Oncorete: Sharing and Innovation System

Firenze, 25 Febbraio 2019

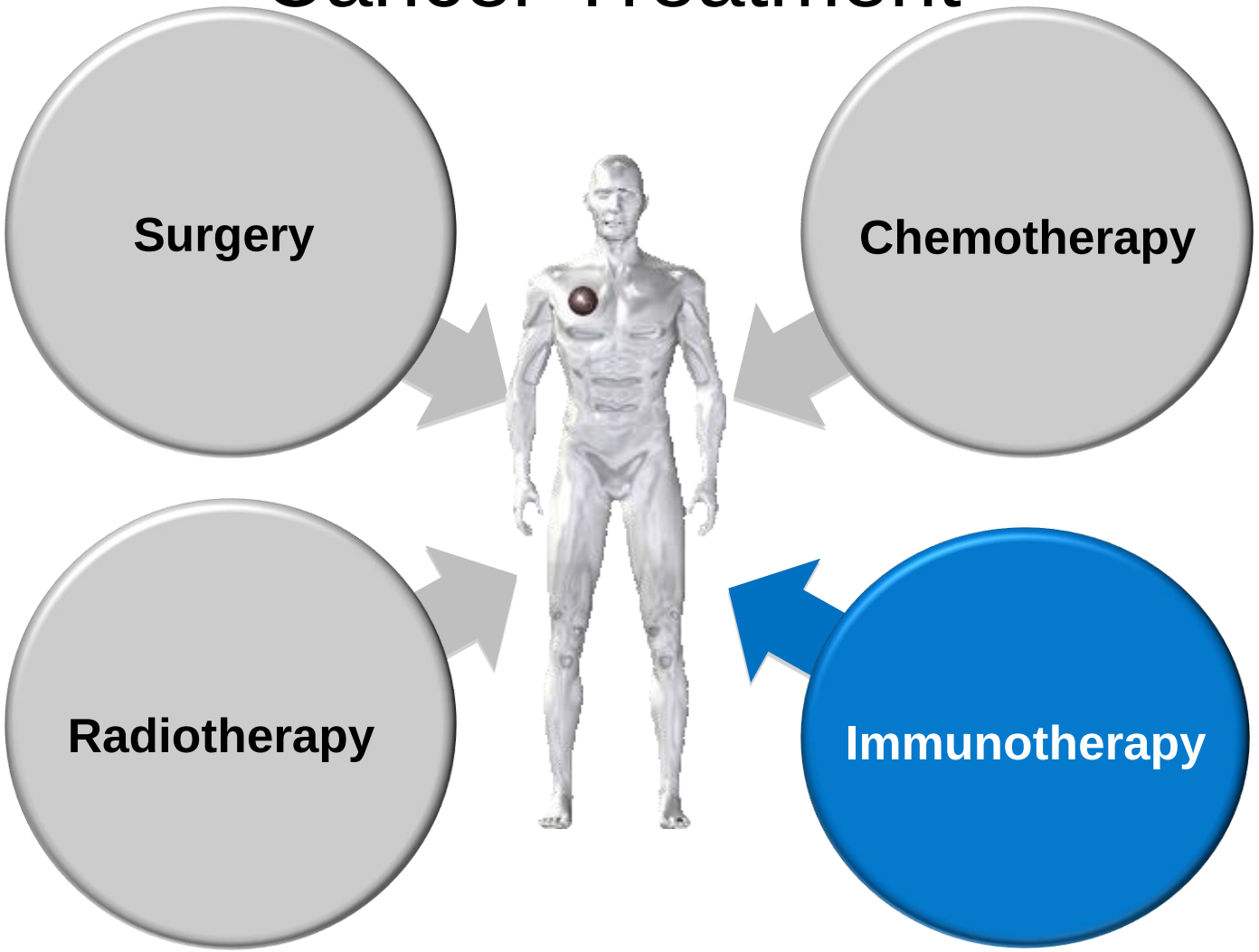
Immunoterapia Oncologica: attese del paziente e opportunità di cura

Anna Maria Di Giacomo

Center for Immuno-Oncology

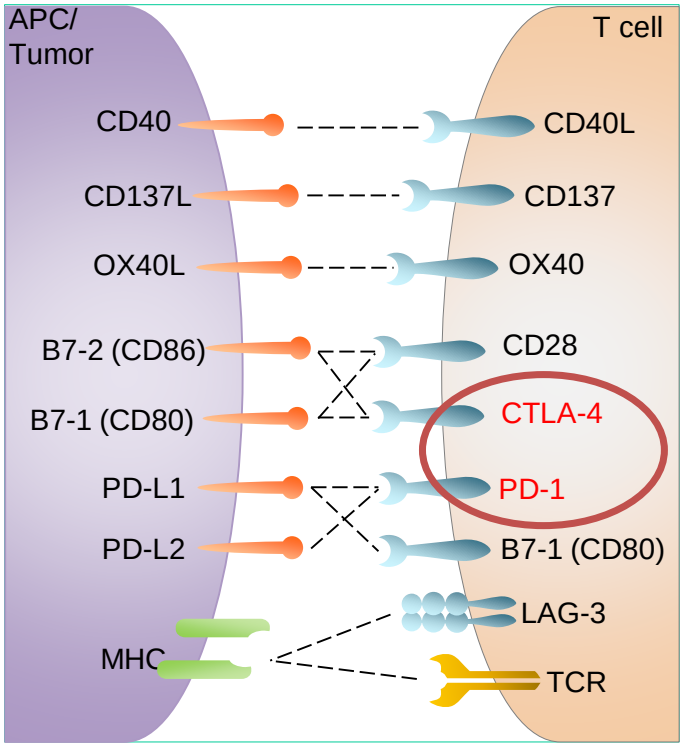
SIENA, ITALY

Evolving Therapeutic Options for Cancer Treatment



Pioneering cancer immunotherapy researchers awarded Nobel Prize in medicine 2018

T-cell Checkpoint and Co-stimulatory Pathways



Adapted from Pardoll DM 2012.

Activation
Activation
Activation
Activation

These pathways can be activated via I-O agents to counteract tumor-mediated inhibition

Inhibition
Inhibition
Inhibition
Inhibition

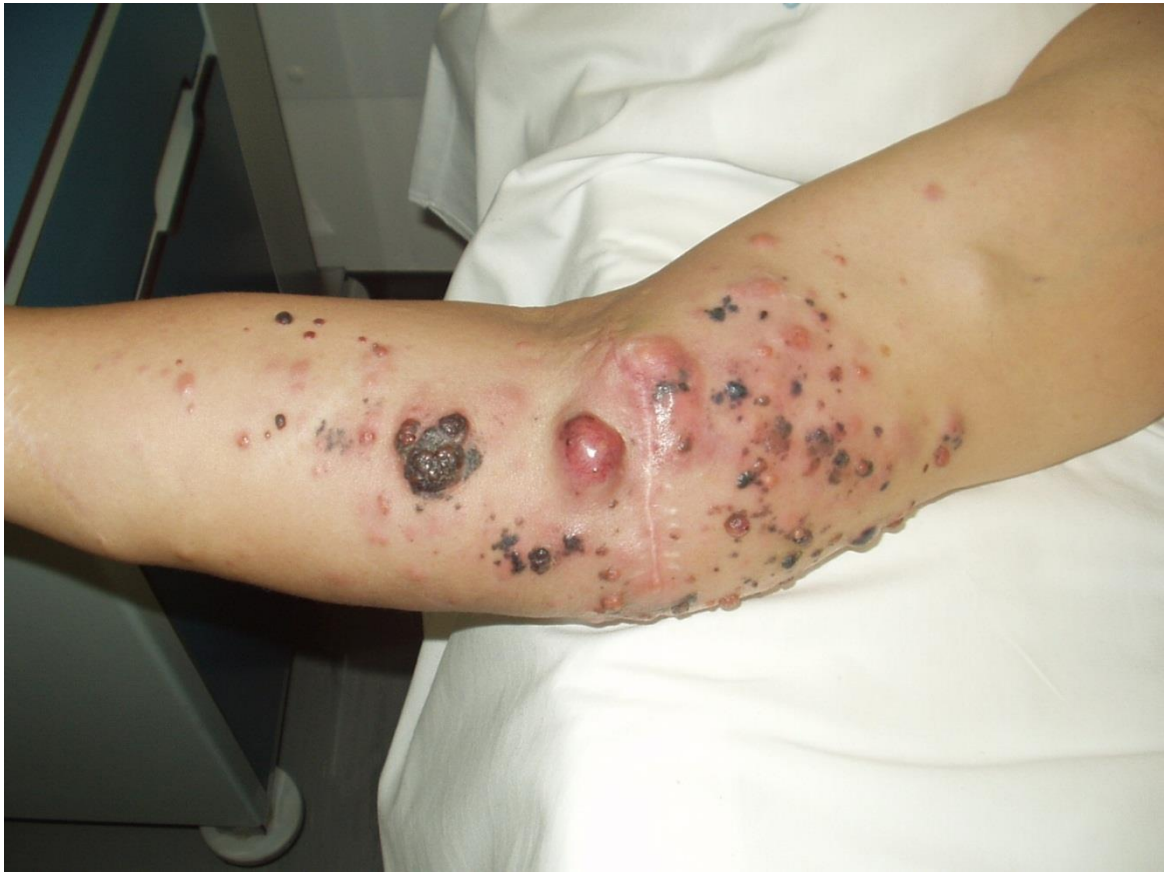
These pathways can be blocked via I-O agents to counteract tumor-mediated inhibition

APC=antigen-presenting cell; CTLA-4=cytotoxic T-lymphocyte antigen-4; LAG-3=lymphocyte activation gene-3; MHC=major histocompatibility complex;
PD-1=programmed death-1; PD-L1=PD ligand-1; PD-L2=PD ligand-2; TCR=T-cell receptor.

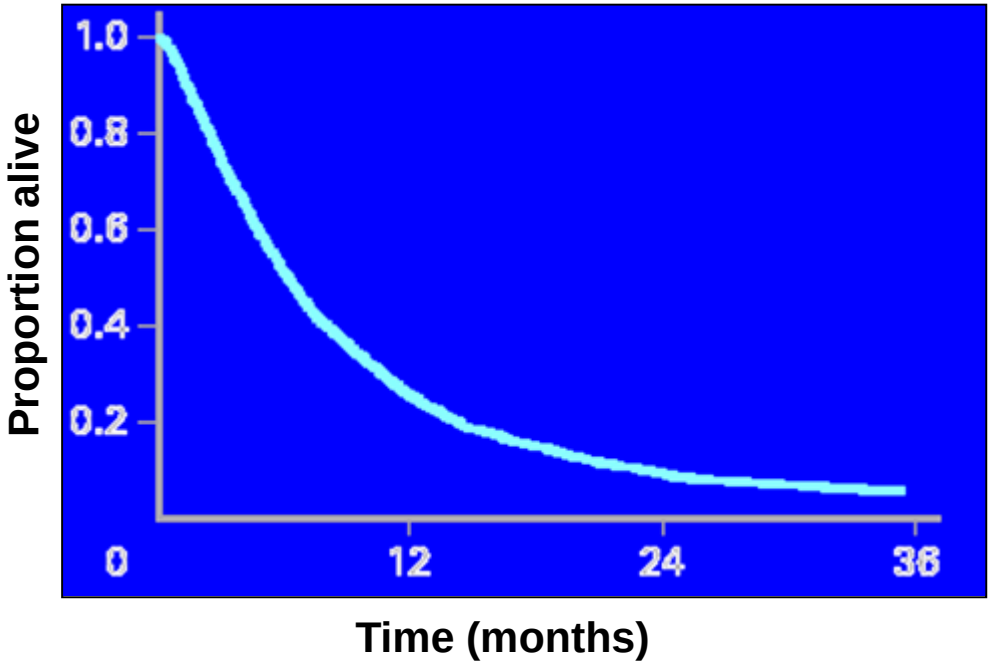
Pardoll DM. Nat Rev Cancer. 2012;12:252-264.

Melanoma as a tool for cancer research

- ✓ Tissue samples readily accessible
- ✓ Adaptable to tissue culture
- ✓ Amenable to testing of novel therapies



Overall Survival for Metastatic Melanoma



Adapted from Korn 2008

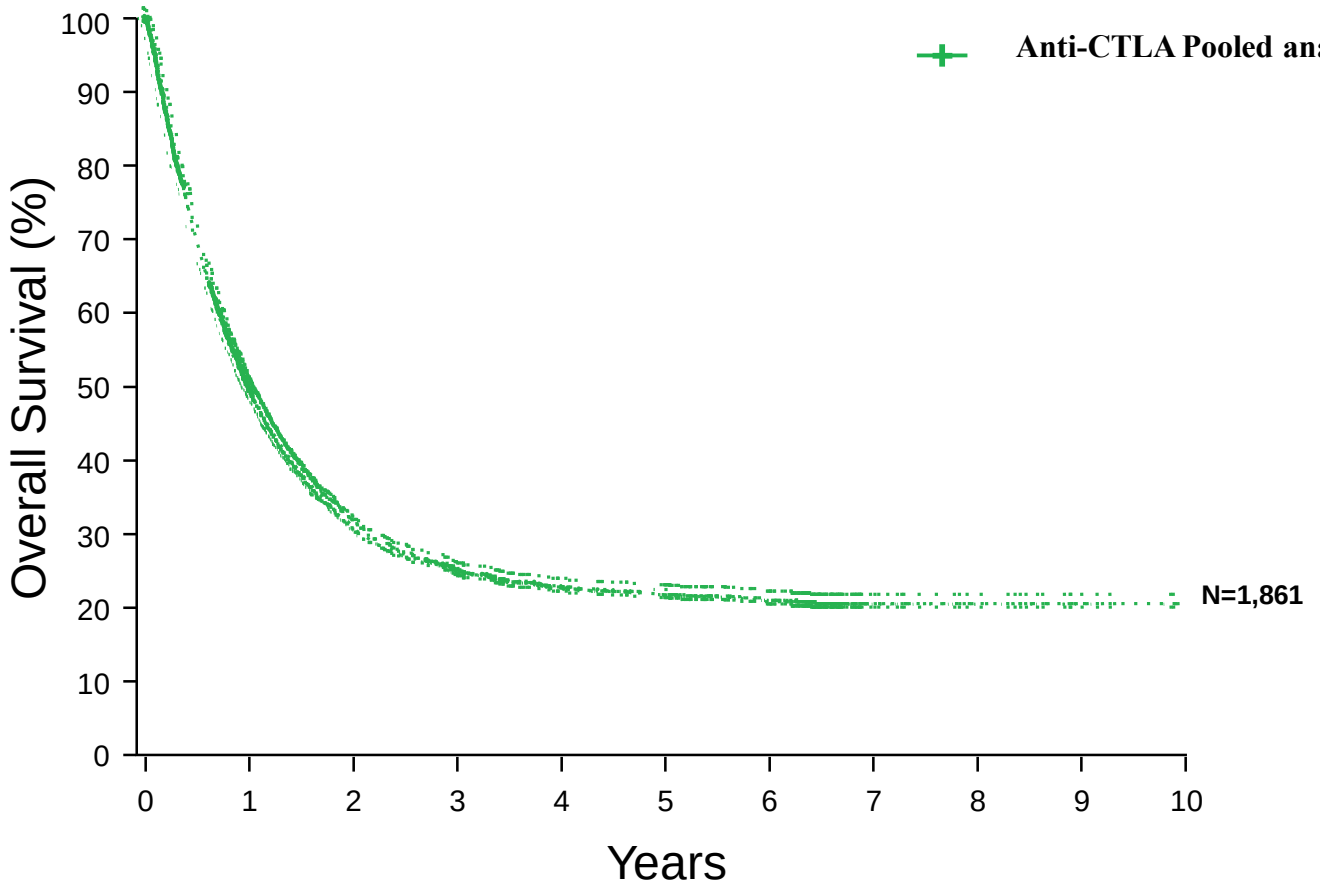
Survival data from 42 Phase II trials with over 2,100 stage IV patients[1]:

12 month OS: 25.5 %, median OS: 6.2 months
(stage IV melanoma including patients with brain metastases)

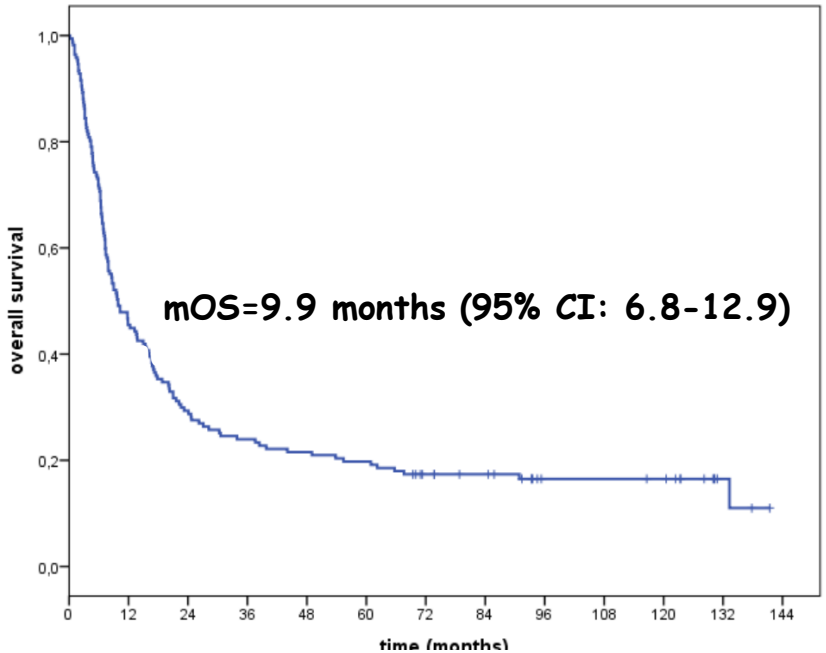
Due to the lack of efficacious therapy, the preferred treatment for metastatic melanoma remains the inclusion in a clinical trial[2]

[1]Korn EL et al. J Clin Oncol 2008;26(4):527-34.
[2]Dummer R, Hauschild A, Jost L. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:ii86-8.

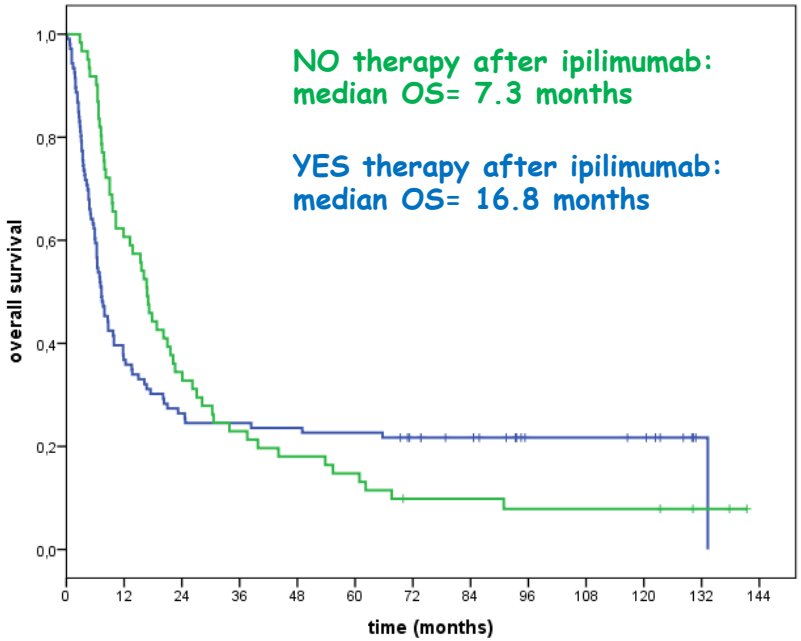
Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



LONG-TERM BENEFITS OF IPILIMUMAB IN ADVANCED MELANOMA:THE CENTER FOR IMMUNO-ONCOLOGY OF SIENA EXPERIENCE



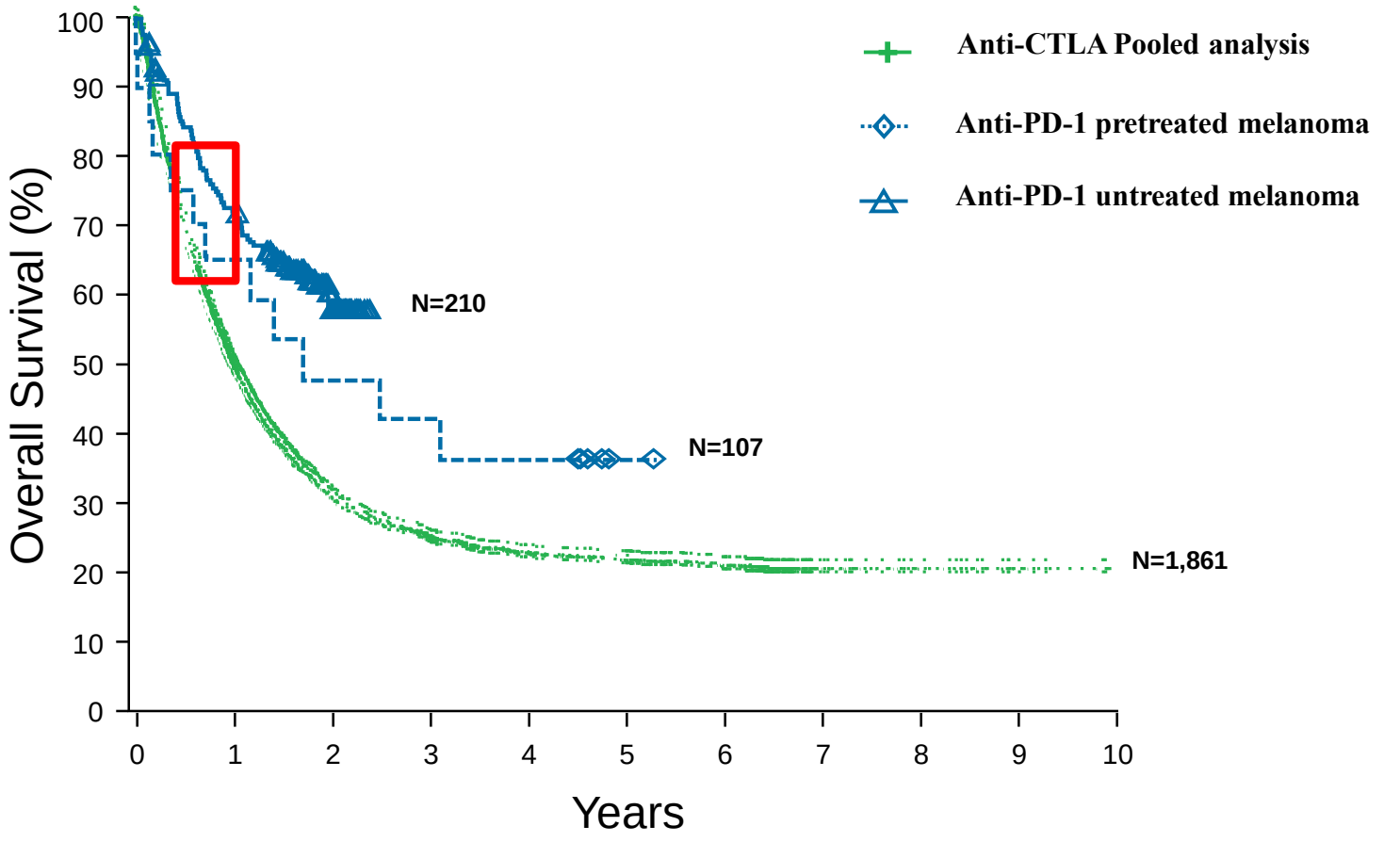
Kaplan–Meier analysis of OS among 167 patients receiving ipilimumab



Kaplan–Meier analysis of OS after subsequent systemic therapies for all patients

Di Giacomo AM et al., Unpublished

Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

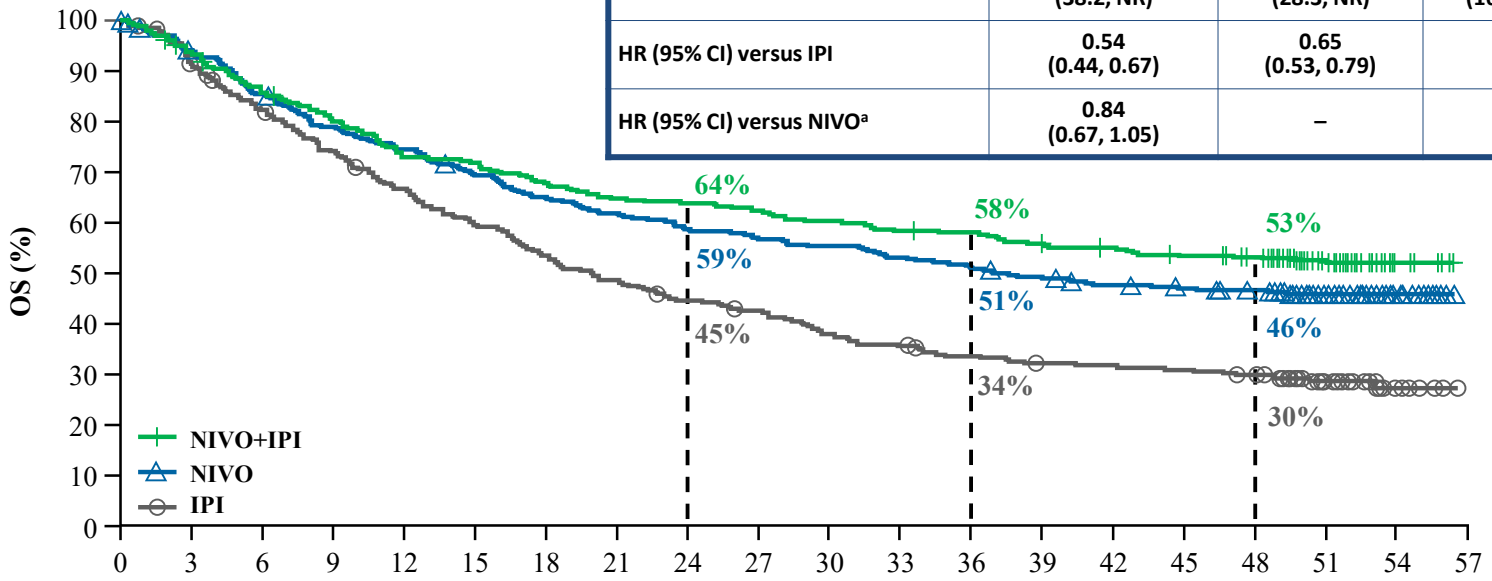
Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.-J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, M. Smylie, R. Dummer, A. Hill, D. Hogg, J. Haanen, M.S. Carlino, O. Bechter, M. Maio, I. Marquez-Rodas, M. Guidoboni, G. McArthur, C. Lebbé, P.A. Ascierto, G.V. Long, J. Cebon, J. Sosman, M.A. Postow, M.K. Callahan, D. Walker, L. Rollin, R. Bhore, F.S. Hodi, and J. Larkin

CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4 ; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.

Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2, NR)	36.9 (28.3, NR)	19.9 (16.9, 24.6)
HR (95% CI) versus IPI	0.54 (0.44, 0.67)	0.65 (0.53, 0.79)	–
HR (95% CI) versus NIVO[a]	0.84 (0.67, 1.05)	–	–

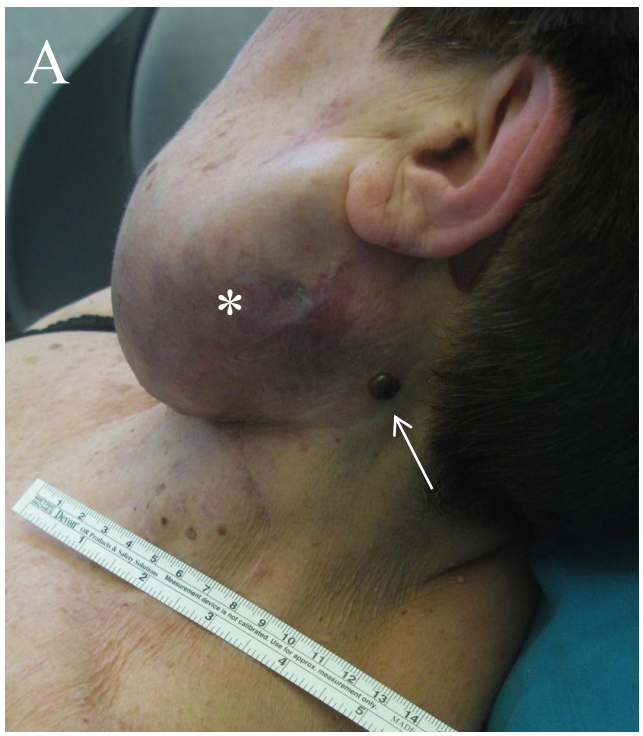


Patients at risk:

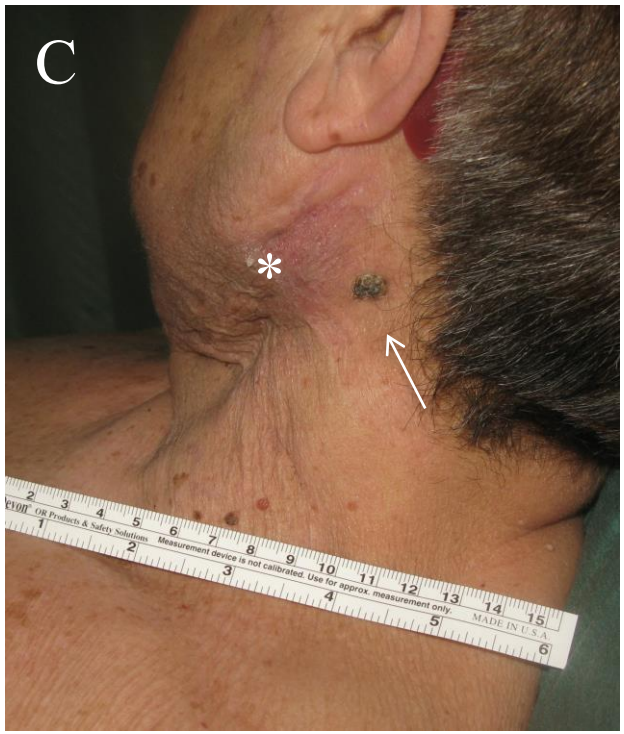
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	186	180	178	171	166	160	154	96	13	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	144	140	135	85	18	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	99	94	93	90	86	50	11	0

[a]Descriptive analysis

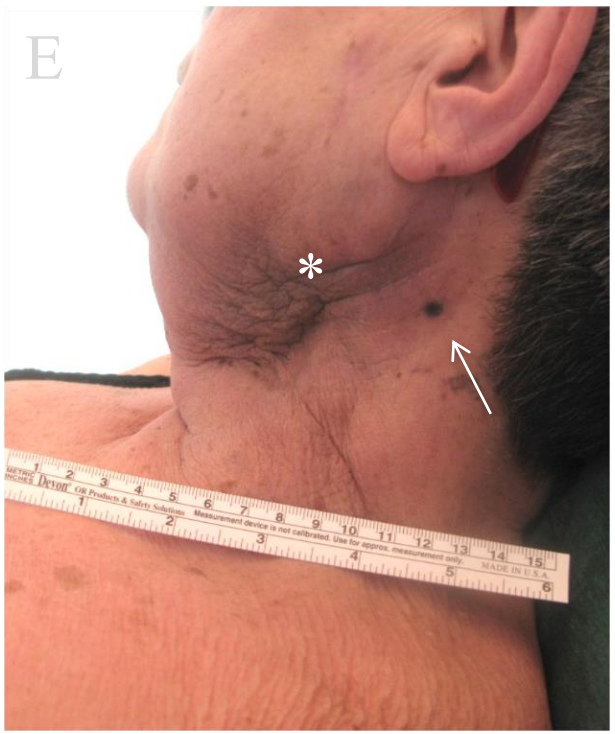
Hodi FS et al. Lancet Oncol 2018



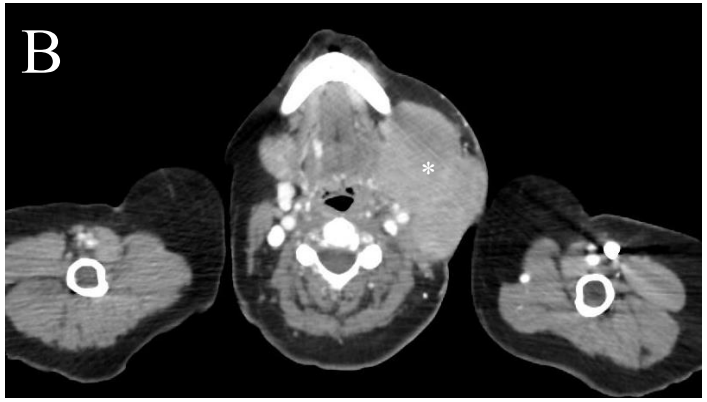
Baseline



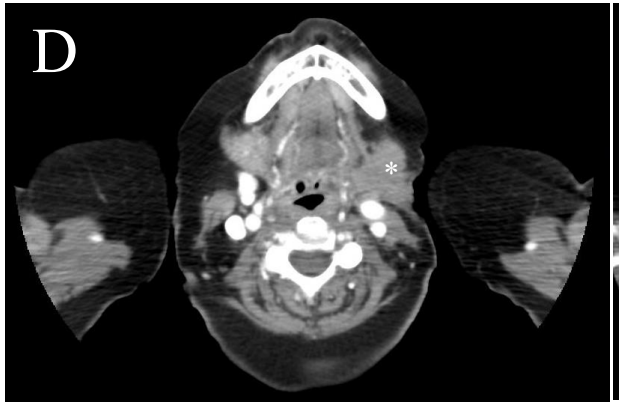
3 weeks after the first dose



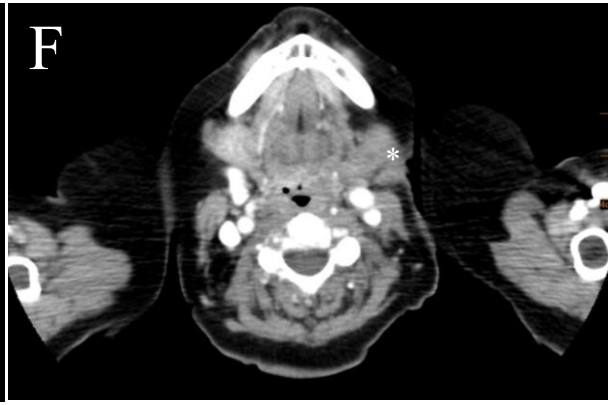
20 weeks after the first dose



Baseline

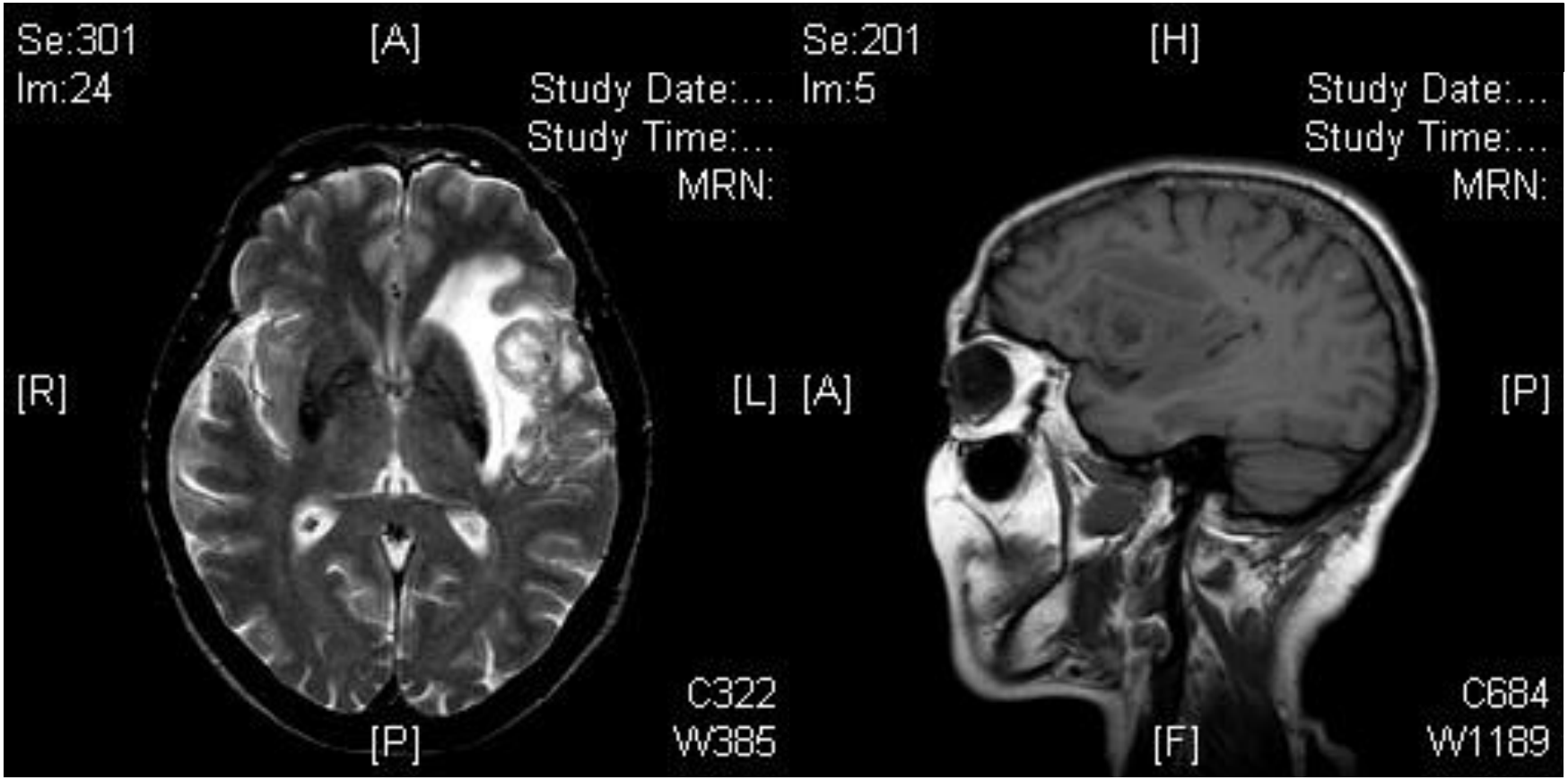


9 weeks after the first dose



20 weeks after the first dose

Immunotherapy in melanoma brain metastases



Immunotherapy in melanoma brain metastases

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
Global disease control	9 (18%, 8–31)	13 (25%, 14–40)	1 (5%, 0·1–24)	2 (10%, 1–30)
CNS disease control	12 (24%, 13–38)	13 (25%, 14–40)	2 (10%, 1–30)	2 (10%, 1–30)
Non-CNS disease control	14 (27%, 16–42)	17 (33%, 21–48)	1 (5%, 0·1–24)	2 (10%, 1–30)
Global objective response	5 (10%, 3–21)	5 (10%, 3–21)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
CNS objective response	8 (16%, 7–29)	8 (16%, 7–29)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
Non-CNS objective response	7 (14%, 6–26)	7 (14%, 6–26)	1 (5%, 0·1–24)	1 (5%, 0·1–24)

Data are n (%, 95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

***Table 3*: Disease control and objective response after 12 weeks**

Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial

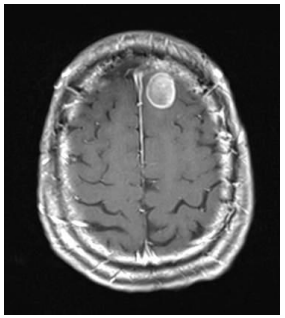
Anna Maria Di Giacomo, Paolo A Ascierto, Lorenzo Pilla, Mario Santinami, Pier Francesco Ferrucci, Diana Giannarelli, Antonella Marasco, Licia Rivoltini, Ester Simeone, Stefania V L Nicoletti, Ester Fonsatti, Diego Annesi, Paola Queirolo, Alessandro Testori, Ruggero Ridolfi, Giorgio Parmiani, Michele Maio

	Study population (n=86)	Patients with brain lesions (n=20)
Immune-related disease control	40 (46·5% [35·7–57·6])	10 (50·0% [27·2–72·8])
Immune-related complete response	6 (6·9% [2·6–14·6])	2 (10·0% [1·2–31·7])
Immune-related partial response	19 (22·1% [13·8–32·3])	6 (30·0% [11·9–54·3])
Immune-related stable disease	15 (17·4% [10·1–27·1])	2 (10·0% [1·2–31·7])
Immune-related progressive disease	46* (53·4% [42·4–64·3])	10 (50·0% [27·2–72·8])
Immune-related major durable disease control†	17 (19·7% [11·9–29·7])	6 (30·0% [11·9–54·3])

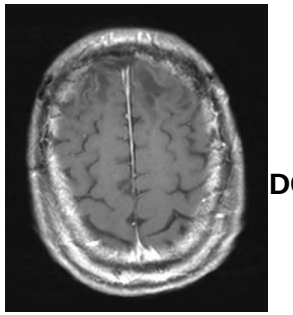
Data are n (% [95% CI]). *Because of early progression, follow-up scans were not available for 15 (17%) patients who were defined as having progressive disease as per protocol. †Immune-related disease control lasting at least 24 weeks.

***Table 2*: Primary and secondary endpoints**

Subject 6-202, PR in brain and PR in total tumor burden



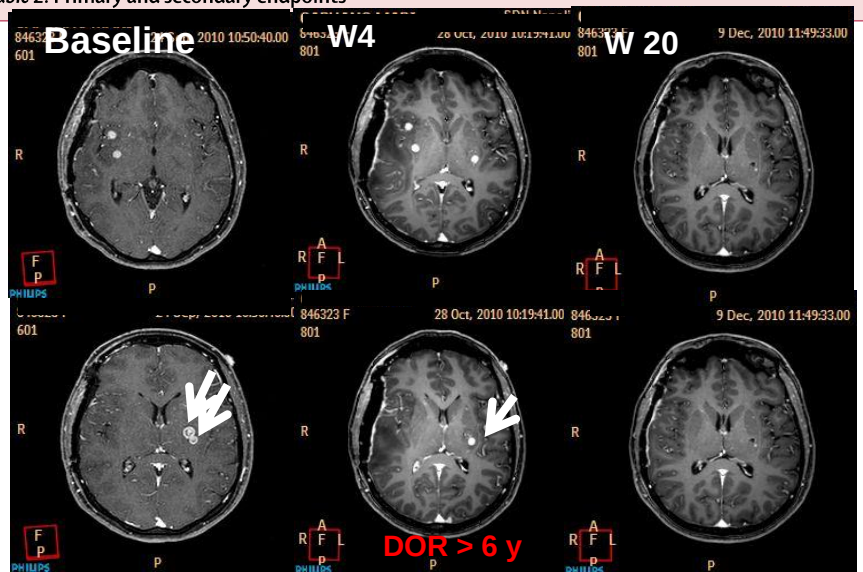
Baseline



Week 16

DOR 11+ mo

Courtesy of Kim Margolin



Immunotherapy in melanoma brain metastases

original articles

Annals of Oncology

Annals of Oncology 26: 798–803, 2015
doi:10.1093/annonc/mdu577
Published online 23 December 2014

Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II study

A. M. Di Giacomo[1], P. A. Ascierto[2], P. Queirolo[3], L. Pilla[4,†], R. Ridolfi[5], M. Santinami[6], A. Testori[7], E. Simeone[2], M. Guidoboni[5], A. Maurichi[6], L. Orgiano[3], G. Spadola[7], M. Del Vecchio[8], R. Danielli[1], L. Calabrò[1], D. Annesi[1], D. Giannarelli[9], C. Maccalli[1,10], E. Fonsatti[1], G. Parmiani[4,†‡] & M. Maio[1*]

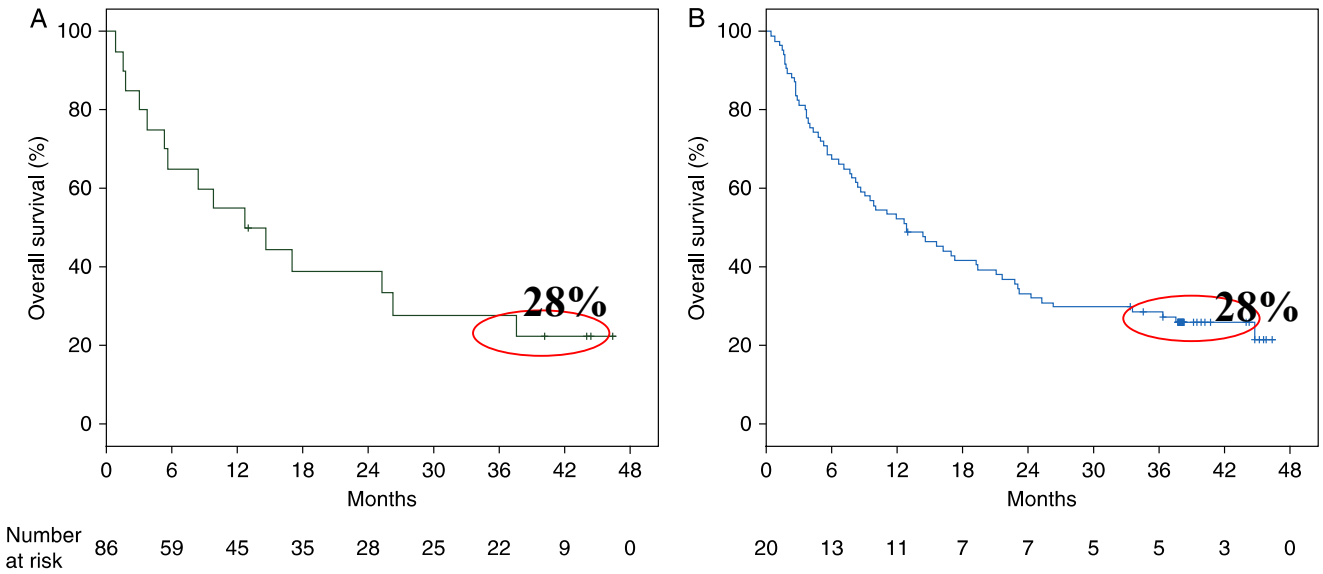
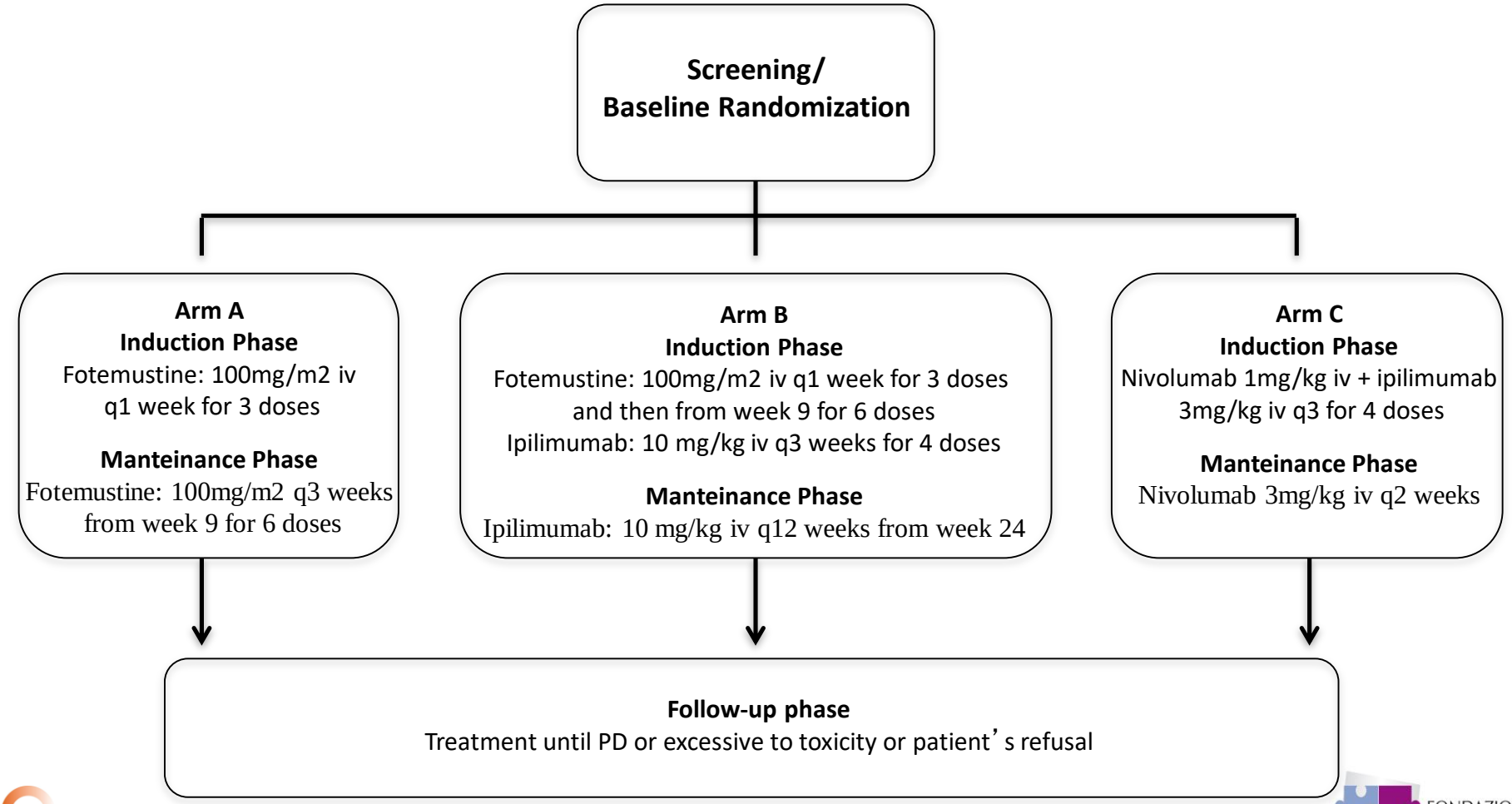


Figure 1. Kaplan–Meier plot of overall survival for all patients (A) and for patients with brain metastases (B). Vertical lines indicate censoring.

5/20 complete regressions of BM. Duration of brain CR was: 16, 28, 39,80+,94+ months

Immunotherapy in melanoma brain metastases

The NIBIT-M2 study design



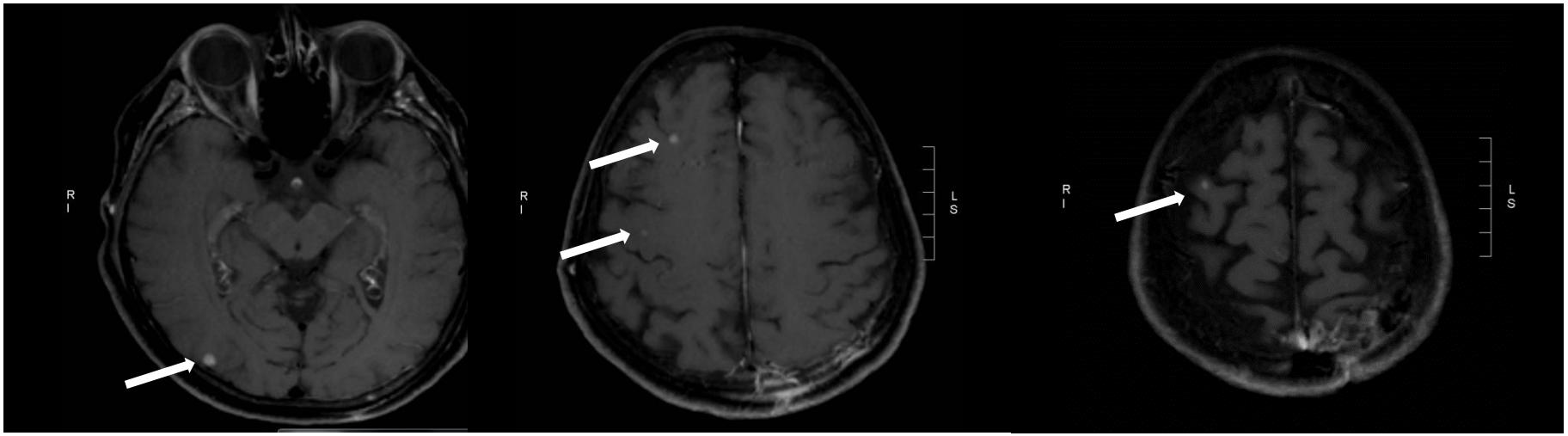
Center for Immuno Oncology

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

Immunotherapy in melanoma brain metastases

CLINICAL CASE - Stage IV cutaneous melanoma

Baseline



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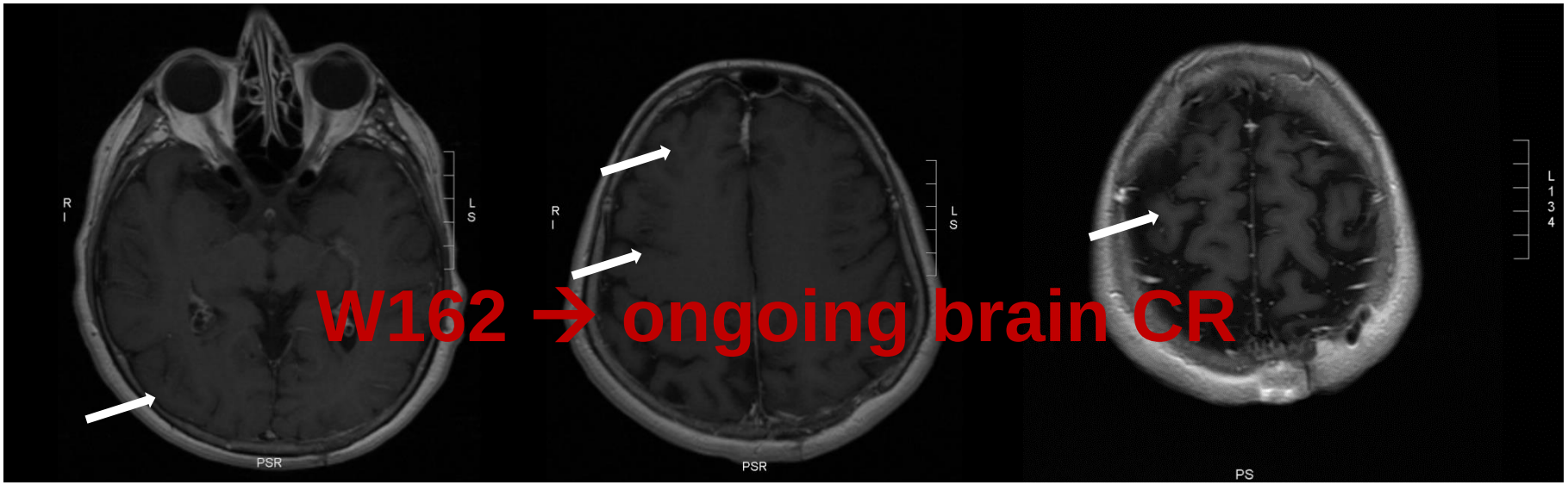


Di Giacomo and Maio, unpublished

IO Combination in melanoma brain metastases

The NEW ENGLAND JOURNAL of MEDICINE

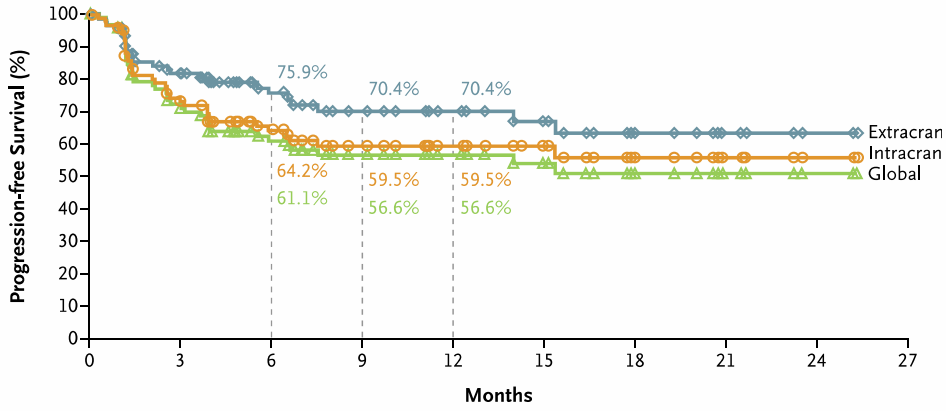
ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

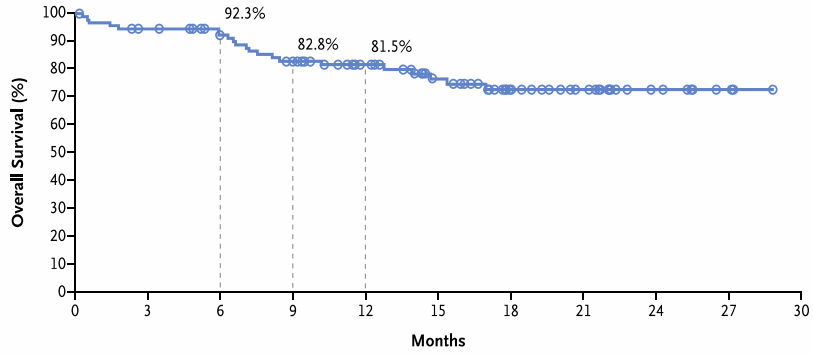
Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.

Table 2. Response to Treatment.

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

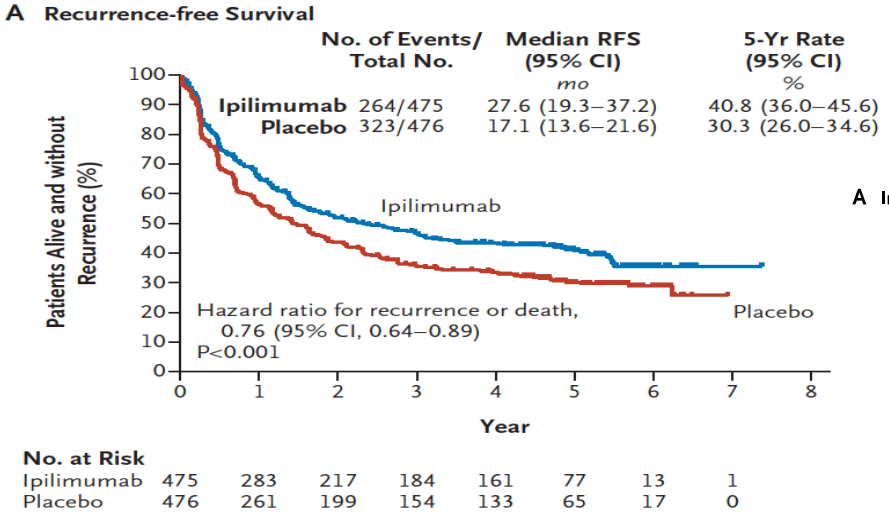


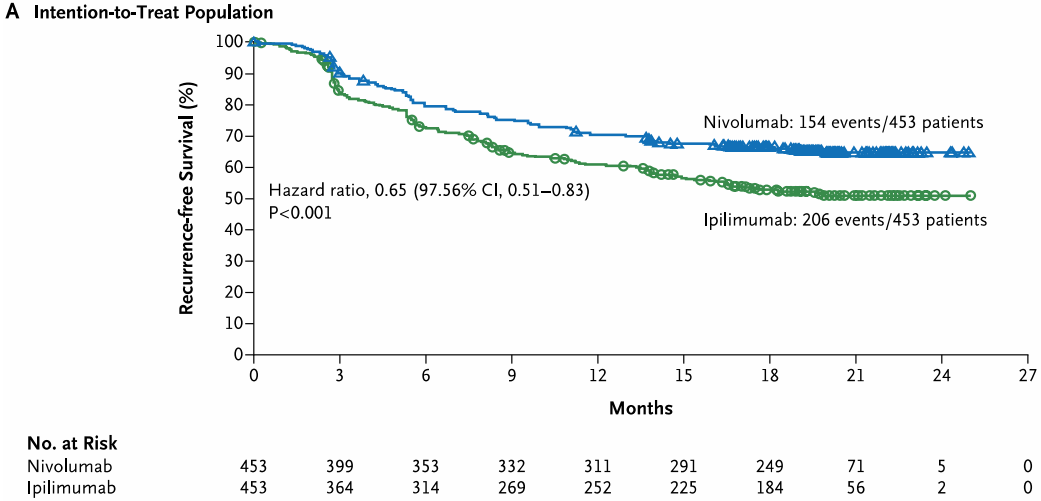
No. at Risk										
Extracranial	94	66	45	32	25	19	11	6	2	0
Intracranial	94	61	45	32	25	19	11	6	2	0
Global	94	60	44	32	25	19	11	6	2	0

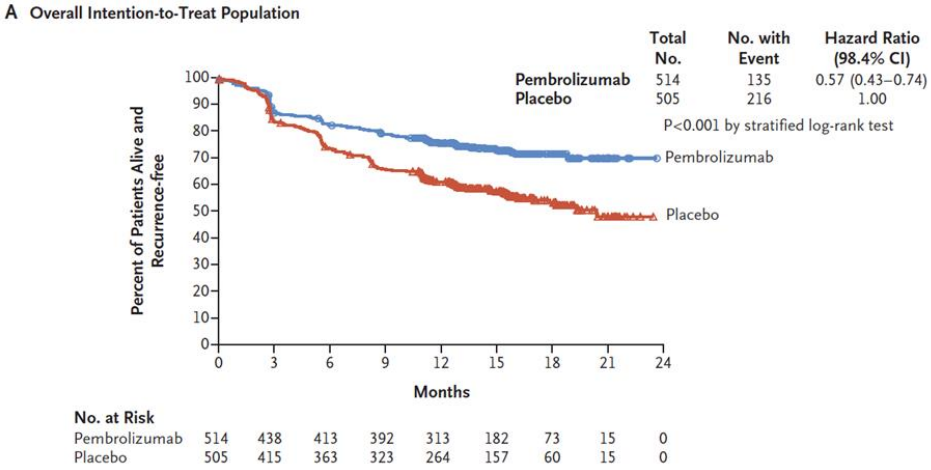


No. at Risk											
	94	86	78	69	54	41	27	19	9	3	0

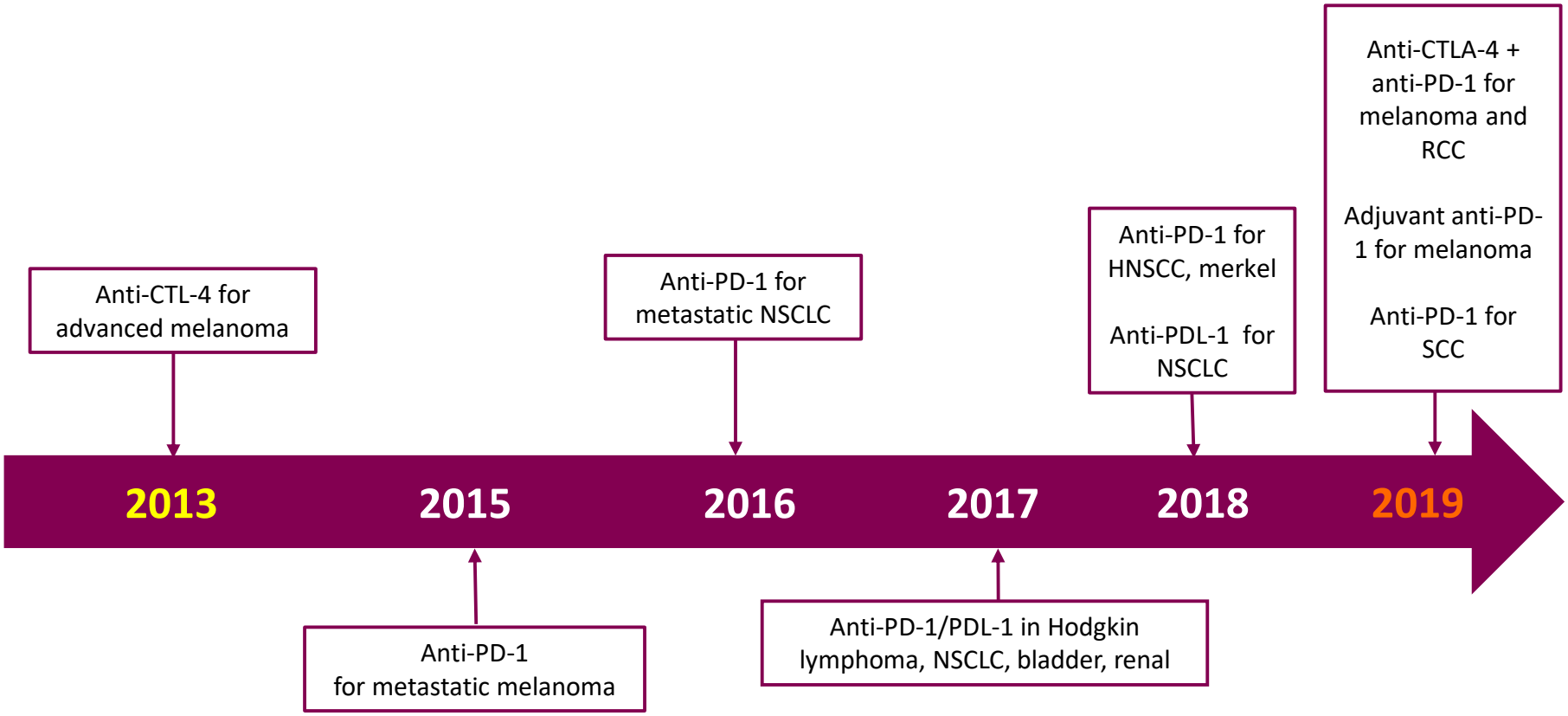
Bringing I-O to earlier disease stage







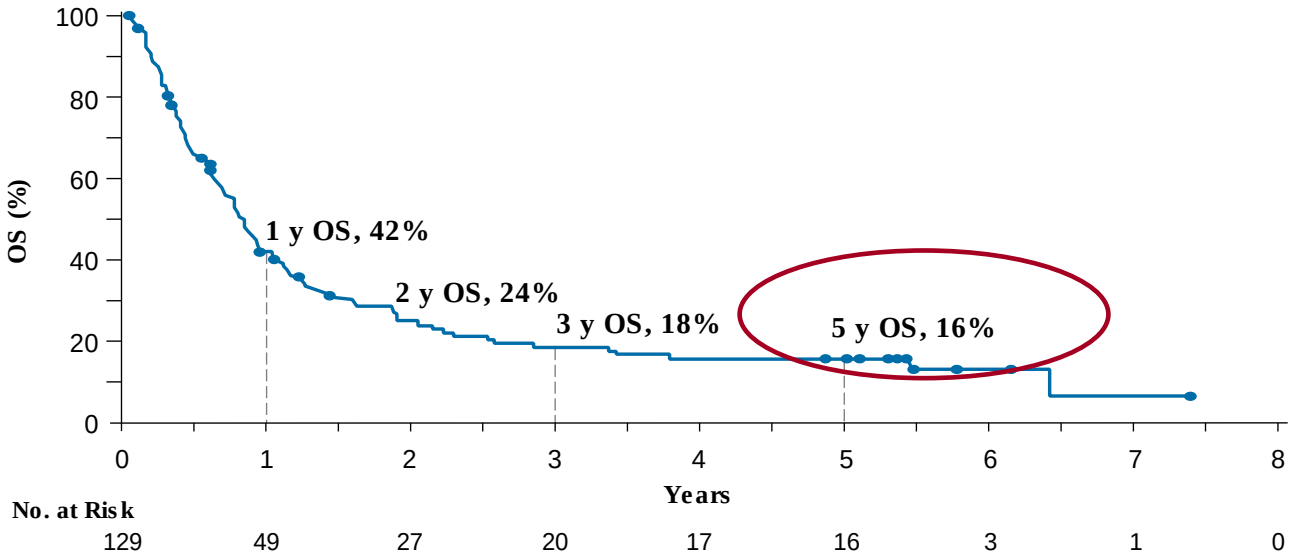
A historical view of immunotherapy in Italy



5-Year Estimates of OS

BMS CA209-003: phase 1 dose finding study in NSCLC

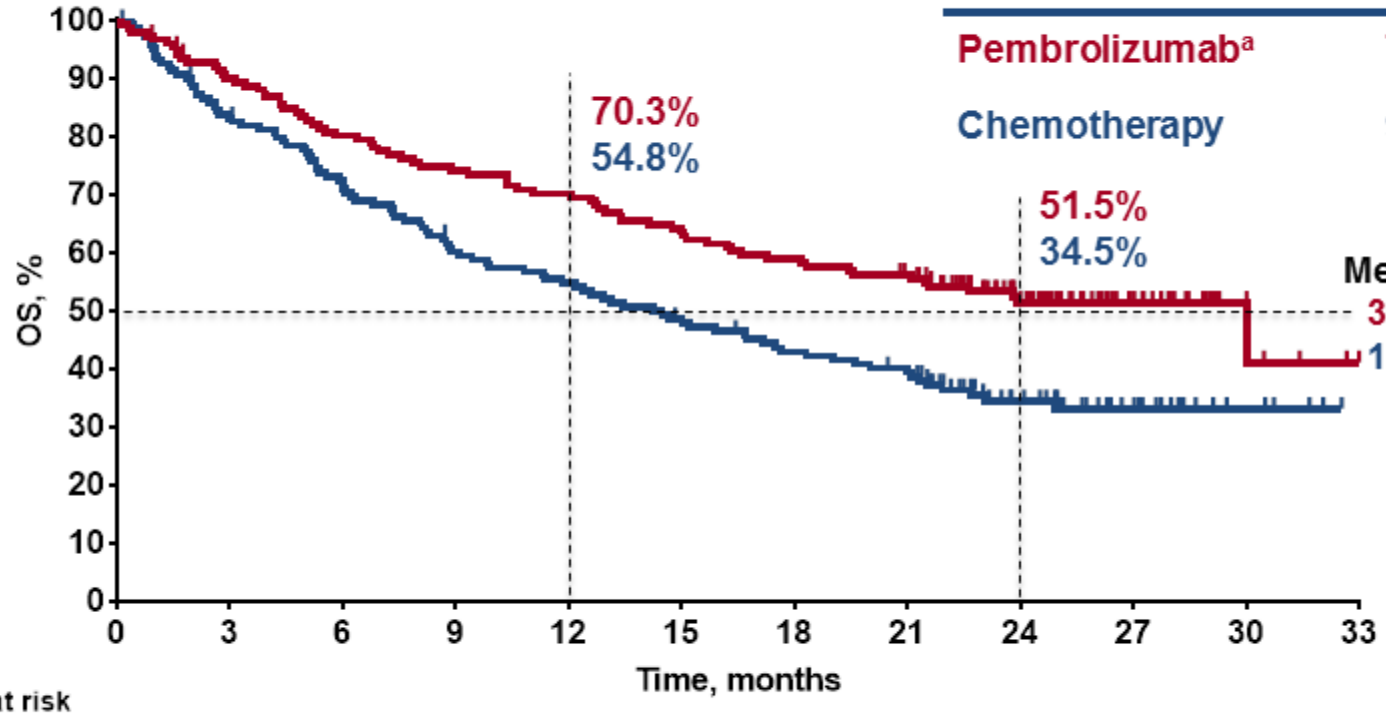
	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)



[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

Brahmer WCLC 2017

Overall Survival: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86)
Chemotherapy	96	*P* = 0.002[b]

Median (95% CI)

30.0 mo (18.3 mo–NR)

14.2 mo (9.8 mo–19.0 mo)

No. at risk

Pembro	154	136	121	112	106	96	89	83	52	22	5	0
Chemo	151	123	107	88	80	70	61	55	31	16	5	0

[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

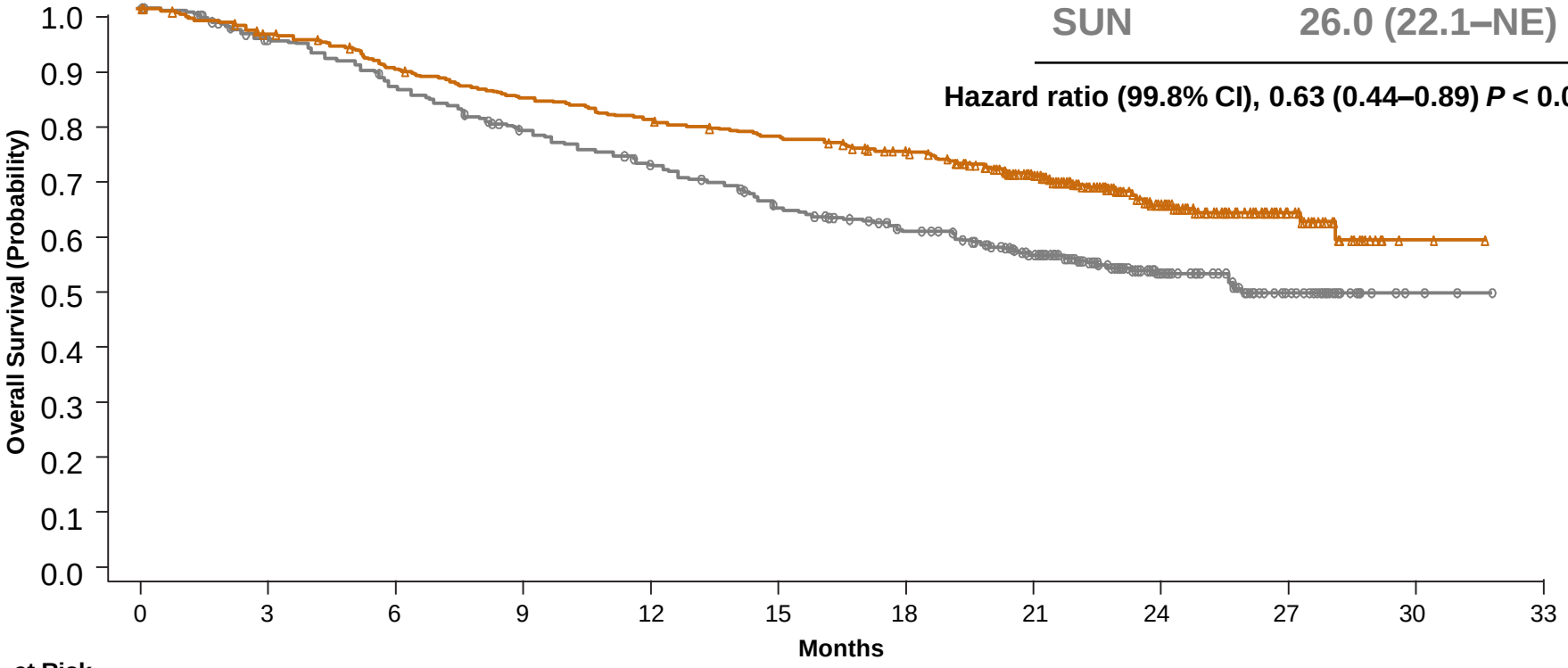
P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, 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

OS: IMDC intermediate/poor risk

Median OS, months (95% CI)

NIVO + IPI	NR (28.2–NE)
SUN	26.0 (22.1–NE)

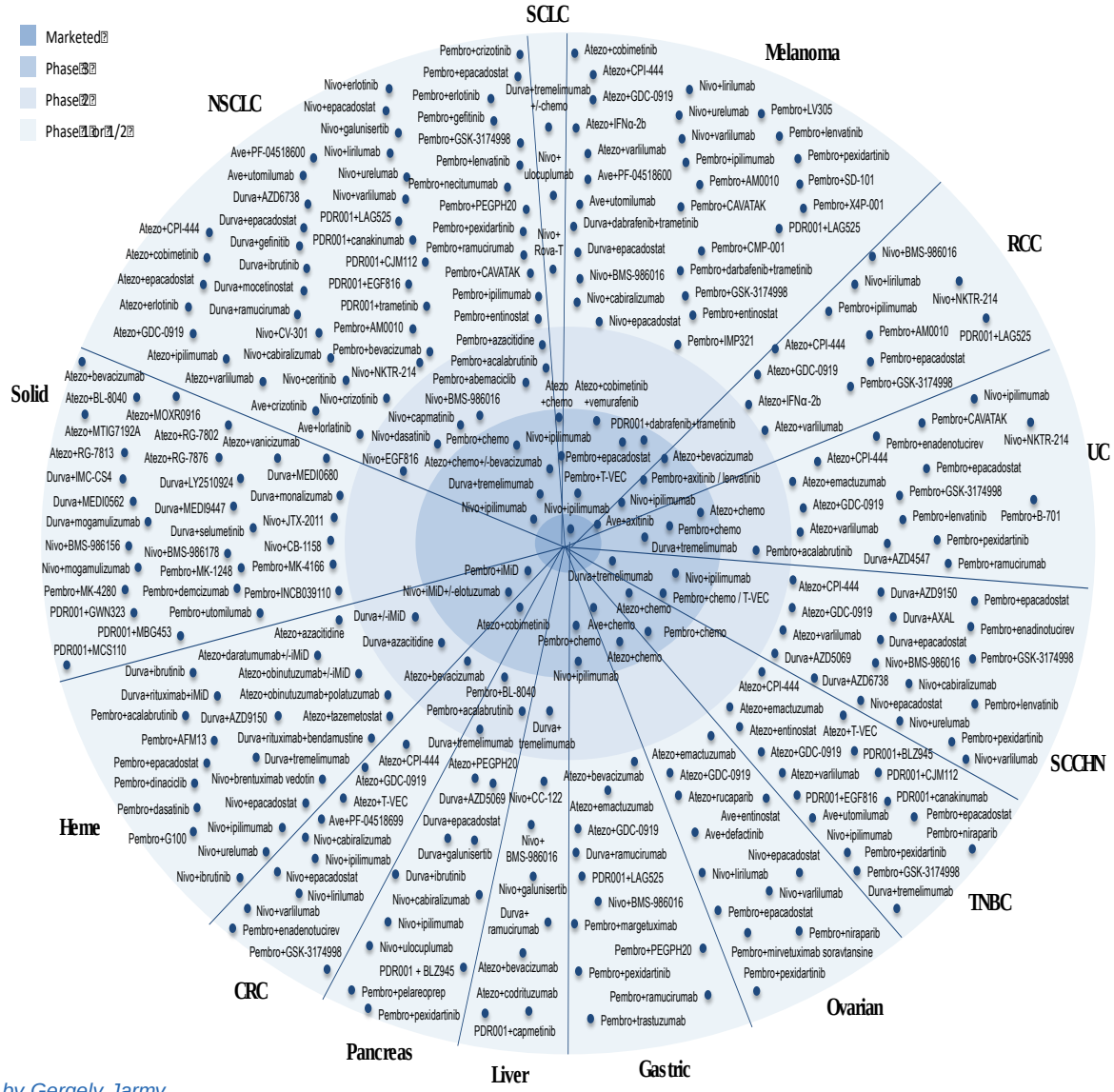
Hazard ratio (99.8% CI), 0.63 (0.44–0.89) *P* < 0.0001



No. at Risk												
NIVO + IPI	425	399	372	348	332	318	300	241	119	44	2	0
SUN	422	387	352	315	288	253	225	179	89	34	3	0

The evolving Cancer Immunotherapy Landscape

>800 clinical combinations with PD-L1/PD-1 inhibitors



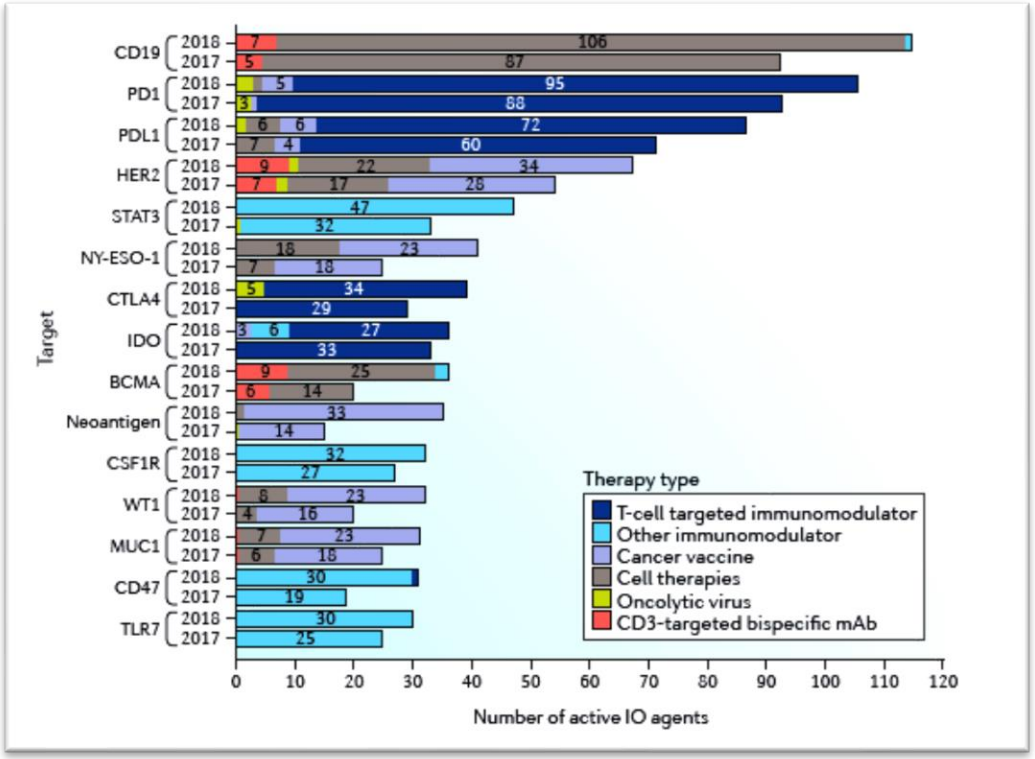
Adapted from Vanessa Lucey of CRI by Gergely Jarmy Chen and Mellman, Nature 2017

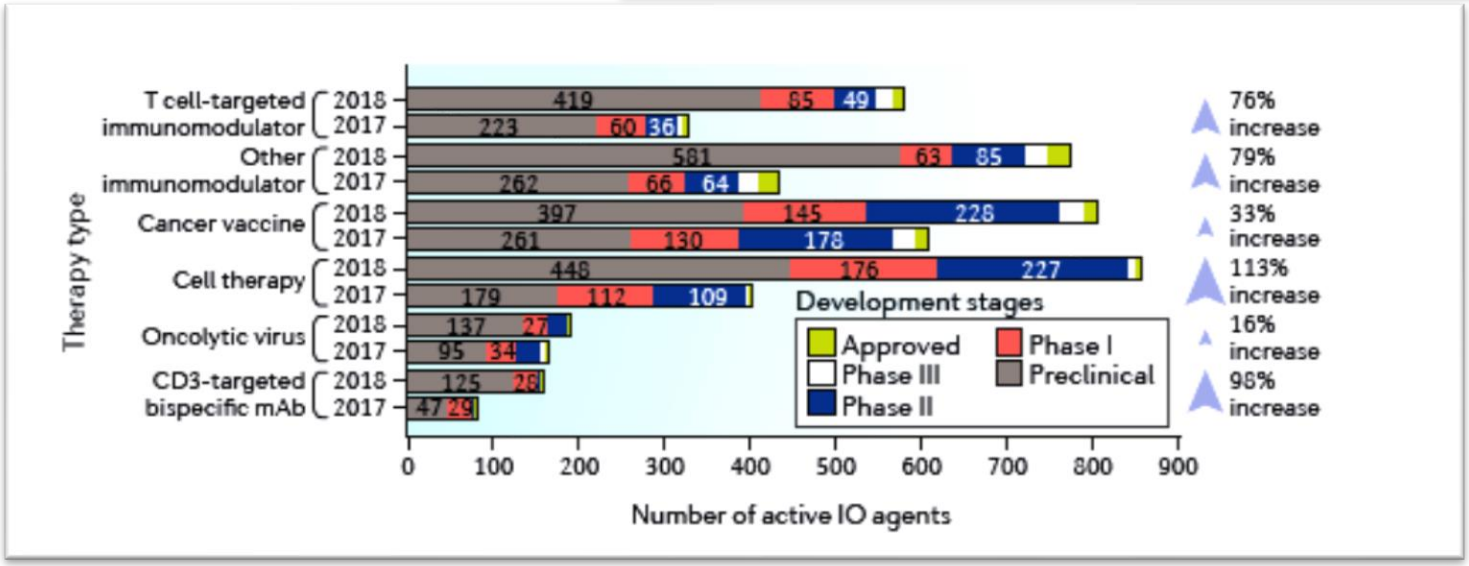
Hegde PS, AAADV, Washington DC, 2017

FROM THE ANALYST'S COUCH

Trends in the global immuno-oncology landscape

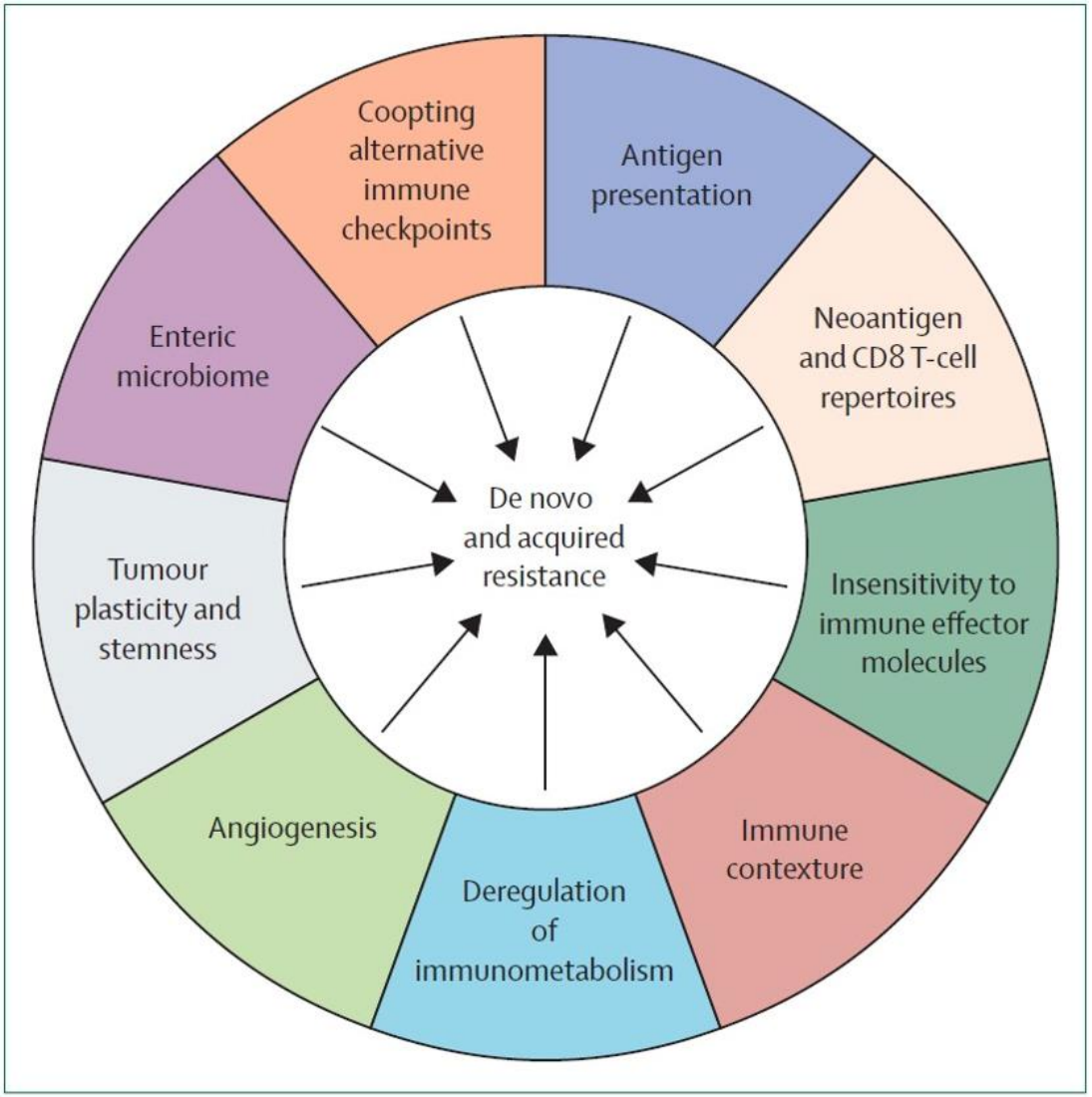
Jun Tang, Laura Pearce, Jill O'Donnell-Tormey and Vanessa M. Hubbard-Lucey





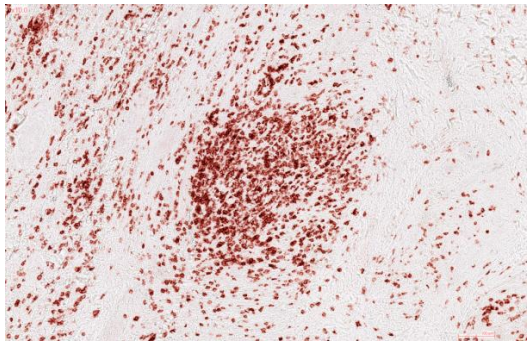
The future of Melanoma Immunotherapy

Mechanisms of primary and secondary immuno-resistance

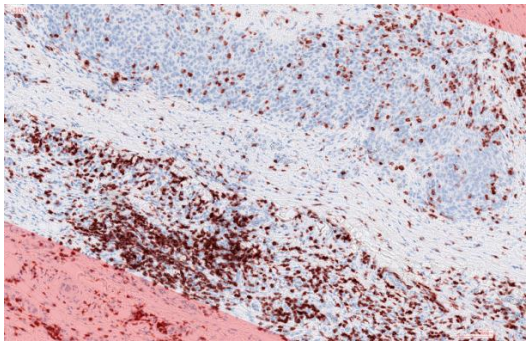


Syn et al, *Lancet Oncol 2017*

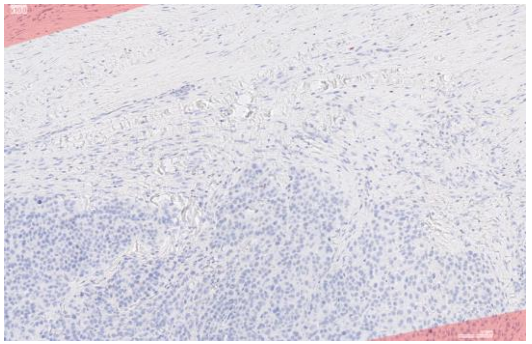
Inflamed tumor — **Non-inflamed tumor**



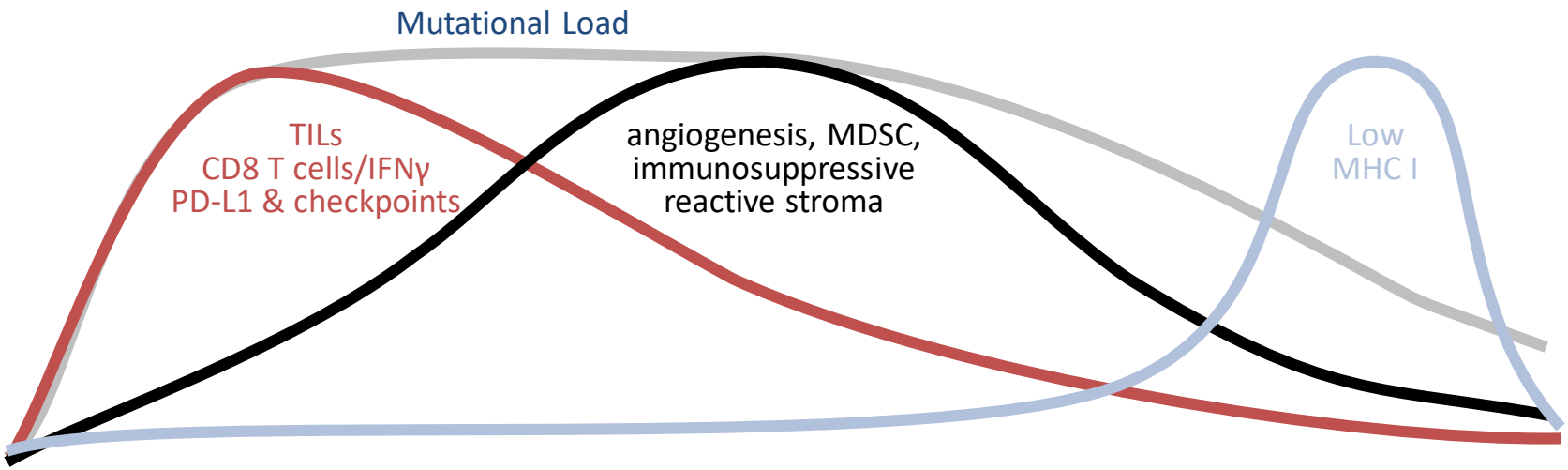
pre-existing immunity



T-cell migration defect

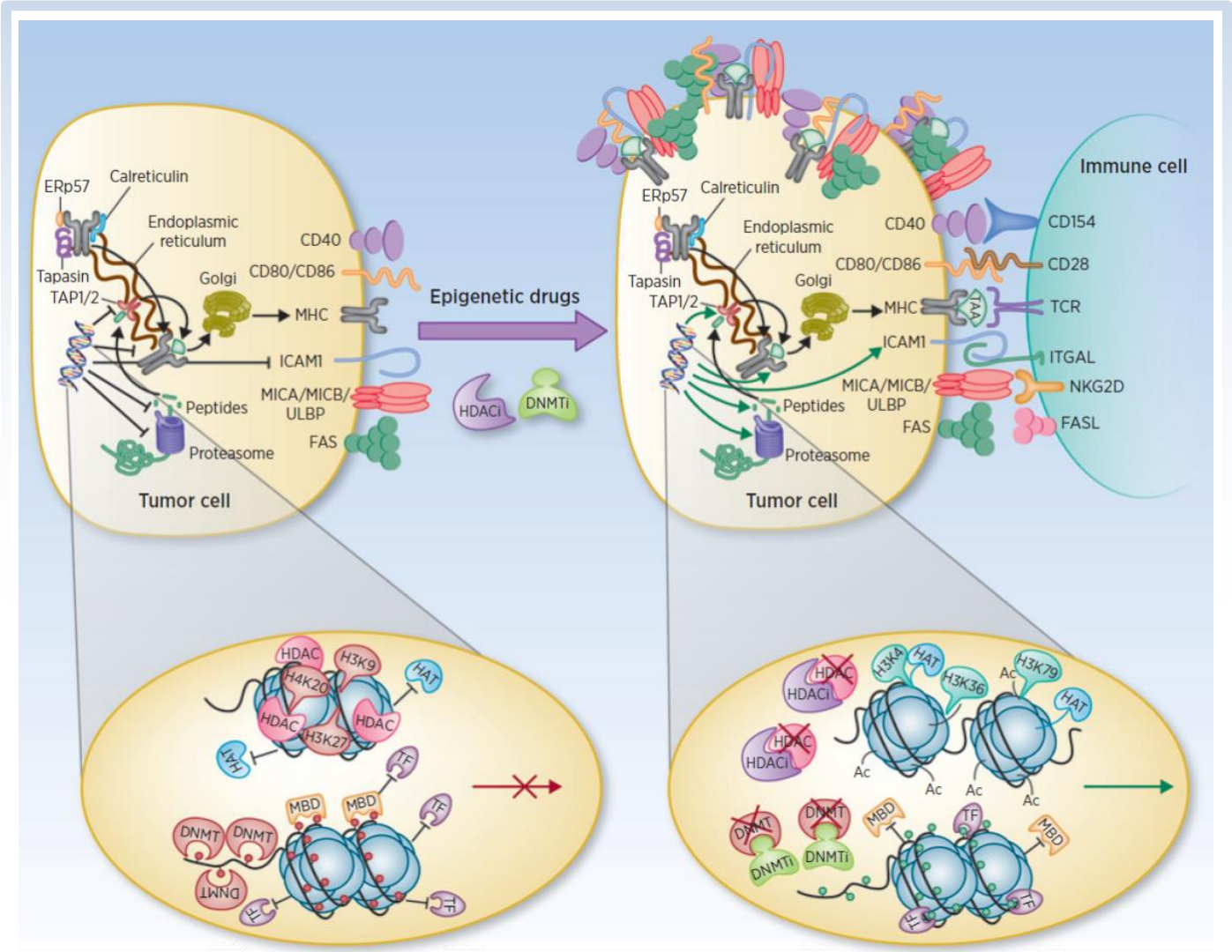


Immune desert tumors



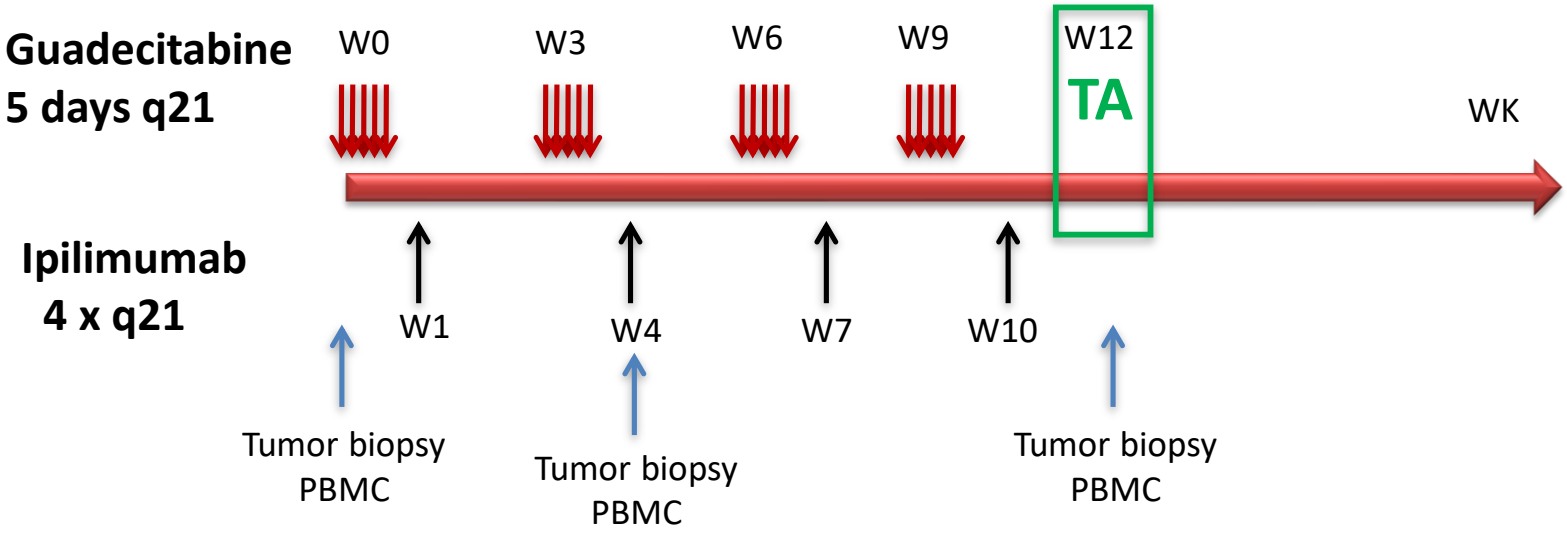
- Adapted from Hegde PS et al. Clin Cancer Res 2016;22(8):1865-1874.

Epigenetic Immunomodulation of Cancer cell

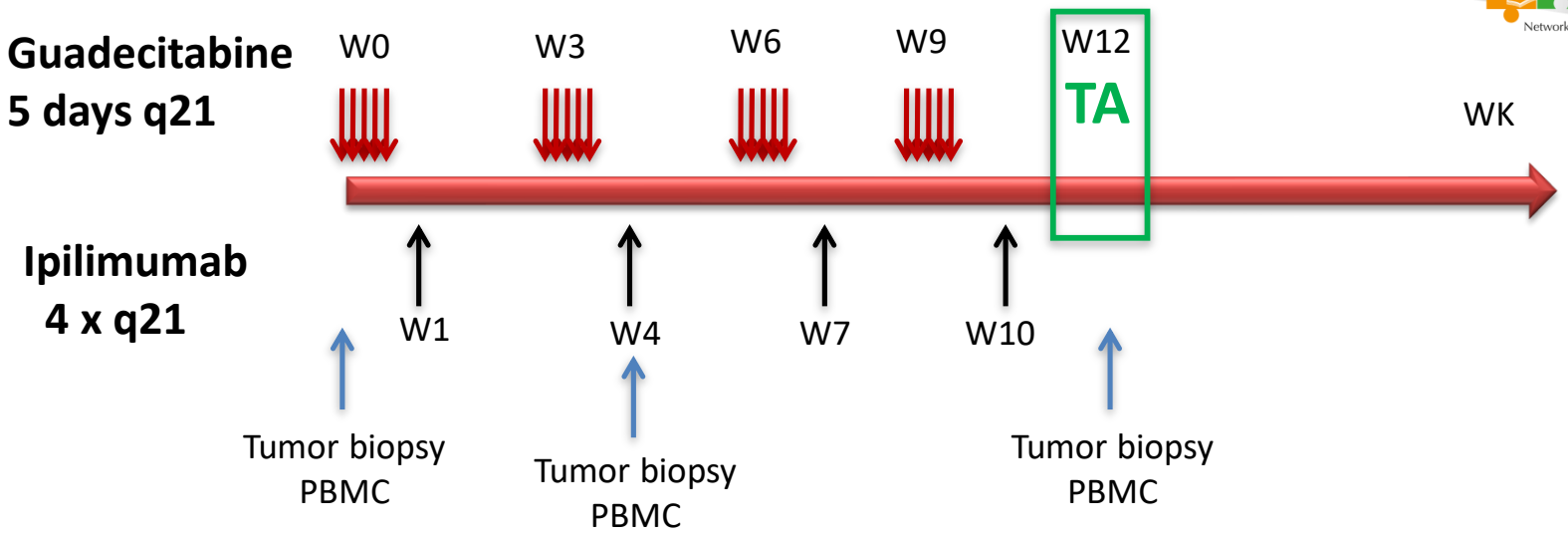


- Maio M et al. CCR 2015

Epigenetic immuno-sequencing: the NIBIT-M4 Study NCT02608437



Epigenetic immuno-sequencing: the NIBIT-M4 Study
NCT02608437



NGS analyses

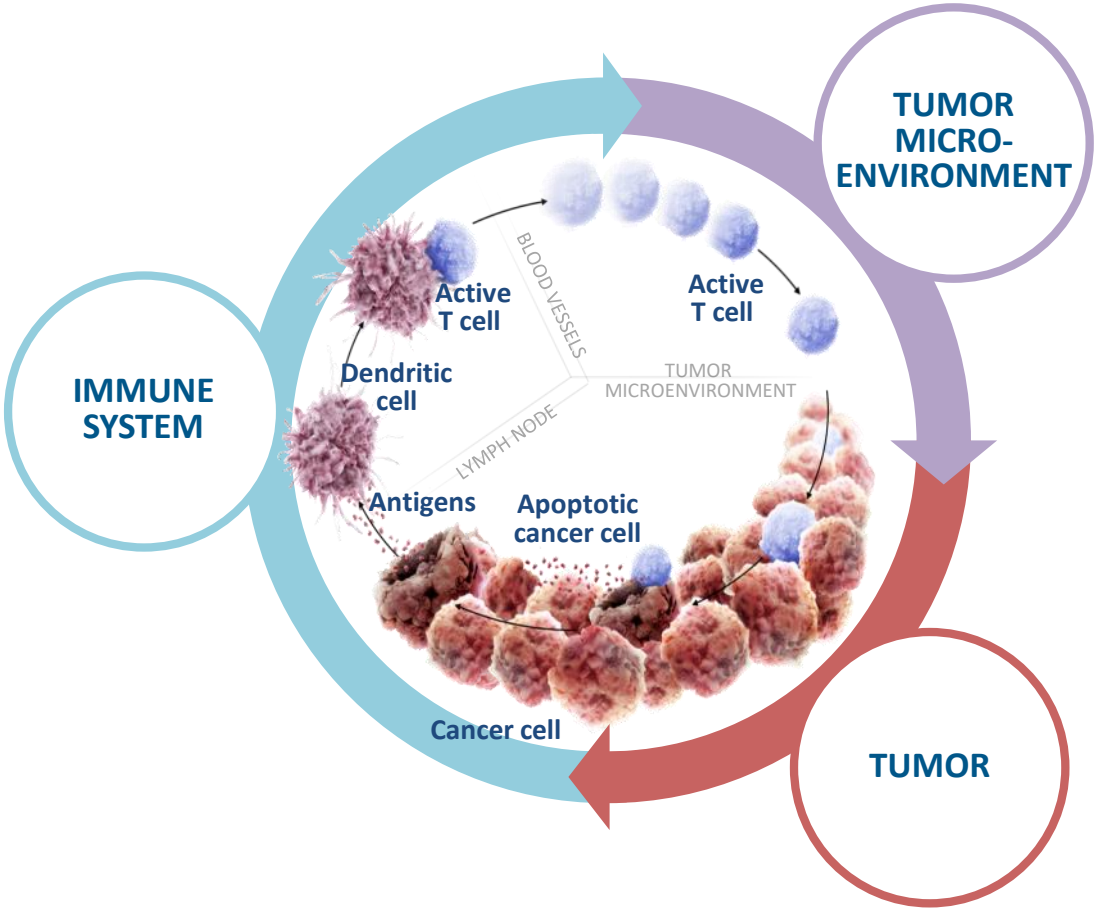
- **Transcriptome** — RNA
- **Methylome** — DNA
- **Exome** — DNA

Peripheral and tumor immunophenotype

- **Phenotipic, functional analyses of PBMC**
- **IMMUNE-CONTEXTURE** density, location, organization and functional orientation of tumor-infiltrating immune cells — **FFPE**

The future of Melanoma Immunotherapy

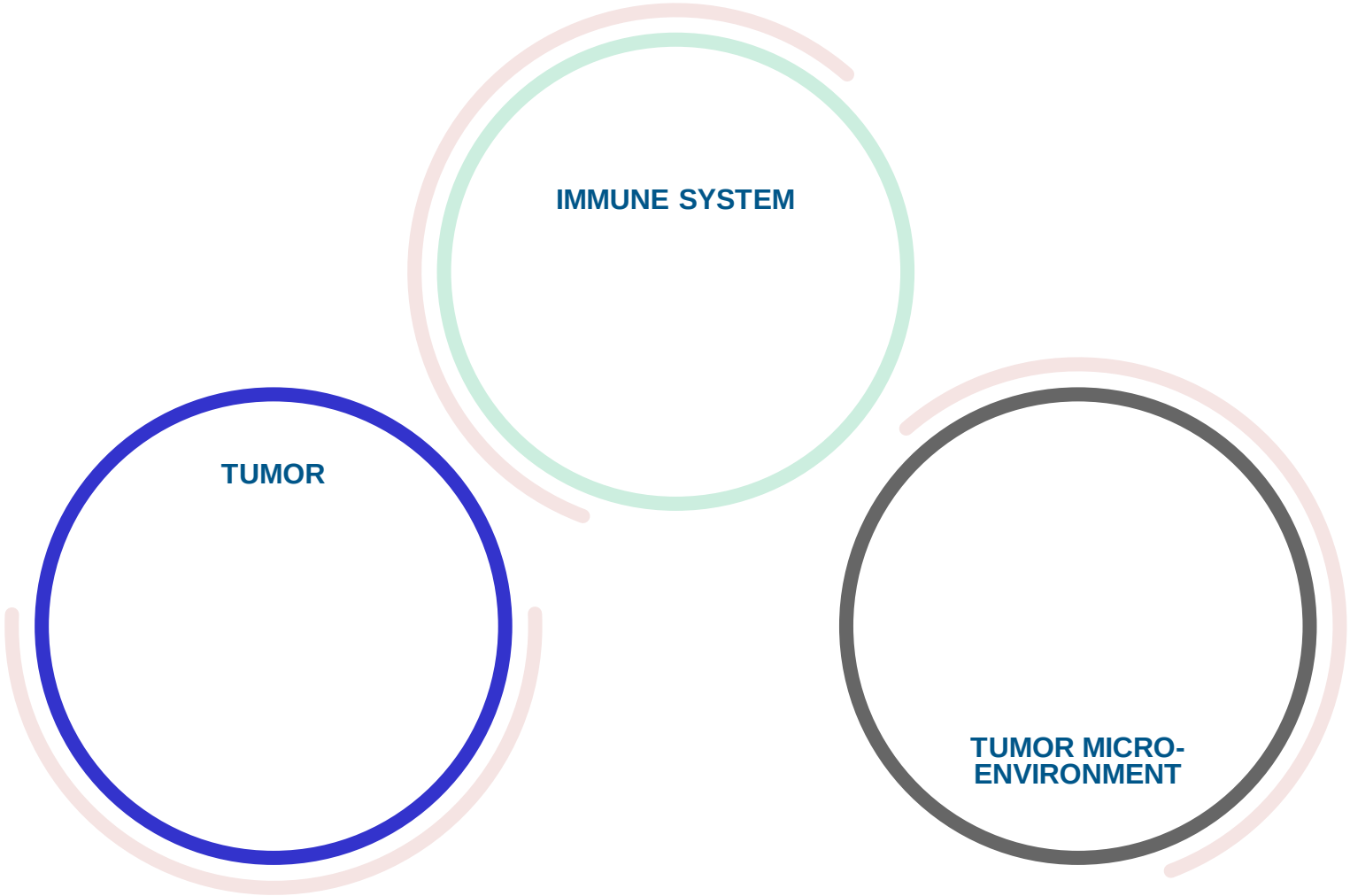
Targeting and modulating multiple compartments



The future of Cancer Immunotherapy

Patient-tailored immunotherapeutic approaches

Targeting and modulating multiple compartments



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