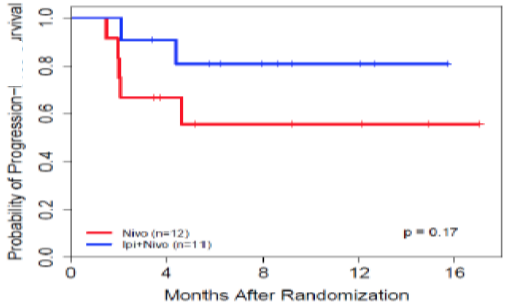
Molecular & immune profiling in longitudinal tissue and blood samples

Treatment with neoadjuvant Ipi Nivo was associated with a higher RECIST / pCR rate, and improved RFS over Nivo monotherapy



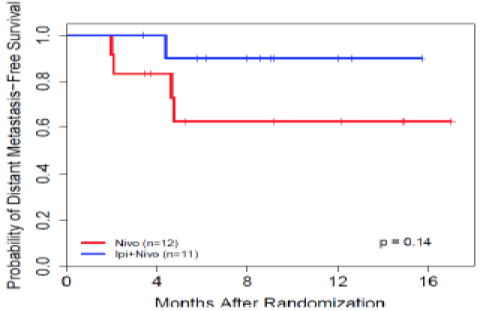


Progression-Free Survival



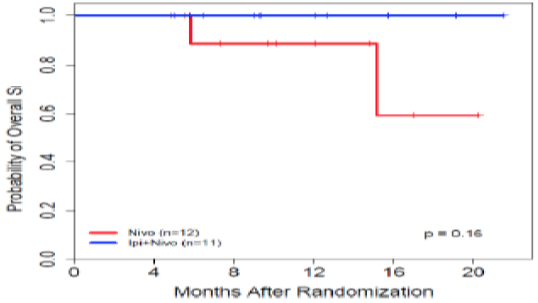
Nivo	12	6	4	3	1
Ipi+Nivo	11	9	5	3	0

Distant Metastasis Free Survival



Nivo	12	8	5	4	1
Ipi+Nivo	11	10	6	3	0

Overall Survival



Nivo	8	12	7	5	2	1
Ipi+Nivo	13	11	8	5	2	1

However treatment with combined therapy was associated with a high rate of adverse events

Select Treatment Related Adverse Events During Neoadjuvant Treatment

	Nivolumab (n=12)		Ipilimumab + Nivolumab (n=11)	
	Any Grade, %	Grade 3-4, %	Any Grade, %	Grade 3-4, %
Any Treatment Related Adverse Events	**92**	**8**	**91**	**73**
Fatigue	67	0	55	0
Rash	17	0	73	0
Fevers/chills/flu like	8	0	64	0
Weight loss/anorexia	17	0	27	0
Transaminitis	17	0	55	27
Colitis/diarrhea	17	0	64	18
Hyperthyroidism	8	0	27	9
Hypothyroidism	0	0	36	0
Myositis/myalgias	8	0	18	9
Pain	25	8	27	0

Inibidor de Checkpoint Neoadjuvante

nature medicine

LETTERS

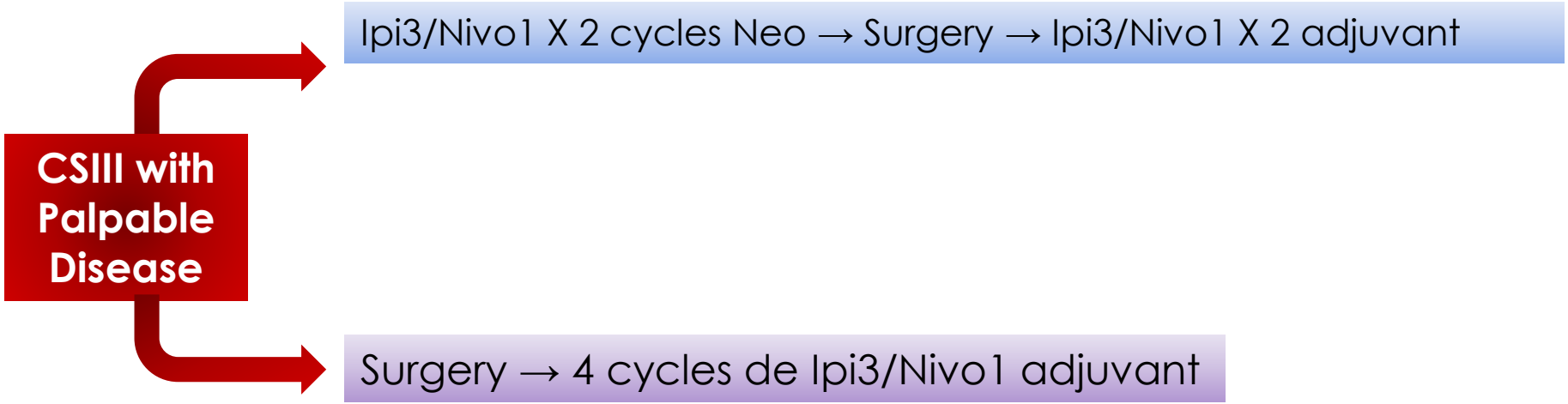
https://doi.org/10.1038/s41591-018-0198-0

Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma

Christian U. Blank[1,2]*, Elisa A. Rozeman[1,2], Lorenzo F. Fanchi[2], Karolina Sikorska[3], Bart van de Wiel[4], Pia Kvistborg[2], Oscar Krijgsman[2], Marlous van den Braber[2], Daisy Philips[2], Annegien Broeks[4], Johannes V. van Thienen[1], Henk A. Mallo[1], Sandra Adriaansz[1], Sylvia ter Meulen[5], Loes M. Pronk[3], Lindsay G. Grijpink-Ongering[3], Annemarie Bruining[6], Rachel M. Gittelman[7], Sarah Warren[8], Harm van Tinteren[3], Daniel S. Peeper[2], John B. A. G. Haanen[1,2], Alexander C. J. van Akkooi[5] and Ton N. Schumacher[2]*

Blank et al Nature Medicine, 2018

Neoadjuvant vs Adjuvant Ipi3/Nivo1. Pilot Study



Blank et al Nature Medicine, 2018

Neoadjuvant vs Adjuvant Ipi3/Nivo1. Efficacy Data

- Of the 10 pts treated with neoadjuvant therapy, 9 were evaluable for response
- 6 of 9 had a profound histologic response
  - 3/9 - pCR
  - 3/9 - Near pCR
  - 1/9 - < 50% viable tumor
- Very high toxicity rate – 90% G3/4 in both arms

Blank et al Nature Medicine, 2018

Toxicity data

Four patients developed clinically severe treatment-related adverse events: Steven–Johnson syndrome (onset after three cycles); severe colitis (onset after two cycles) requiring four lines of immune suppressive therapy and 10 weeks to recover to grade 1; polyradiculitis (onset after two cycles) requiring three lines of immune suppression and 12 months of rehabilitation to fully recover; and diabetes type 1 (onset after two cycles)

Blank et al Nature Medicine, 2018

Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial

Elisa A Rozeman, Alexander M Menzies, Alexander C J van Akkooi, Chandra Adhikari, Carolien Bierman, Bart A van de Wiel, Richard A Scolyer, Oscar Krijgsman, Karolina Sikorska, Hanna Eriksson, Annegien Broeks, Johannes V van Thienen, Alexander D Guminski, Alex Torres Acosta, Sylvia ter Meulen, Anne Miek Koenen, Linda J W Bosch, Kerwin Shannon, Loes M Pronk, Maria Gonzalez, Sydney Ch'ng, Lindsay G Grijpink-Ongering, Jonathan Stretch, Stijn Heijmink, Harm van Tinteren, John B A G Haanen, Omgo E Nieweg, Willem M C Klop, Charlotte L Zuur, Robyn P M Saw, Winan J van Houdt, Daniel S Peeper, Andrew J Spillane, Johan Hansson, Ton N Schumacher, Georgina V Long, Christian U Blank

Lancet Oncol 2019; 20: 948–60

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See Comment page 892

Summary

Background The outcome of patients with macroscopic stage III melanoma is poor. Neoadjuvant treatment with ipilimumab plus nivolumab at the standard dosing schedule induced pathological responses in a high proportion of patients in two small independent early-phase trials, and no patients with a pathological response have relapsed after a median follow up of 32 months. However, toxicity of the standard ipilimumab plus nivolumab dosing schedule was high, preventing its broader clinical use. The aim of the OpACIN-neo trial was to identify a dosing schedule of ipilimumab plus nivolumab that is less toxic but equally effective.

OPACIN-NEO:
A MULTICENTER PHASE 2 STUDY TO IDENTIFY THE OPTIMAL NEO-ADJUVANT COMBINATION SCHEME OF IPILIMUMAB (IPI) AND NIVOLUMAB (NIVO)

EA Rozeman, AM Menzies, BA van de Wiel, C Adhikari, K Sikorska, O Krijgsman, H Eriksson, C Biermans, LG Grijpink-Ongering, M Gonzalez, A Broeks, AD Guminski, AJ Spillane, WM Klop, RPM Saw, RA Scolyer, ACJ van Akkooi, J Hansson, GV Long and CU Blank

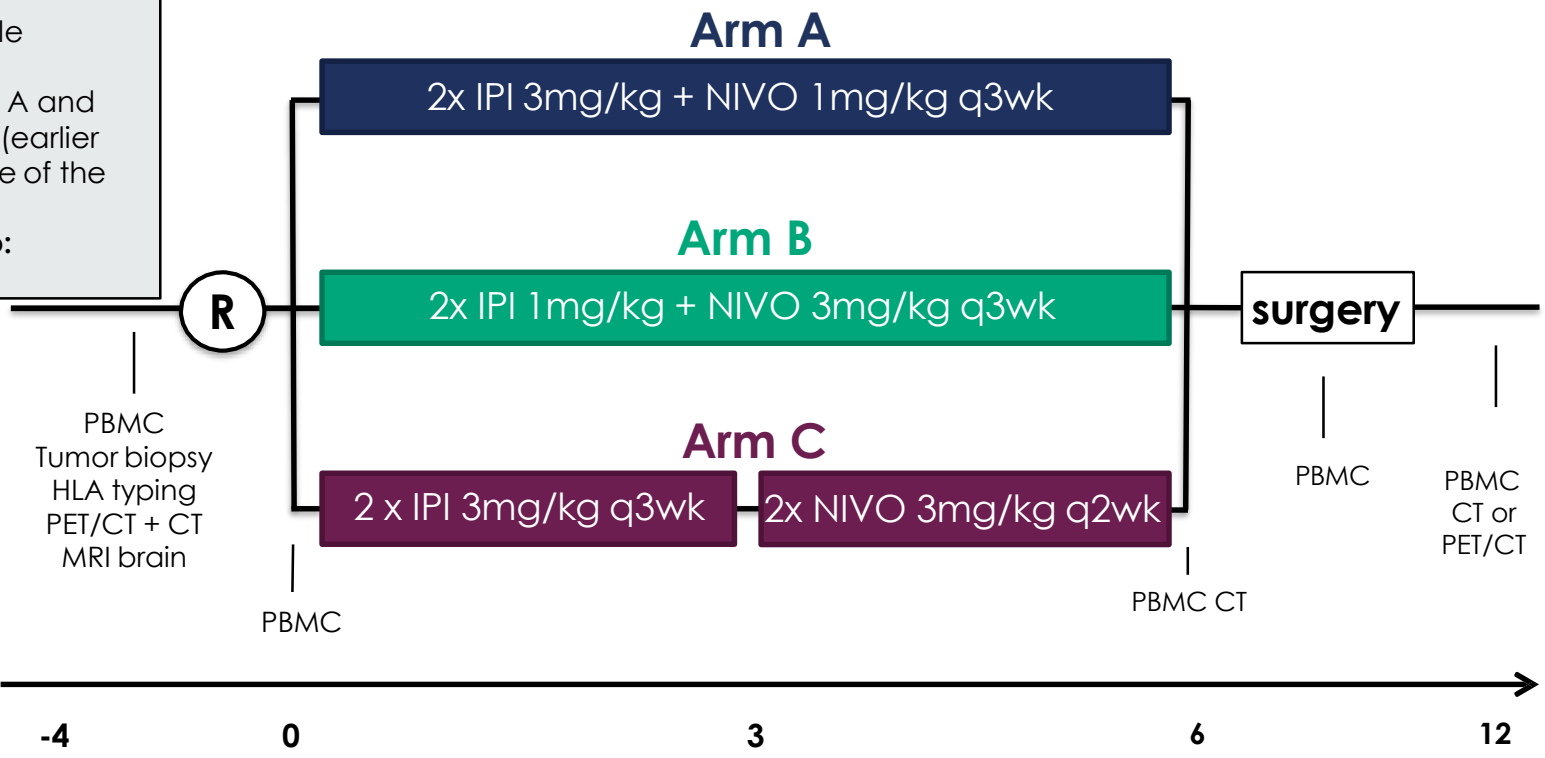
ESMO 2018

OPACIN-NEO: Study design

Study design:
- Multi-center phase 2 trial

Study cohort:
- Stage IIII measurable melanoma
- 86 patients, 30 Arm A and Arm B, 26 in Arm C (earlier closed upon advice of the DSMB)

Stratified according to:
- Study center



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

Data lock: 28 Sep 2018
Median follow-up 8.3 months

Pathologic response – Central revision

	Treatment arm		
	A: 2 x I3+N1 (n=30)	B: 2 x I1+N3 (n=30)	C: 2 x I3-2xN3 (n=26)
pRR	24 (80)	23 (77)	17 (65)
pCR	14 (47)	17 (57)	6 (23)
pPR	7 (23)	2 (7)	15 (17)
pNR	6 (20)	7 (23)[a]	8 (31)
Not evaluable	-	-	1 (4)[b]

[a] One patient had only palliative resection of largest lymph node, [b] Surgery was not performed because of toxicity, this patient had a radiologic CR Data are presented as n, (%).

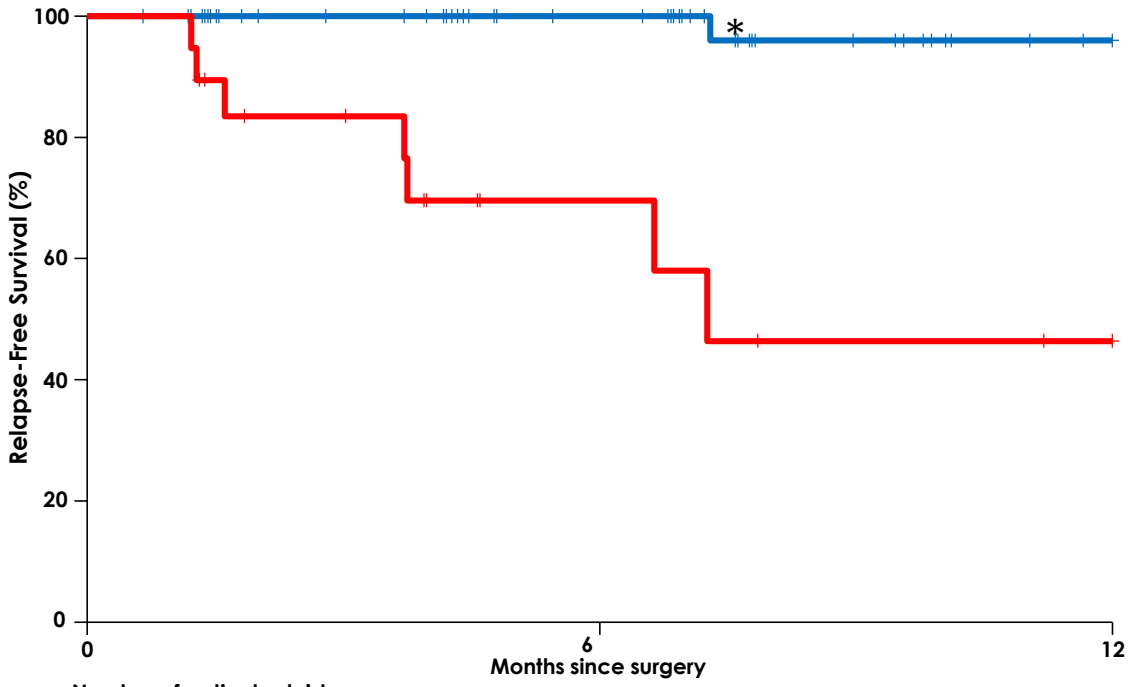
Immune-related adverse events in the first 12 weeks

Adverse Event	A: 2xI3+N1		B: 2xI1+N3		C: 2xI3-2xN3	
	All grade	Grade 3-4	All grade	Grade 3-4	All grade	Grade 3-4
Any adverse event	29 (97)	12 (40)	29 (97)	6 (20)	26 (100)	13 (50)
Fatigue	19 (63)	-	[illegible]		14 (54)	-
Rash	18 (60)	2 (			18 (69)	3 (12)
Pruritus	12 (40)	-	10 (33)	-	10 (38)	-
ALT increased	12 (40)	6 (20)	6 (20)	1 (3)	9 (35)	2 (8)
Hyperthyroidism	12 (40)	-	2 (7)	-	9 (35)	1 (4)
Diarrhea	7 (23)	1 (3)	4 (13)	1 (3)	11 (42	3 (12)
Headache	8 (27)	1 (3)	5 (17)	-	4 (15)	-
Fever	4 (13)	-	4 (13)	1 (3)	7 (27)	-
Dry mouth	6 (20)	-	3 (10)	-	3 (12)	-
Colitis	2 (7)	2 (7)	1 (3)	-	7 (27)	5 (19)
Hypothyroidism	5 (17)	-	2 (7)	-	3 (12)	-
Nausea	4 (13)	-	1 (3)	-	4 (15)	1 (4)
Arthralgia	2 (7)	-	3 (10)	-	4 (15)	-
Dry eye	2 (7)	-	3 (10)	-	2 (8)	-
Flu-like symptoms	1 (3)	-	4 (13)	-	2 (8)	-
Infusion related reaction	-	-	5 (17)	-	2 (8)	-
Serum amylase increased	3 (10)	1 (3)	2 (7)	1 (3)	1 (4)	-
Hyponatremia	-	-	2 (7)	1 (3)	1 (4)	-
Lipase increased	2 (7)	1 (3)	2 (7)	-	1 (4)	-
Adrenal insufficiency	1 (3)	-	-	-	2 (8)	1 (4)
Radiculitis	-	-	1 1(3)	-	1 (4)	1 (4)
Hypotension	1 (3)	1 (3)	-	-	-	-
Hyperglycemia	-	-	-	-	1 (4)	1 (4)
Meningitis	-	-	1 1(3)	1 (3)	-	-

Arm A vs Arm B p=0.158

Adverse events that occurred in ≥ 7 patients or were grade 3-4 are displayed in the table. Data are presented as n, (%)

Relapse free survival according to pathologic response



Number of patients at risk			
Response	64	34	10
No Response	19	6	2

* This pCR patient died due to complication of immune-related encephalitis

Neoadjuvant Targeted Therapy

Neoadjuvant Dabrafenib + Trametinib. Experiência da Australia

Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB–C, *BRAF*^{V600} mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial

Georgina V Long, Robyn P M Saw, Serigne Lo, Omgo E Nieweg, Kerwin F Shannon, Maria Gonzalez, Alexander Guminski, Jenny H Lee, Hansol Lee, Peter M Ferguson, Robert V Rawson, James S Wilmott, John F Thompson, Richard F Kefford, Sydney Ch'ng, Jonathan R Stretch, Louise Emmett, Rony Kapoor, Helen Rizos, Andrew J Spillane, Richard A Scolyer, Alexander M Menzies

Summary

Background Adjuvant dabrafenib plus trametinib therapy improves relapse-free survival in patients with resected stage III melanoma. We aimed to ascertain the proportion of patients who would have a pathological response and a response according to Response Evaluation Criteria in Solid Tumors (RECIST) after neoadjuvant dabrafenib plus trametinib therapy for resectable clinical stage III melanoma.

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Neoadjuvant Dabrafenib + Trametinib. Experiência da Australia

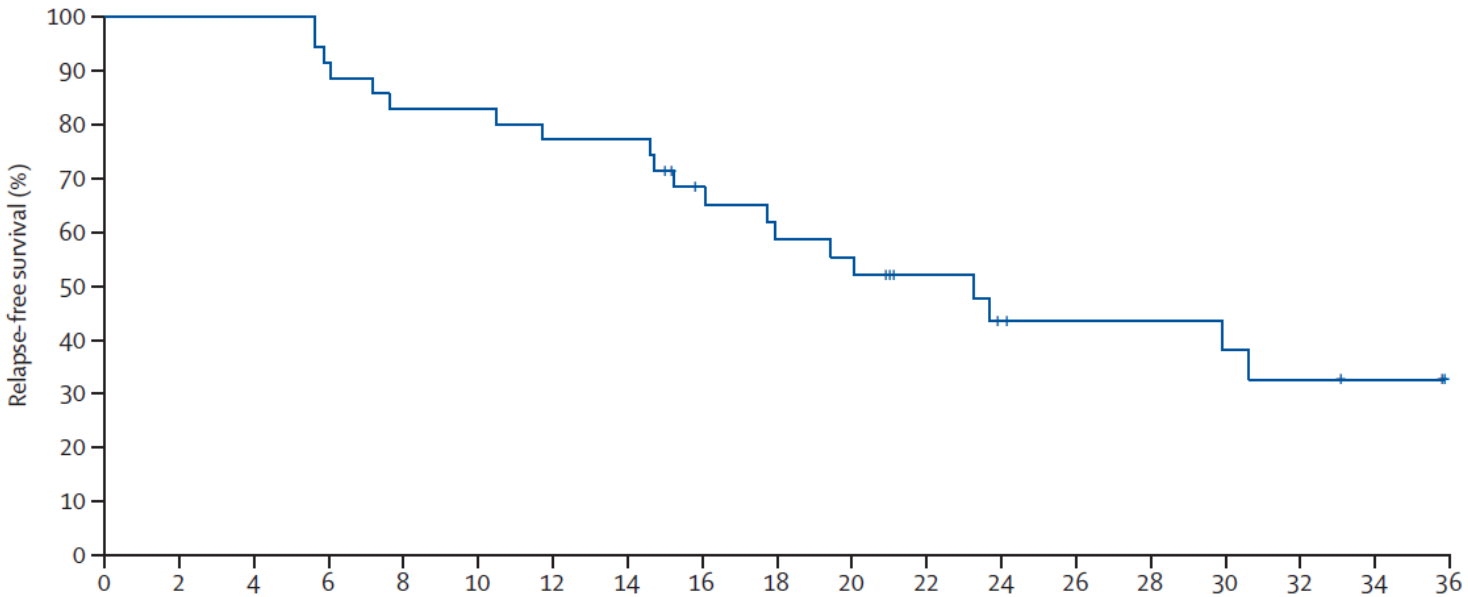
	Total population (n=35)
Median age at enrolment, years (IQR)	56·0 (46·0–64·0)
Sex	
Female	15 (43%)
Male	20 (57%)
BRAF genotype	
BRAF^{V600E}	34 (97%)
BRAF^{V600K}	1 (3%)
ECOG performance status	
0	32 (91%)
1	3 (9%)
Elevated serum lactate dehydrogenase	13 (37%)
AJCC clinical stage (7th edition)	
IIIB	6 (17%)
IIIC in-transit metastasis only	7 (20%)
IIIC lymph node positive or negative in-transit metastasis	22 (63%)

Neoadjuvant Dabrafenib + Trametinib. Experiência da Australia

	Study population (n=35)
Pathological response	
Complete	17 (49%; 95% CI 31–66)
Non-complete	18 (51%; 95% CI 34–69)
RECIST response	
Complete response	16 (46%; 95% CI 29–63)
Partial response	14 (40%; 95% CI 24–58)
Stable disease	5 (14%; 95% CI 5–30)
Metabolic response	
Complete	18 (51%; 95% CI 34–69)
Non-complete	17 (49% 95% CI 31–61)

Data are n (%; 95% CI). RECIST=Response Evaluation Criteria in Solid Tumors.

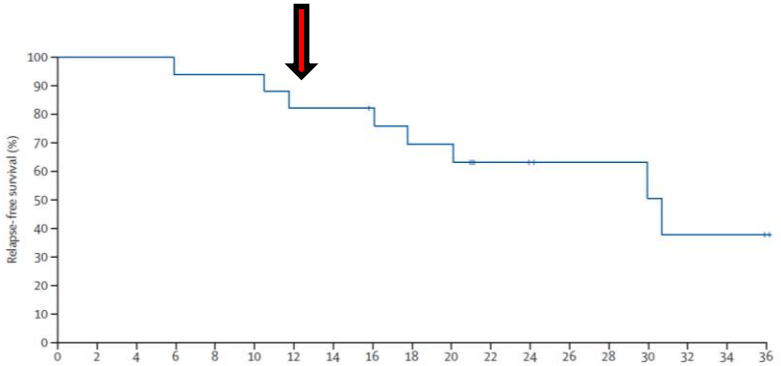
RFS. All Patients



Number at risk (number censored)																		
All patients	35 (0)	35 (0)	35 (0)	32 (0)	29 (0)	29 (0)	27 (0)	27 (0)	21 (3)	18 (3)	17 (3)	12 (7)	9 (8)	8 (9)	8 (9)	7 (9)	6 (9)	5 (10)	3 (12)

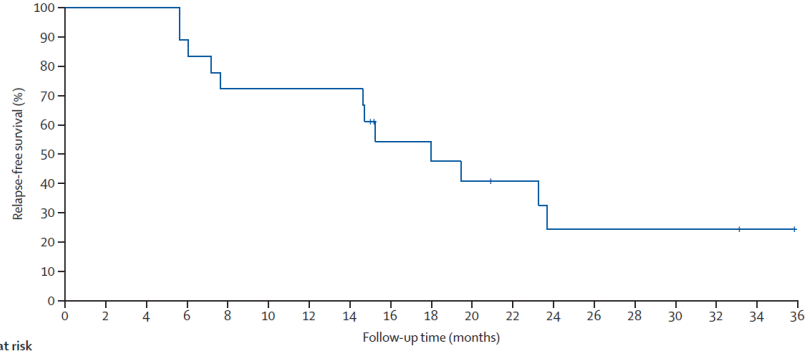
RFS in Patients with and without pCR

with pCR



Number at risk (number censored)																			
Patients with a complete pathological response	17 (0)	17 (0)	17 (0)	16 (0)	16 (0)	16 (0)	14 (0)	14 (0)	13 (1)	11 (1)	11 (1)	7 (4)	6 (5)	5 (6)	5 (6)	4 (6)	3 (6)	3 (6)	2 (7)

without pCR



Number at risk (number censored)																			
Patients with a non-complete pathological response	18 (0)	18 (0)	18 (0)	16 (0)	13 (0)	13 (0)	13 (0)	13 (0)	8 (2)	7 (2)	6 (2)	5 (3)	3 (3)	3 (3)	3 (3)	3 (3)	3 (3)	2 (4)	1 (5)

Neoadjuvant Dabrafenib + Trametinib. MDACC Study

Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial

Rodabe N Amaria*, Peter A Prieto*, Michael T Tetzlaff, Alexandre Reuben, Miles C Andrews, Merrick I Ross, Isabella C Glitza, Janice Cormier, Wen-Jen Hwu, Hussein A Tawbi, Sapna P Patel, Jeffrey E Lee, Jeffrey E Gershenwald, Christine N Spencer, Vancheswaran Gopalakrishnan, Roland Bassett, Lauren Simpson, Rosalind Mouton, Courtney W Hudgens, Li Zhao, Haifeng Zhu, Zachary A Cooper, Khalida Wani, Alexander Lazar, Patrick Hwu, Adi Diab, Michael K Wong, Jennifer L McQuade, Richard Royal, Anthony Lucci, Elizabeth M Burton, Sangeetha Reddy, Padmanee Sharma, James Allison, Phillip A Futreal, Scott E Woodman, Michael A Davies†, Jennifer A Wargo†

Summary

Background Dual BRAF and MEK inhibition produces a response in a large number of patients with stage IV *BRAF*-mutant melanoma. The existing standard of care for patients with clinical stage III melanoma is upfront surgery and consideration for adjuvant therapy, which is insufficient to cure most patients. Neoadjuvant targeted therapy with BRAF and MEK inhibitors (such as dabrafenib and trametinib) might provide clinical benefit in this high-risk p opulation.

Lancet Oncol 2018

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See Online/Comment
http://dx.doi.org/10.1016/

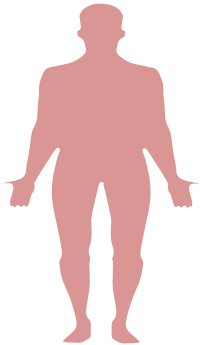
Lancet Oncol Epub ehead of print Jan 17, 2018

Eligibility

- CSIII with at least one palpable lymph node of at least 1.5 cm or at least one intransit met of at least 1 cm
- Oligometastatic stage IV (4 or less potentially resectable sites of metastases)

Lancet Oncol Epub ehead of print Jan 17, 2018

Phase II trial to test the hypothesis that treatment with neoadjuvant (+ adjuvant) BRAF/MEK inhibitors would improve RFS over SOC upfront surgery



Patients with resectable stage IIIB/IIIC melanoma, + BRAF mutation

n=28

Arm A
SOC - Upfront surgery

Surgical resection

Pathologic assessment (pCR rate)

SOC adjuvant therapy

Clinical and radiographic follow up

n=56

Arm B
Neoadjuvant BRAFi/MEKi x 8 weeks

CT scans with RECIST, Surgical resection

Adjuvant BRAF/MEK x 44 weeks

Clinical and radiographic follow up

Assess relapse-free survival, overall survival, toxicity

Biopsy & blood draw

Biopsy & blood draw on-treatment (wk 3, 5)

Biopsy & blood draw at surgery

Blood draws q 3 months with restaging

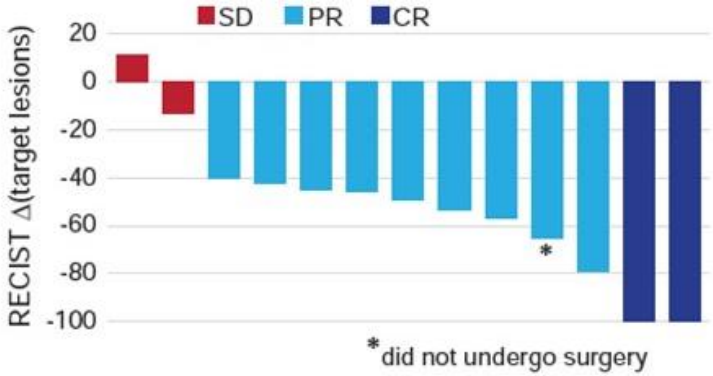
Biopsy & blood draw on relapse

Molecular & immune profiling in longitudinal tissue and blood samples

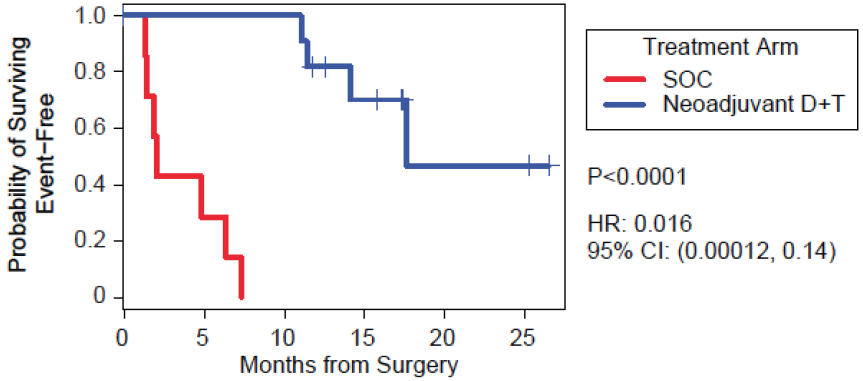
Amaria et al, Lancet Oncology 2018

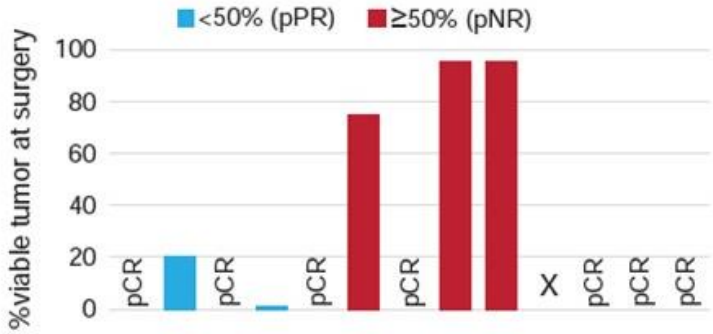
NCT02231775

Treatment with neoadjuvant BRAF/MEKi was associated with a high RECIST / pCR rate, and improved RFS over SOC surgery

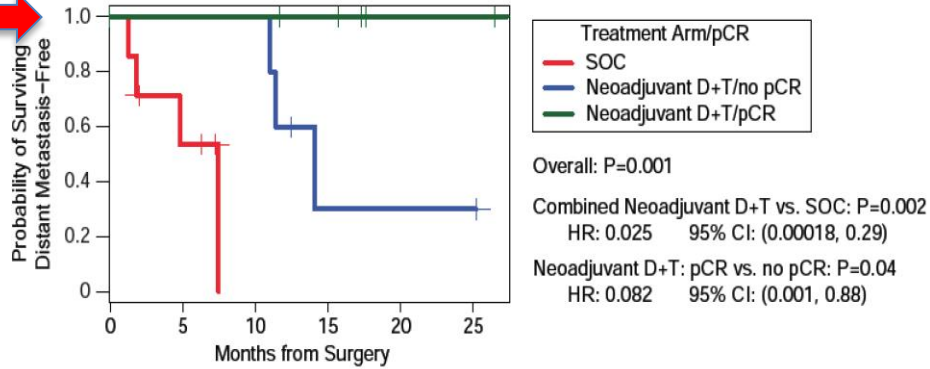


RECIST response rate 85%





Path CR rate 58%



Amaria et al, Lancet Oncology 2018

Toxicity

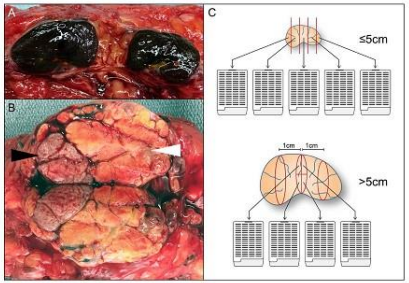
- 12 of 13 required temporary treatment discontinuation due to fever
- 38% required dose reduction
- There was no grade 4 toxicity
- Of 11 patients who received adjuvant therapy, 4 required discontinuation due to toxicity

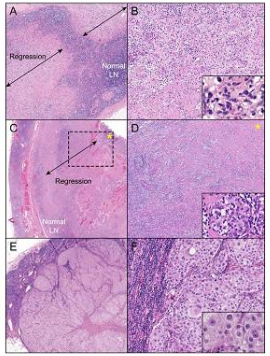
Lancet Oncol Epub ehead of print Jan 17, 2018

International Neoadjuvant Melanoma Consortium

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†]





Ann Oncol. 2018;29(8):1861-8.

White Paper

Shaping the Future of Neoadjuvant Systemic Therapy in Melanoma: Recommendations of the International Neoadjuvant Melanoma Consortium (INMC)

Agreed principles for neoadjuvant trials:
- Population
- Duration of therapy
- Biospecimens
- Endpoints

Amaria, Menzies, Burton et al Lancet Oncology, 2019 in press

Modern melanoma NST trials

Trial	Regimen	N	pCR (%)	med RFS (mo)	med FU (mo)
Amaria Lancet Oncol 2018	Dab/Tram	21	58	19.7	18.6
Long Lancet Oncol 2019*	Dab/Tram	35	49	23.0	27.0
Blank Nat Med 2018	Ipi+nivo	10	33	NR	32
Amaria Nat Med 2018	Nivo Ipi+nivo	12 11	25 45	NR NR	20
Huang Nat Med 2019	Pembro	30	19	NR	18
Rozeman Lancet Oncol 2019*	Ipi+nivo	86	57^	NR	8.3

* In press

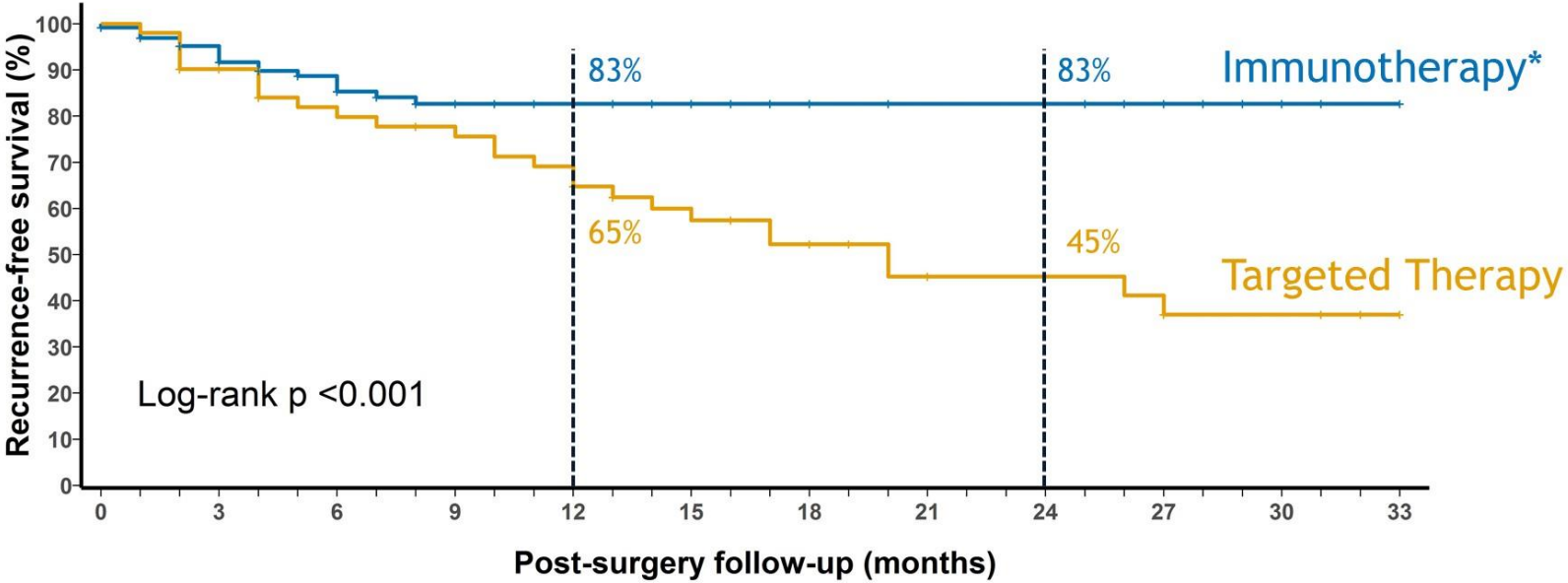
^arm B = I1N3

Results – Patient Characteristics

	Total N=184
Median age (range) (yrs)	57 (18-87)
AJCC v7 clinical stage at baseline	
IIIB	100 (54.3%)
IIIC	84 (45.7%)
Disease sites*	
neck	31 (16.8%)
axilla	78 (42.4%)
groin	63 (34.2%)
multiple basins	12 (6.5%)
Med. time to surgery (weeks, range)	7 (2-217)
Med. F/U post-op (months, 95% CIs)	13 (12–16)

*1 pt epitrochlear node
*2 pts nodes + ITMs

RFS by drug class

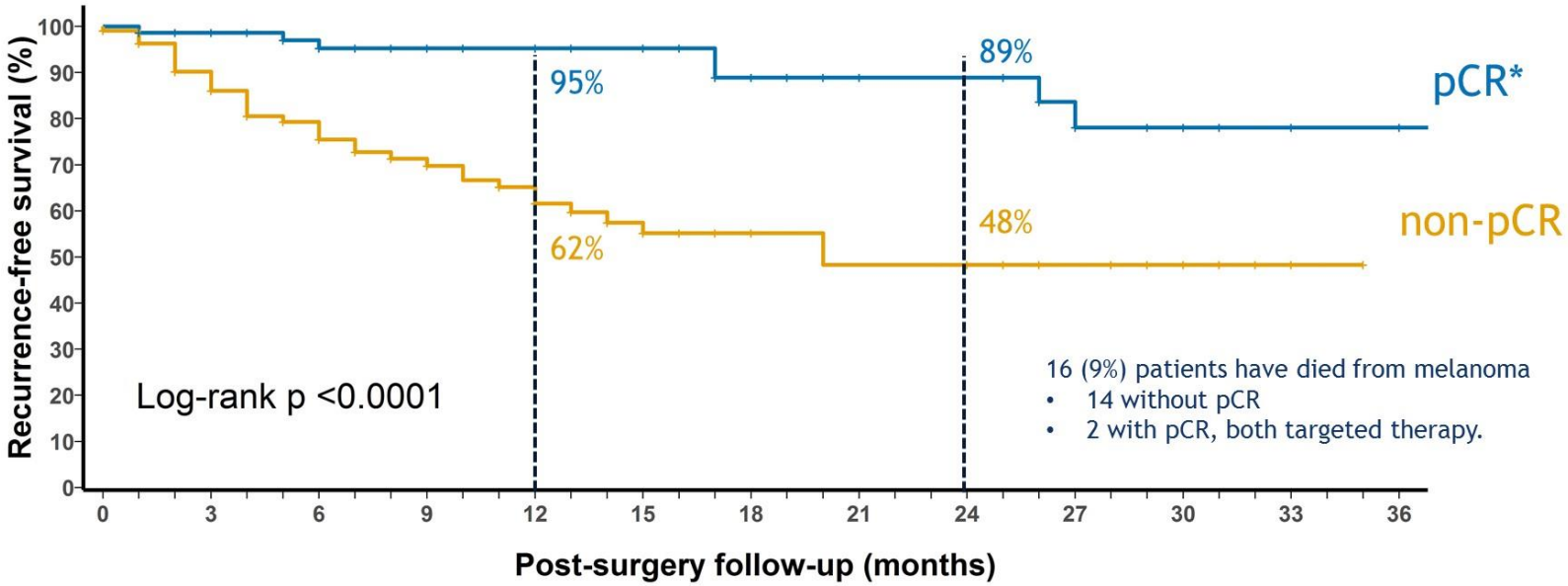


Numbers at risk

Immunotherapy*	133	107	79	56	45	35	24	22	22	13	7	3	Med f/u 10 mo
Targeted Therapy	51	45	39	36	32	24	20	13	11	10	8	6	Med f/u 22 mo

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

RFS by pathological response



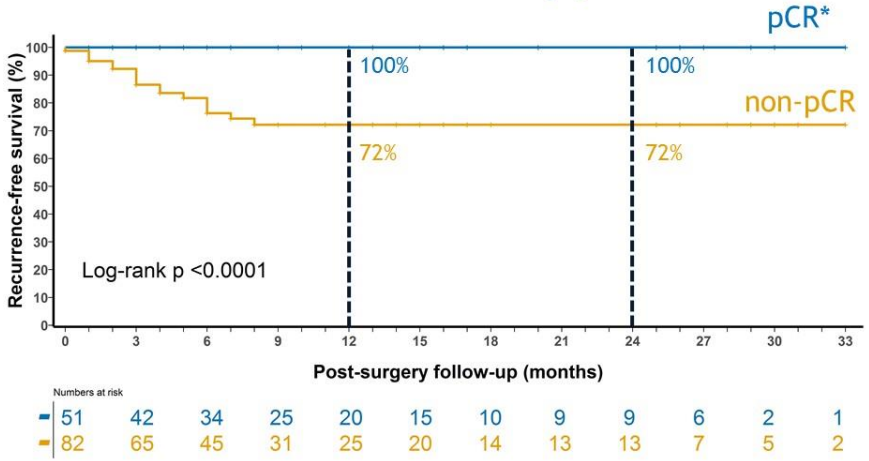
Numbers at risk

pCR*	75	65	56	45	40	34	26	21	19	15	9	7	3
non-pCR	109	87	62	47	37	25	18	14	14	8	6	2	0

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

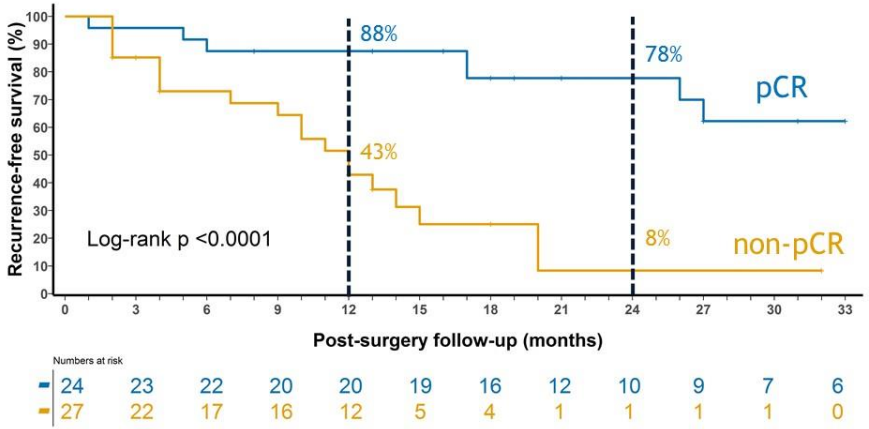
RFS by pathological response and drug

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

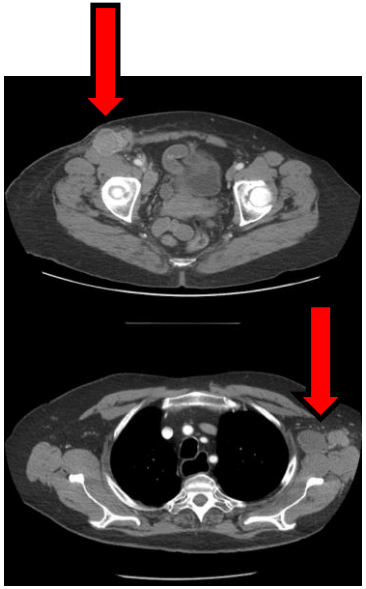
Conclusions

- Neoadjuvant immunotherapy and targeted therapy
  - active regimens in resectable stage III melanoma
  - associated with high pCR rate
- The ability to achieve pCR correlates with improved RFS
  - New benchmark for rapid drug development and regulatory approval
- No patient with pCR from immunotherapy has recurred to date.

Data Compilation of Immunotherapy and Targeted Therapy

Series	Therapy	pCR
Holland (n=10)	Ipi3/Nivo1 X 2	3/9 (33%)
MDACC (n=11)	Ipi3/Nivo1 X 4	5/11 (45%)
Holland/Australia (n=60)	Ipi3/Nivo1 X 2	13/30 (47%)
	Ipi1/Nivo3 X 2	17/30 (57%)
Australia (n=30)	Dabrafenib/Trametinib X 12 weeks	15/30 (50%)
MDACC (n=12)	Dabrafenib/Trametinib X 8 weeks	7/12 (58%)

My treatment algorithm of neoadjuvant therapy for bulky regional disease



Neo Ipi1/Nivo3 X 2 cycles

SURGERY

- pCR → Follow-up only
- Near-pCR → Follow-up only?
- No response
  - BRAF mutated → Adjuvant antiBRAF therapy
  - BRAF wild type → Follow-up only?


Thank you