Immunoterapia del cancro

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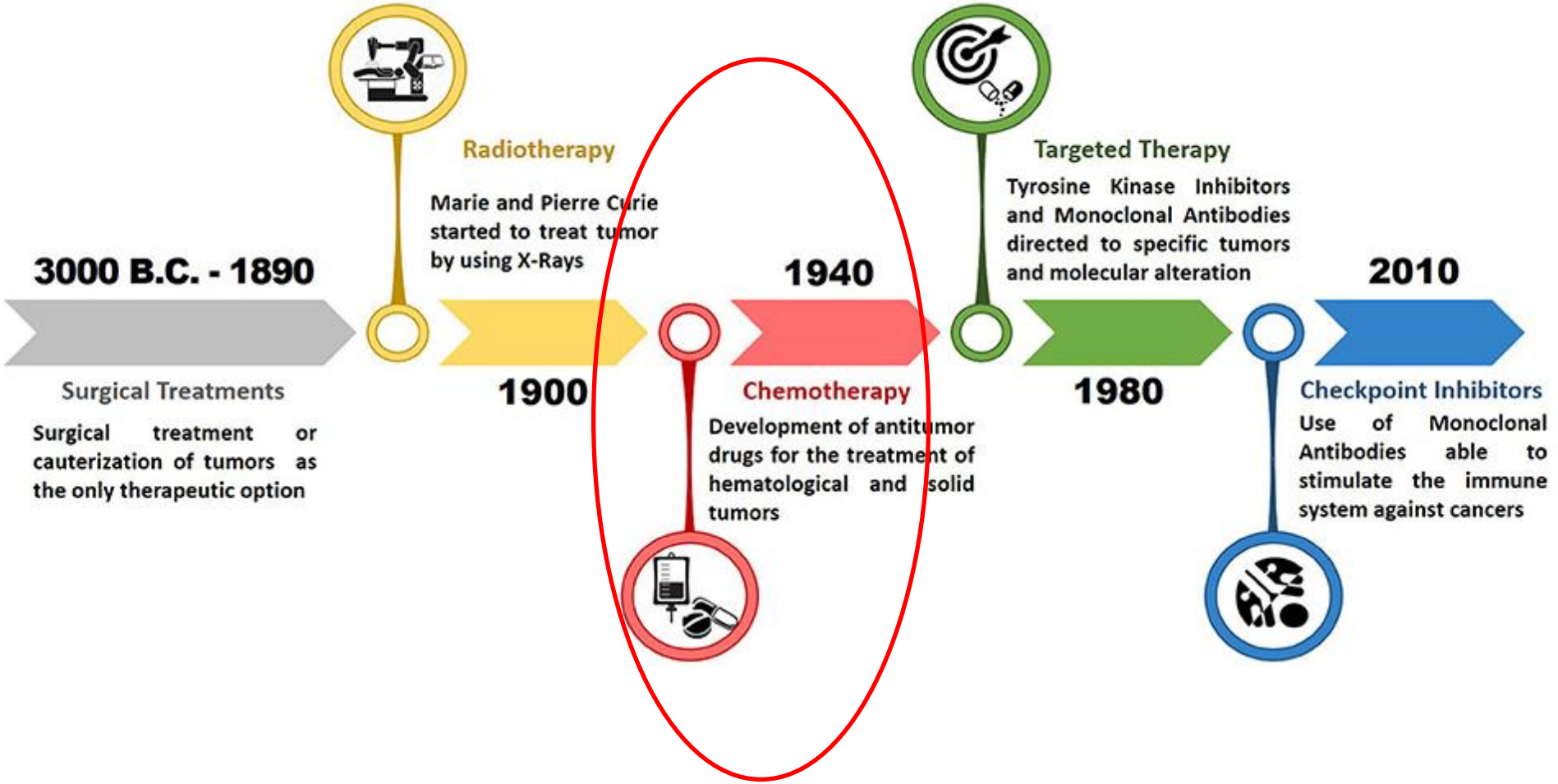
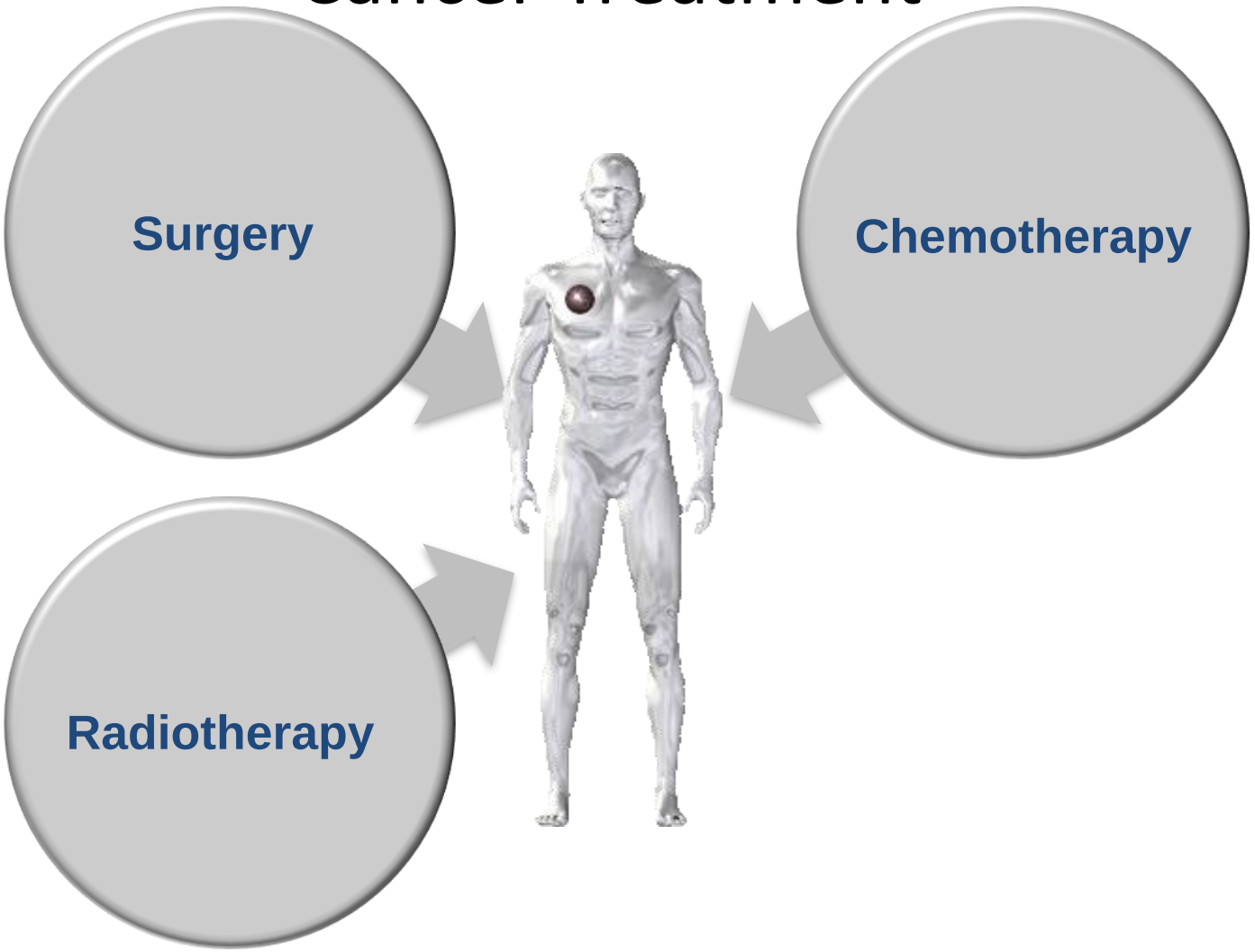
Come è cambiato il ruolo dell'immunoterapia nel trattamento del cancro?

Evolution of cancer treatment

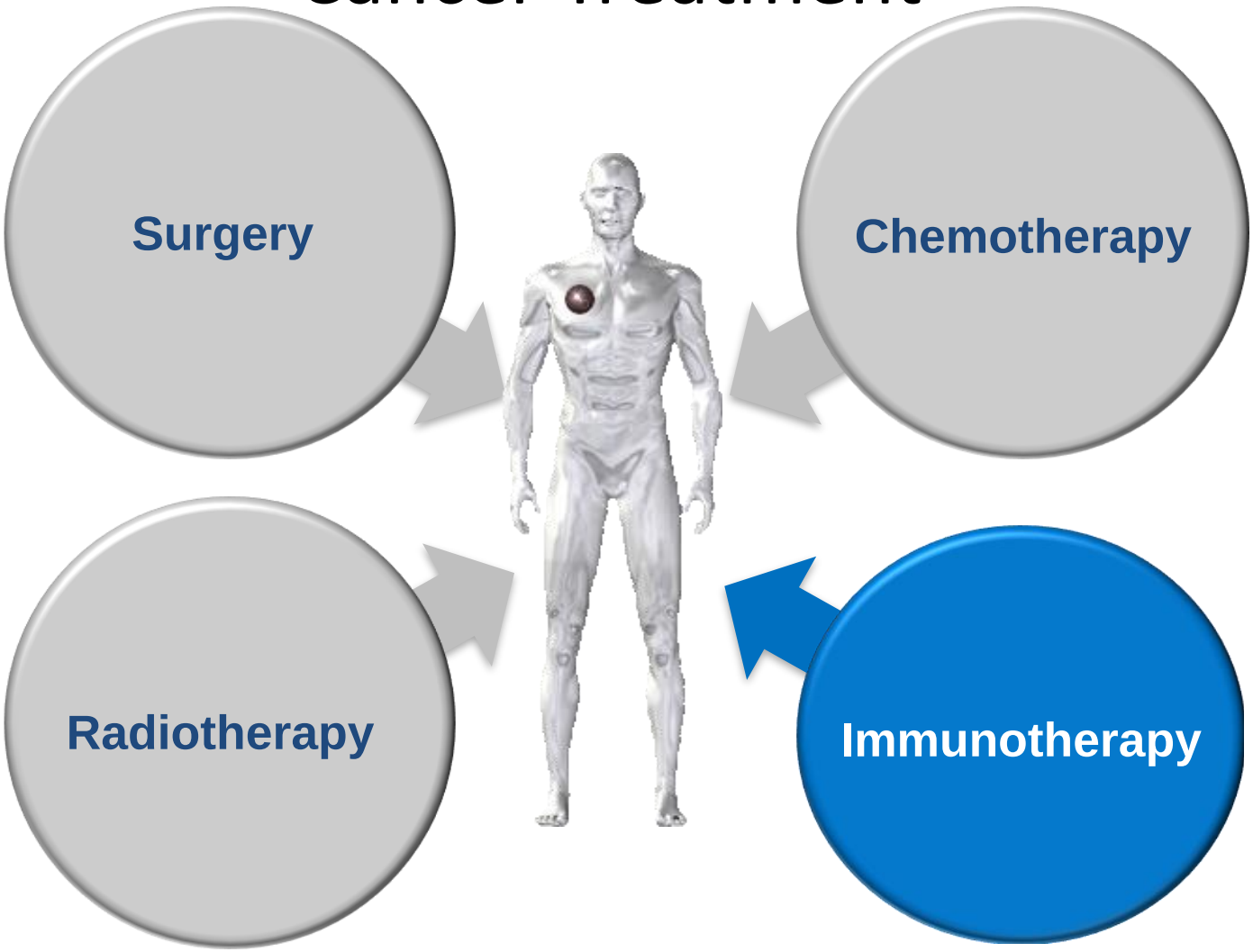


Evolving Therapeutic Options for Cancer Treatment



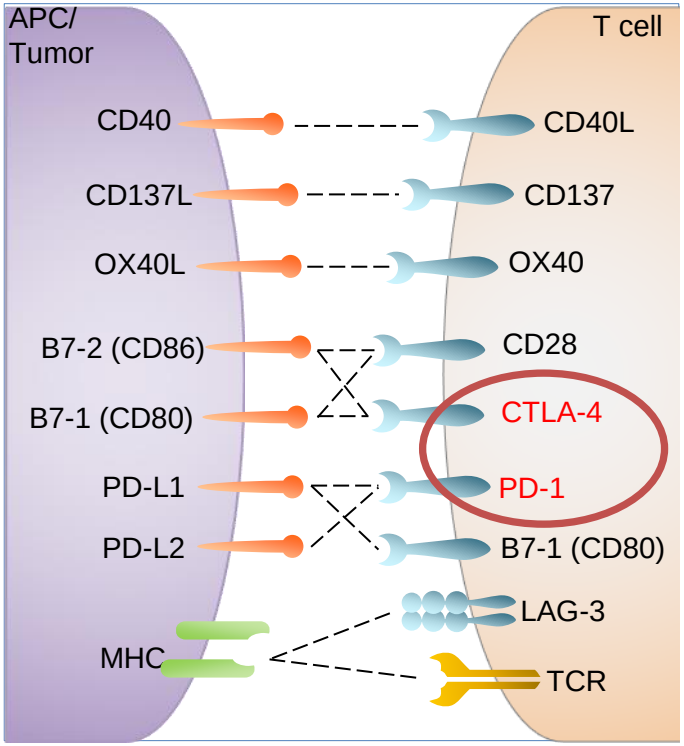
Maio M. Di Giacomo AM, Seminars in Oncol 2015

Evolving Therapeutic Options for Cancer Treatment



Maio M. Di Giacomo AM, Seminars in Oncol 2015

T-cell Checkpoint and Co-stimulatory Pathways



Adapted from Pardoll DM 2012.

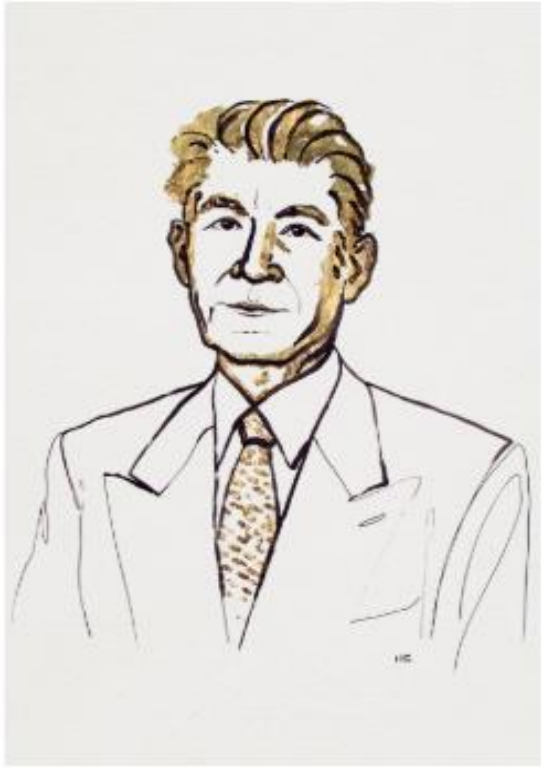
APC=antigen-presenting cell; CTLA-4=cytotoxic T-lymphocyte antigen-4; LAG-3=lymphocyte activation gene-3; MHC=major histocompatibility complex;
PD-1=programmed death-1; PD-L1=PD ligand-1; PD-L2=PD ligand-2; TCR=T-cell receptor.

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

The Nobel Prize in Physiology or Medicine 2018

Ill. Niklas Elmehed. © Nobel Media

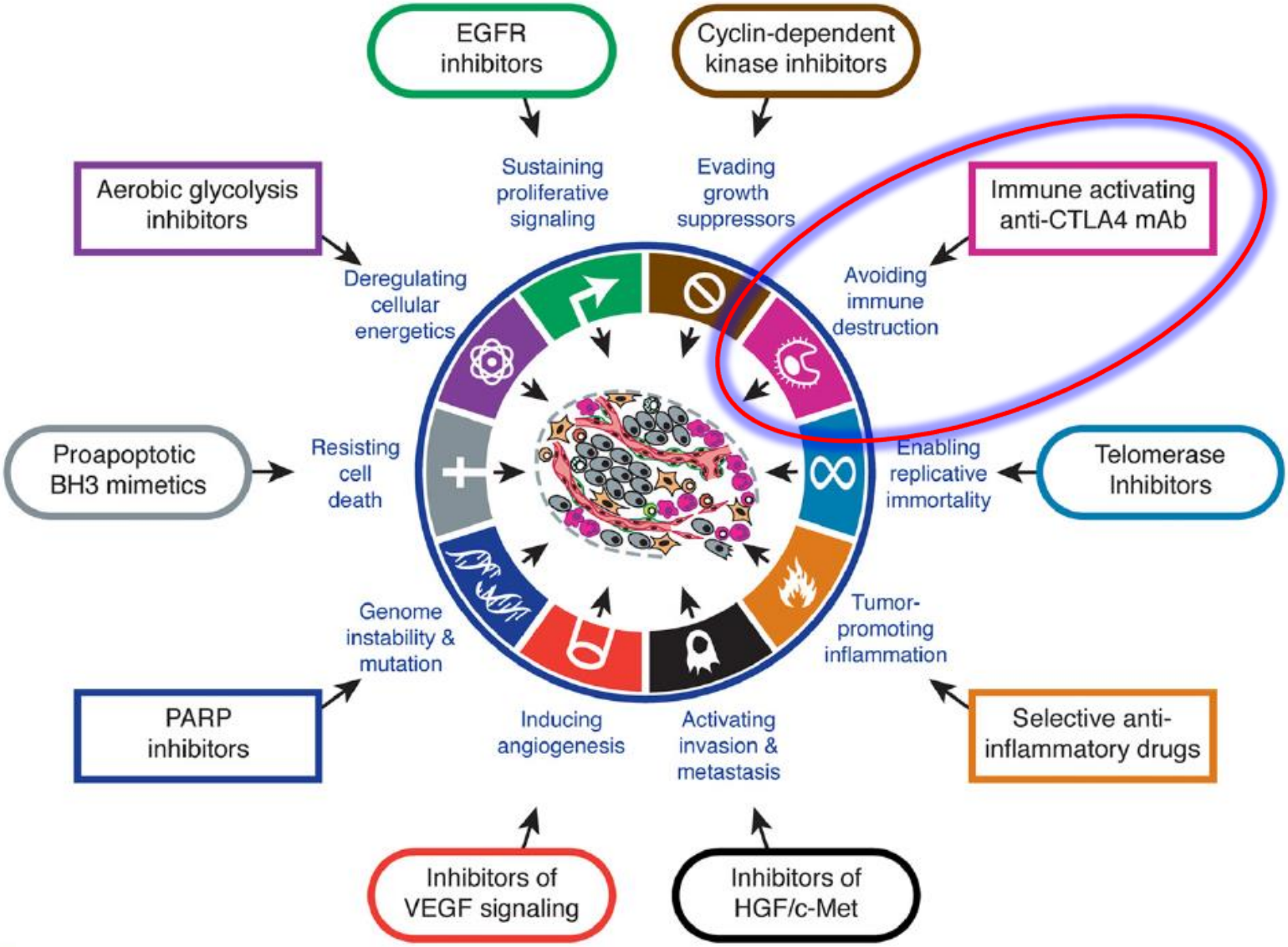
James P. Allison



Ill. Niklas Elmehed. © Nobel Media

Tasuku Honjo

Hallmarks of cancer
2011: immune mechanisms recognized



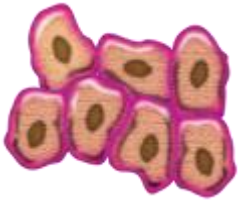
Hanahan D, Weinberg RA, Cell 2011; 144: 646-674

Cosa differenzia l'immunoterapia dai trattamenti di chemioterapia o dai farmaci a bersaglio molecolare?

Cancer-Cell Directed vs Immune-System Directed Cancer Treatment: a Matter of Time

TIME

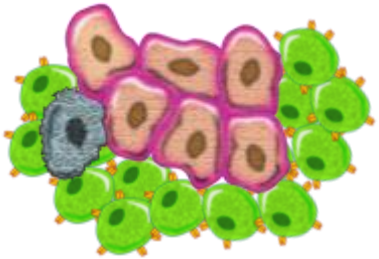
Chemotherapy/ Target Therapy



Tumor Cell Destruction

Immunotherapy

Immune System Activation

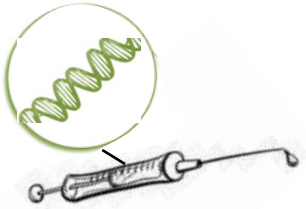


Tumor Cell Destruction

“Unconventional” clinical responses with I-O agents

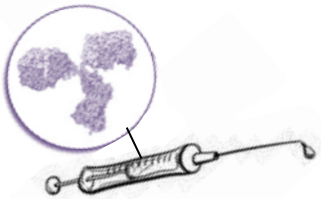
(i.e., PD followed by OR)

Vaccines

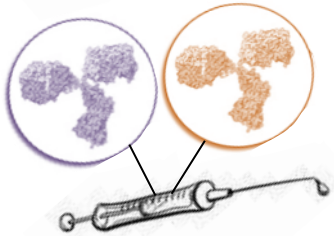


CTLA-4

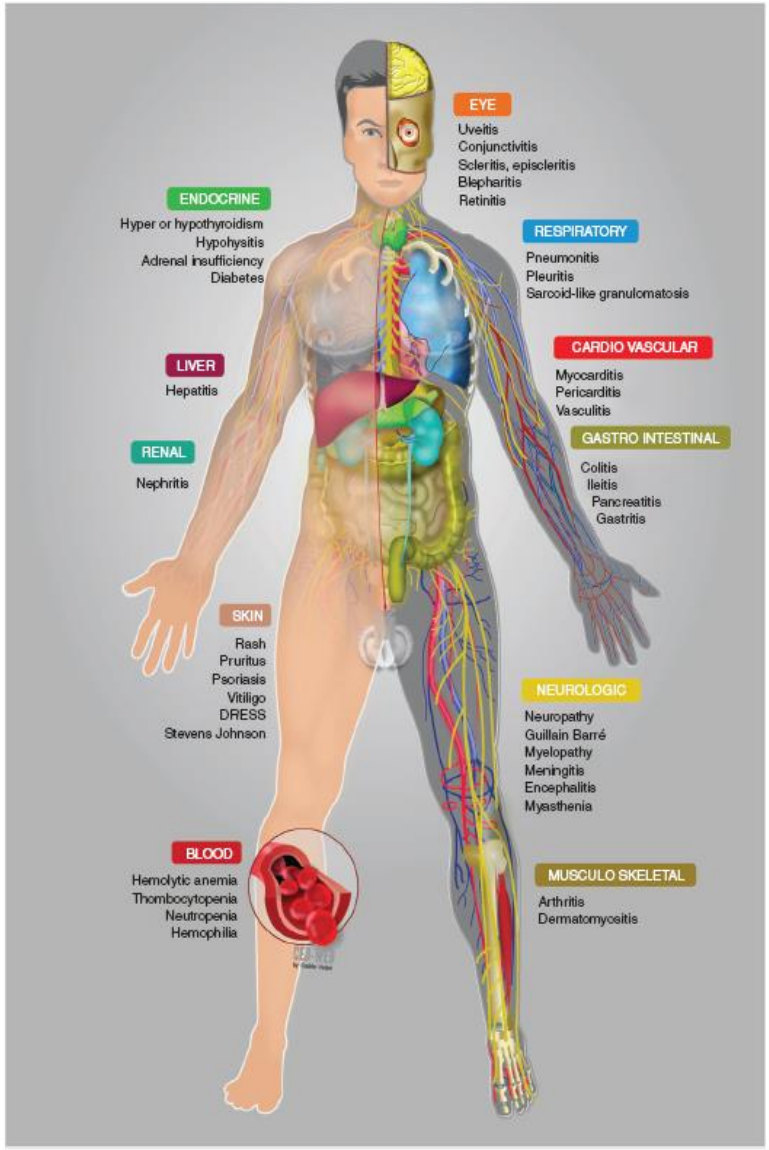
PD1/PDL1



PD1/PDL1
+
CTLA-4



Immune-related Advers Events



- Unique spectrum of side effects (timing and profile is different then chemotherapy)

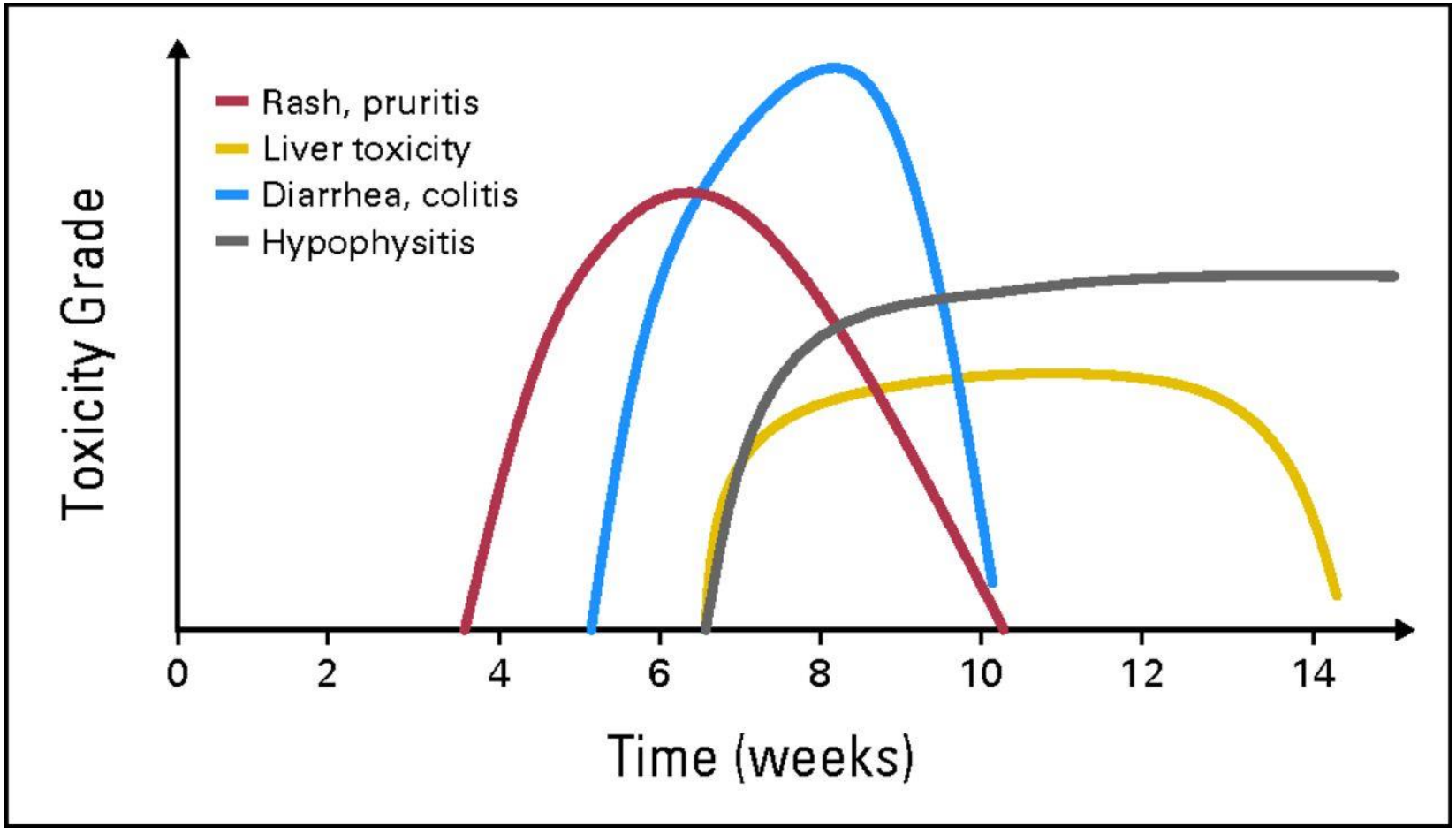
- Quite broad spectrum of toxicity in terms of organ system involvement and severity

-Highly unpredictable and often difficult to distinguish between normal oncologic complications, progression of disease, infection (may require biopsy).

- Require careful surveillance and early intervention to mitigate adverse outcomes and often a multidisciplinary management

Champiat S, et al, Annal Oncol 2016

Kinetics of appearance of immune-related adverse event

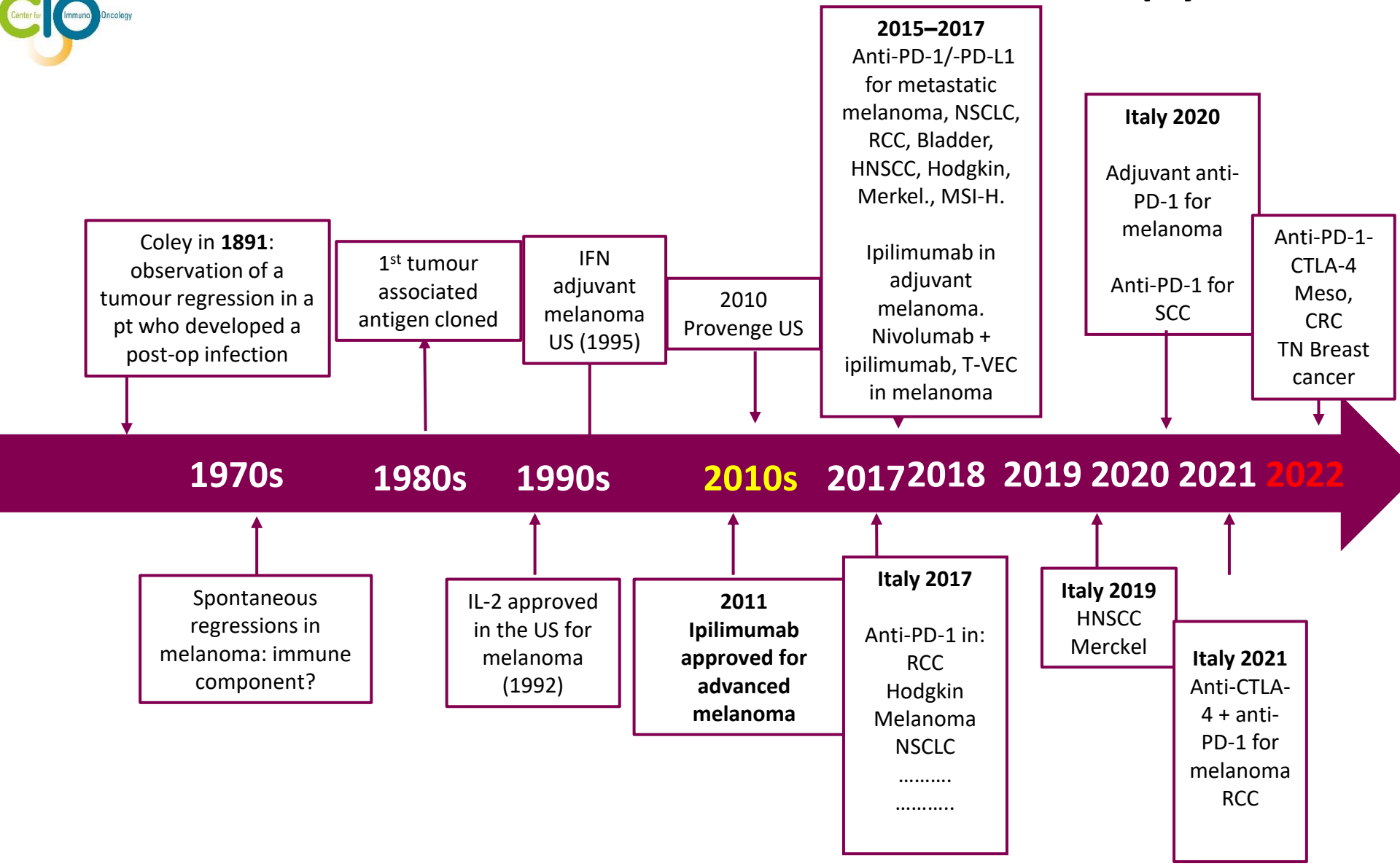


Weber J S et al. JCO 2012;30:2691-2697

JOURNAL OF CLINICAL ONCOLOGY

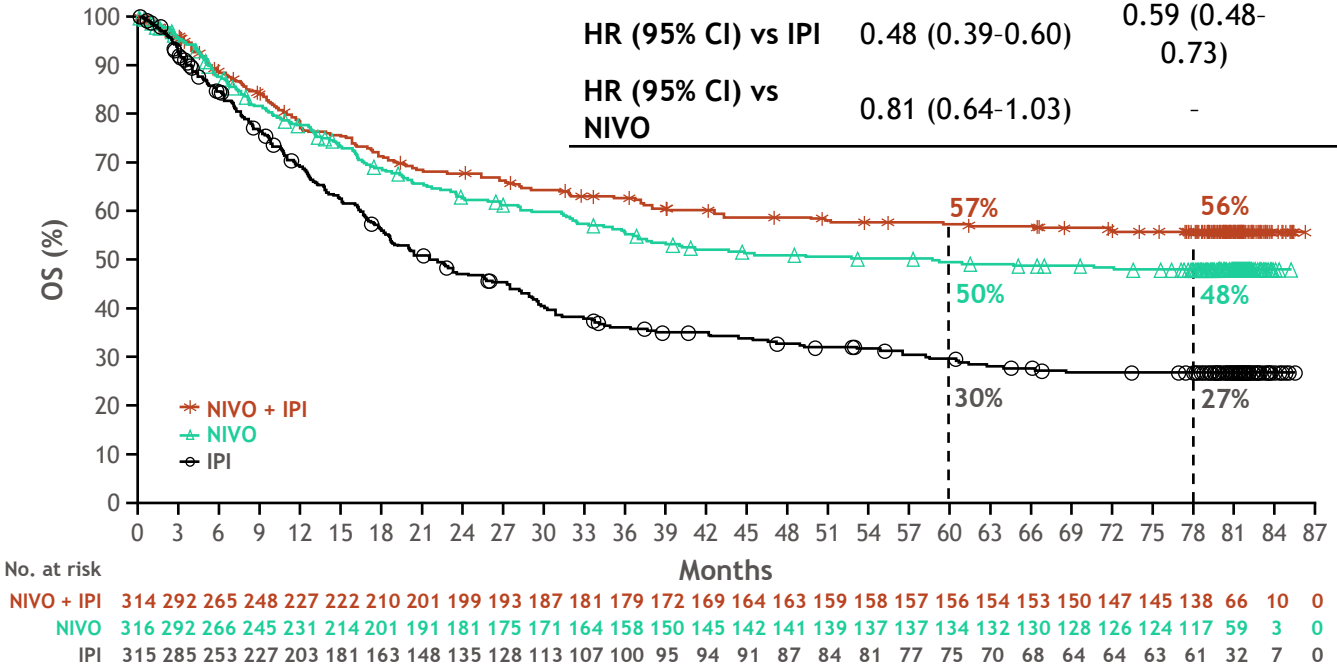
In quali patologie l'immunoterapia è oggi un trattamento standard di provata efficacia clinica?

A historical view of immunotherapy



Melanoma-specific survival (post hoc analysis)[a]

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	NR (71.9-NR)	58.7 (35.9-NR)	21.9 (18.1-27.4)
HR (95% CI) vs IPI	0.48 (0.39-0.60)	0.59 (0.48-0.73)	-
HR (95% CI) vs NIVO	0.81 (0.64-1.03)	-	-



[a]In this descriptive analysis, an event was defined as death due to melanoma and deaths for any other reason were censored.

JCO 2021

Nivolumab plus ipilimumab in melanoma brain metastases

In their Article in *The Lancet Oncology*, Hussein Tawbi and colleagues[1] report a remarkable 71·9% 3-year overall survival rate for patients with melanoma and asymptomatic brain metastases treated with nivolumab plus ipilimumab in the CheckMate 204 trial. These findings strongly support the activity of the nivolumab plus ipilimumab combination, recently reported in the same clinical setting by the anti-PD-1 brain collaboration (ABC) study,[2] in which the 5-year survival rate was 51%, and by the Italian Network for Tumor Biotherapy-Melanoma 2 (NIBIT-M2) study,[3] in which the 5-year survival rate was 41%. Notably, this exciting new clinical scenario for patients with melanoma and asymptomatic brain metastases has been achieved thanks to these unique multicentre clinical trials, all conceived by non-profit organisations. Indeed, the Cytokine Working Group in the USA, the Melanoma Institute in Australia, and the NIBIT Foundation in Europe asked the question about the activity of the nivolumab plus ipilimumab combination in a population of patients with melanoma who, to date, have been hard to treat, with very poor therapeutic chances. Notably, until now, patients with melanoma and brain metastases were systematically excluded from industry-sponsored clinical trials with immune checkpoint inhibitors because of their poor prognosis and the prevailing dogma that the blood–brain barrier would prevent effector immune cells from trafficking to the brain.[4]

This substantial change in the therapeutic landscape for patients with melanoma and asymptomatic brain metastases highlights the crucial role of independent clinical research in specific oncology settings in which, although the clinical need is unquestionable, industry-sponsored trials are not prioritised. Consequently, a virtuous collaboration and exchange of goals between non-profit organisations and pharmaceutical industry could eventually benefit small groups of patients in specific clinical settings. However, to fully achieve this task, independent clinical research has to ask highly relevant medical questions, thus fulfilling the mission to help patients who are excluded from industry-sponsored trials, as has happened since the advent of immune checkpoint inhibitor-based clinical trials for patients with melanoma and brain metastases.[4] Along this line, the striking long-term survival observed in these three independent studies identify the nivolumab plus ipilimumab combination as the standard of care for patients with melanoma and asymptomatic brain metastases. Once the dogma that the brain is an immune-privileged organ is definitively broken, the next step forwards for investigator-sponsored clinical trials could be to broaden knowledge on the efficacy of immune checkpoint inhibitor therapy on brain metastases from other tumour types, and in even more challenging clinical settings, such as symptomatic brain metastases or leptomeningeal tumour spreading.

AMDG has served as a consultant or advisor to Incyte, Pierre Fabre, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp Dohme, and Sanofi and has received compensated educational activities from Bristol-Myers Squibb, Merck Sharp Dohme, Pierre Fabre, and Sanofi. MM has served as a consultant or advisor to Roche, Bristol-Myers Squibb, Merck Sharp Dohme, Incyte, AstraZeneca, Amgen, Pierre Fabre, Eli Lilly, GlaxSmithKline, Sciclone, Sanofi, Alfasigma, and Merck Serono and own shares in Epigen Therapeutics.

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1 Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol* 2021; **22:** 1692–704.

2 Long GV, Atkinson V, Lo S, et al. Five-year overall survival from anti-PD-1 brain collaboration (ABC study): randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). *Proc Am Soc Clin Oncol* 2021; **39** (suppl 15): 9508 (abstr).

3 Di Giacomo AM, Chiarion-Sileni V, Del Vecchio M, et al. Primary analysis and 4-year follow-up of the phase III NIBIT-M2 trial in melanoma patients with brain metastases. *Clin Cancer Res* 2021; **27:** 4737–45.

4 Di Giacomo AM, Valente M, Cerase A, et al. Immunotherapy of brain metastases: breaking a "dogma". *J Exp Clin Cancer Res* 2019; **38:** 419.

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., Sergios 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.

Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study

Georgina V Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Alexander D Guminski, Michael P Brown, James S Wilmott, Jarem Edwards, Maria Gonzalez, Richard A Scolyer, Alexander M Menzies, Grant A McArthur**

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Primary Analysis and Four-Year Follow-Up of the Phase III NIBIT-M2 Trial in Melanoma Patients With Brain Metastases

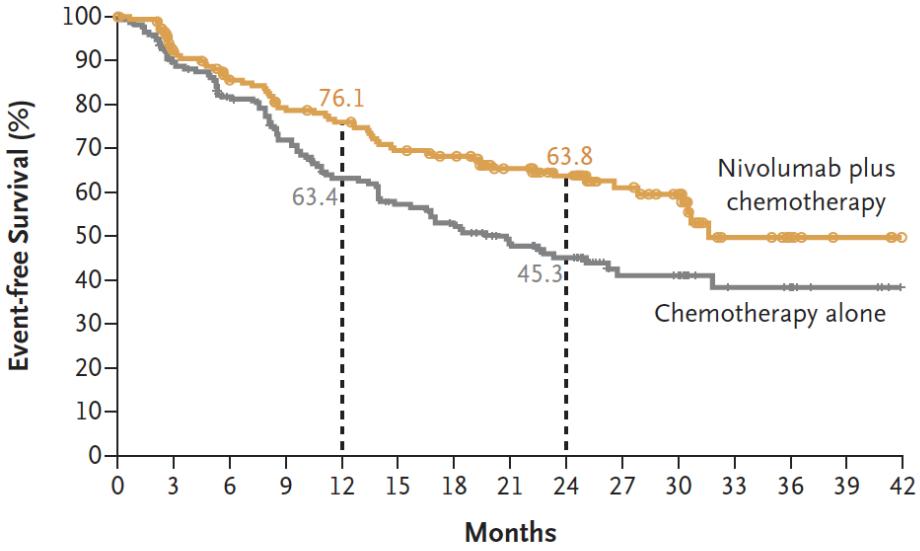
Anna Maria Di Giacomo[1], Vanna Chiarion-Sileni[2], Michele Del Vecchio[3], Pier Francesco Ferrucci[4], Michele Guida[5], Pietro Quaglino[6], Massimo Guidoboni[7], Paolo Marchetti[8], Ornella Cutaia[1], Giovanni Amato[1], Alessia Covre[1], Roberto Camerini[9], Luana Calabrò[1], Monica Valente[1], Diana Giannarelli[10], Mario Mandalà[11], and Michele Maio[1,9,12]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

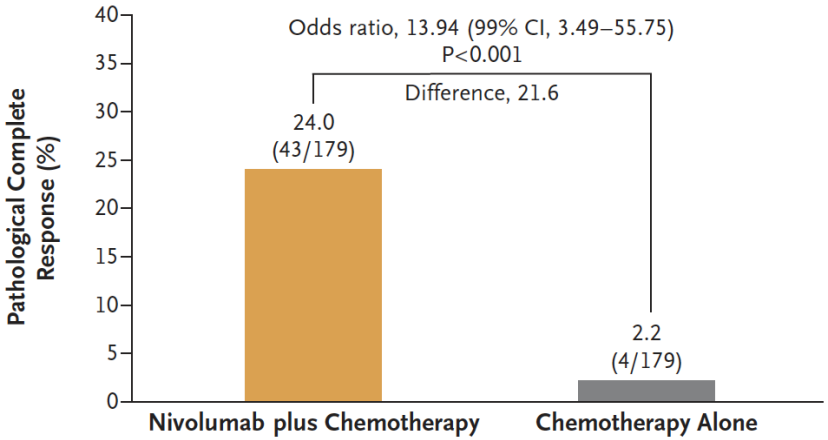
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

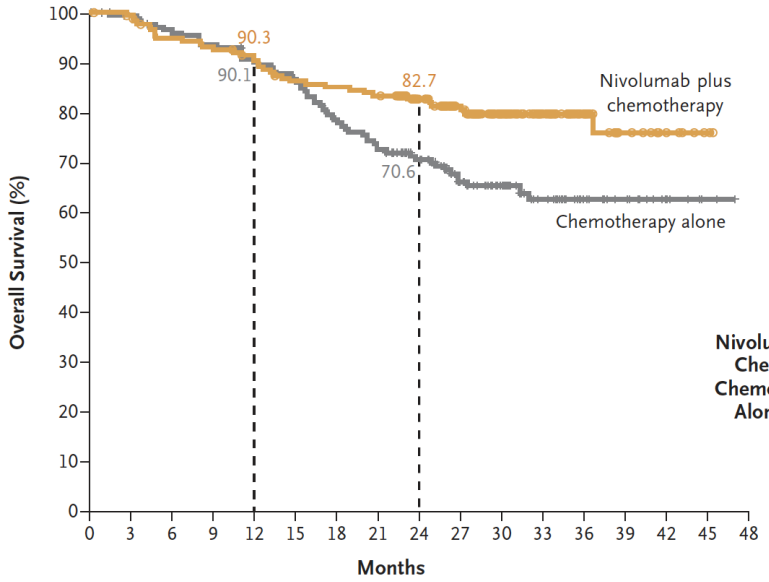
No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

Forde PM et al, NEJM 2022

Neoadjuvant Nivolumab plus Chemotherapy in NSCLC





	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

No. at Risk

Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

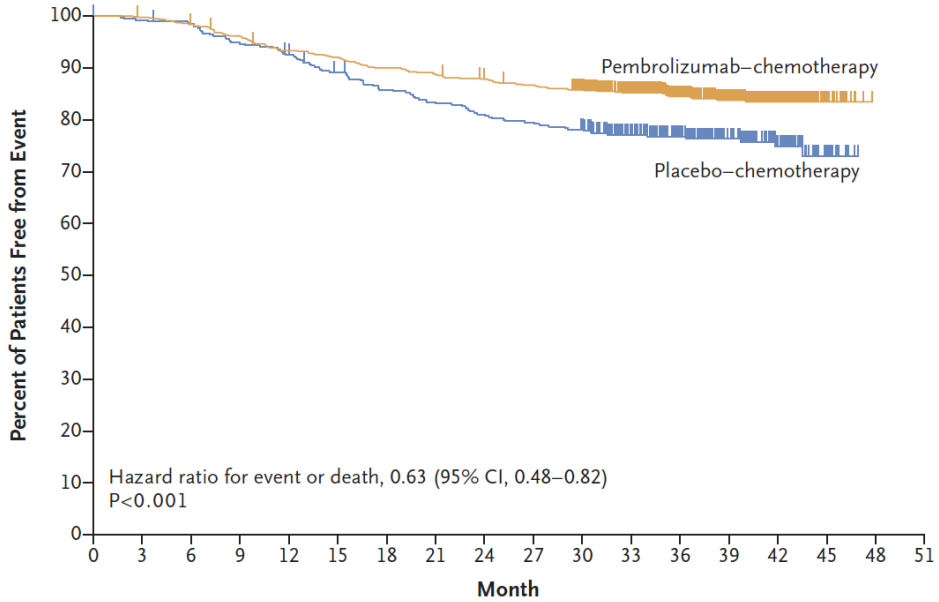
Forde PM et al, NEJM 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, J. Andersen, D. Patt, M. Danso, M. Ferreira, M.-A. Mouret-Reynier, S.-A. Im, J.-H. Ahn, M. Gion, S. Baron-Hay, J.-F. Boileau, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

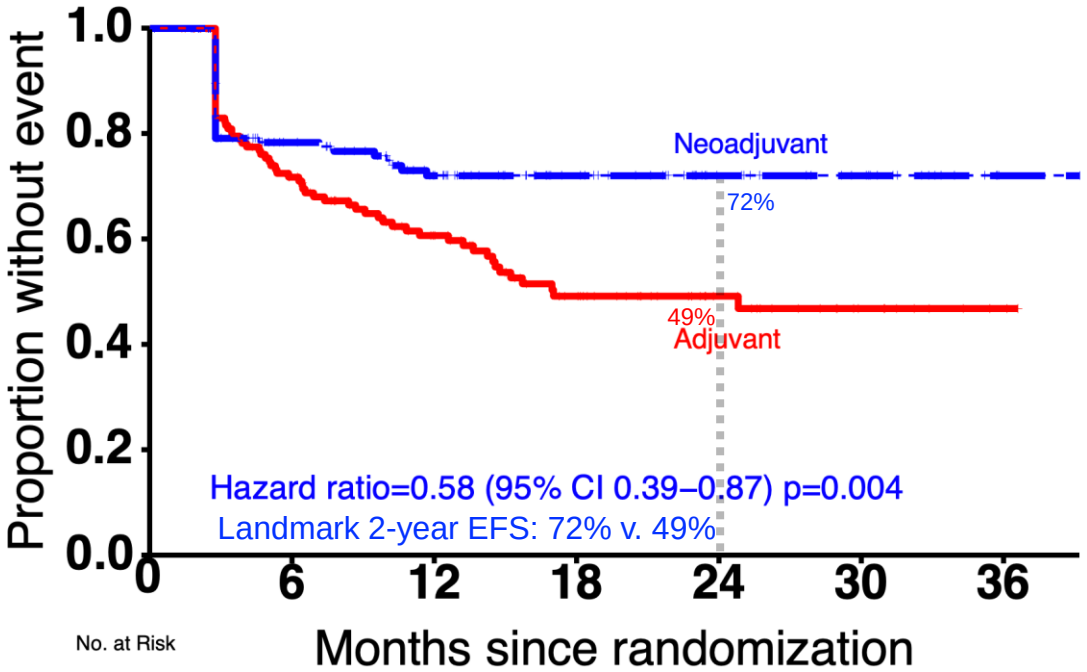


No. at Risk

Pembrolizumab–chemotherapy	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo–chemotherapy	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

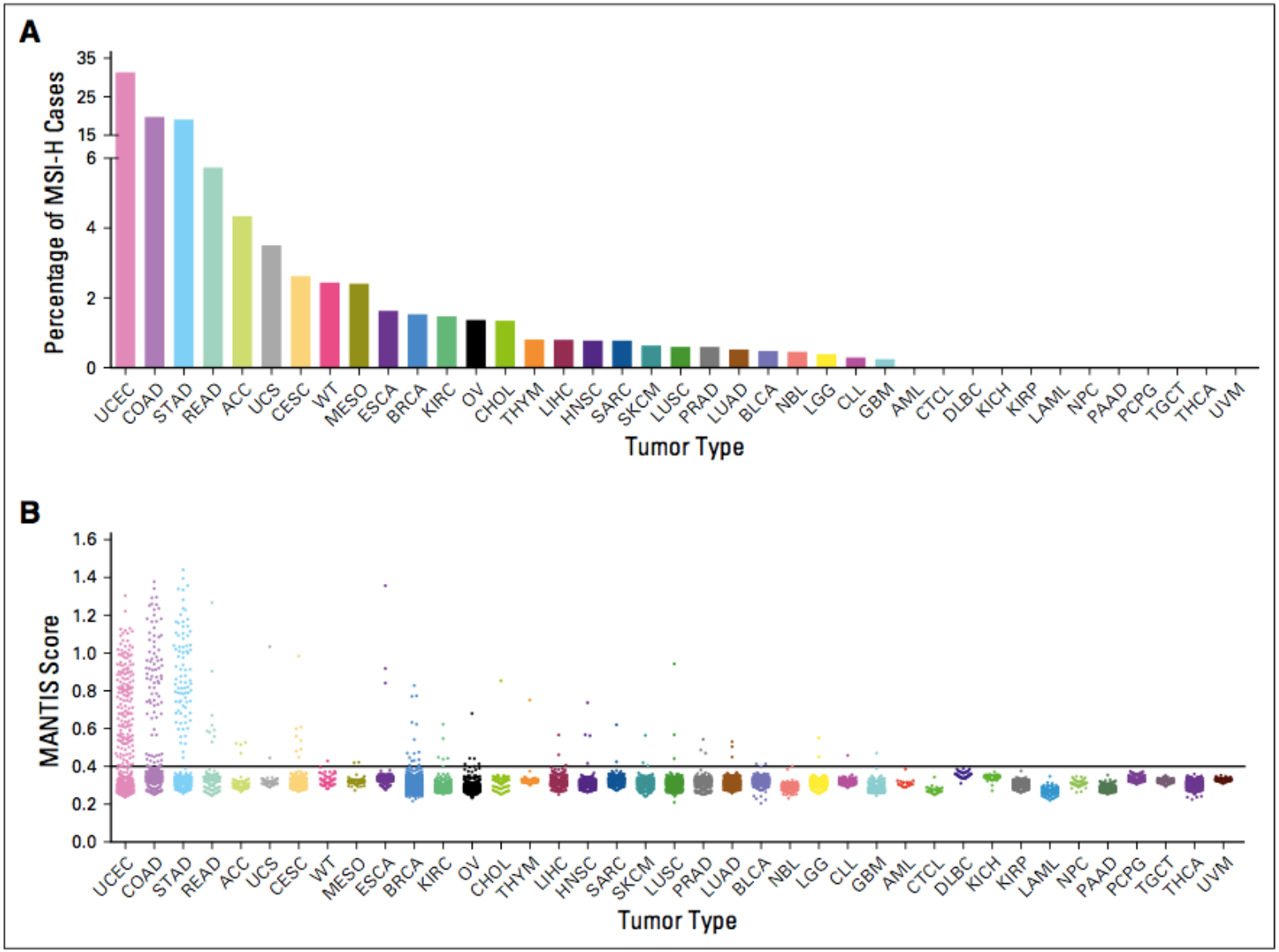
Schmid P et al NEJM 2022

S1801 primary endpoint: Event-free survival in melanoma



Sapna P. Patel, MD

Prevalence of microsatellite instability (MSI) across 39 human cancer types

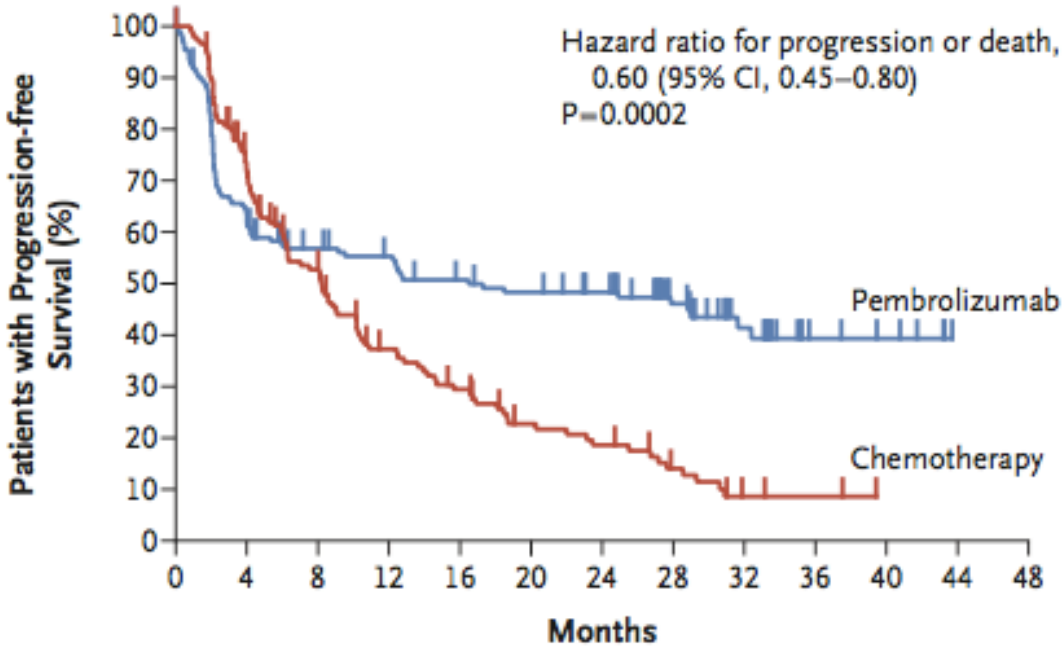


Boneville R. et al, JCO Precision Oncology 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

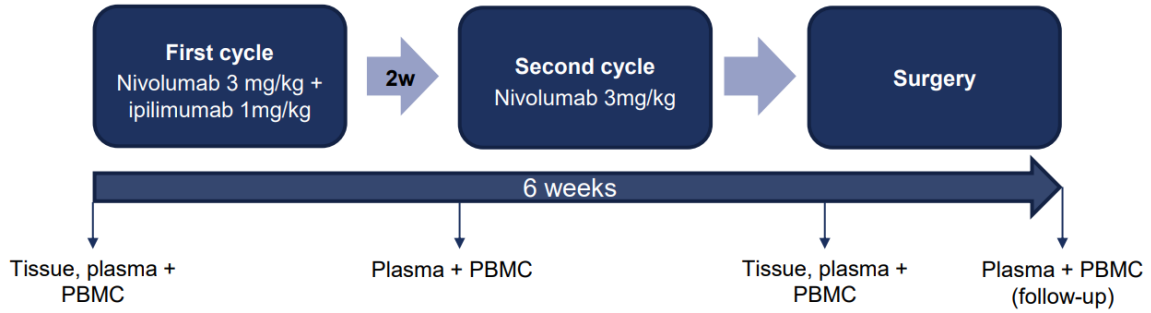


No. at Risk

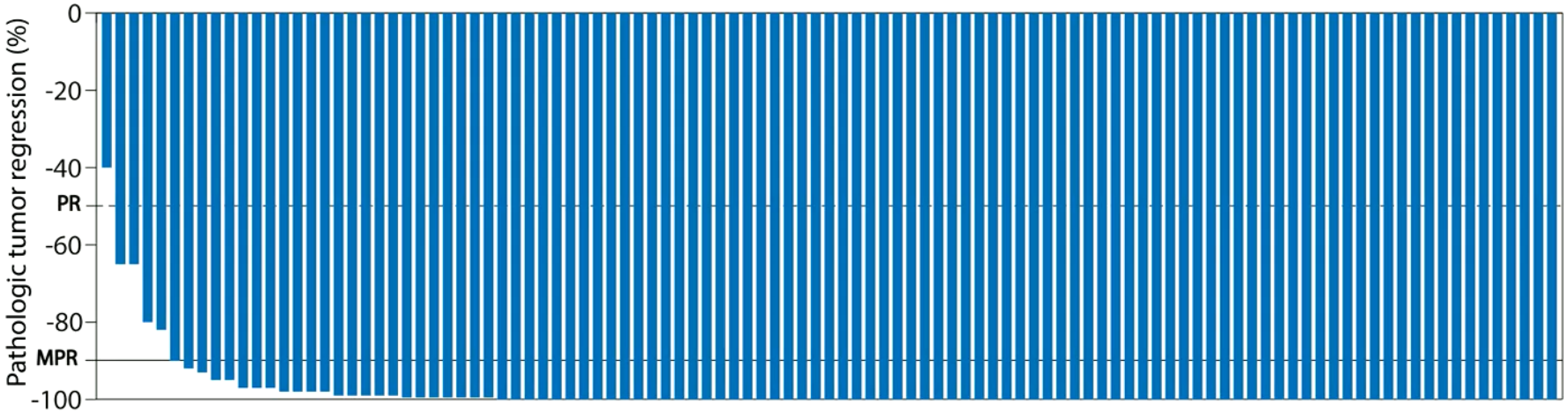
Pembrolizumab	153	96	77	72	64	60	55	37	20	7	5	0	0
Chemotherapy	154	100	68	43	33	22	18	11	4	3	0	0	0

Andrè T et al, NEJM 2020

Neoadjuvant Phase II NICHE-2 trial in untreated dMMR CC



Major pathologic response in 95% of patients; 67% pCR



M Shalabi et al, ESMO 2022

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445

CLINICAL PROBLEM

Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

RESULTS

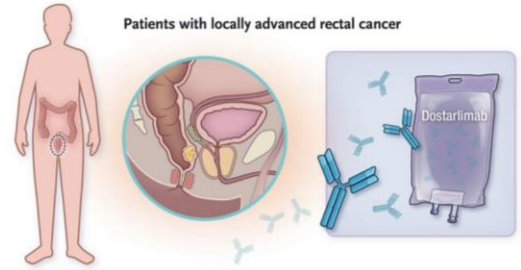
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

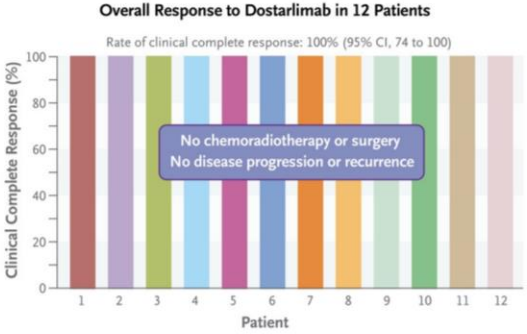
Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

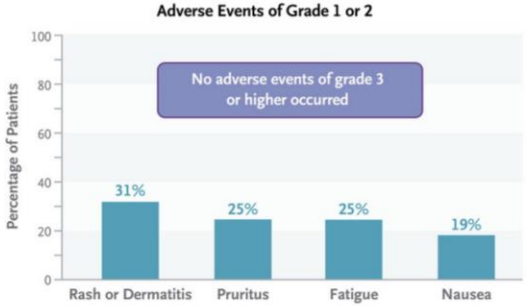
LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.

Links: Full Article | NEJM Quick Take | Editorial



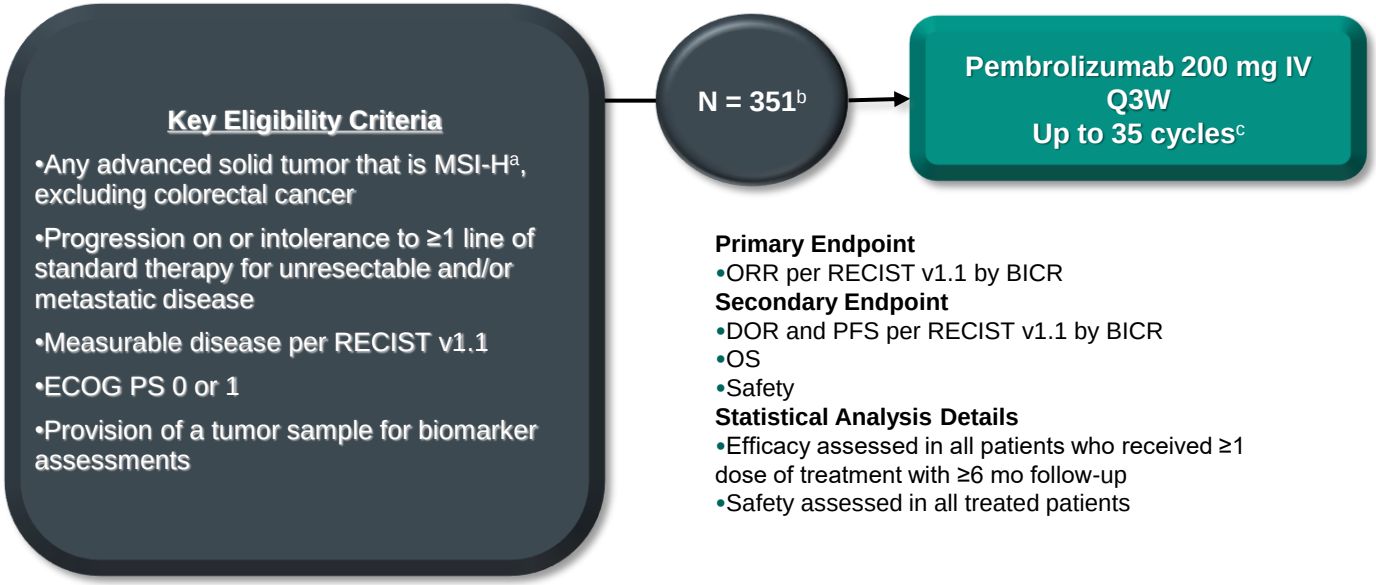




CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

KEYNOTE-158 (NCT02628067)
Cohort K – MSI-H Solid Tumors



Primary Endpoint
- ORR per RECIST v1.1 by BICR

Secondary Endpoint
- DOR and PFS per RECIST v1.1 by BICR
- OS
- Safety

Statistical Analysis Details
- Efficacy assessed in all patients who received ≥1 dose of treatment with ≥6 mo follow-up
- Safety assessed in all treated patients

Median (range) time from first dose to database cutoff: 37.5 (0.2–55.6) mo

BICR, blinded independent central review; IV, intravenous; PCR, polymerase chain reaction.
[a]MSI-H/dMMR status was assessed locally from a tumor tissue sample and defined as ≥1 of 4 MMR proteins absent by immunohistochemistry or ≥2 allelic loci size shifts of 5 microsatellite markers by PCR. [b]Tumor types occurring in ≥5% of patients were endometrial (22.5%), gastric (14.5%), small intestine (7.4%), ovarian (7.1%), cholangiocarcinoma (6.3%), pancreatic (6.3%), and brain (6.0%). [c]Treatment continued until PD, unacceptable toxicity, investigator decision, or withdrawal of consent. Data cutoff: October 5, 2020.

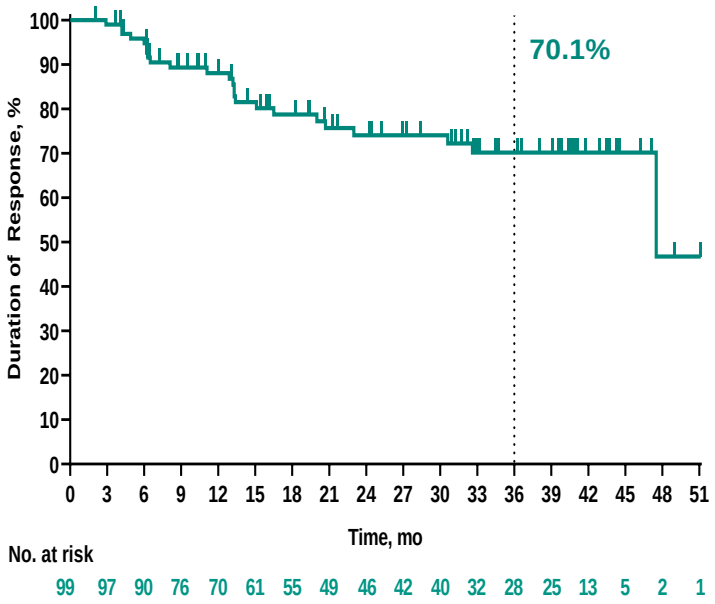
Maio M et al, Ann Oncol, 2022

Antitumor Activity

Efficacy Analysis Population	N = 321
ORR, % (95% CI)	**30.8 (25.8–36.2)**
CR	27 (8.4)
PR	72 (22.4)
SD	61 (19.0)
PD	131 (40.8)
Nonevaluable	3 (0.9)
No assessment[a]	27 (8.4)

CI, confidence interval. "+" indicates no PD by the time of last disease assessment.
[a]Patients who had no postbaseline imaging assessment.
Data cutoff: October 5, 2020

Duration of Response



Maio M et al, Ann Oncol, 2022

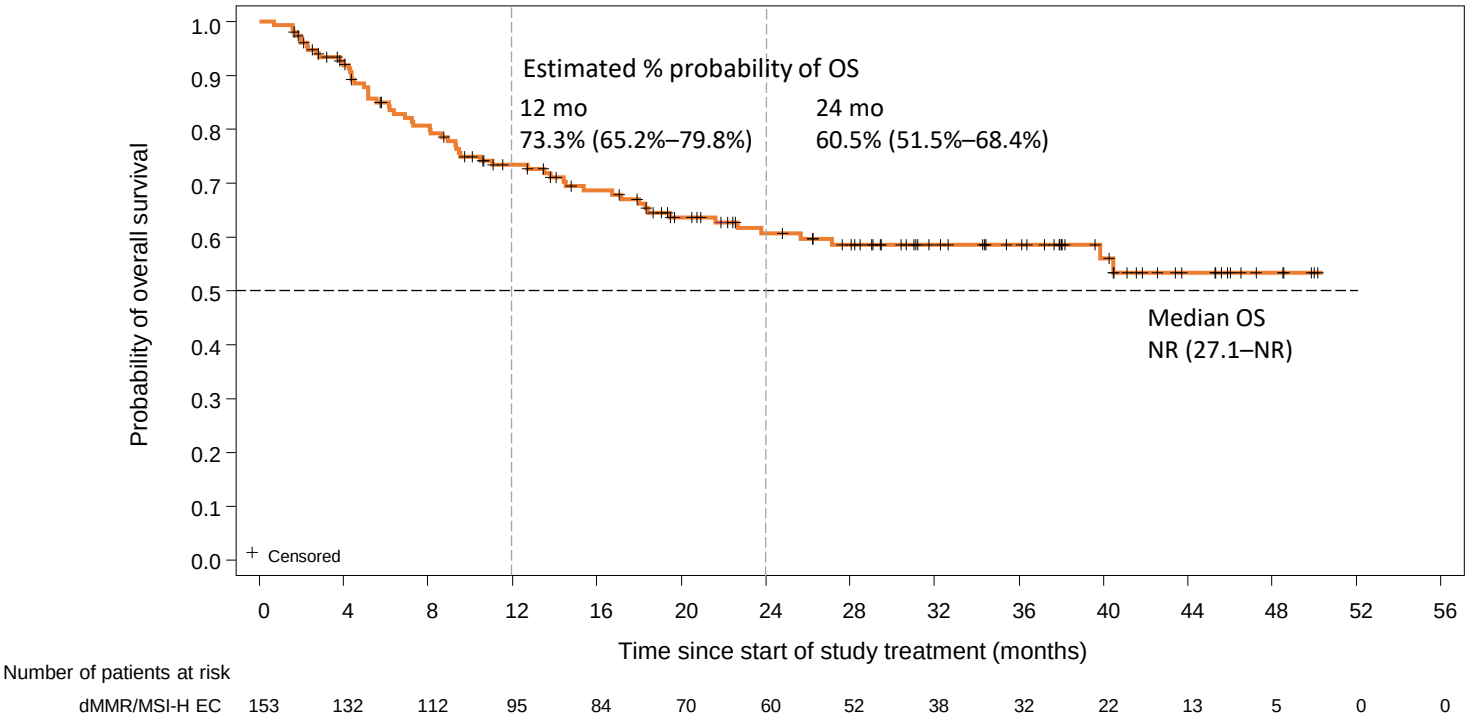
Dostarlimab in Advanced/Recurrent Mismatch Repair Deficient/Microsatellite Instability–High or Proficient/Stable Endometrial Cancer: the GARNET study

Ana Oaknin,[1] Bhavana Pothuri,[2] Lucy Gilbert,[3] Renaud Sabatier,[4] Sharad Ghamande,[5] Adriano Gravina,[6] Emiliano Calvo,[7] Susana Banerjee,[8] Rowan E. Miller,[9] Joanna Pikiel,[10] Mansoor R. Mirza,[11] Tao Duan,[12] Sybil Zildjian,[13] Eleftherios Zografos,[14] Jennifer Veneris,[13] Anna V. Tinker[15]

[1]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d' Hebron, Vall d' Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]Gynecologic Oncology Group (GOG) and Department of Obstetrics/Gynecology, Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [3]Division of Gynecologic Oncology, McGill University Health Centre, Montreal, Quebec, Canada; [4]Department of Medical Oncology, Institut Paoli Calmettes, Aix-Marseille University, Marseille, France; [5]Department of Obstetrics & Gynecology, Georgia Cancer Center, Augusta University, Augusta, GA, USA; [6]Clinical Trial Unit, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [7]START Madrid–CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [8]Gynaecology Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [9]University College London, St. Bartholomew' s Hospitals London, London, UK; [10]Department of Chemotherapy, Regional Center of Oncology, Gdansk, Poland; [11]Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark, Nordic Society of Gynaecologic Oncology–Clinical Trial Unit, Copenhagen, Denmark; [12]GlaxoSmithKline, Pennington, NJ, USA; [13]GlaxoSmithKline, Waltham, MA, USA; [14]GlaxoSmithKline, London, UK; [15]Department of Medicine, British Columbia Cancer, Vancouver Centre, University of British Columbia, Vancouver, British Columbia, Canada

ASCO 2022

Probability of Overall Survival: dMMR/MSI-H



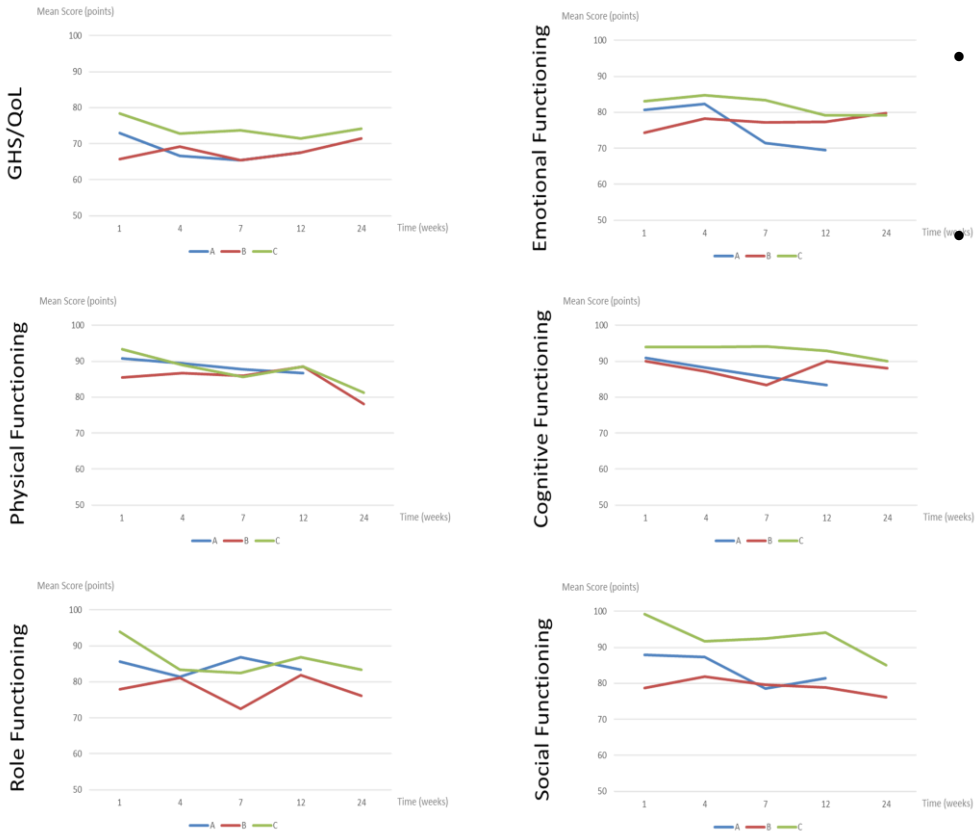
dMMR, mismatch repair deficient; EC, endometrial cancer; MSI-H, microsatellite instability–high; NR, not reached; OS, overall survival.

Ana Oaknin, ASCO 2022

Quanto l’utilizzo dell’immunoterapia impatta sulla qualità di vita del paziente oncologico?

Patient-reported outcomes and quality of life in melanoma patients with asymptomatic brain metastases: results from the phase III NIBIT-M2 trial

Anna Maria Di Giacomo, MD[1,2,3], Vanna Chiarion-Sileni, MD[4], Michele Del Vecchio, MD[5], Pier Francesco Ferrucci, MD[6], Michele Guida, MD[7], Pietro Quaglino, MD[8], Massimo Guidoboni, MD[9], Paolo Marchetti, Prof[10], Elena Simonetti, MD[1], Giovanni Amato, PhD[2], Alessia Covre, PhD[1], Roberto Camerini, MD[3], Luana Calabrò, MD[11], Monica Valente, MD[2], Mario Mandalà, MD[12], Diana Giannarelli, PhD[13], Michele Maio, Prof[1,2,3,†]



- **HRQoL** was comprehensively **preserved** in all treatment arms of the NIBIT-M2 study.
- Treatment with **ipilimumab plus nivolumab** in melanoma pts with asymptomatic BM **led to a lower decrease in the mean QLQ-C30 scores** as compared to pts treated with ipilimumab and fotemustine and fotemustine alone.

Di Giacomo AM et al, SMR 2022

European Journal of Cancer 169 (2022) 1–10

Available online at www.sciencedirect.com

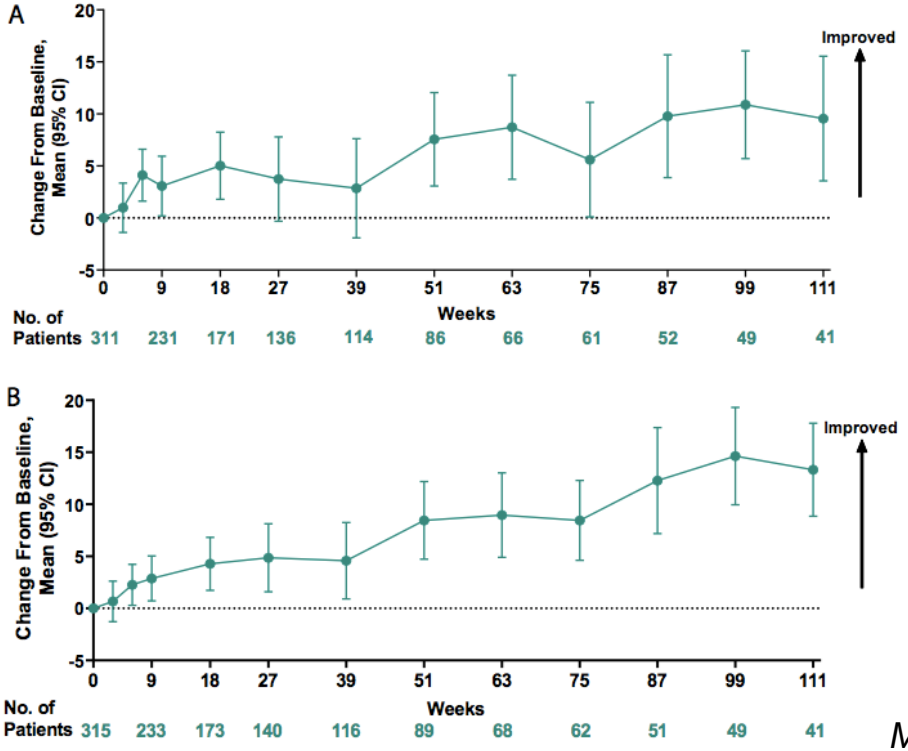
ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Health-related quality of life in patients treated with pembrolizumab for microsatellite instability–high/mismatch repair–deficient advanced solid tumours: Results from the KEYNOTE-158 study

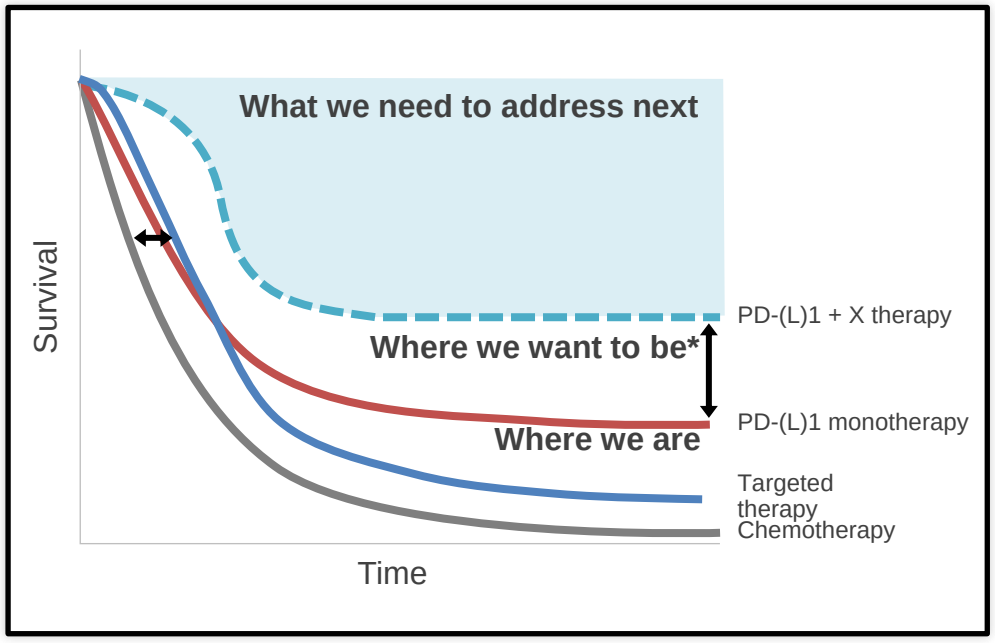
Change from baseline in (A) EORTC QLQ-C30 GHS/QoL scores and (B) EQ-5D-3L visual analogue scale scores



Maio M et al, Eur J Cancer 2022

Cosa dobbiamo fare per migliorare l’efficacia di questa strategia?

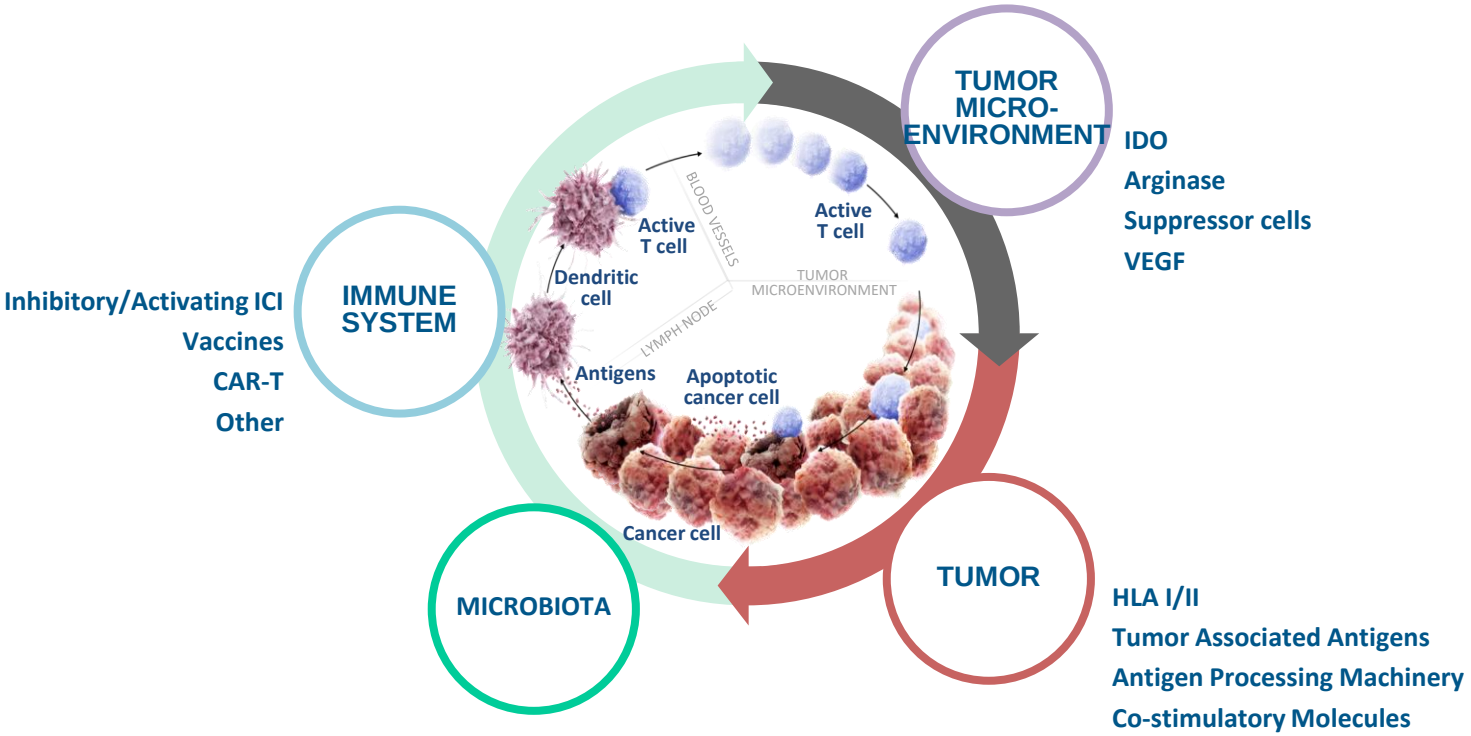
Anti-PD-(L)1 Therapies Have Improved OS in Various Tumor Types But Not All Patient Shown Responses



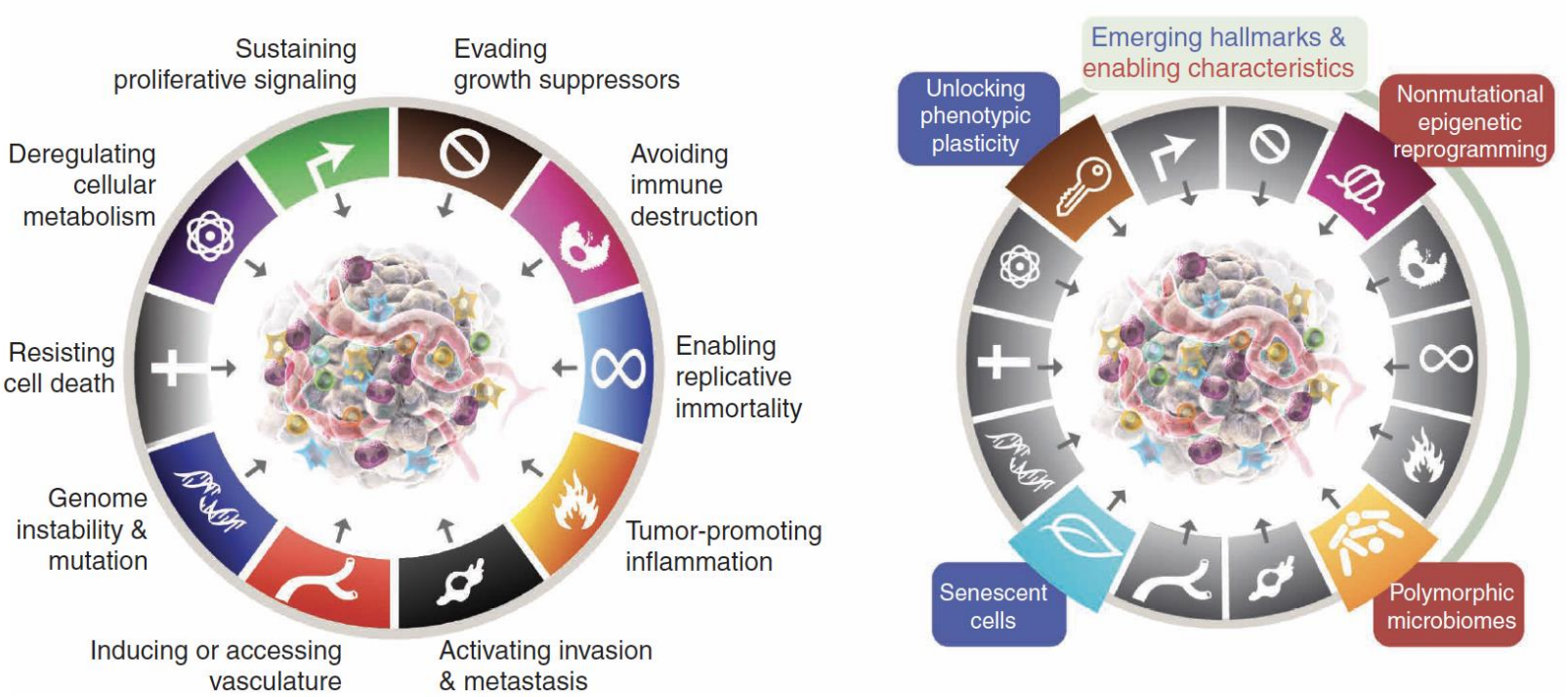
- Some tumors have **primary resistance mechanisms** and escape the immune response[1]
- **Several tumor types** with low frequency of response (e.g. breast, prostate, colon, or pancreatic)[1,2]
- Tumors may develop novel **escape mechanisms** leading to **secondary resistance**[2]
- **Secondary resistance** has been documented across a variety of tumor types[2]

The future of Immunotherapy

Targeting and modulating multiple compartments



EPIGENETIC REMODELING



Cancer Discovery 2022

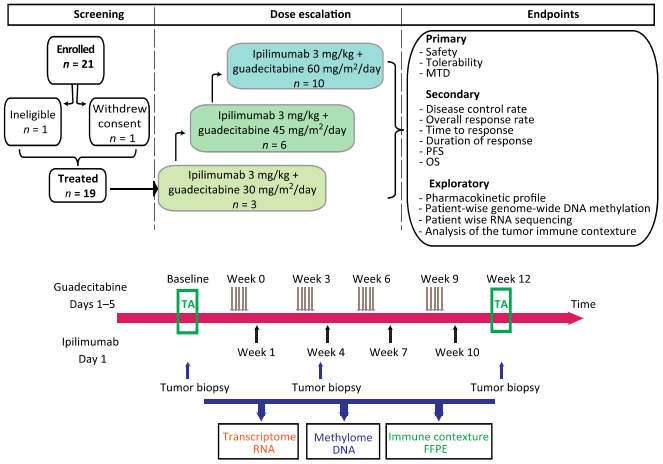
Epigenetic immuno-sequencing: the NIBIT-M4 Study NCT02608437

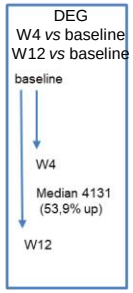
Clinical Trials: Immunotherapy

Clinical Cancer Research

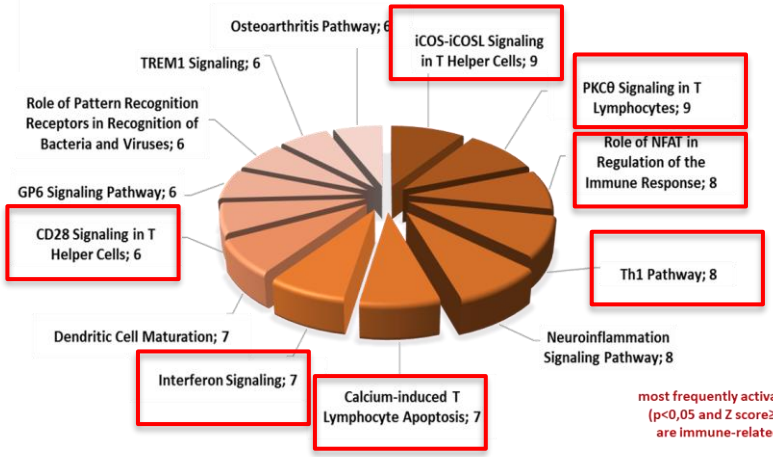
Guadecitabine Plus Ipilimumab in Unresectable Melanoma: The NIBIT-M4 Clinical Trial

Anna Maria Di Giacomo[1], Alessia Covre[1], Francesca Finotello[2], Dietmar Rieder[2], Riccardo Danielli[1], Luca Sigalotti[3], Diana Giannarelli[4], Florent Petitprez[5,6,7,8], Laetitia Lacroix[5,6,7], Monica Valente[1], Ornella Cutaia[1], Carolina Fazio[1], Giovanni Amato[1], Andrea Lazzeri[1], Santa Monterisi[1], Clelia Miracco[9], Sandra Coral[1], Andrea Anichini[10], Christoph Bock[11,12,13], Amelie Nemc[11], Aram Oganesian[14], James Lowder[14], Mohammad Azab[14], Wolf H. Fridman[5,6,7], Catherine Sautès-Fridman[5,6,7], Zlatko Trajanoski[2], and Michele Maio[1]





Differentially expressed pathways most frequently modulated at W4 and/or W12 vs. baseline



most frequently activated (p<0,05 and Z score≥2) are immune-related

Di Giacomo AM, Covre A et al. Clin Cancer Res 2019

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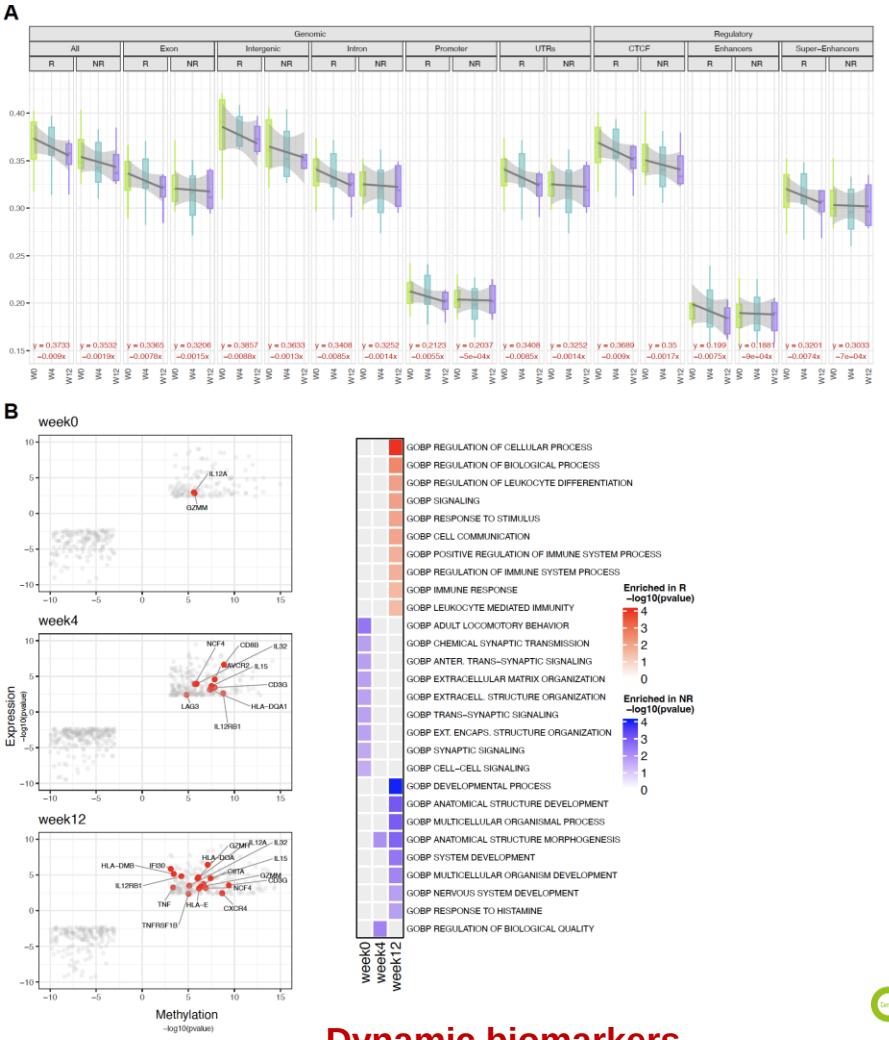
Article | Open Access | Published: 22 September 2023

Guadecitabine plus ipilimumab in unresectable melanoma: five-year follow-up and integrated multi-omic analysis in the phase 1b NIBIT-M4 trial

Teresa Maria Rosaria Noviello, Anna Maria Di Giacomo, Francesca Pia Caruso, Alessia Covre, Roberta Mortarini, Giovanni Scala, Maria Claudia Costa, Sandra Coral, Wolf H. Fridman, Catherine Sautès-Fridman, Silvia Brich, Giancarlo Pruneri, Elena Simonetti, Maria Fortunata Lofiego, Rossella Tufano, Davide Bedognetti, Andrea Anichini, Michele Maio ✉ & Michele Ceccarelli

Clinical activity N=19	
Ir-Objective response	
Ir-Complete Response	2/19 (10.5%)
Ir-Partial Response	3/19(15.8%)
Ir-Stable Disease	3/19(15.8%)
Ir-Disease progression	11/19 (57.9%)
Ir-ORR	5/19 [26%; 95% CI: 10.1–51.4
Ir-DCR	8/19 (42%; 95% CI: 21.1–66.0)
m-DoR	20.6 mo (95% CI, 12.4-28.8)
mOS	26.2 mo (95% CI: 3.8-48.6)]
1-year OS	73.3%
2-year OS	50.1%
3-year OS	38.5%
4-year OS	37%
5-year OS	29%



Dynamic biomarkers

NIBIT-ML1 clinical trial: study design

EUDRACT Number:2019-002986-36

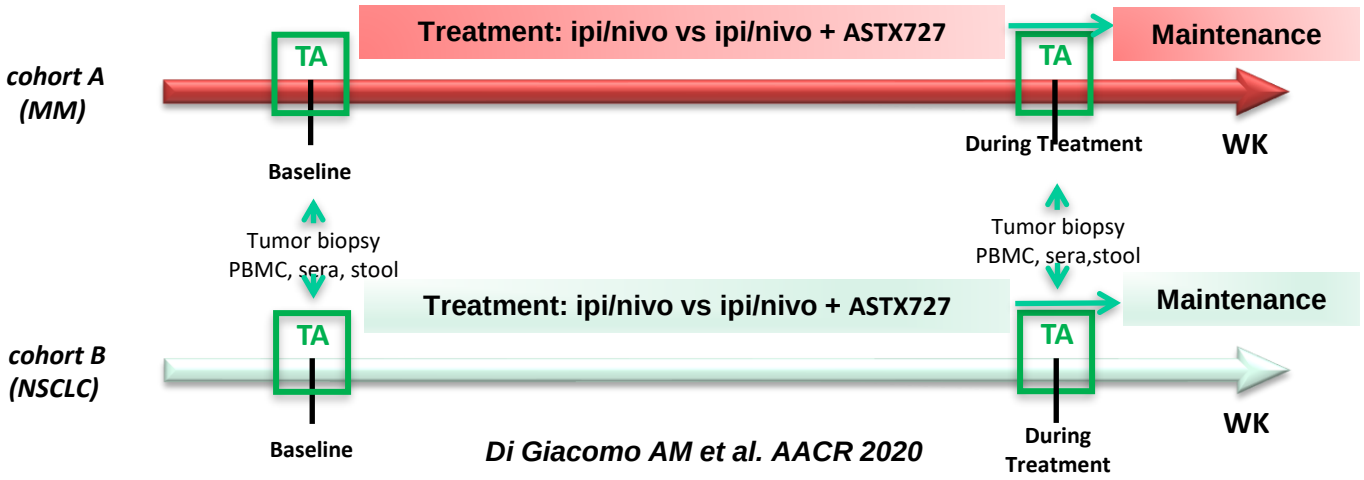
Run-in phase	Stage 1	Stage 2
cohort A (MM)	**ARM A n=18** **IPI+NIVO+ ASTX727**	**ARM A n=25** **IPI+NIVO+ ASTX727**
IPI+NIVO+ASTX727 **Cohort of 6 pts**	**ARM B n=18** **IPI+NIVO**	**ARM B n=25** **IPI+NIVO**
cohort B (NSCLC)	**ARM A n=18** **IPI+NIVO+ ASTX727**	**ARM A n=25** **IPI+NIVO+ ASTX727**
IPI+NIVO+ ASTX727 **Cohort of 6 pts**	**ARM B n=18** **IPI+NIVO**	**ARM B n=25** **IPI+NIVO**

Endpoints

Primary
ORR *according to iRECIST*

Secondary
Safety, tolerability
DCR, TTR, DOR, PFS,OS

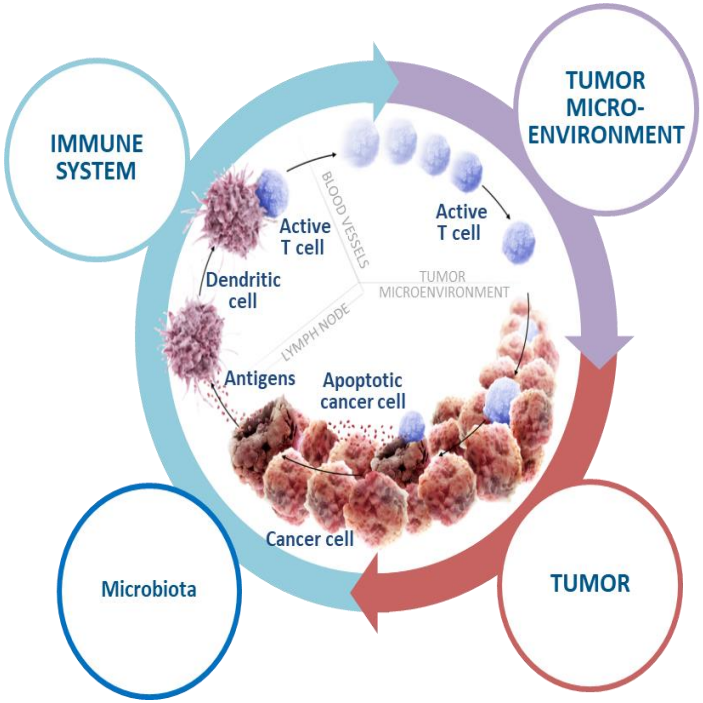
Exploratory
PK
Patient-wise genome-wide DNA methylation
Patient wise RNA sequencing –
Analysis of the tumour immune contexture



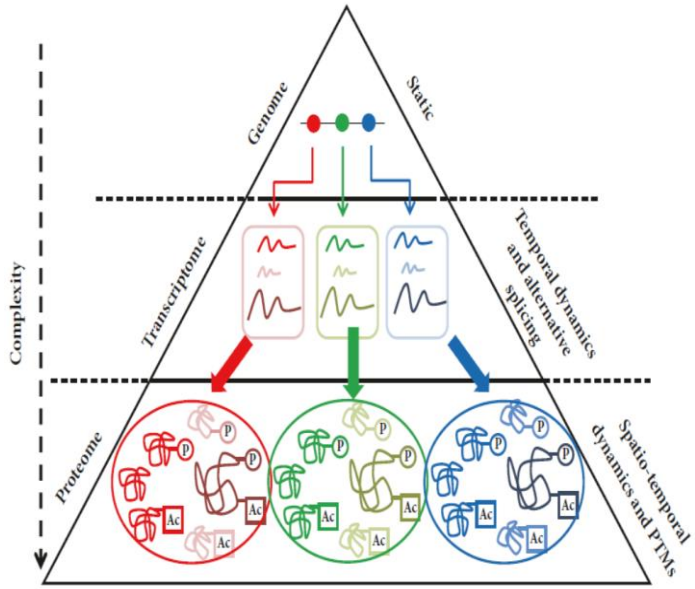
Di Giacomo AM et al. AACR 2020

Untangling the threads of Immunotherapy research

- Targeting and modulating multiple compartments to identify novel therapeutic strategies



- Identify biomarkers predictive of response and toxicity to improve efficacy of IO strategies



Chakraborty S et al, Biomed Res International 2018