MEETING DELLE NEUROSCIENZE TOSCANE

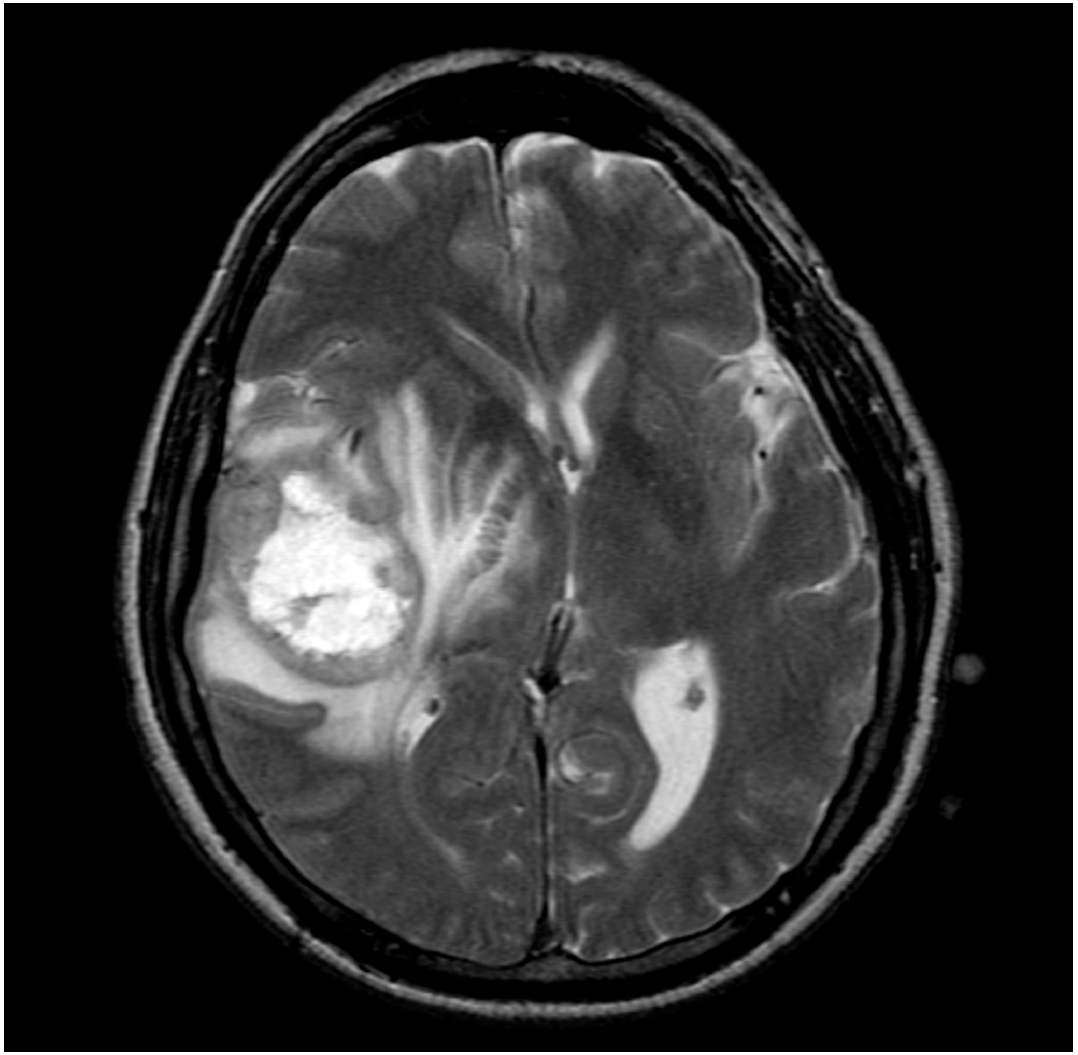
Grosseto, 6-8 Aprile, 2017

Nuovi approcci terapeutici nei tumori cerebrali

Anna Maria Di Giacomo

Medical Oncology and Immunotherapy
Center for Immuno-Oncology
University Hospital of Siena

Glioblastoma



Glioblastoma (GMB)

- GBM represent about 17% of all primary brain tumors; approximately 5,000 new cases/year in US
- Without therapy patients with GBM die within 3 months
- Patients treated with optimal therapy have a mOS of 12 months, with fewer than 25% surviving up to 2 years and fewer than 10% up to 5 years

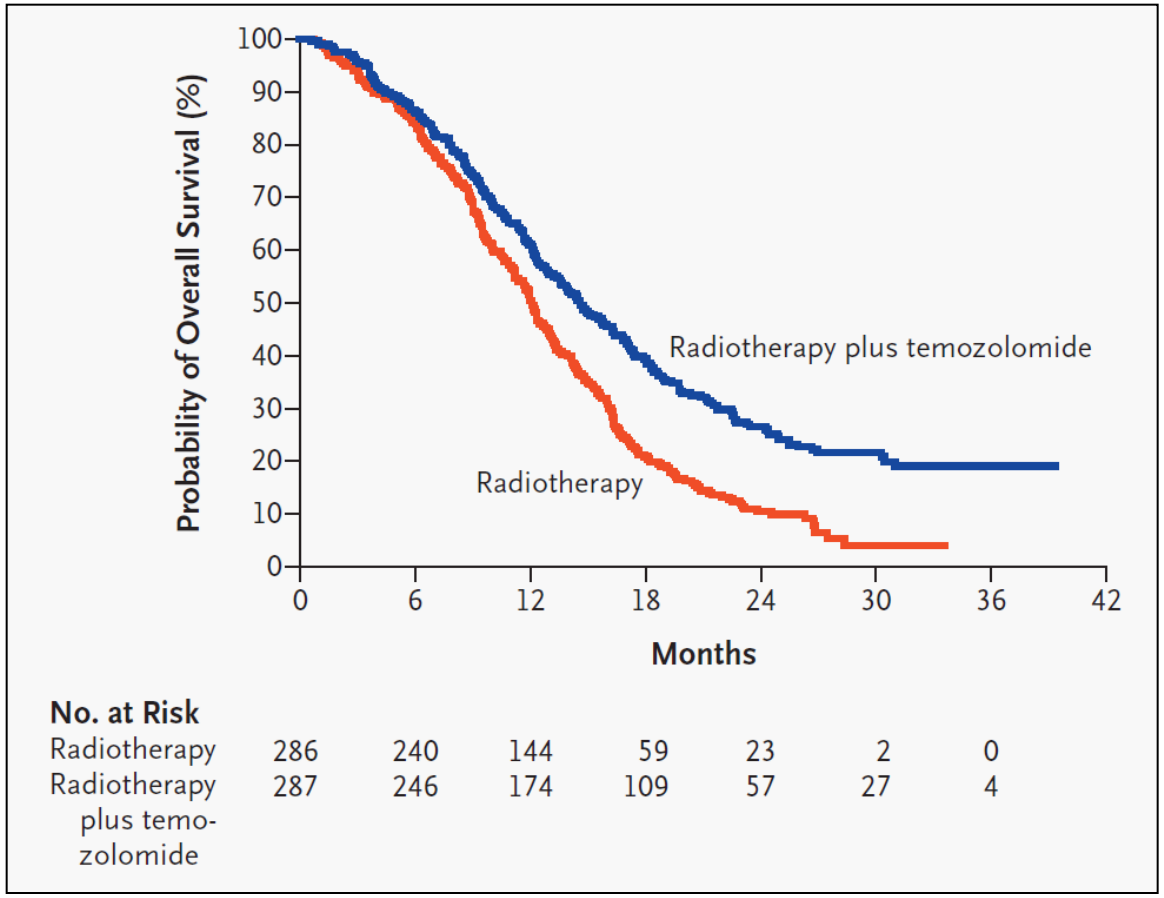
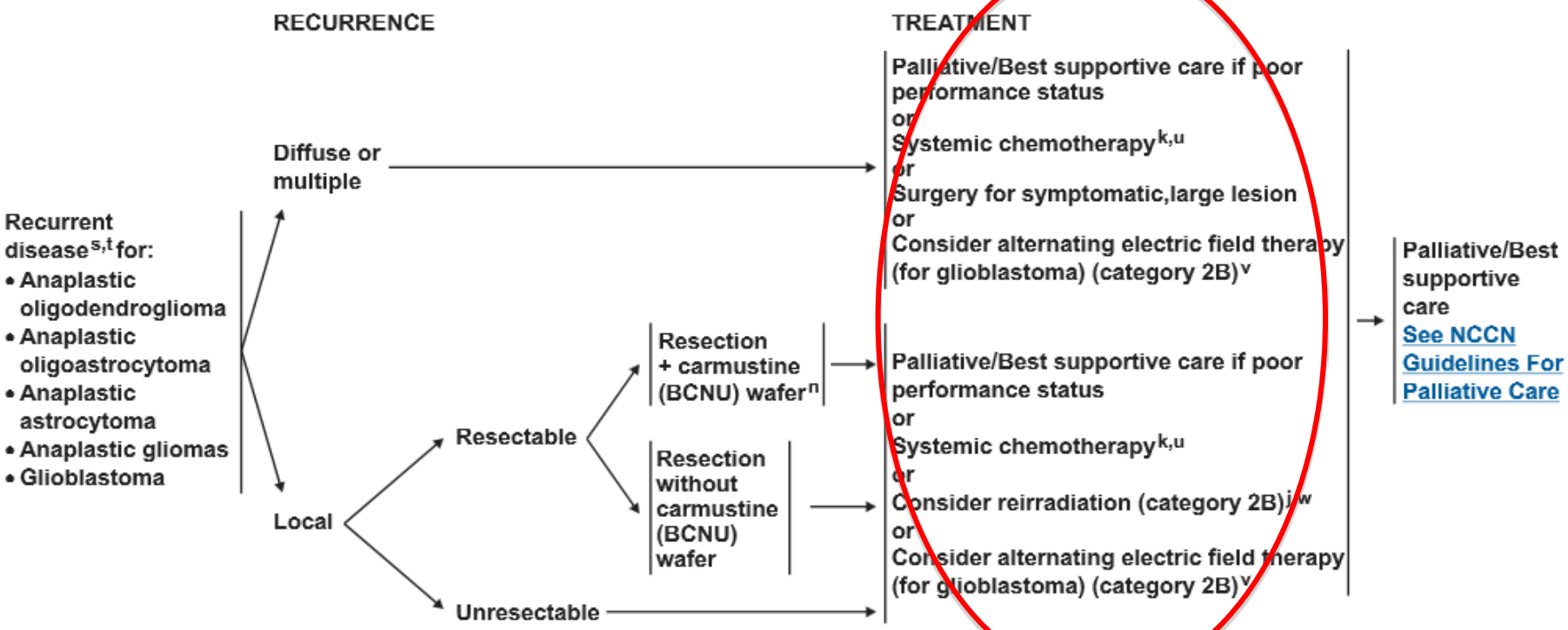


Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

Stupp R et al. N Engl J Med,2005;352-987

NCCN Guidelines Version 2.2013
Anaplastic Gliomas/Glioblastoma[a]



CLINICAL TRIAL

[a] This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

[j] See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

[k] See Principles of Brain Tumor Systemic Therapy (BRAIN-D).

[n] Treatment with carmustine wafer, reirradiation, or multiple prior systemic therapies, may impact enrollment in some adjuvant clinical trials.

[s] Consider MR spectroscopy, MR perfusion, or brain PET to rule out radiation necrosis.

[t] Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging. With pseudoprogression, stabilization or improvement should be expected within 3 mo of the end of radiotherapy.

[u] Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.

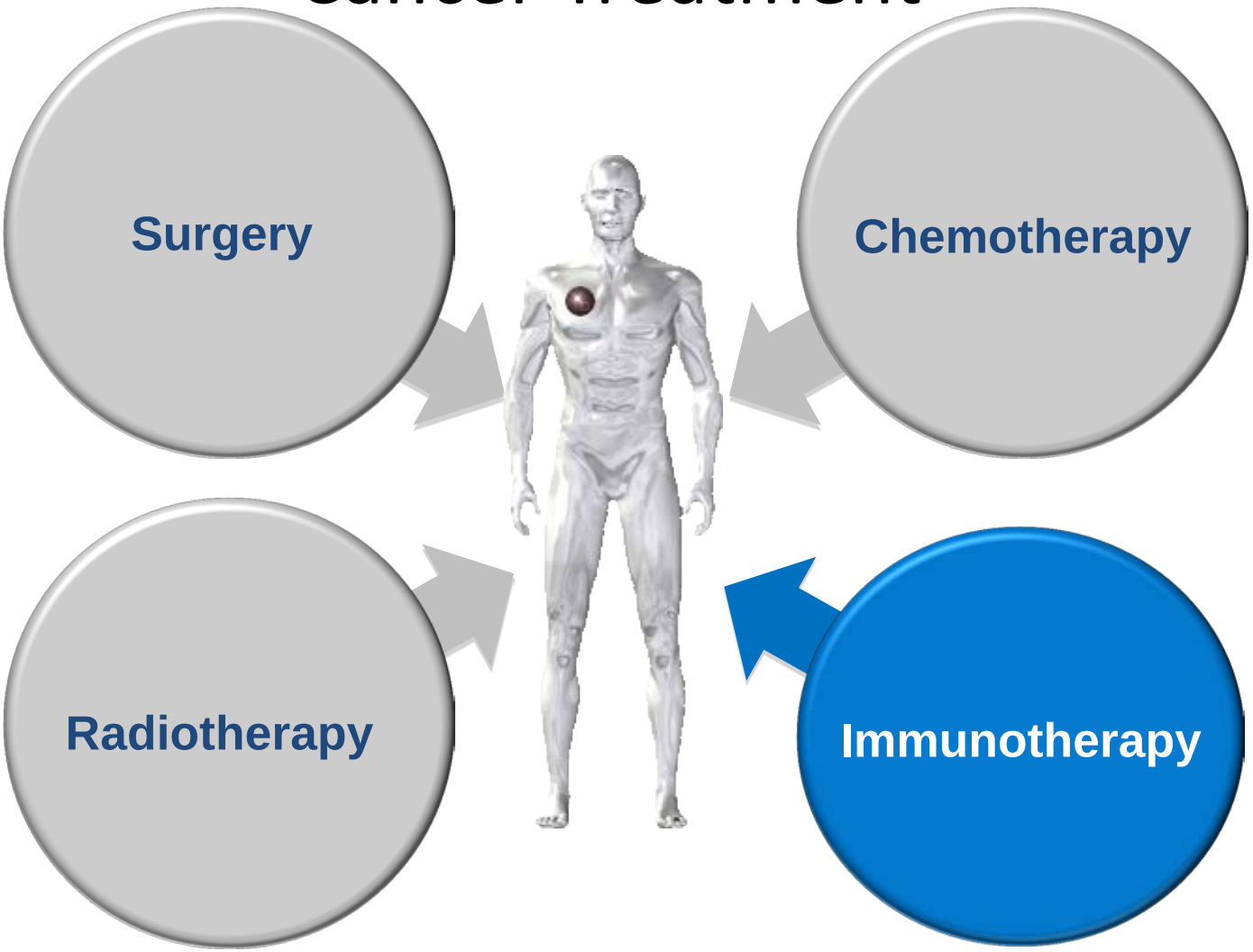
[v] Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality. European Journal of Cancer 2012;48:2192-2202.

[w] Especially if long interval since prior RT and/or if there was a good response to prior RT.

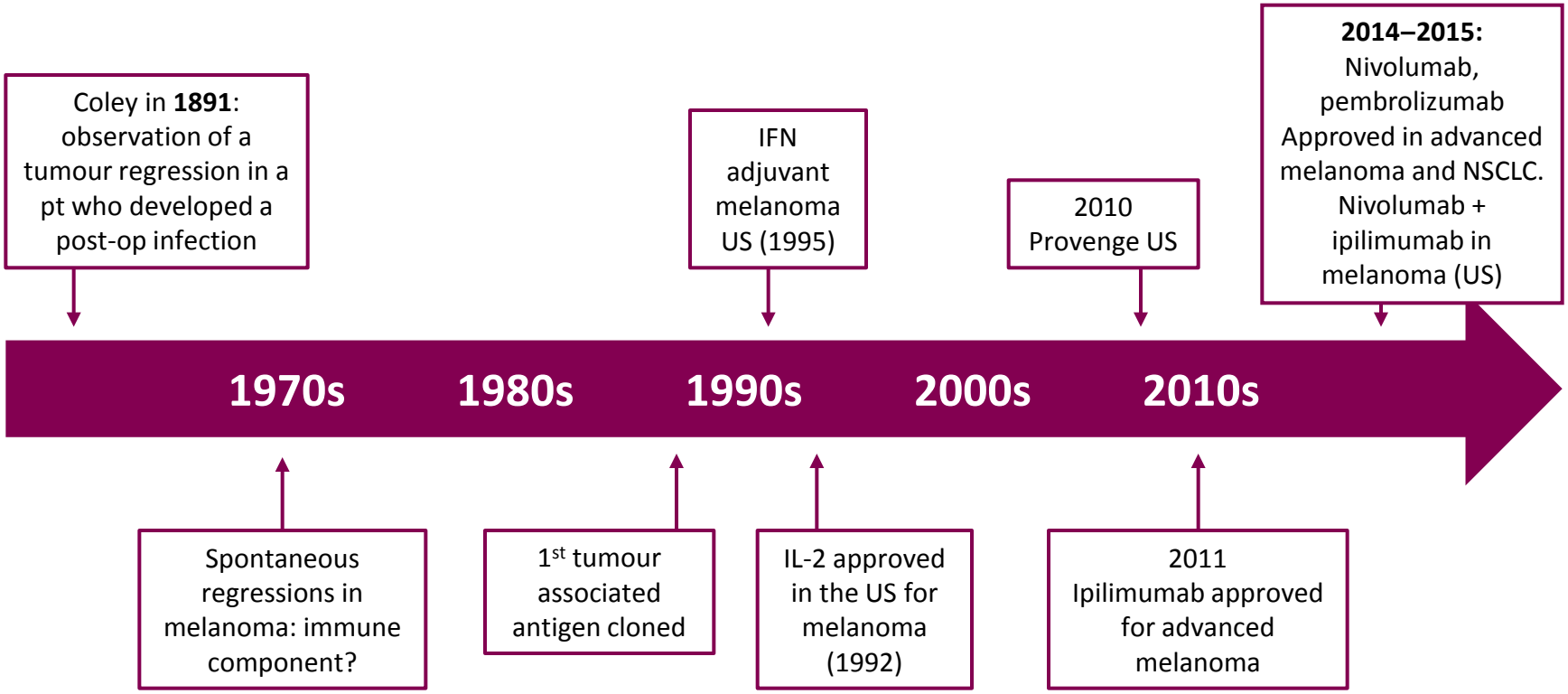
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2013, 04/25/13 © National Comprehensive Cancer Network, Inc. 2013, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

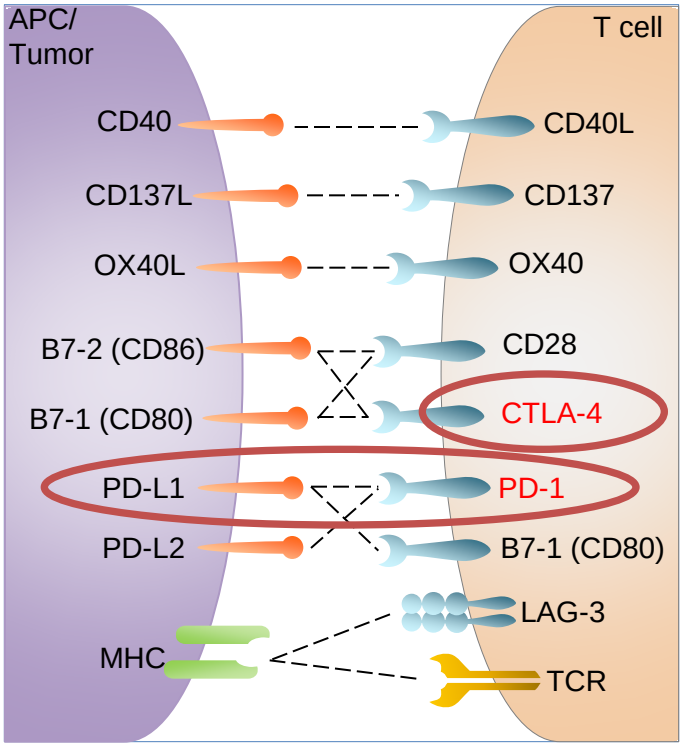
Evolving Therapeutic Options for Cancer Treatment



A historical view of immunotherapy…



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

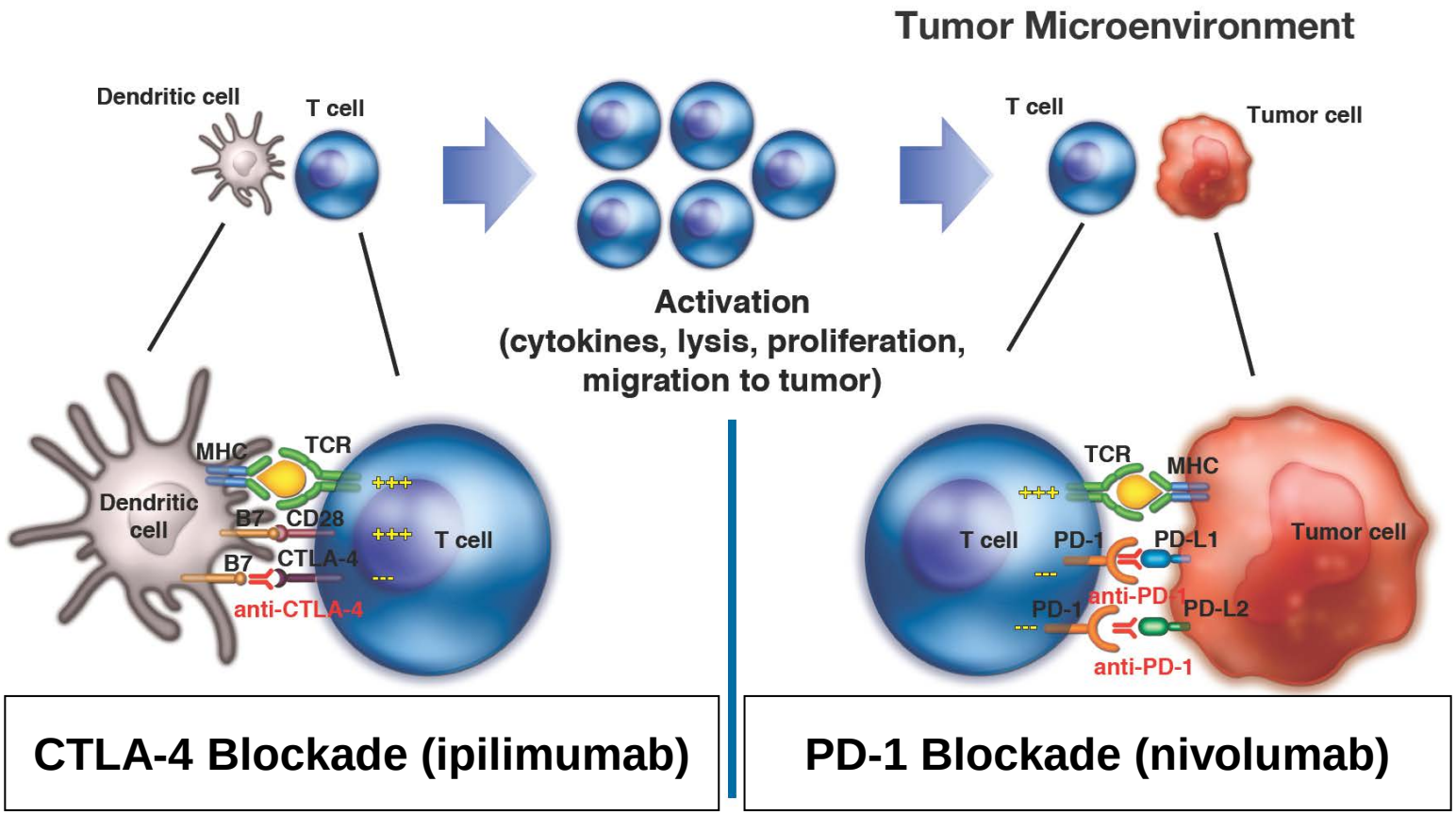
Inhibition
Inhibition
Inhibition
Inhibition

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.

Immune Checkpoint Pathways

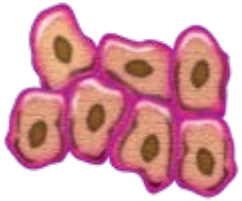


CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4 ; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.

Cancer-cell directed vs immune-system directed cancer treatment: a matter of time

TIME

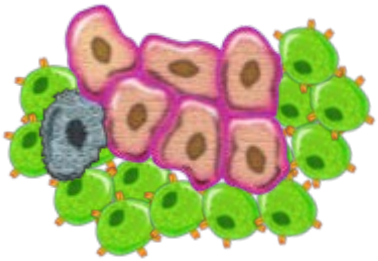
Chemotherapy/ target therapy



Tumour cell destruction

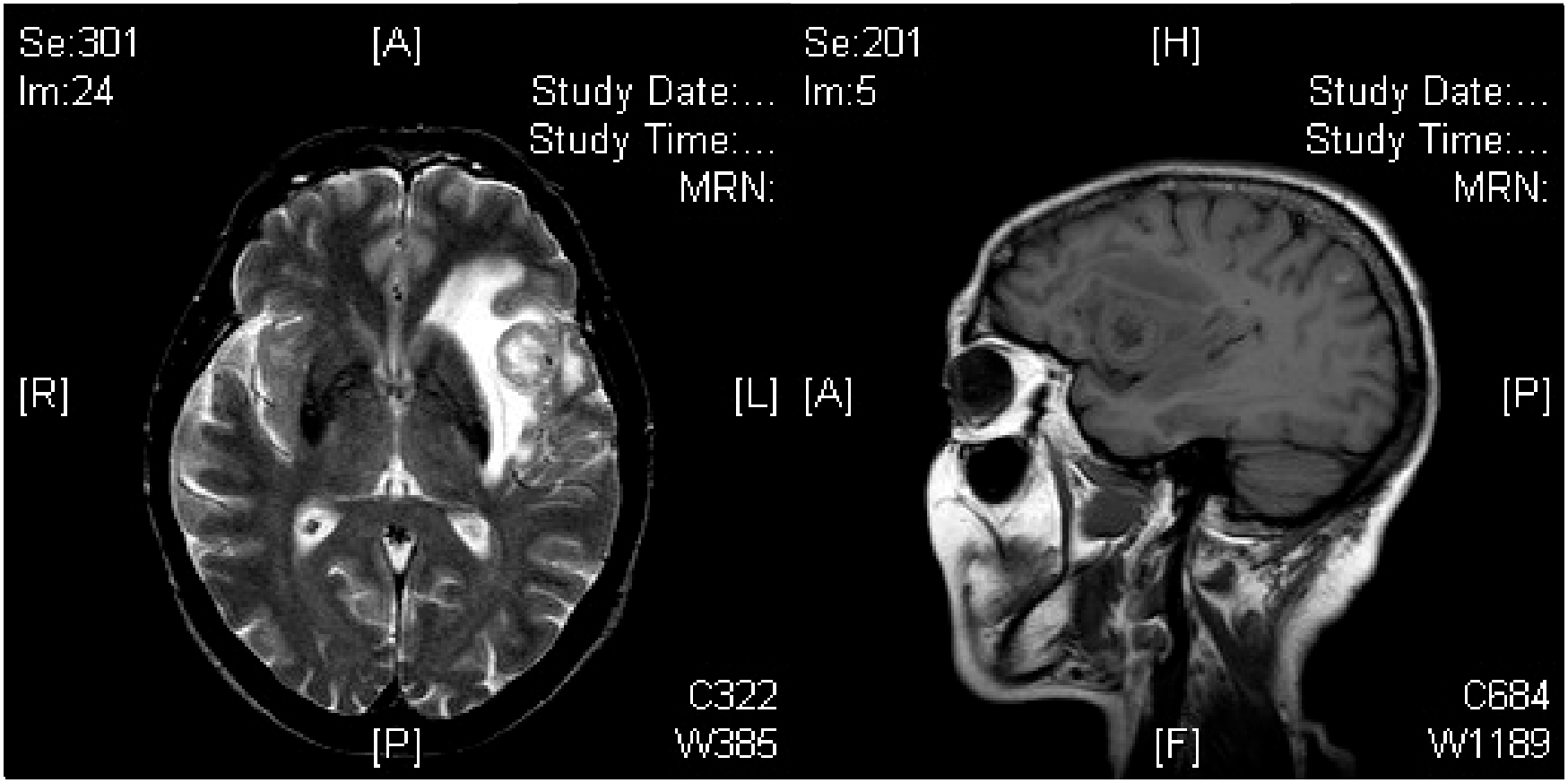
Immunotherapy

Immune system activation



Tumour cell destruction

Effect in the CNS?



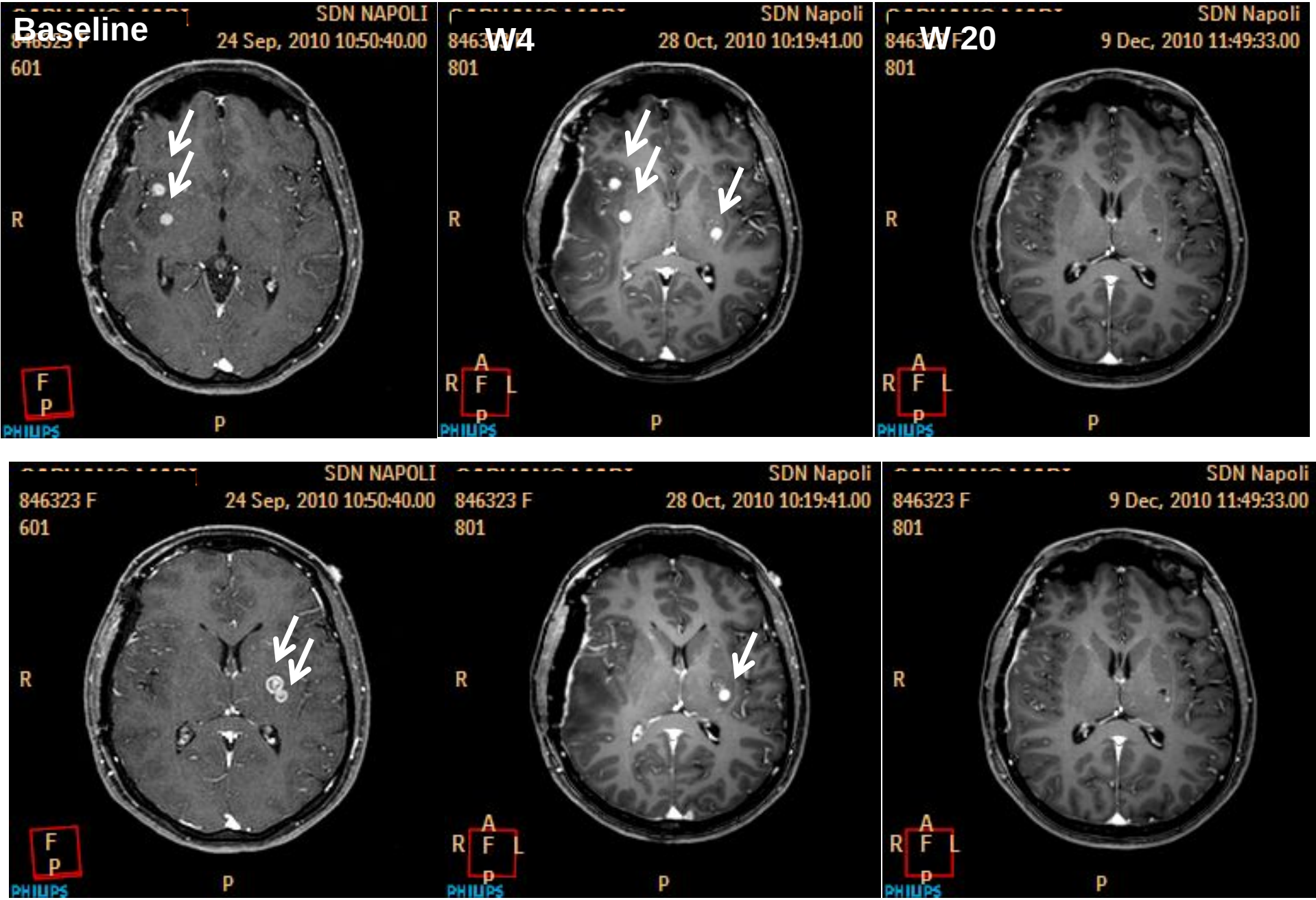
THE LANCET Oncology
Volume 13, Issue 9; September 2012, Pages 879-886

Articles

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

NIBIT M1– Patient 2014

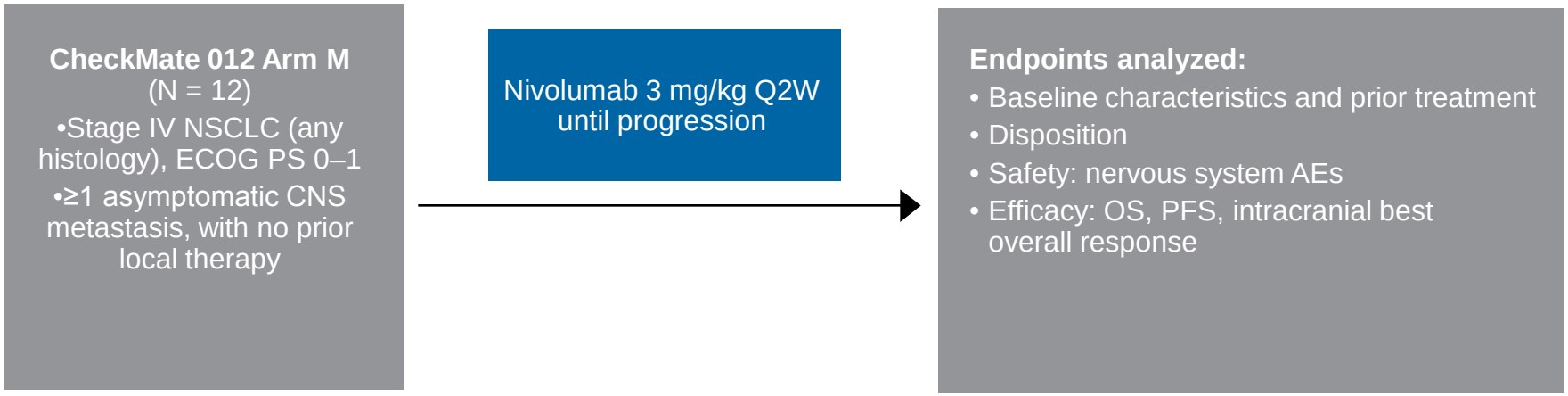


NIBIT - M1
3-years survival update

Secondary Endpoints	**Study population (N=86)**	**Patients with MBM (N=20)**
Median OS, months (95% CI)	12.9 (7.1-18.7)	12.7 (2.7-22.7)
3-year survival rate, % (95% CI)	28.5 (20.1-41.3)	27.8 (17.2-60.6)
Median ir-PFS, months (95% CI)	4.5 (3.1-5.9)	3.4 (2.3-4.5)

Di Giacomo AM et al., Annals Oncol 2015

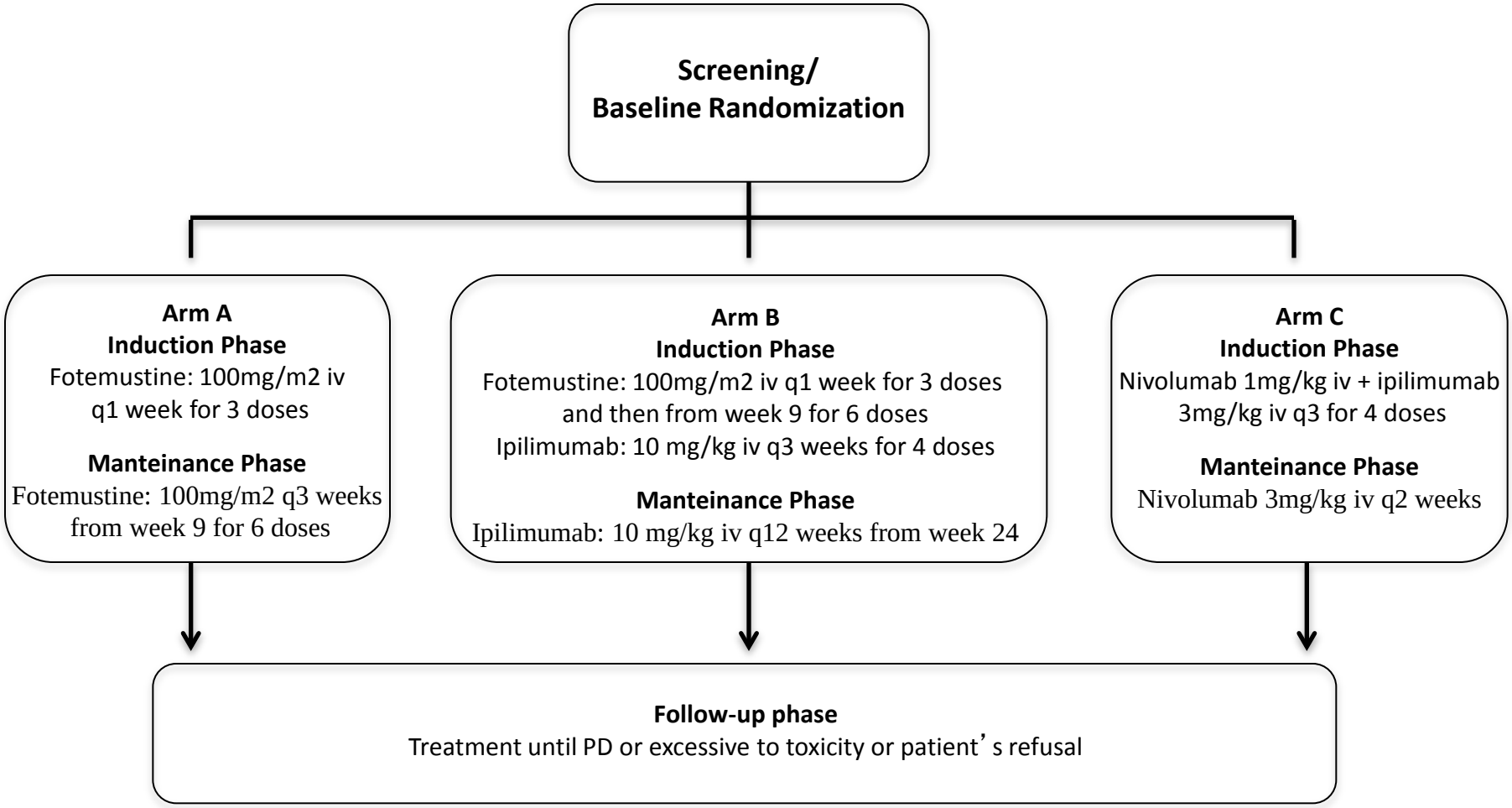
CheckMate 012 Arm M: Nivolumab in NSCLC Patients With Untreated CNS Metastases



2/12 pts (16.7%) achieved intracranial responses, including one CR long-lasting (>10.5 mo)

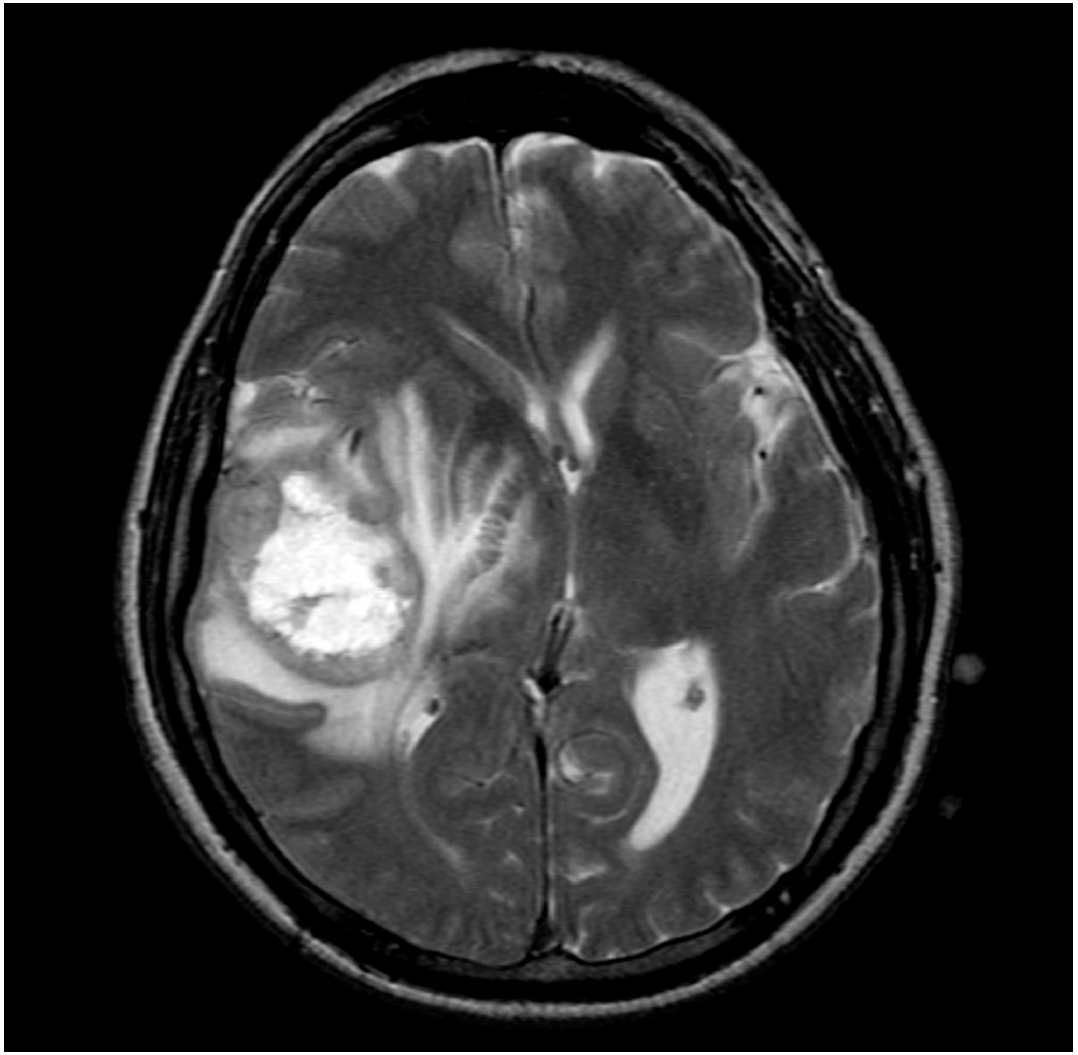
FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

The NIBIT-M2 study design



Ongoing Clinical Trials	NCT	Phase	Status	Treatment(s)
Anti-PD 1 Brain Collaboration for Patients With Melanoma Brain (ABC)	NCT02374242	II	Recruiting	Nivolumab
Nivolumab in Symptomatic Brain Metastases (CA209-322)	NCT02621515	II	Recruiting	Nivolumab
A randomized, Phase III study of Fotemustine versus the Combination of Fotemustine and Ipilimumab in Patients with Metastatic Melanoma with brain metastasis (NIBIT-M2 Study)	NCT02460068	III	Recruiting	Fotemustine Ipilimumab+Fotemustine Ipilimumab+Nivolumab
GEM STUDY: Radiation and Yervoy in pts with melanoma and brain mts (GRAY-B)	NCT021151390	II	Recruiting	Ipilimumab+WBRT
SRS plus Ipilimumab	NCT01950195	I	Recruiting	Ipilimumab+SRS
A Multi-Center Phase 2 Open-Label Study to Evaluate Safety, Efficacy in Subjects With MM to the Brain Treated With Nivolumab in Combination With Ipilimumab Followed by Nivolumab (CheckMate 204)	NCT02320058	II	Recruiting	Ipilimumab+Nivolumab
MK-3475 in Melanoma and NSCLC Patients With Brain Metastases	NCT02085070	II	Recruiting	Nivolumab

Glioblastoma



VOLUME 34 · NUMBER 19 · JULY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency

Eric Bouffet, Valérie Larouche, Brittany B. Campbell, Daniele Merico, Richard de Borja, Melyssa Aronson, Carol Durno, Joerg Krueger, Vanja Cabric, Vijay Ramaswamy, Nataliya Zhukova, Gary Mason, Roula Farah, Samina Afzal, Michal Yalon, Gideon Rechavi, Vanan Magimairajan, Michael F. Walsh, Shlomi Constantini, Rina Dvir, Ronit Elhasid, Alyssa Reddy, Michael Osborn, Michael Sullivan, Jordan Hansford, Andrew Dodgshun, Nancy Klauber-Demore, Lindsay Peterson, Sunil Patel, Scott Lindhorst, Jeffrey Atkinson, Zane Cohen, Rachel Laframboise, Peter Dirks, Michael Taylor, David Malkin, Steffen Albrecht, Roy W.R. Dudley, Nada Jabado, Cynthia E. Hawkins, Adam Shlien, and Uri Tabori

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on March 21, 2016.

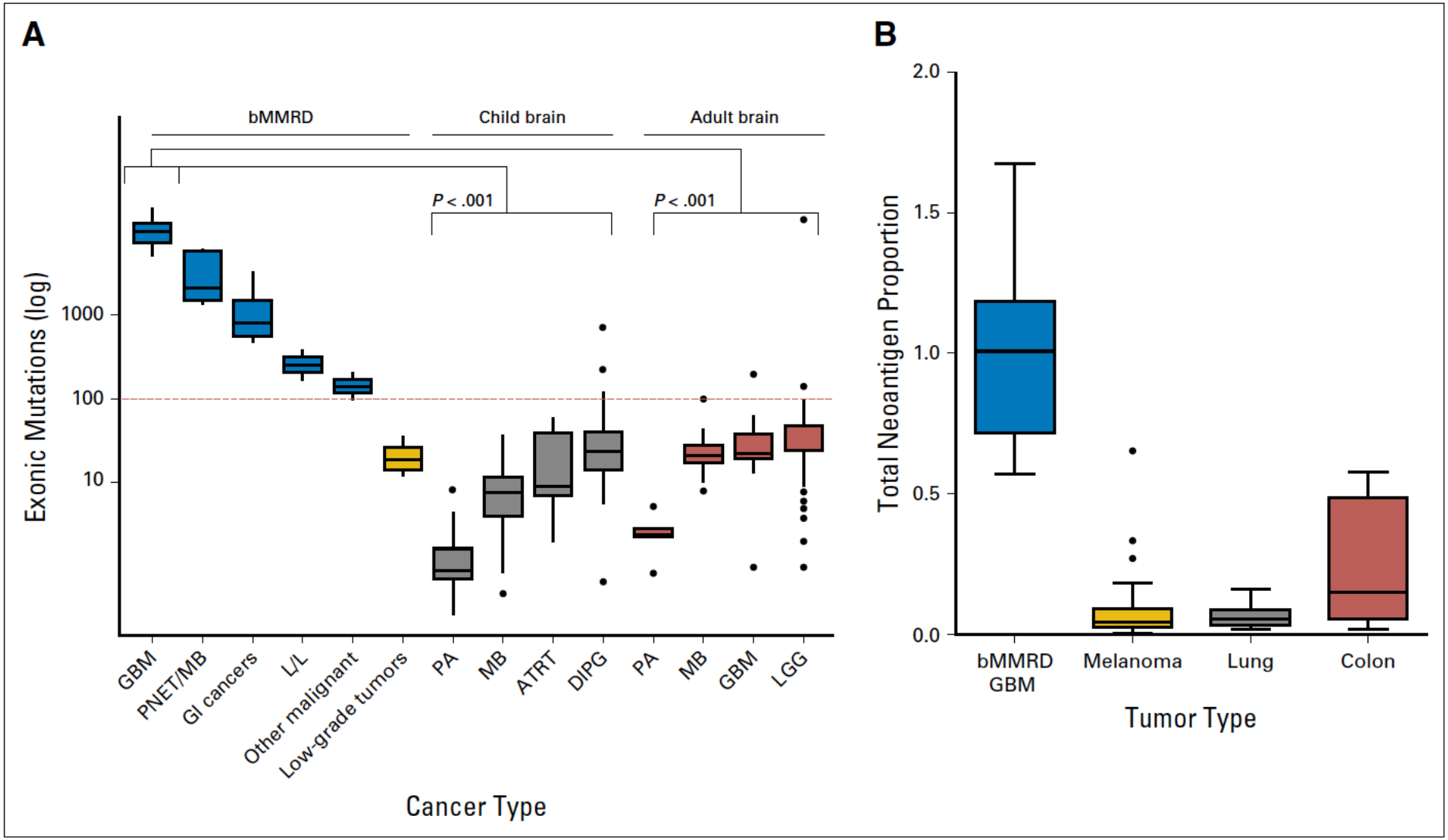
Written on behalf of the International Biallelic Mismatch Repair Deficiency Consortium and KiCS, the SickKids Cancer Sequencing Program.

ABSTRACT

Purpose

Recurrent glioblastoma multiforme (GBM) is incurable with current therapies. Biallelic mismatch repair deficiency (bMMRD) is a highly penetrant childhood cancer syndrome often resulting in GBM characterized by a high mutational burden. Evidence suggests that high mutation and neoantigen loads are associated with response to immune checkpoint inhibition.

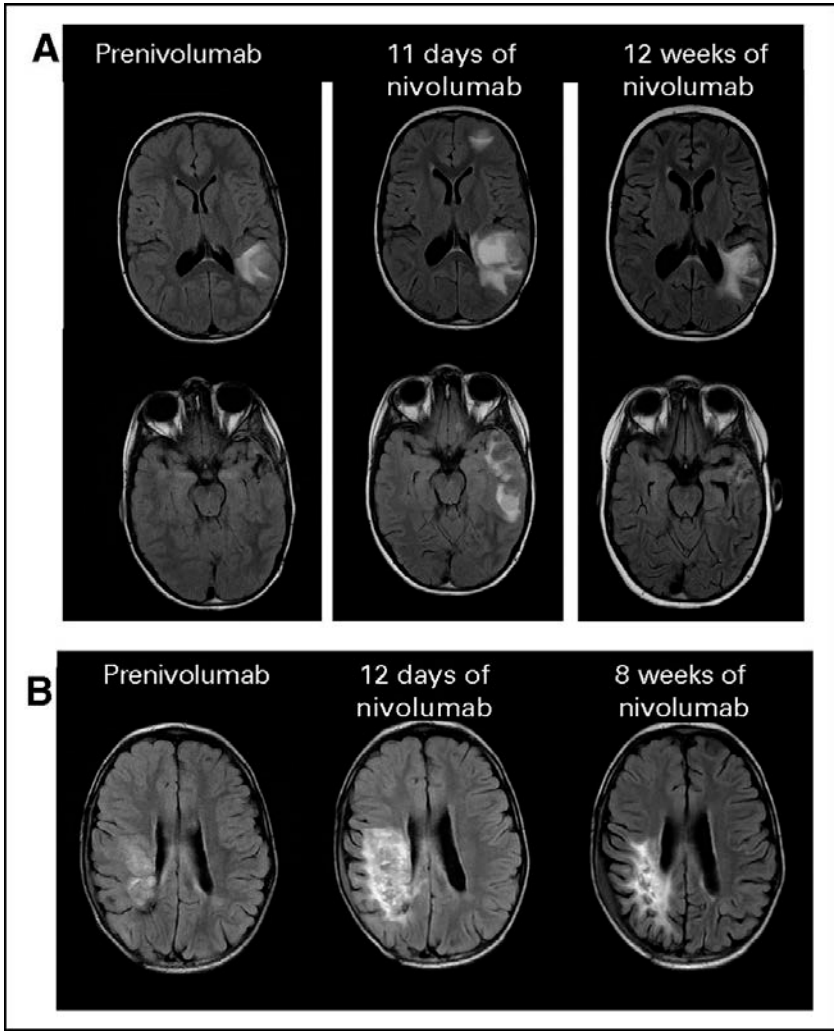
GBM from germline biallelic Mismatch Repair Deficiency (bMMRD) have higher mutational load and neoantigen



Case report: Two siblings with recurrent multifocal GBM treated with anti-PD1 nivolumab showing clinically significant durable responses.

Bouffet e., et al. J Clin Oncol 2016

MRI of two siblings with biallelic Mismatch Repair Deficiency treated with nivolumab



Eric Bouffet et al. JCO 2016;34:2206-2211

©2016 by American Society of Clinical Oncology

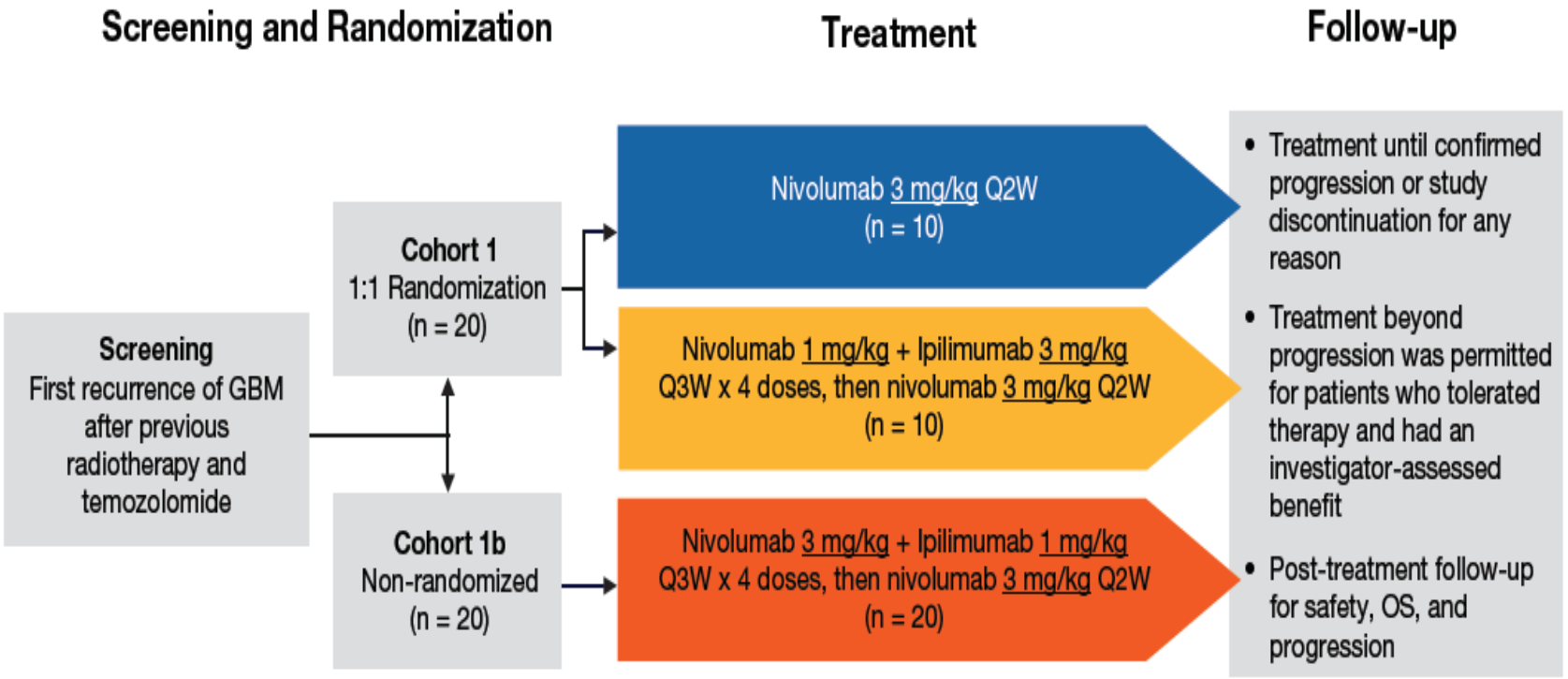
Safety and Activity of Nivolumab Monotherapy and Nivolumab in Combination With Ipilimumab in Recurrent Glioblastoma: Updated Results From CheckMate 143

• David A. Reardon,[1] John Sampson,[2] Solmaz Sahebjam,[3]Michael Lim,[4] Joachim Baehring,[5] Gordana Vlahovic,[2]
Timothy Cloughesy,[6] Lewis Strauss,[7] Robert Latek,[7] Prashni Paliwal,[7]
Chris Harbison,[7] Alfredo Voloschin,[8] Antonio Omuro[9]

• [1]Dana-Farber Cancer Institute and Harvard University School of Medicine, Boston, MA, USA;
[2]Duke University Medical Center, Durham, NC, USA; [3]Moffitt Cancer Center, Tampa, FL, USA;
[4]The Johns Hopkins Hospital, Baltimore, MD, USA; [5]Yale School of Medicine, New Haven, CT, USA;
[6]University of California, Los Angeles, Los Angeles, CA, USA; [7]Bristol-Myers Squibb, Princeton, NJ, USA;
[8]Emory University School of Medicine, Atlanta, GA, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA

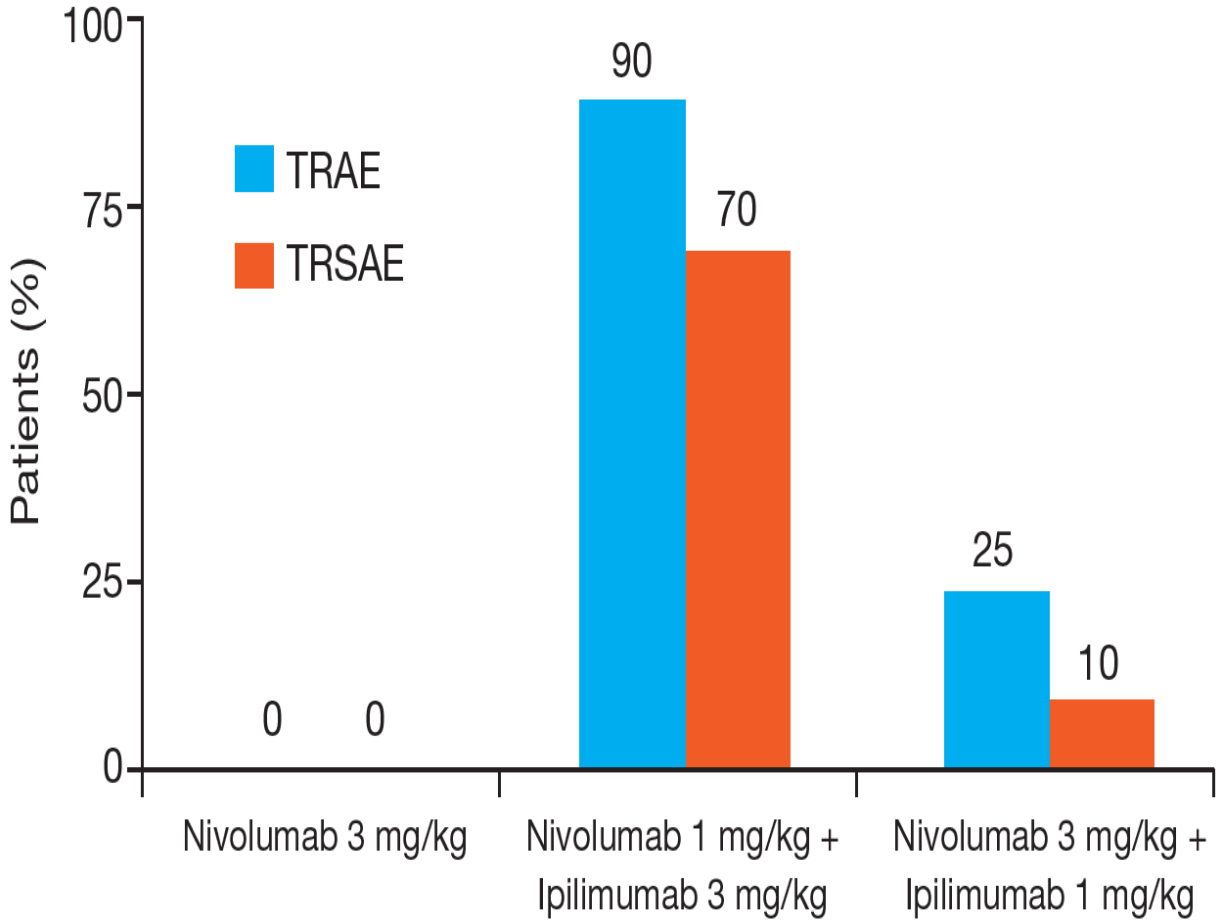
• ASCO 2016

CheckMate 143
Study Design



OS = overall survival; Q2W = every 2 weeks; Q3W = every 3 weeks.

Percentage of Patients with Grade 3–4 TRAEs and TRSAEs



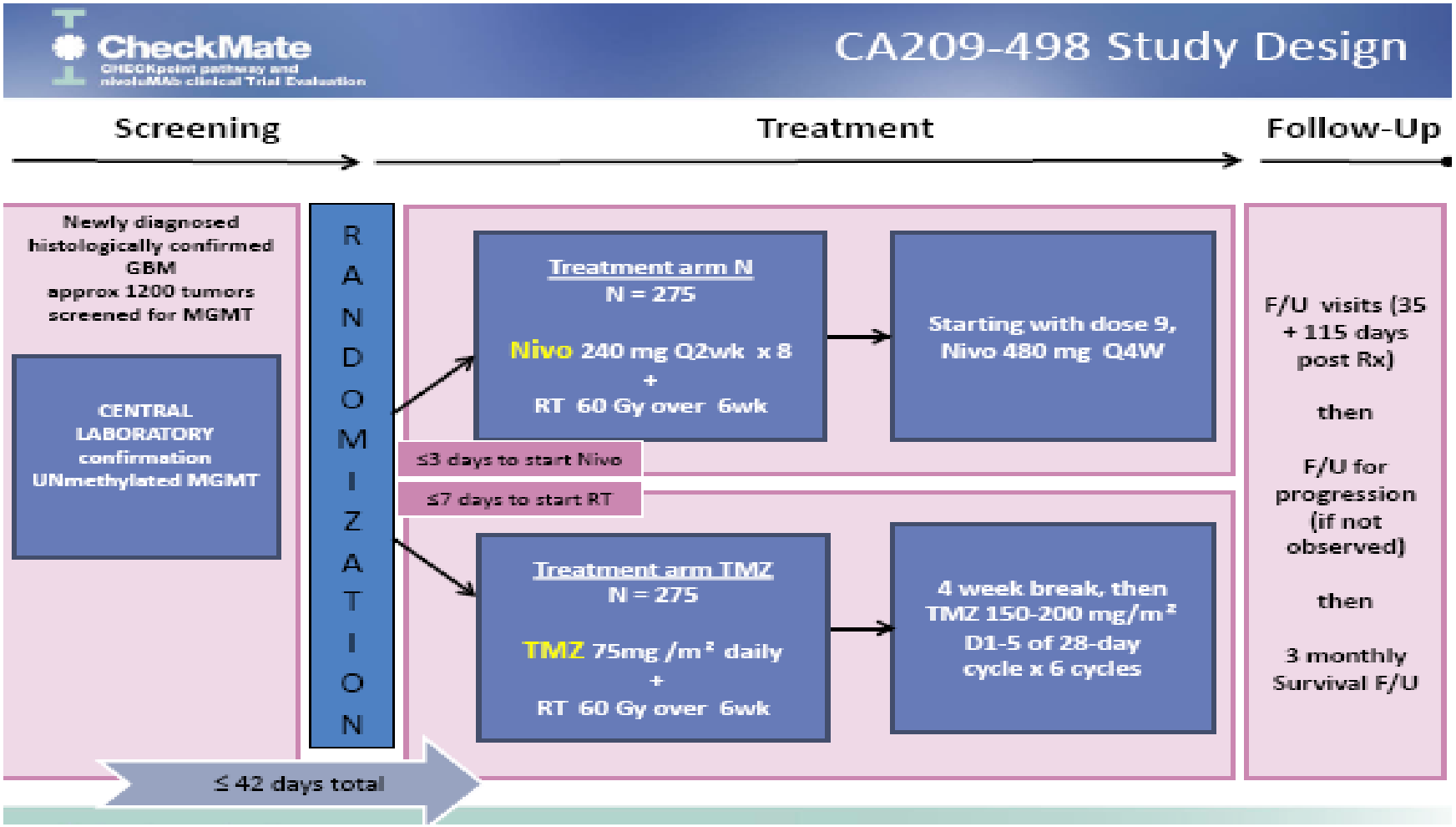
Investigator-assessed Best Overall Response and Objective Response Rate per RANO Criteria

	Cohort 1		Cohort 1b
	Nivolumab 3 mg/kg (n = 10)	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 10)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 20)
Best overall response,[a] n (%)			
Complete response	0	0	0
Partial response	1 (10)	0	0
Stable disease	5 (50)	4 (40)	10 (50)
Progressive disease	3 (30)	6 (60)	9 (45)
Not reported	1 (10)	0	1 (5)
ORR,[b] n (%) (95% CI)	1 (10) (0.3, 44.5)	0 (0.0, 30.8)	0 (0.0, 16.8)

[a]Per RANO criteria
[b]Complete response + partial response; confidence interval (CI) based on the Clopper and Pearson method

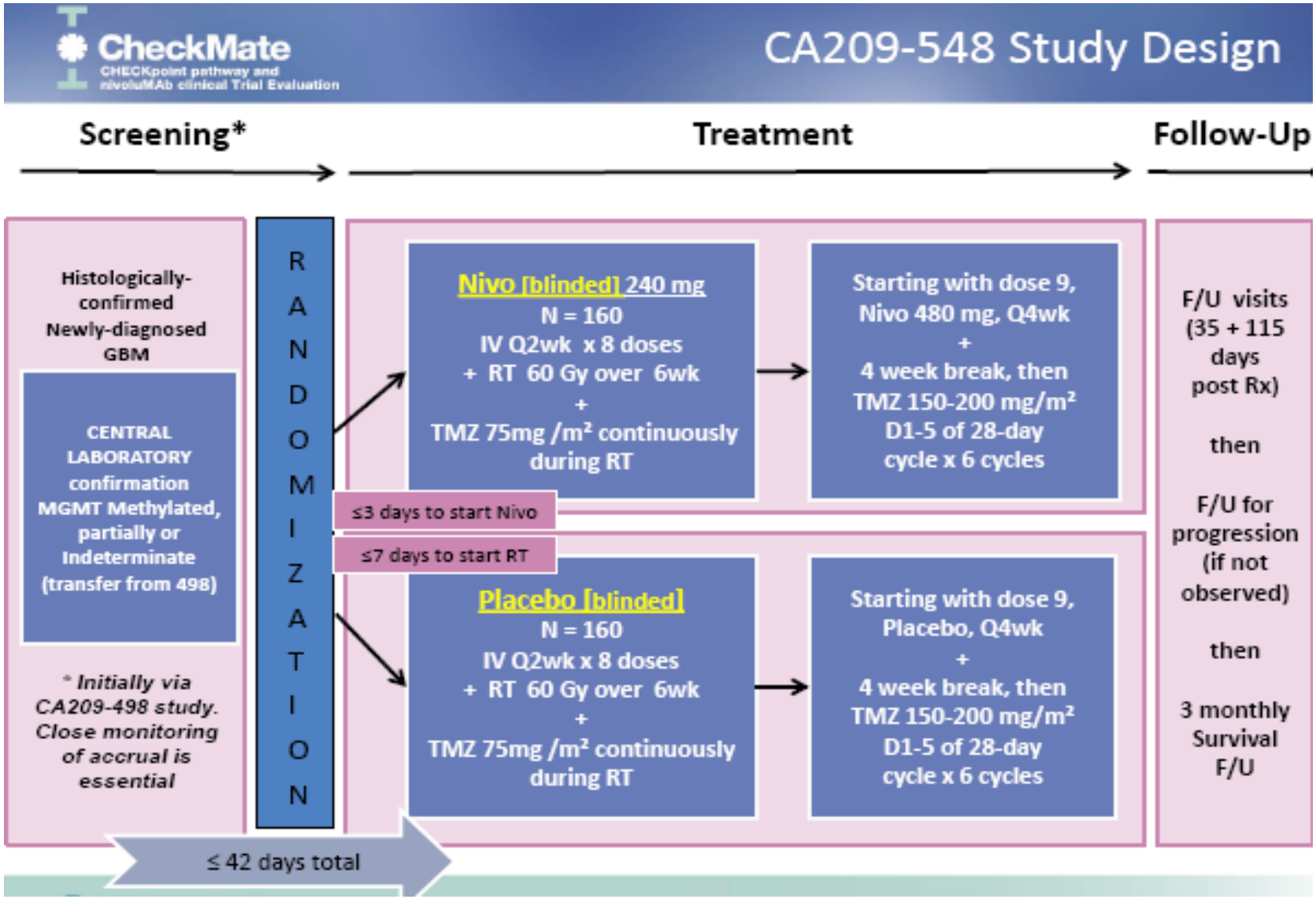
CheckMate 143

Ongoing randomized studies will address the efficacy of nivolumab versus bevacizumab in a previously treated population


CheckMate
CHECKpoint pathway and nivoLUMAb clinical Trial Evaluation
CA209-498 Study Design
Screening
Treatment
Follow-Up
Newly diagnosed histologically confirmed GBM
approx 1200 tumors screened for MGMT
CENTRAL LABORATORY confirmation UNmethylated MGMT
RANDOMIZATION
Treatment arm N
N = 275
Nivo 240 mg Q2wk x 8
+
RT 60 Gy over 6wk
Starting with dose 9, Nivo 480 mg Q4W
≤3 days to start Nivo
≤7 days to start RT
Treatment arm TMZ
N = 275
TMZ 75mg /m² daily
+
RT 60 Gy over 6wk
4 week break, then TMZ 150-200 mg/m²
D1-5 of 28-day cycle x 6 cycles
F/U visits (35 + 115 days post Rx)
then
F/U for progression (if not observed)
then
3 monthly Survival F/U
≤ 42 days total

CheckMate
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

CA209-548 Study Design

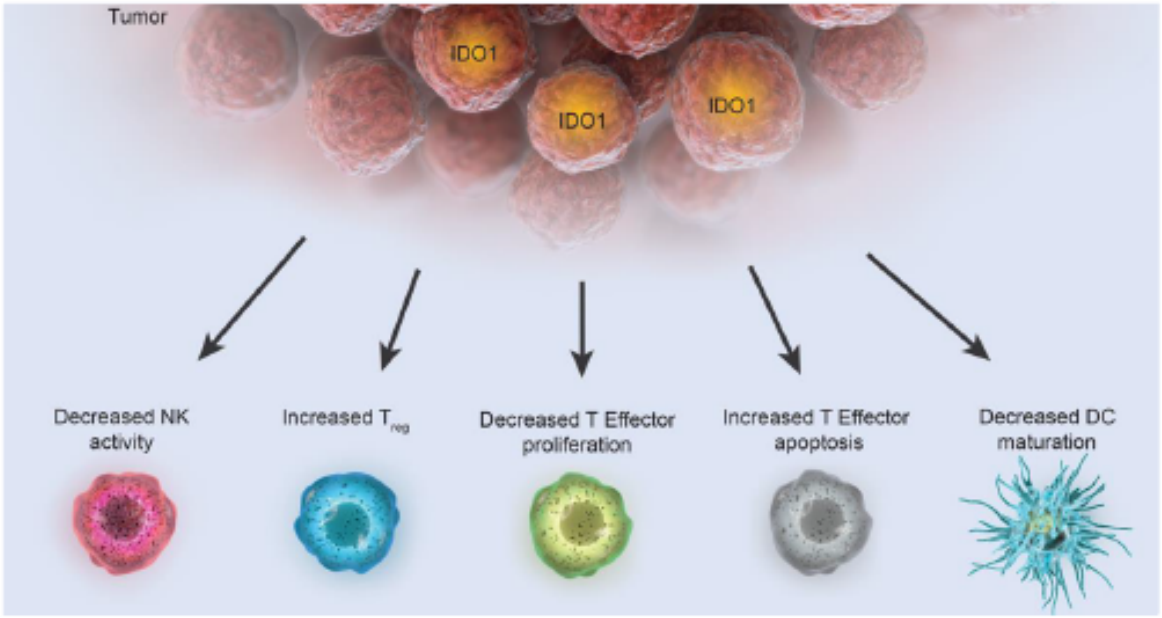


Immune check-point(s) blockade-based combinations/sequences holding the most promise for future development

- Vaccines
- Cytokines
- Tumor microenvironment modulating agents
- Selected chemotherapeutic agents
- Targeted therapies
- Epigenetic therapies

IDO-mediated immunesuppression

- IDO1 is a tryptophan-catabolizing enzyme that is overexpressed in many cancers[1-3] and induces immune tolerance by suppressing T-cell responses[4]
  - IDO1 is expressed in human tumors and in dendritic cells within tumor draining lymph nodes[5]
  - IDO1 expression is associated with more rapid tumor progression and reduced survival[5]
  - IDO1 inhibition exhibits antitumor activity through the reactivation of effector T cells[3] and is synergistic with PD-1 blockade[6]



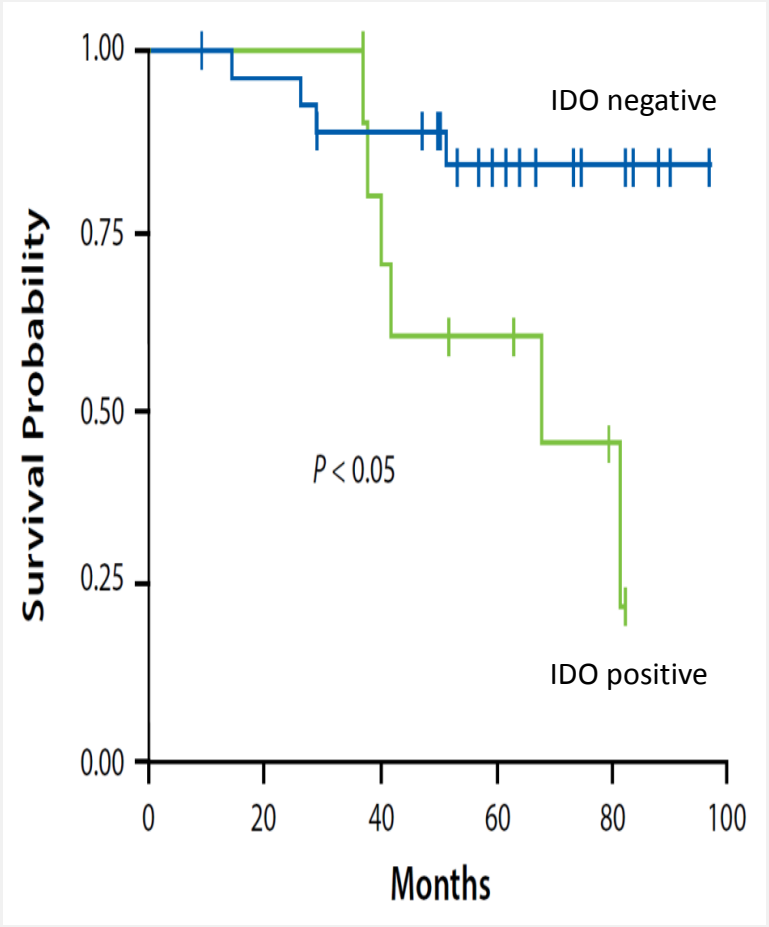
IDO1, indoleamine 2,3 dioxygenase 1.

1. Moretti et al. *J Clin Endocrinol Metab*. 2014:jc20133351; **2.** Yu et al. *Clin Dev Immunol*. 2011;2011:469135; **3.** Uyttenhove et al. *Nat Med*. 2003; 9(10):1269-1274; **4.** Munn et al. *J Clin Invest*. 2007;117(5):1147-1154; **5.** Godin-Ethier et al. *Clin Cancer Res*. 2011;17(22):6985-6991; **6.** Spranger et al. *J Immunother Cancer*. 2014 Feb 18;2:3.

IDO1 Expression Is Associated With Poor Patient Outcome in Various Tumor Types

- IDO1 is highly expressed in multiple tumor types
  - Melanoma
  - NSCLC
  - Ovarian cancer
  - Pancreatic cancer
  - CRC
  - Glioblastoma
  - Squamous cell carcinoma
  - Endometrial carcinoma
  - DLBCL
  - RCC
  - TCC
  - TNBC

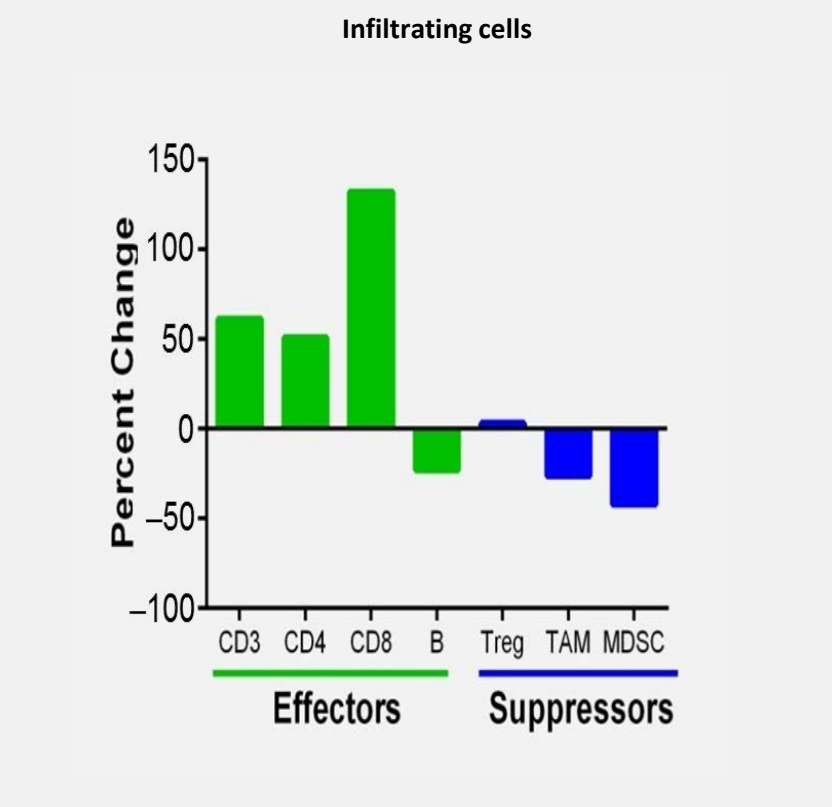
Kaplan-Meier survival curves in melanoma based on IDO1 accumulation in the lymph node[1]

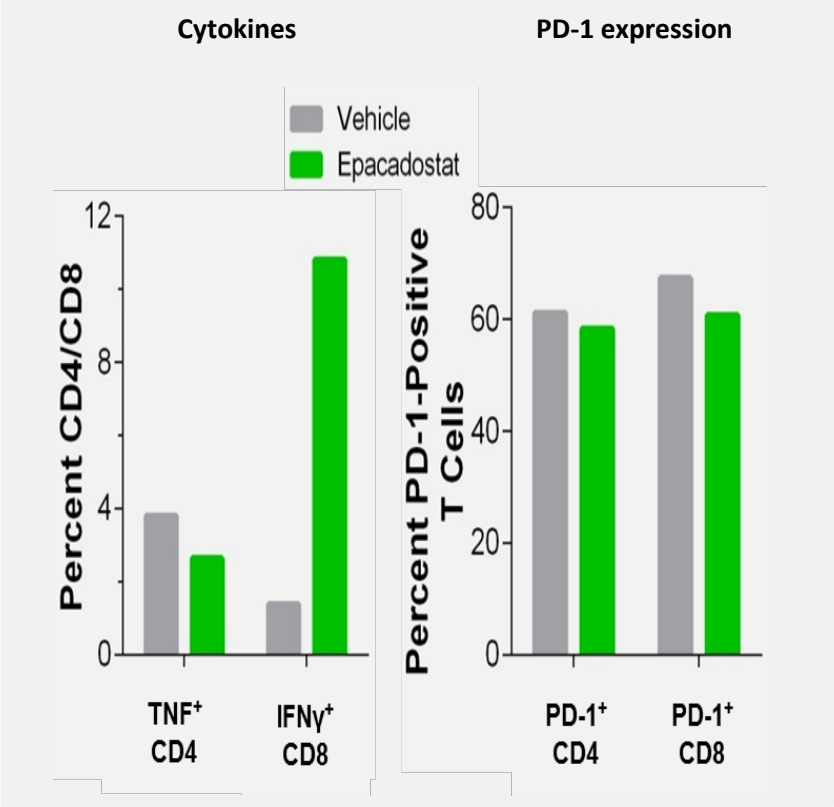


TCC=transitional cell carcinoma; TNBC=triple negative breast cancer

1. Munn DH, et al. *J Clin Invest* 2004;114(2):280-90

IDO1 Inhibition Correlates With Increases in TIL Number and Function





- IDO1 inhibition leads to increased number of TILs and decreased suppressor cells in tumors
- Enhanced IFN-γ secretion from TILs was observed following IDO1 inhibitor treatment

IFN=interferon

Koblish HK, et al. AACR 2015. Poster 1336

Inhibition of IDO1 with epacadostat enhances anti-tumor efficacy of PD-1 blockade in a syngeneic glioblastoma (GBM) model

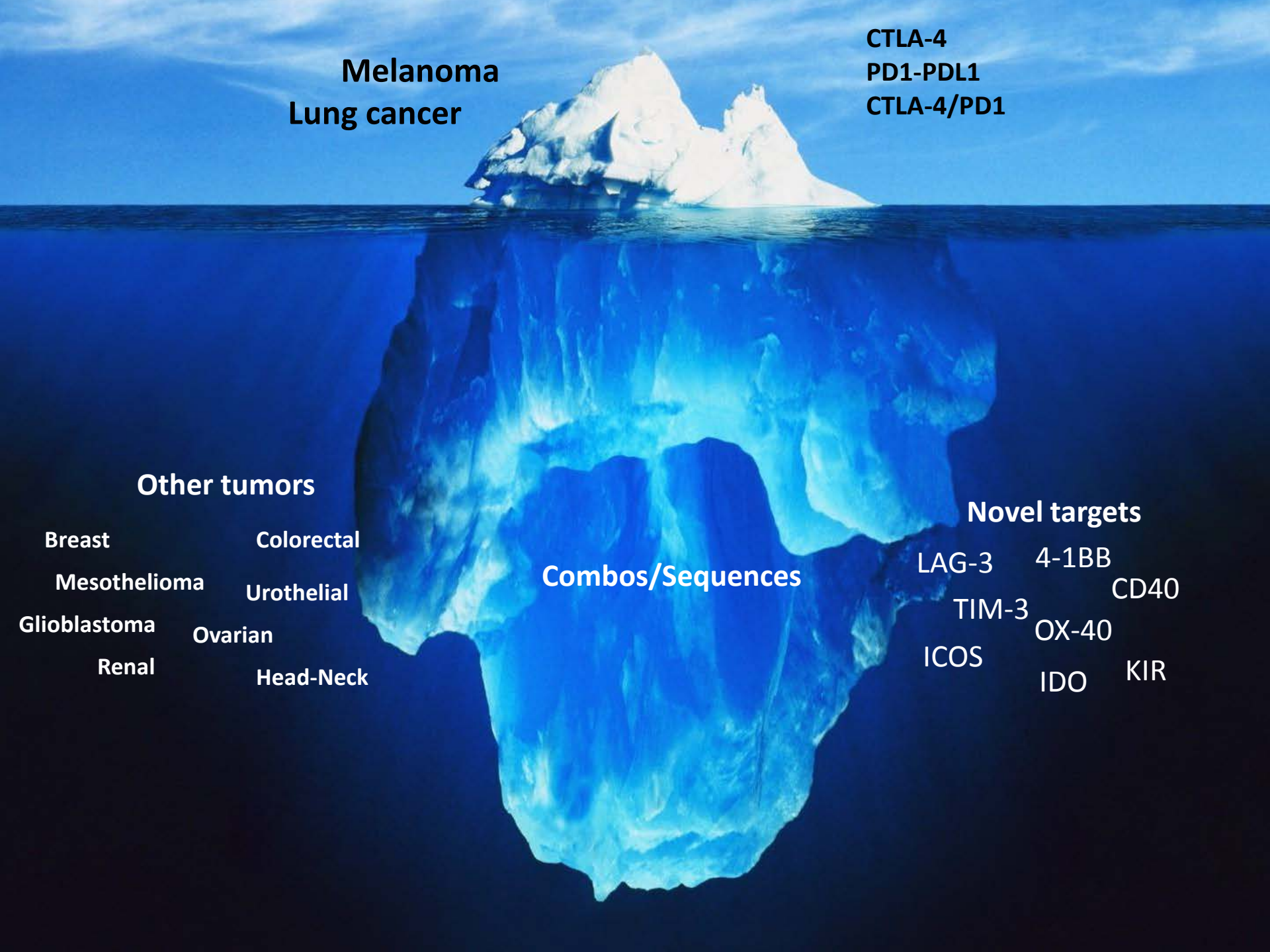
•GL261 cells, a murine GBM tumor line derived from intracerebral methylcholanthrene implantation, were stereotactically implanted intracranially in albino syngeneic C57BL/6 mice.

•Mice were randomized (n=8/group) to receive treatment:

- anti-PD-1;
- epacadostat;
- anti-PD-1 + epacadostat;
- control

•IDO1 inhibition with epacadostat increased the eradication rate of anti-PD-1(1% *vs* 50%) therapy in an orthotopic syngeneic GBM model and long term survivors rejected tumor following orthotopic re-challenge.

Reardon A, et al. AACR 2017. Poster 572


Melanoma
Lung cancer
CTLA-4
PD1-PDL1
CTLA-4/PD1
Other tumors
Breast
Colorectal
Mesothelioma
Urothelial
Glioblastoma
Ovarian
Renal
Head-Neck
Combos/Sequences
Novel targets
LAG-3
4-1BB
CD40
TIM-3
OX-40
ICOS
IDO
KIR

MEDICAL ONCOLOGY AND IMMUNOTHERAPY
DEPT. OF MEDICAL ONCOLOGY
UNIVERSITY HOSPITAL OF SIENA

Michele Maio *and*

- Maresa Altomonte
- Erika Bertocci
- Luana Calabrò
- Ornella Cutaia
- Riccardo Danielli
- Anna Maria Di Giacomo
- Carolina Fazio
- Ester Fonsatti

- Francesca Colizzi
- Sandra Coral
- Alessia Covre
- Elisabetta Fratta
- Hugues Nicolay
- Giulia Parisi
- Aurora Rizzo
- Luca Sigalotti

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

astex pharmaceuticals

Bristol-Myers Squibb

Pfizer

HARRY J. LLOYD CHARITABLE TRUST

AIRC

Ministero della Salute

AstraZeneca

MedImmune

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

NIBIT
Network Italiano per la Bioterapia dei Tumori

Cancer Bio-Immunotherapy in **Siena**

XV NIBIT MEETING

For more information, updates and useful links, please visit our website:

www.sienameeting-nibit.org

october 5-7 2017