Improving Patient Selection in Cellular Therapy Studies and Neoadjuvant Trials

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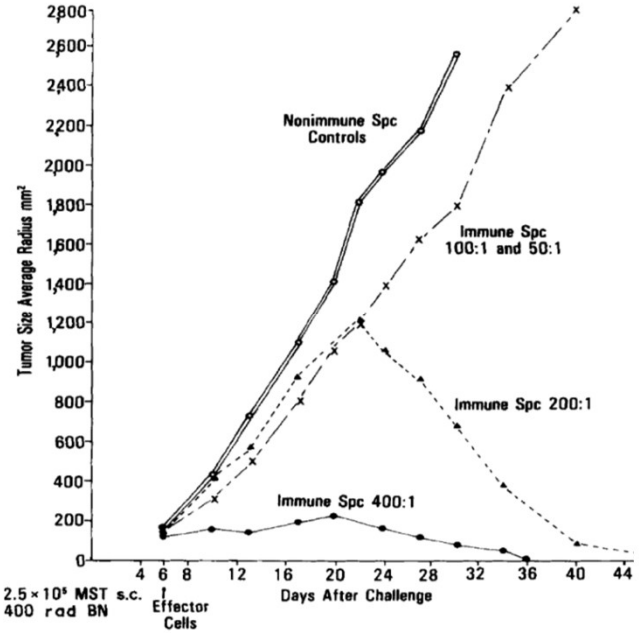
Disclosures

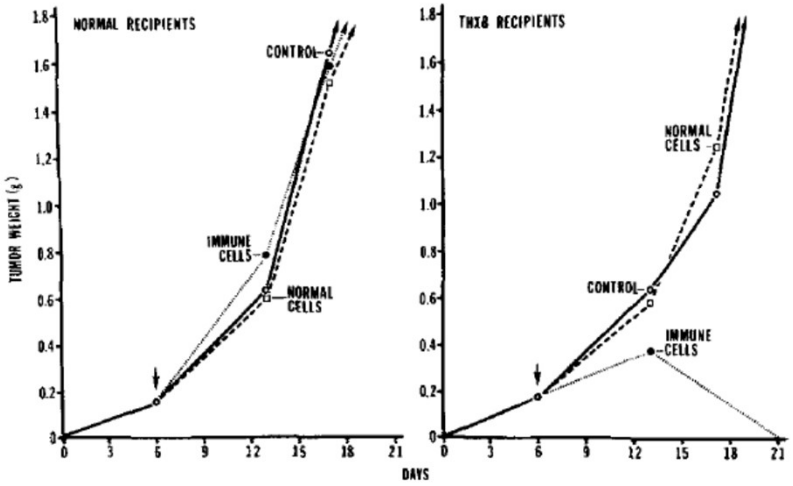
Research funding: Merck, Bristol Myers-Squibb, Genentech, Novartis, Iovance
Advisory board: Iovance, Nektar
Steering committee: Bristol Myers-Squibb, Novartis

Cellular Therapy

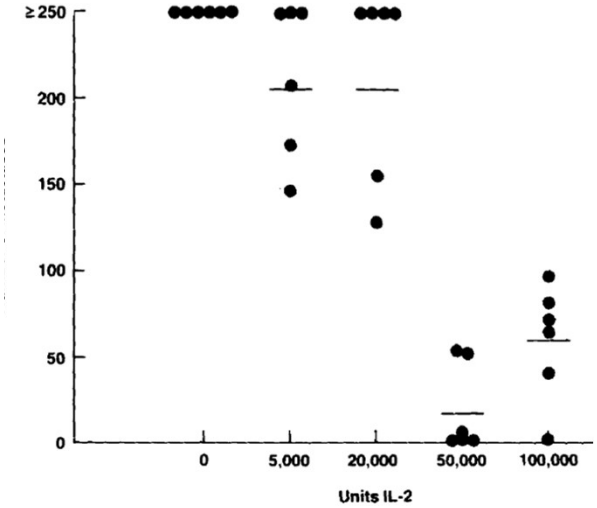
Early Pre-Clinical Studies Demonstrate that T Cells can Mediate Tumor Growth, Importance of Lymphodepletion and IL-2



Infusion of splenocytes can control tumor growth



Splenocyte infusion regresses tumors in immune deficient mice

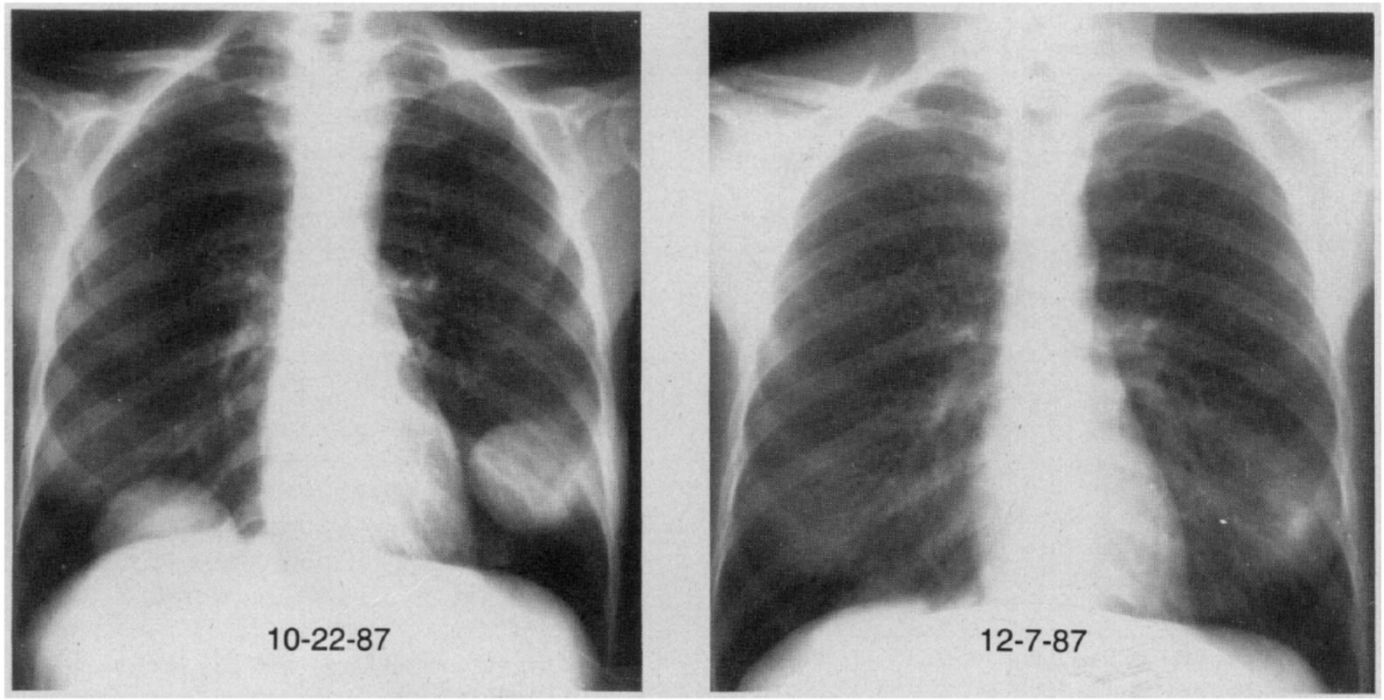


High dose IL-2 can kill murine lung metastases

Fernandez-Cruz et al. JEM 1980 152: 823-41; Berendt and North JEM 1980 151; 69-80; Rosenberg et al. JEM 1985 161: 1169-88

Initial TIL Patient Experience Yields 60% Response Rates

Lymphodepletion → TIL Infusion → High dose IL2



Rosenberg et al. NEJM 1988; 319: 1676-80

Iovance C-144-01 Study Design: Metastatic Melanoma

Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)

Patient Population: **Unresectable or metastatic melanoma treated with at least 1 systemic prior therapy including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF or BRAF/MEK**

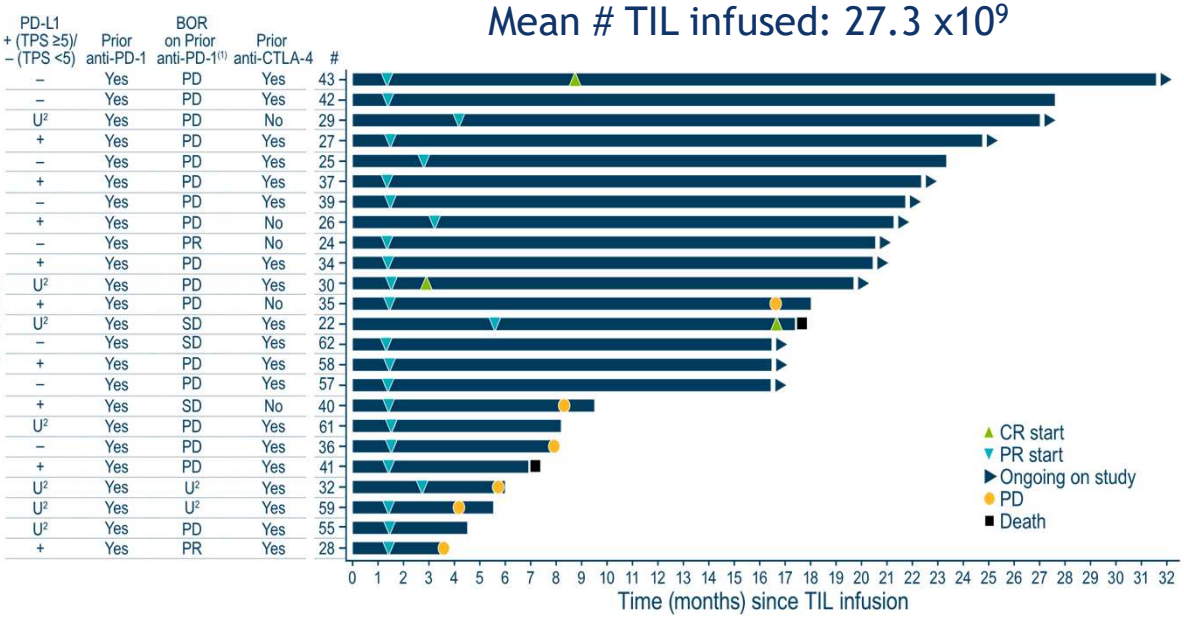
~~Cohort 1:~~ Non-cryopreserved TIL product (Gen 1) N=30
Closed to enrollment

Cohort 2: Cryopreserved TIL product (Gen 2) N=60
Closed to enrollment

~~Cohort 4~~ (Pivotal): Cryopreserved TIL product (Gen 2) N=75
Closed to enrollment

Cohort 3: TIL re-treatment N=10

ORR 36.4%
Median DOR not yet achieved with median 18 mo follow up
Mean # TIL infused: 27.3 x10^9

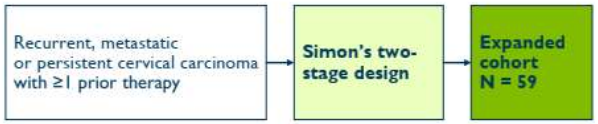


PRESENTED BY: Amod Sarnaik, MD
H. Lee Moffitt Cancer Center, Tampa, FL, USA

Iovance innova TIL-04 Study: Cervical Cancer

innovaTIL-04 Study Design

Phase 2, multicenter study to evaluate the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (LN-145) in patients with recurrent, metastatic or persistent cervical carcinoma (NCT03108495)



Endpoints

- Primary: Objective Response Rate (ORR) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
- Secondary: safety and efficacy

Key updates

- Protocol amended to increase total to 59 patients, and ORR as determined by Blinded Independent Review Committee (BIRC)
- Fast Track and Breakthrough designations received

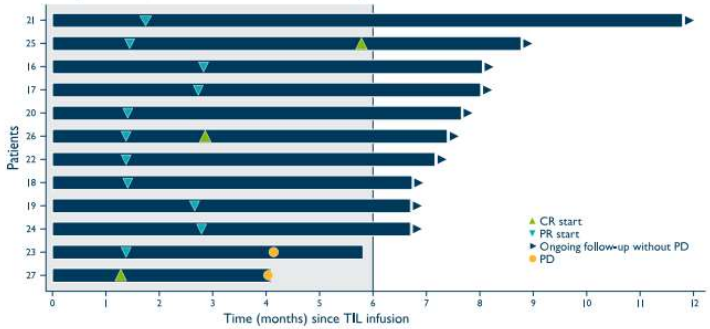
- 78% of patients had a reduction in tumor burden
- Median follow up is 7.4 months
- Mean number of TIL cells infused: 28 x 10^9
- Median number of IL-2 doses administered was 6.0

and represent the total number of patients dosed

Table 3. Efficacy

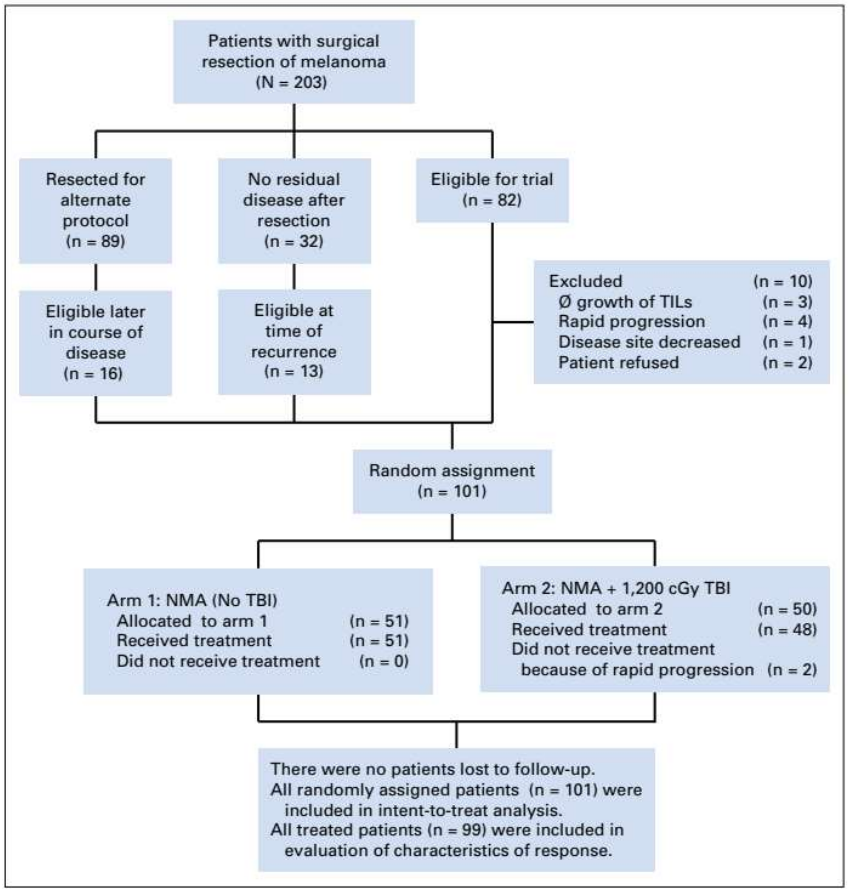
RESPONSE (RECIST v1.1)	PATIENTS, N=27 n (%)
Objective Response Rate (ORR)	**12 (44.4%)**
Complete Response (CR)	3 (11.1%)
Partial Response (PR)	9 (33.3%)
Stable Disease (SD)	11 (40.7%)
Progressive Disease (PD)	4 (14.8%)
Non-Evaluable	0
Disease Control Rate (DCR)	23 (85.2%)
Median Duration of Response (DOR)	**Not Reached**
Min, Max (range)	2.6+ to 9.2+ months

Figure 3. Time to First Response, Duration of Response, Time on Efficacy Assessment



- Mean time to first response 1.9 months
- Mean time to best response 2.4 months

Jazaeri et al. Abstract 2358 ASCO 2019



Goff et al. J Clin Oncol 2016 342389-2397

Patient Characteristics by Response

Table 4. Patient Characteristics by Response

Characteristic	Total, No.	CR, No. (%)	PR, No. (%)	NR*, No.	P†	
					CR *v* PR + NR	CR + PR *v* NR
Patients	101	24	30	47		
Sex						
Female	37	9 (24)	12 (32)	16	1.0	.68
Male	64	15 (23)	18 (28)	31		
Age, years						
Median		52.5	46	46	.024	.37
18-30	11	0 (0)	4 (36)	7	.12‡	.60‡
31-45	34	8 (24)	10 (29)	16		
46-60	51	15 (29)	16 (31)	20		
61-65	5	1 (20)	0 (0)	4		
HLA						
A2	43	15 (35)	8 (19)	20	.03	1.0
Non-A2	58	9 (16)	22 (38)	27		
Stage						
M1a	9	2 (22)	5 (56)	2	.37	.03
M1b	16	6 (38)	6 (38)	4		
M1c	76	16 (21)	19 (25)	41		
Prior systemic treatments					1.00	1.00
None	26	5 (19)	7 (27)	14		
1 systemic therapy	41	12 (29)	14 (34)	15		
≥ 2 systemic therapies	34	7 (21)	9 (26)	18		
Immunotherapy						
High-dose IL-2	29	8 (28)	9 (31)	12	.61	.66
Anti–CTLA-4 only	31	9 (29)	10 (32)	12	.45	.39
Anti–PD-1 only	3	1 (33)	1 (33)	1	.56	.14
Anti–CTLA-4 and anti–PD-1	8	1§ (13)	1 (13)	6§	.68	.54
Adjuvant (IFN-α, vaccine, etc)	38	9 (24)	13 (34)	16	1.0	1.0
Chemotherapy						
Dacarbazine or temozolomide	11	1 (9)	4 (36)	6	.45	.75
Small-molecule inhibitor	9	0 (0)	2 (22)	7	.11	.078
Other (including biochemotherapy)	10	3 (30)	0 (0)	7	.70	.18
Select baseline values, median (25th to 75th percentile						
LDH, U/L		157 (145-212)	179 (154-230)	211 (158-322)	.04	.02
NLR		1.99 (1.23-3.18)	2.69 (1.66-3.96)	3.12 (2.24-5.23)	.004	.002
Platelets, K/μL		227 (197-316)	229 (171-282)	237 (201-326)	.75	.34

Higher LDH = poorer efficacy

Higher NLR = poorer efficacy

Goff et al. J Clin Oncol 2016 342389-2397

Treatment Characteristics by Response

Characteristic	Total, No.	CR, No. (%)	PR, No. (%)	NR, No.	P*	
					CR *v* PR + NR	CR + PR *v* NR
Patients treated	99	24	30	45		
Source of TIL						
Subcutaneous deposit	31	7 (23)	13 (42)	11	.47	.31
Lymph node	33	6 (18)	9 (27)	18		
Viscera	35	11 (31)	8 (23)	16		
Fresh TIL	15	4 (26)	3 (20)	8	.75	.58
Cryopreserved TIL	84	20 (24)	27 (32)	37		
Treatment characteristic						
$CD3^+$ cells						
$< 5 \times 10^{10}$	21	3 (14)	5 (24)	13	.16	.005
$5.1\text{-}7.0 \times 10^{10}$	26	6 (23)	6 (23)	14		
$7.1\text{-}9.0 \times 10^{10}$	18	4 (22)	6 (33)	8		
$9.1\text{-}11.0 \times 10^{10}$	16	5 (31)	4 (25)	7		
$> 11 \times 10^{10}$	18	6 (33)	9 (50)	3		
Cell phenotype, median (25th to 75th percentile $\times 10^{-9}$)						
$CD3^+$		87.7 (61.1-117)	83.3 (54.8-114)	65.7 (46.4-86.3)	.10	.0059
$CD8^+$		79.7 (49.5-96.5)	61.2 (31.5-106)	39.4 (25.7-58)	.014	.0007
$CD4^+$		8.9 (4.8-17.4)	11.1 (4.3-22.8)	12.0 (7.5-25.8)	.19	.13
T-cell subsets, median (25th to 75th percentile), %						
T_N		0.02 (0.007-0.08)	0.02 (0.005-0.13)	0.07 (0.02-0.20)	.26	.013
T_{CM}		0.37 (0.22-0.51)	0.33 (0.20-0.40)	0.36 (0.22-0.58)	.82	.31
T_{EM}		96.3 (93.6-98.7)	97.1 (90.9-98.6)	91.7 (80.7-97.2)	.21	.002
T_{EMRA}		3.3 (1.0-6.0)	2.6 (1.0-8.9)	8.2 (2.5-18.9)	.20	.002
IL-2 doses						
0-2	11	0 (0)	3 (27)	8	.46	.53
3-5	39	12 (31)	13 (33)	14		
6-8	41	10 (24)	11 (27)	20		
> 8	8	2 (25)	3 (38)	3		
Median (25th to 75th percentile)		5.5 (5-7)	5 (4-6.3)	6 (3.5-7)	.34	.55
Laboratory characteristics†						
IL-7, median (25th to 75th percentile), pg/mL		37 (31.9-49.5)	32.5 (27.8-45.8)	39.8 (34.8-51.5)	.98	.07
IL-15, median (25th to 75th percentile), pg/mL		33 (29.4-42)	35.5 (31-51.3)	38.8 (32.9-52.1)	.07	.08
Peak absolute lymphocyte count, cells/μL						
0-500	45	7 (16)	15 (33)	23	.013	.25
501-2,000	34	9 (26)	12 (35)	13		
2,001-5,000	11	4 (36)	0	7		
5,001-10,000	6	1 (17)	3 (50)	2		
>10,000	3	3 (100)	0	0		
Median (25th to 75th percentile), $\times 10^{-3}$/μL		0.9 (0.4-3.5)	0.5 (0.2-1.2)	0.5 (0.2-1.3)	.033	.40

Higher cell count = better efficacy

More CD8 = better efficacy

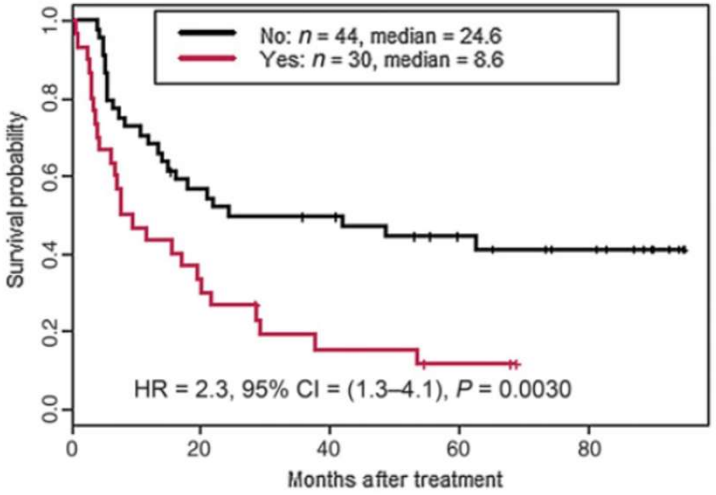
Goff et al. J Clin Oncol 2016 342389-2397.

A

Number of patients	Prior anti-CTLA4	Prior anti-PD1	CR	PR	CR + PR (%)
43	No	No	5	15	20 (47%)
21[1]	Yes	No	3	5	8 (38%)
9[1]	Yes	Yes	0	3	3 (33%)
1	No	Yes	0	0	0

[1] Of the 30 patients treated after anti-CTLA4 therapy, 21 had TIL harvest after anti-CTLA4 and 9 had TIL harvest before anti-CTLA4

B OS post-TIL ACT according to anti-CTLA4 status prior to TIL

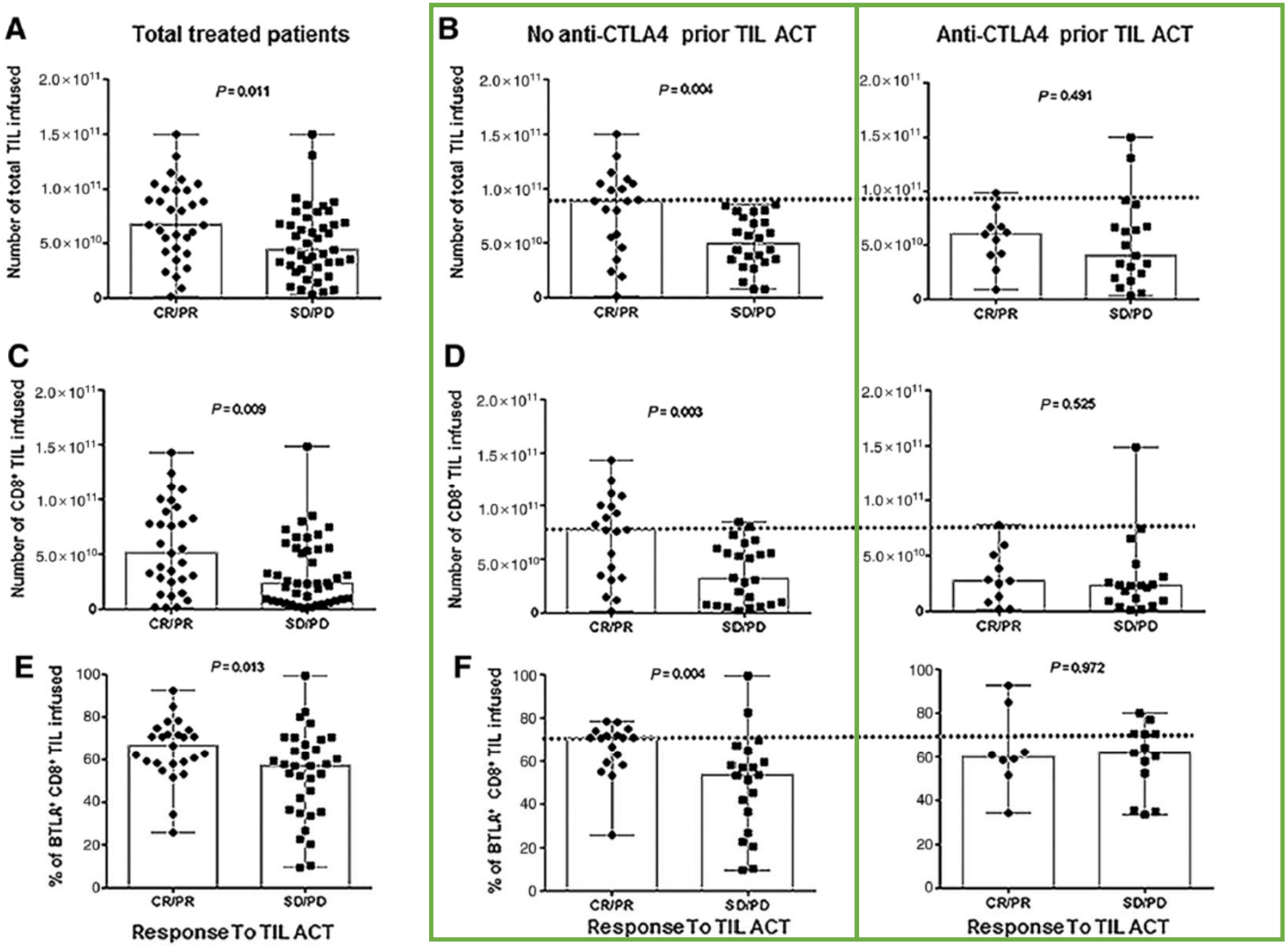


Cox proportional Hazards regression analysis ($n=73$)

Variable	Contrast	HR (95% CI)	P
Prior a-CTLA4	Yes vs. No	1.8 (0.9–3.7)	0.094
LDH	Elev. vs. Not	3.5 (1.7–7.4)	0.0004
# PST*	> 4 vs. 0-4	2.4 (1.1–5.2)	0.047
Brain Met	Yes vs. No	1.0 (0.5–2.1)	0.87
Sex	Male vs. Female	0.9 (0.5–1.8)	0.97
Stage	M1c vs. <M1c	1.0 (0.4–2.4)	0.90
Age	>65 vs. <=65	0.8 (0.4–1.5)	0.60
ECOG	>0 vs. 0	1.0 (0.5–2.0)	0.92

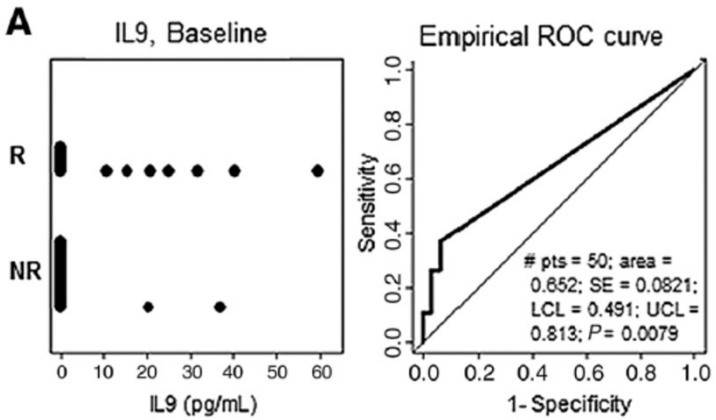
*PST = prior systemic therapies

Forget et al. Clin Cancer Res 2018; 24: 4416-28



Forget et al. Clin Cancer Res 2018; 24: 4416-28

Baseline IL9 Levels May Predict Response



Recursive partitioning analysis identified that the level of IL9 at baseline is predictive of response:

IL9 < 5.3 pg/mL : 12/42 = 29% responders
IL9 > 5.3 pg/mL : 7/9 = 78% responders
(*P* = 0.0090, Fisher exact test)

Forget et al. Clin Cancer Res 2018; 24: 4416-28

Discussion on Patient Selection Criteria for Cellular Therapy in Melanoma

- TIL therapy has evolved over the past 30 years and is potentially on the brink of FDA approval in melanoma, with potential to expand to other solid tumors
- Higher cell counts, higher % CD8 T cells in infusion product seem to correlate best with response to TIL
  - Uncertain if these factors still matter
- Studies to identify factors predictive of response are ongoing

Neoadjuvant Therapy

Pertuzumab for Operable HER2+ Breast Cancer FDA Approved in September 2013

Endpoint/population	Arm A TD	Arm B PTD	Arm C PT	Arm D PD
Comparison		B vs. A	C vs. A	B vs. D
Overall ITT	*N* = 107	*N* = 107	*N* = 107	*N* = 96
pCR (ypT0/is; %)	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)
95% CI	20.6%–38.5%	36.1%–55.7%	10.3%–25.3%	15.8%–33.7%
Difference of response (%; 95% CI)		16.80% (4.1%–29.6%)	−12.20% (−23.3% to −1%)	21.80% (9.0%–34.6%)
Adjusted CMH *P* value		0.0141	0.0198	0.003
pCR (ypT0/is ypN0; %)	23 (21.5%)	42 (39.3%)	12 (11.2%)	17 (17.7%)
95% CI	14.1%–30.5%	30.0%–49.2%	5.9%–18.8%	10.7%–26.8%
Difference of response (%; 95% CI)		17.80% (5.7%–29.9%)	−10.30% (−20.1 to −0.47%)	21.50% (9.6%–33.5%)
Hormone receptor–positive subgroup	*N* = 50	*N* = 50	*N* = 51	*N* = 46
pCR (ypT0/is ypN0; %)	6 (12.0%)	11 (22.0%)	1 (2.0%)	4 (8.7%)
95% CI	4.5%–24.3%	11.5%–36.0%	0.1%–10.5%	2.4%–20.8%
Hormone receptor–negative subgroup	*N* = 57	*N* = 57	*N* = 55	*N* = 50
pCR (ypT0/is ypN0; %)	17 (29.8%)	31 (54.4%)	11 (20.0%)	13 (26.0%)
95% CI	18.4%–43.4%	40.7%–67.6%	10.4%–33.0%	14.6%–40.3%

Gianni L, et al. *Lancet Oncol*. 2012; 13: 25-32; Amiri-Kordestani L, et al. Clin Cancer Res 2014; 20: 5359-5364.

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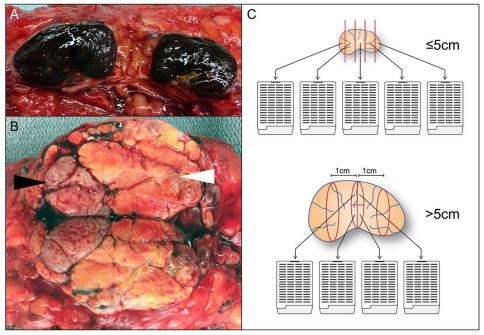
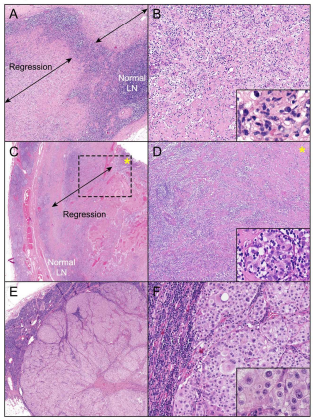
International Neoadjuvant Melanoma Consortium

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†]





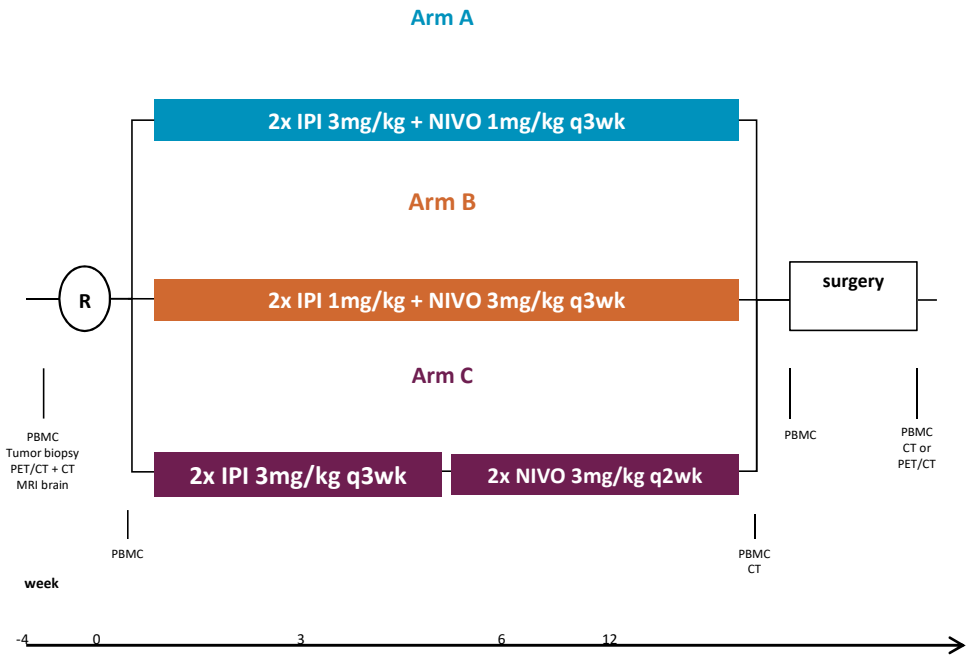
Ann Oncol. 2018;29(8):1861-8.

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

Rodabe N Amaria*, Alexander M Menzies*, Elizabeth M Burton*, Richard A Scolyer*, Michael T Tetzlaff*, Robert Antdbacka, Charlotte Ariyan, Roland Bassett, Brett Carter, Adil Daud, Mark Faries, Leslie A Fecher, Keith T Flaherty, Jeffrey E Gershenwald, Omid Hamid, Angela Hong, John M Kirkwood, Serigne Lo, Kim Margolin, Jane Messina, Michael A Postow, Helen Rizos, Merrick I Ross, Elisa A Rozeman, Robyn P M Saw, Vernon Sondak, Ryan J Sullivan, Janis M Taube, John F Thompson, Bart A van de Wiel, Alexander M Eggermont, Michael A Davies, The International Neoadjuvant Melanoma Consortium members†, Paolo A Ascierto‡, Andrew J Spillane‡, Alexander C J van Akkooi‡, Jennifer A Wargo‡, Christian U Blank‡, Hussein A Tawbi‡, Georgina V Long‡

Lancet Oncol. 2019;20(7):e378-e389.

OpACIN-NEO

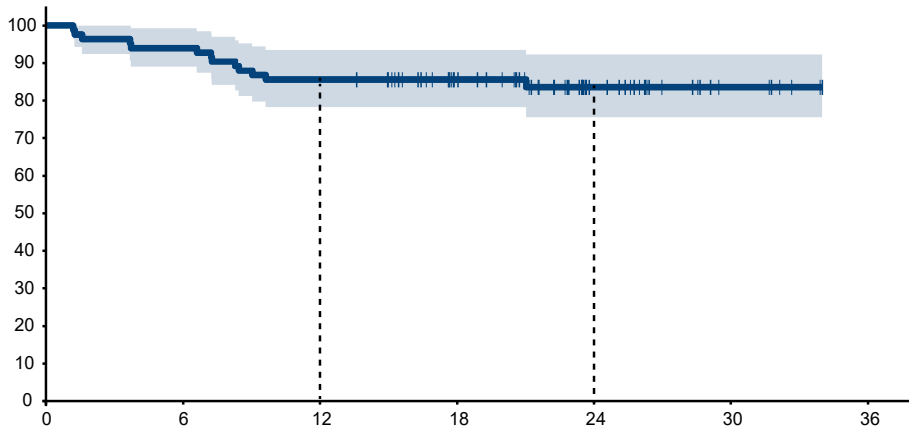


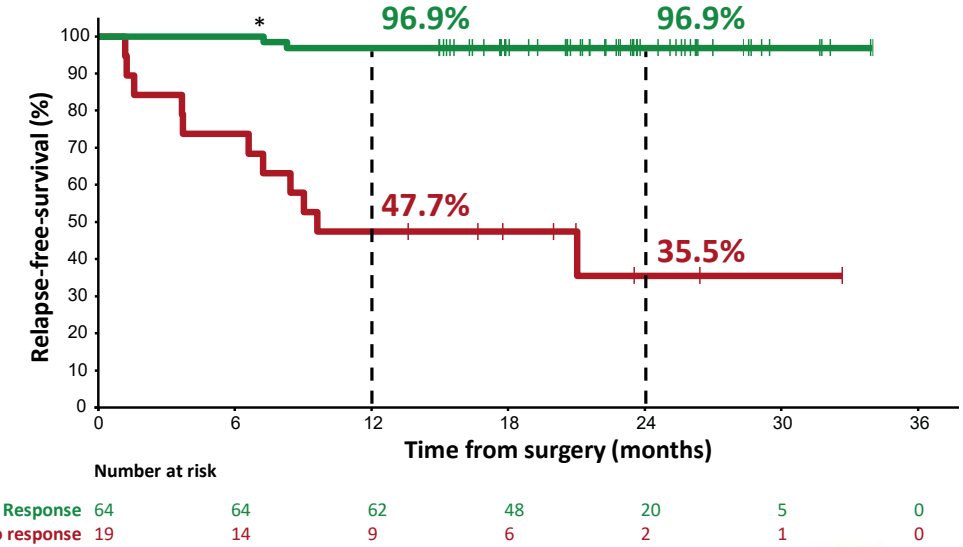
Arm	Grade 3-4 AEs	Pathologic response
A	40%	80%
B	20%	77%
C	50%	65%

Rozeman et al. Lancet Oncol 2019; 20: 948-60

Promising RFS after 2 years follow-up and pathologic response predicts outcome

- **OpACIN-neo:** After a median follow-up of 24.6 months, only 1/64 (2%) patients with pathologic response has relapsed

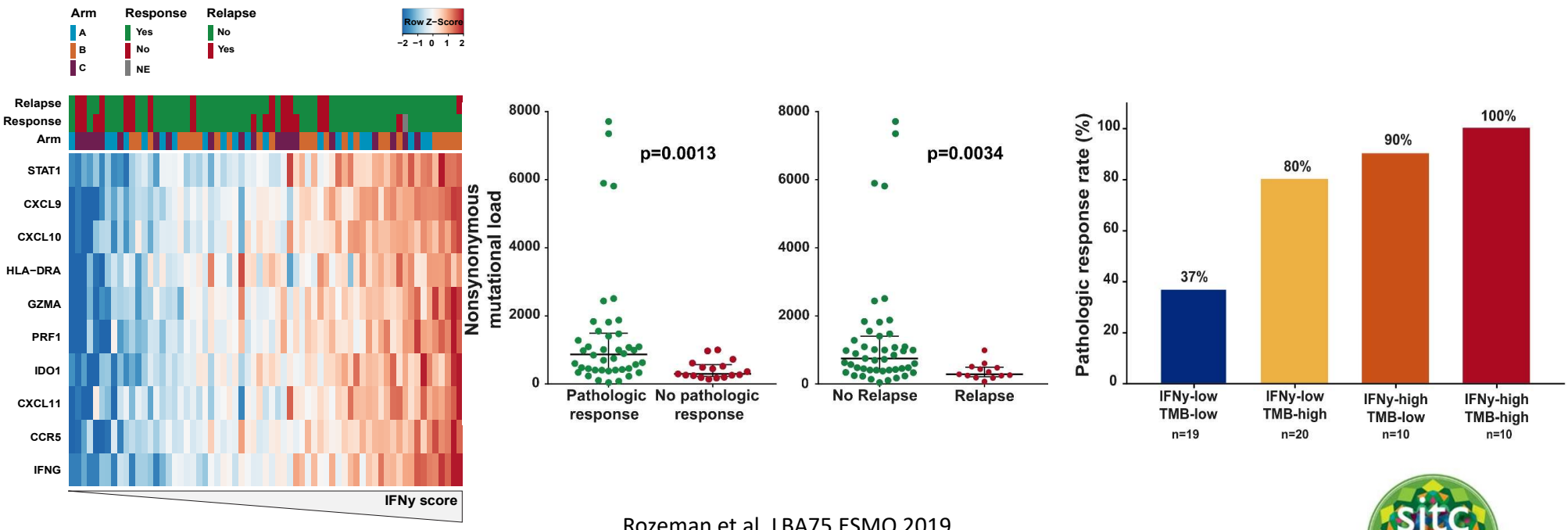




Rozeman et al., abstract 10015, ASCO 2020

(near-)pCR = (near) pathologic complete response, pPR = pathologic partial response, pNR = pathologic non-response

IFN- Signature and Mutational Load are Associated with Response Outcomes



Rozeman et al. LBA75 ESMO 2019

Open access Short report

Journal for ImmunoTherapy of Cancer

Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer

Joshua E Reuss ,[1,2] Valsamo Anagnostou,[1,2] Tricia R Cottrell,[1] Kellie N Smith,[2] Franco Verde,[3] Marianna Zahurak,[1] Mara Lanis,[1] Joseph C Murray,[1,2] Hok Yee Chan,[2] Caroline McCarthy,[4] Daphne Wang,[1,5] James R White,[1] Stephen Yang,[1,6] Richard Battafarano,[1,6] Stephen Broderick,[1,6] Errol Bush,[1,6] Malcolm Brock,[1,6] Jinny Ha,[1,6] David Jones,[7,8] Taha Merghoub,[9,10] Janis Taube,[1,5] Victor E Velculescu,[1,2] Gary Rosner,[1] Peter Illei,[1,5] Drew M Pardoll,[1,2] Suzanne Topalian,[1,2] Jarushka Naidoo ,[1,2] Ben Levy,[1,2] Matthew Hellmann,[4,10] Julie R Brahmer,[1,2] Jamie E Chaft,[4,10] Patrick M Forde[1,2]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

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

Corrected: Author Correction; Publisher Correction

Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

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

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Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma

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Discussion on Patient Selection Criteria for Neoadjuvant Immunotherapy

- Neoadjuvant immunotherapy is still in its infancy
- Best practices for the following should be defined in each disease entity in order to maximize the learning from each trial:
  - Clinical trial design (patient selection, duration of therapy)
  - Collection of biospecimens (which type of specimens at which time-points)
  - Pathologic response assessment (clear and broadly reproducible definition of pCR vs non-pCR)


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