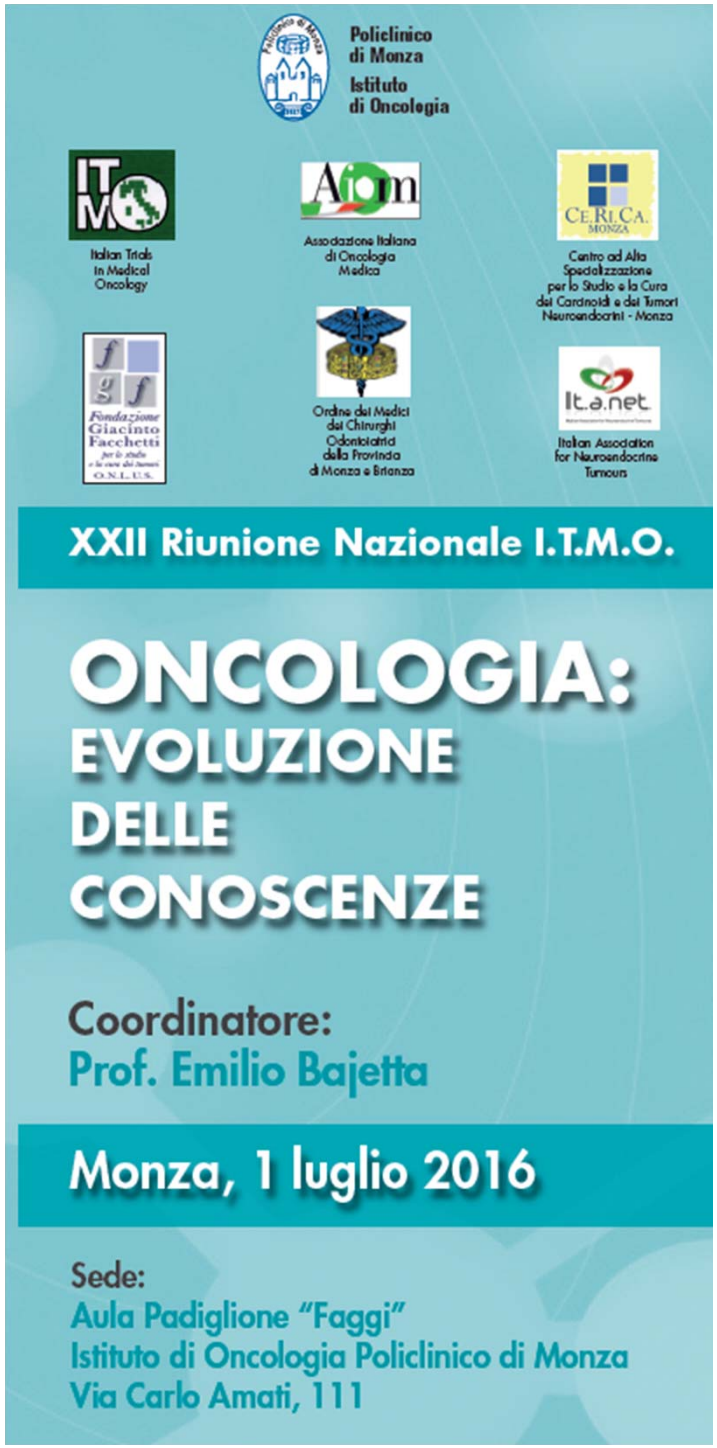


Lettura Giacinto Facchetti

Immuno-Oncologia

Michele Maio
Medical Oncology and Immunotherapy,
University Hospital of Siena, Istituto Toscano Tumori
Siena

PROGRAMMA

XI CONFERENZA NAZIONALE AIOM

ONCOLOGIA MEDICA: TRAGUARDI E PROSPETTIVE

Cosenza

Teatro Rendano
2-4 dicembre 2005

Presidenti

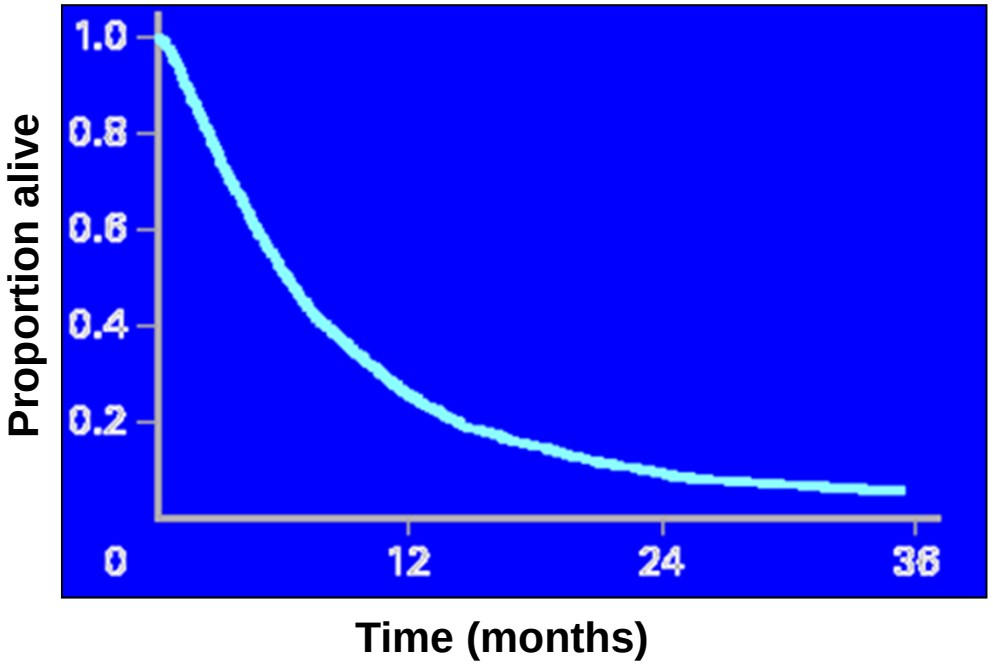
EMILIO BAJETTA
GIANFRANCO FILIPPELLI

Venue: Sala Partenze

Statement: **“*Caro Maio, abbiamo abbracciato questa Croce, non possiamo tirarci indietro*!”**

Author: Emilio Bajetta

Overall Survival for Metastatic Melanoma



Adapted from Korn 2008

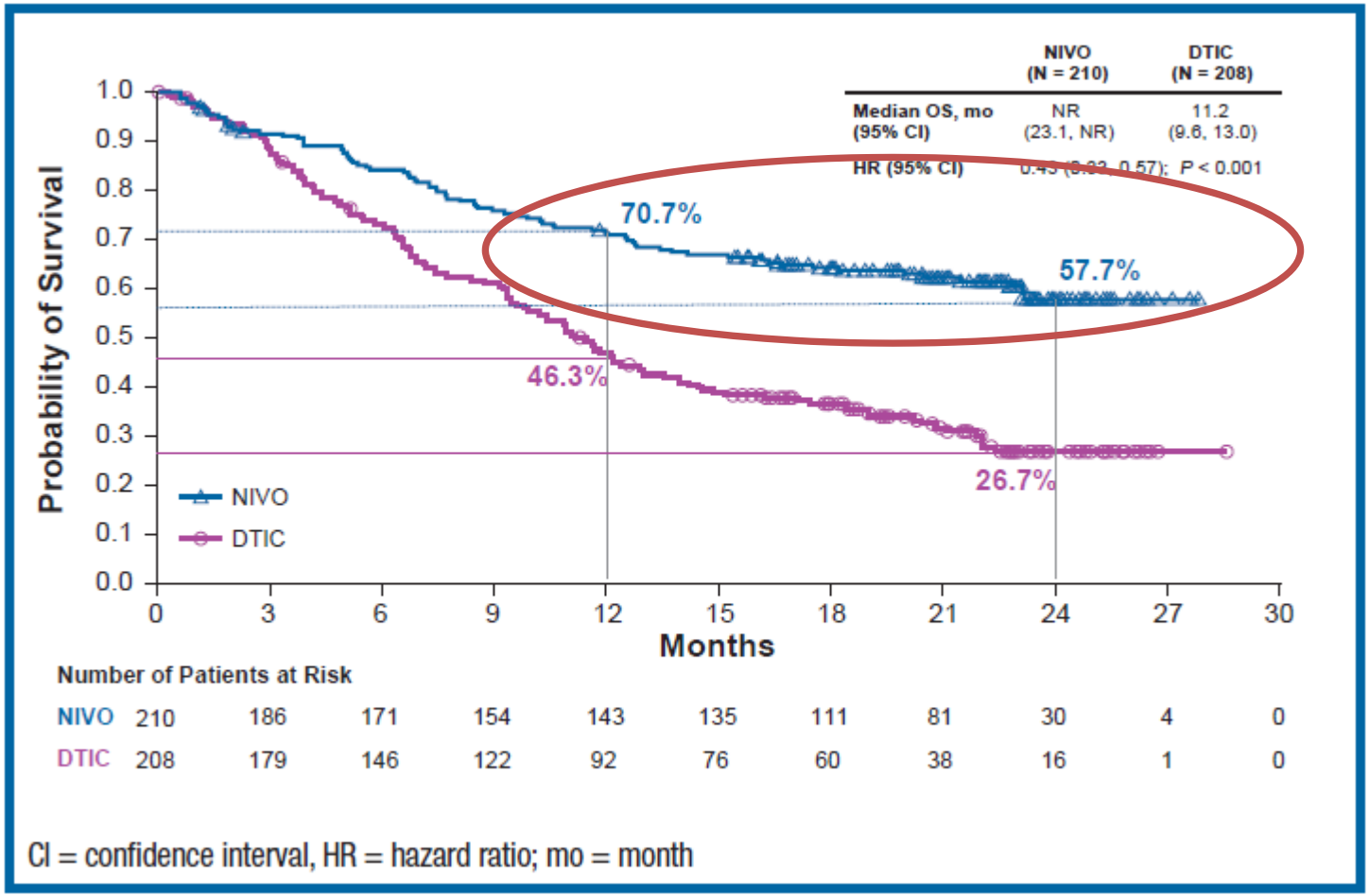
Survival data from 42 Phase II trials with over 2,100 stage IV patients[1]:

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.

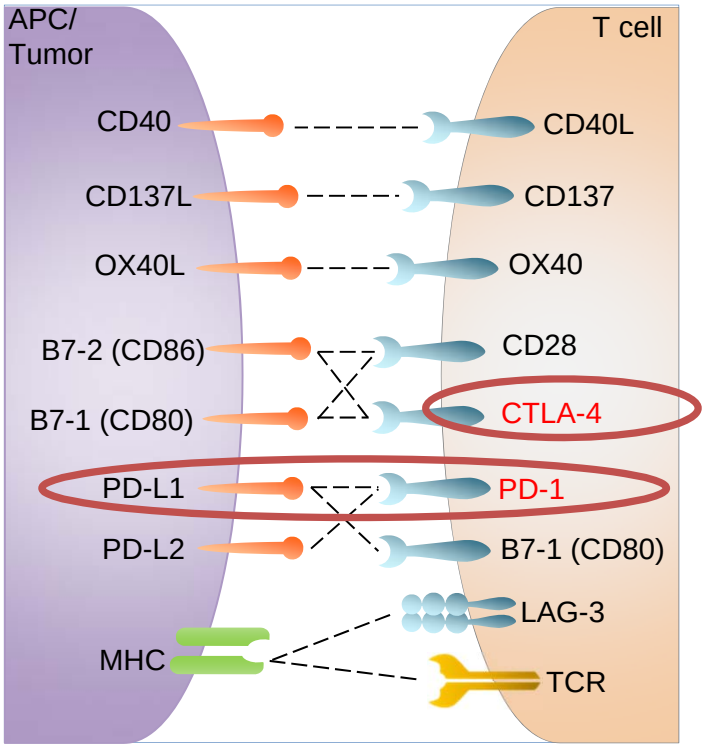
Overall Survival



	NIVO (N = 210)	DTIC (N = 208)
Median OS, mo. (95% CI)	**NR** (23.1, NR)	11.2 (9.6, 13.0)
HR (95% CI)	0.43 (0.33, 0.57); P <0.001	

Minimum survival follow-up of 15.1 months

T-cell Checkpoint and Co-stimulatory Pathways

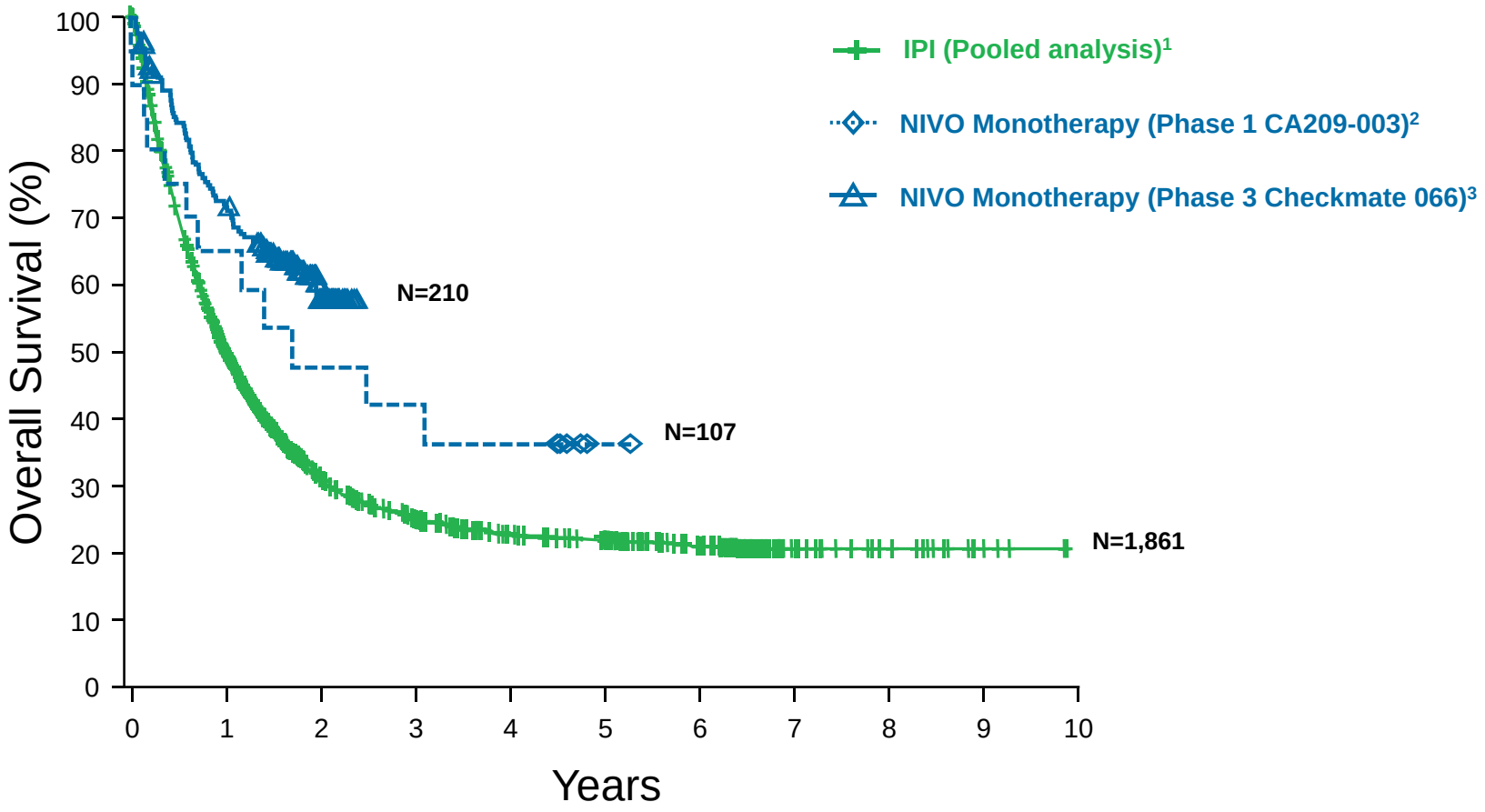


Adapted from Pardoll DM 2012.

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.

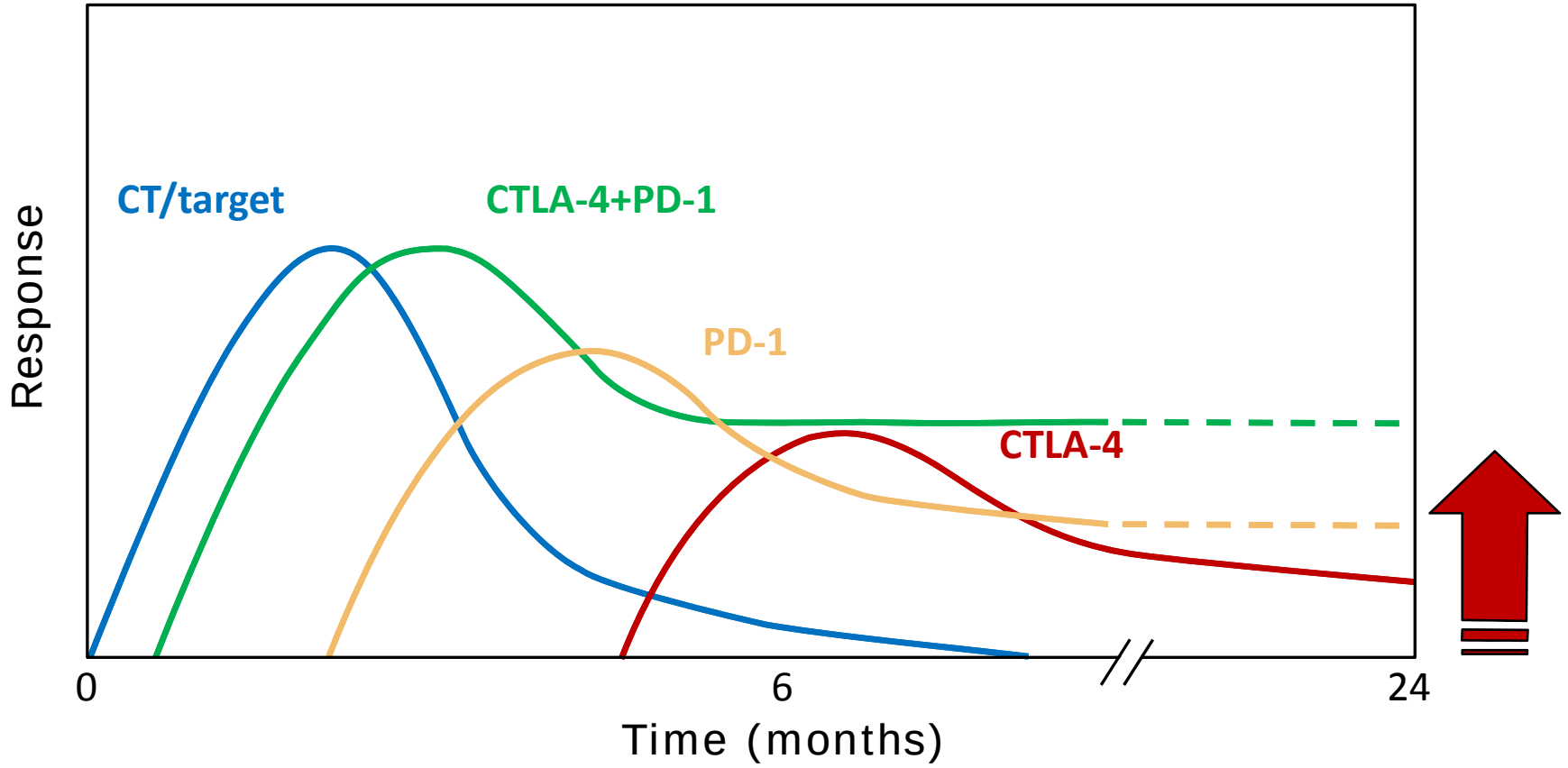
Pardoll DM. Nat Rev Cancer. 2012;12:252-264.

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



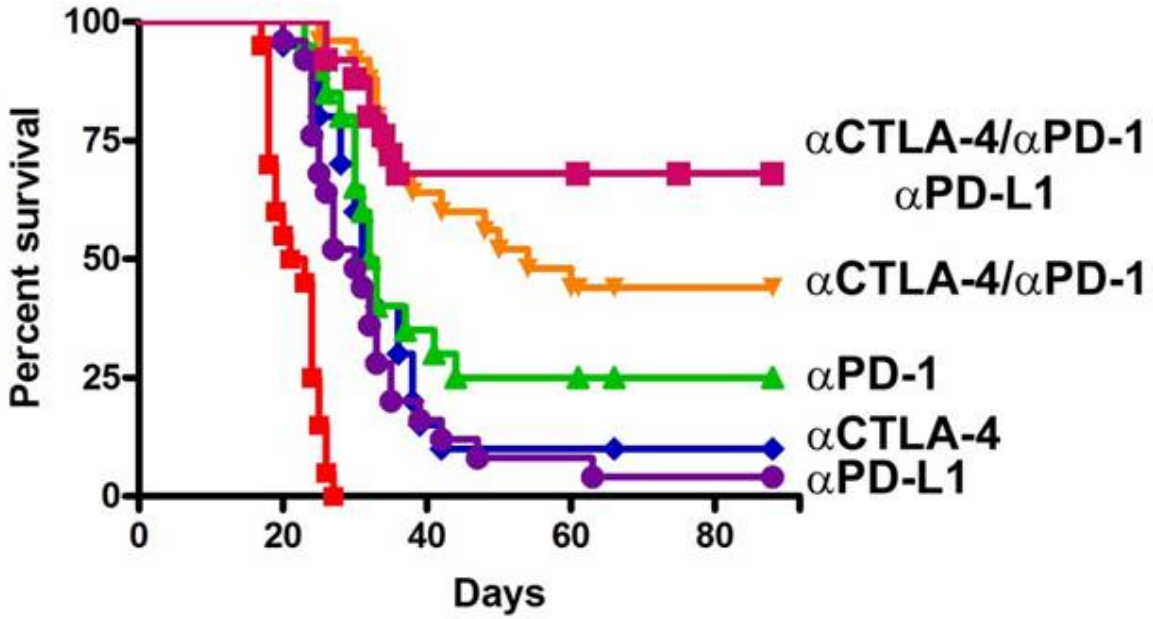
1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

Chemotherapy/Targeted Agents and Immuno-therapy Differ in Action and Outcome



Maio M. et al, unpublished

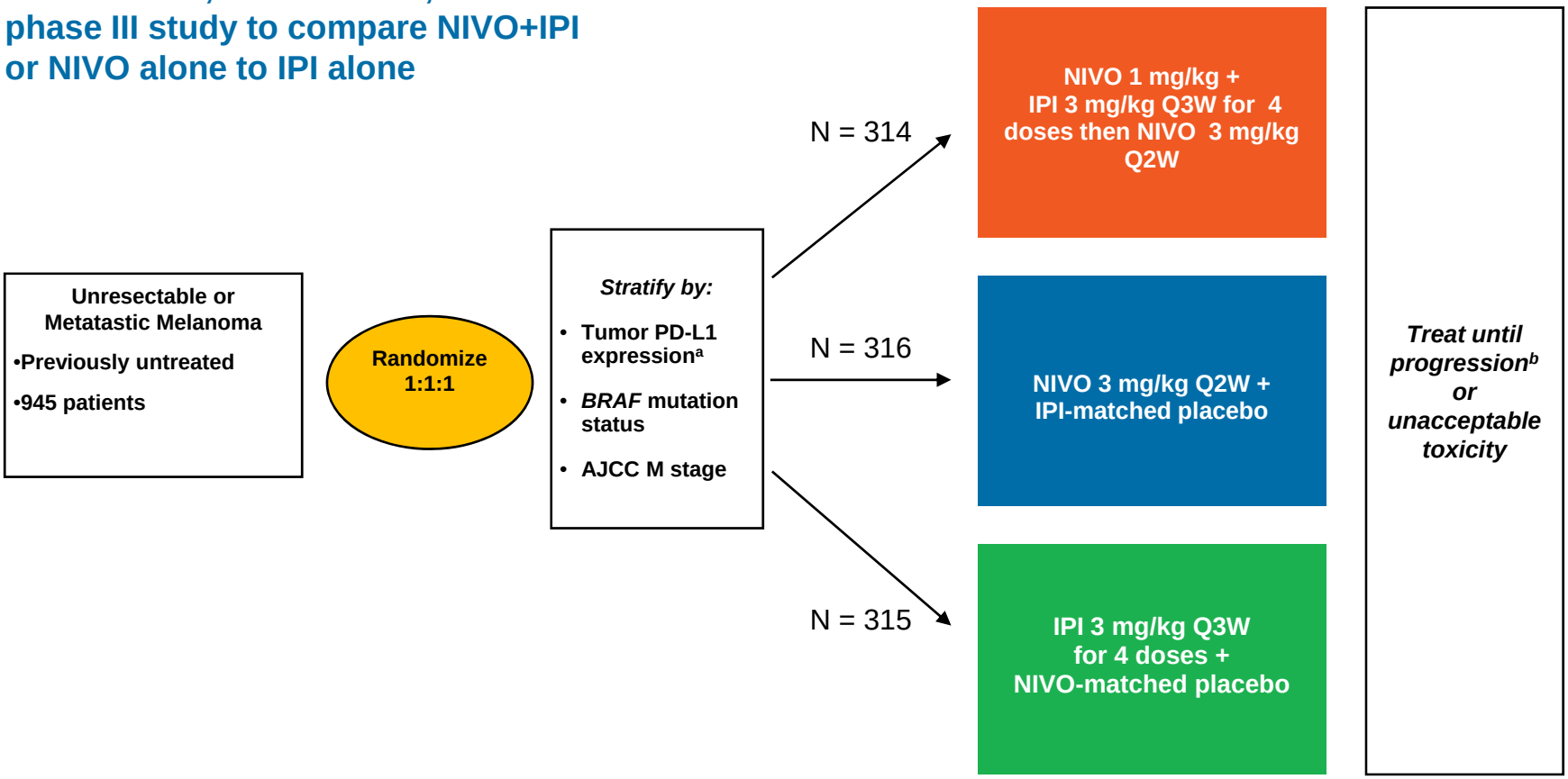
Mouse models with improved tumor rejection and survival due to combination therapy: anti-CTLA-4 plus targeting the PD-1/PD-L1 pathway



Curran et al., *PNAS*, 2010

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone



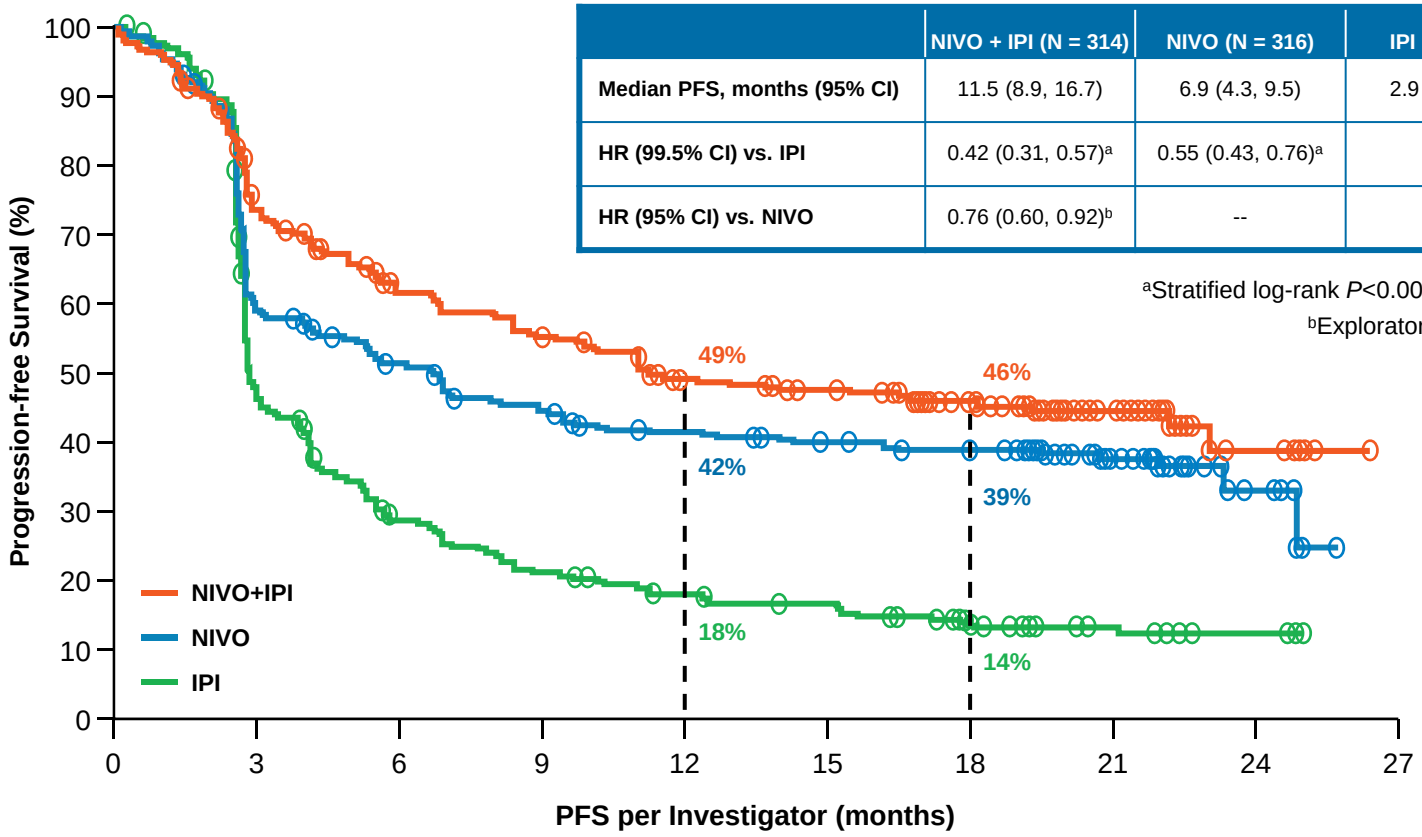
[a]Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses
[b]Patients could have been treated beyond progression under protocol-defined circumstances

Progression-Free Survival (Intent-to-Treat Population)

	NIVO + IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
Median PFS, months (95% CI)	11.5 (8.9, 16.7)	6.9 (4.3, 9.5)	2.9 (2.8, 3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31, 0.57)[a]	0.55 (0.43, 0.76)[a]	--
HR (95% CI) vs. NIVO	0.76 (0.60, 0.92)[b]	--	--

[a]Stratified log-rank *P*<0.00001 vs. IPI

[b]Exploratory endpoint

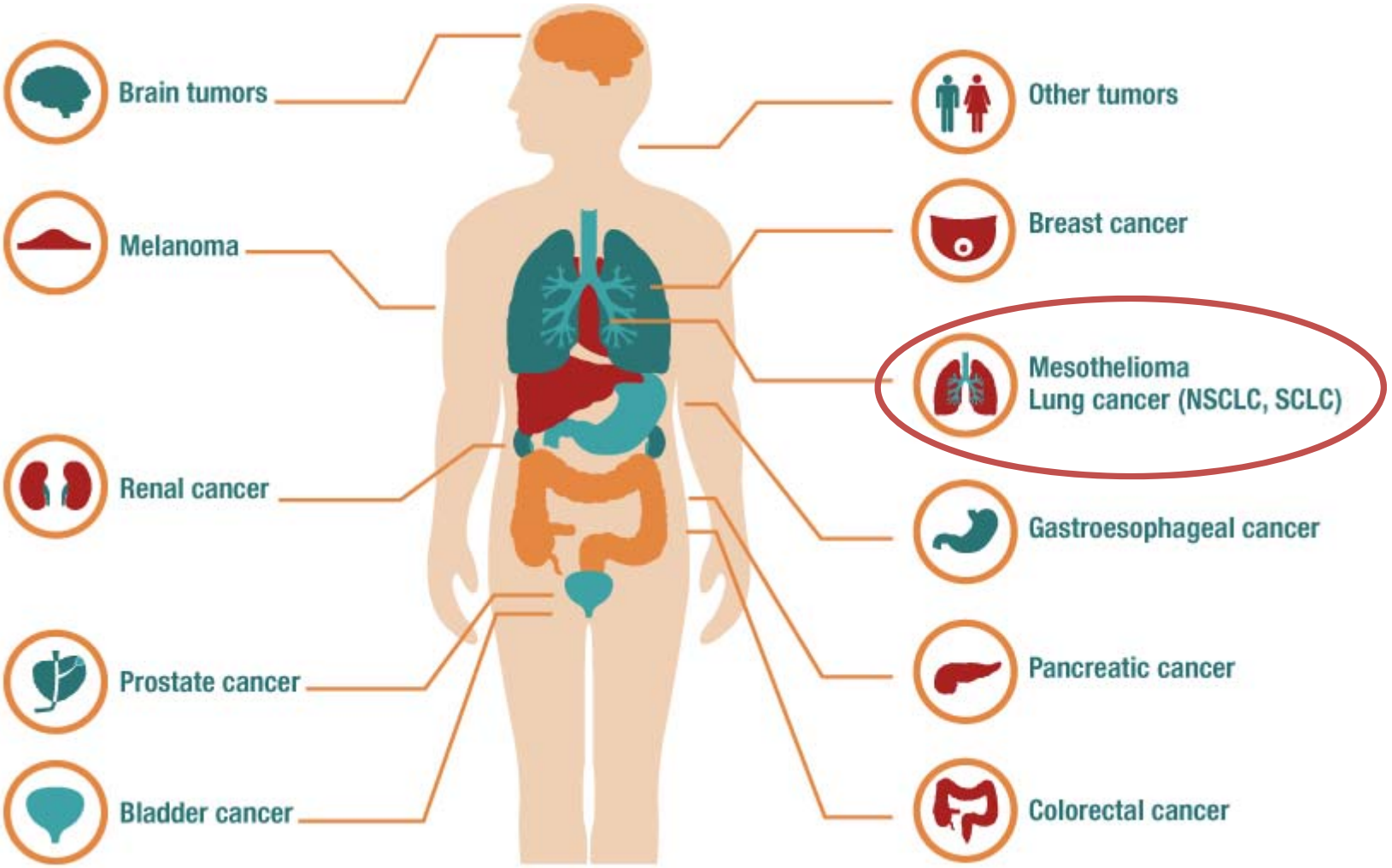


Number of patients at risk:

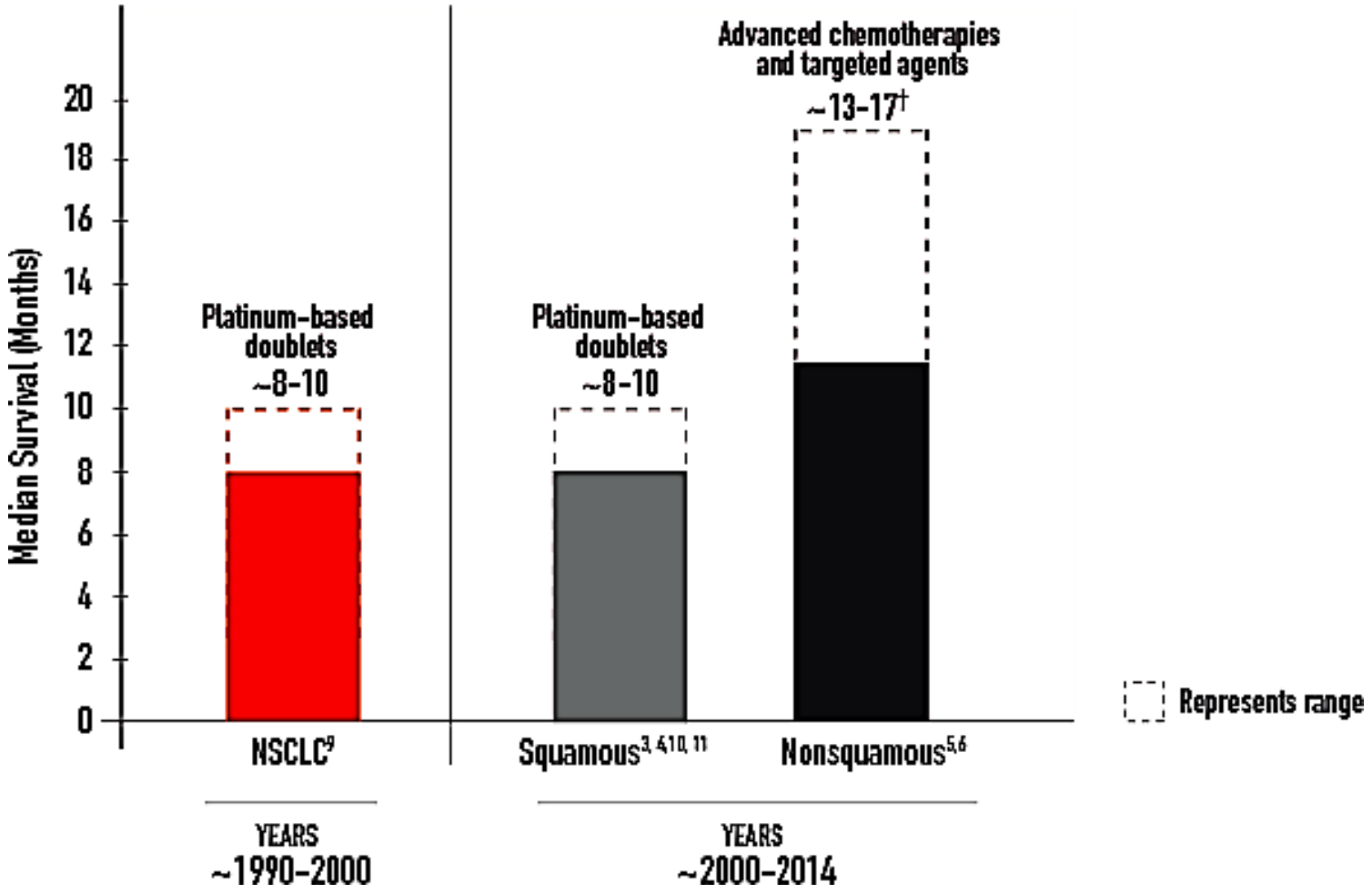
Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

Database lock Nov 2015

Immunotherapy in solid tumours with immunomodulating antibodies

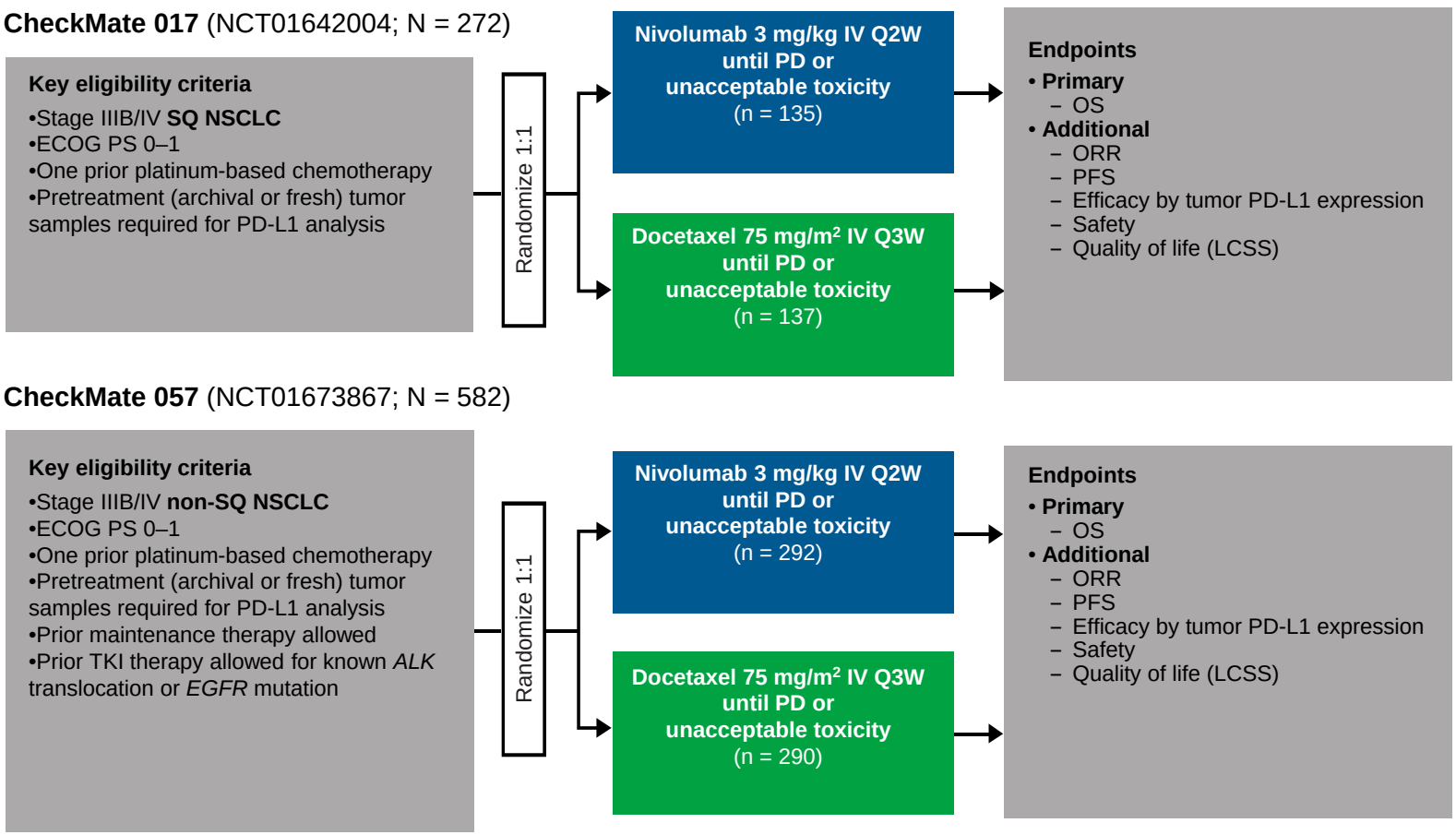


Survival improvement for advanced NSCLC in the last 25 years



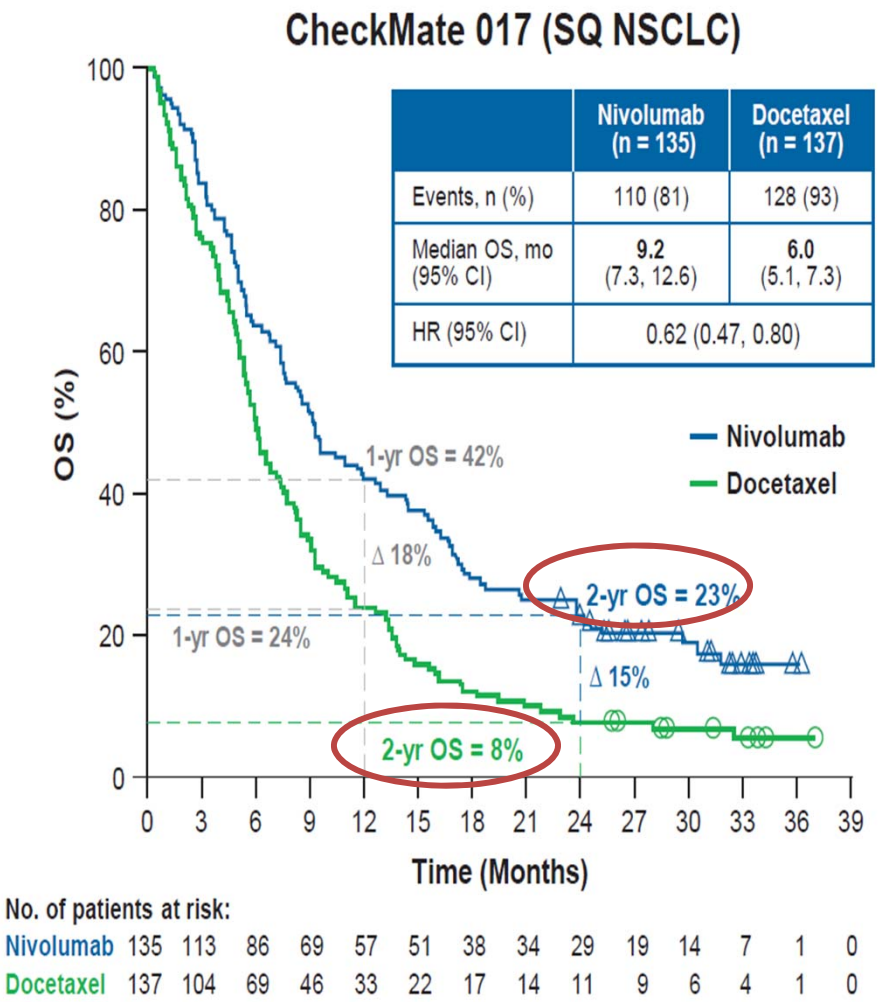
5-years survival < 2-3%

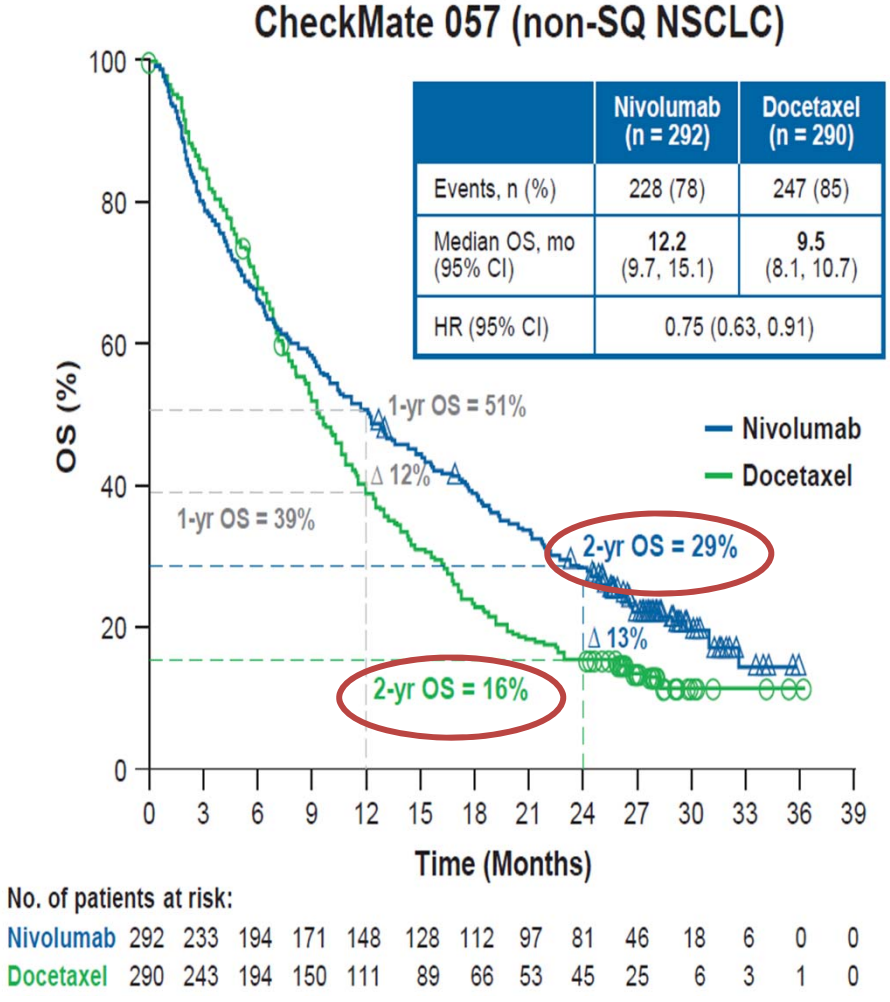
CheckMate 017 and CheckMate 057 Study Designs



LCSS = Lung Cancer Symptom Scale; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; TKI = tyrosine kinase inhibitor

Kaplan–Meier Estimates of OS (2 Years Minimum Follow-up)





MERCK

News Release

Media Contacts: Pamela Eisele (267) 305-3558

Courtney Ronaldo (908) 236-1108

Investor Contacts: Teri Loxam (908) 740-1986

Justin Holko (908) 740-1879

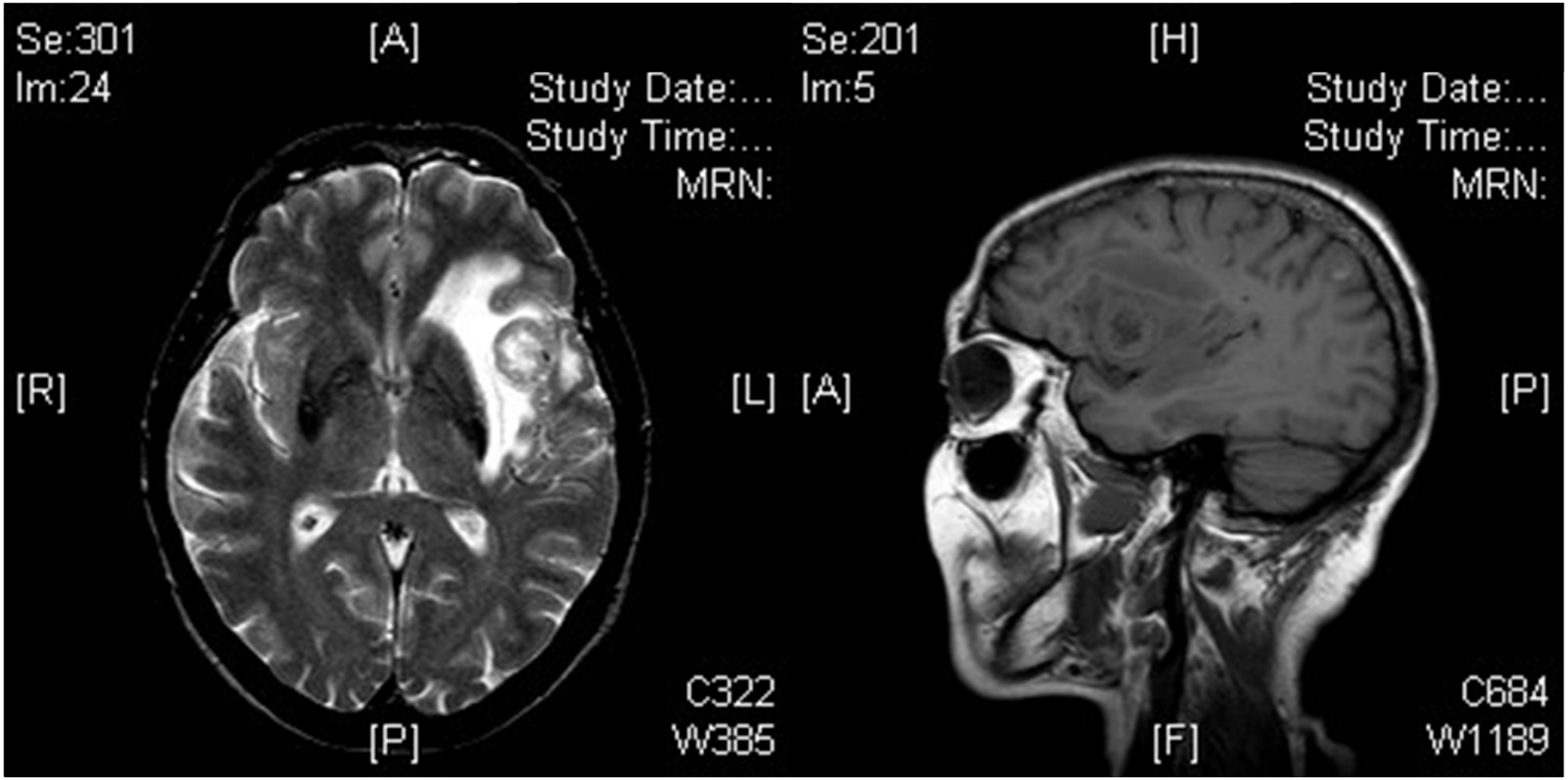
Merck's KEYTRUDA® (pembrolizumab) Demonstrates Superior Progression-Free and Overall Survival Compared to Chemotherapy as First-Line Treatment in Patients with Advanced Non-Small Cell Lung Cancer

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

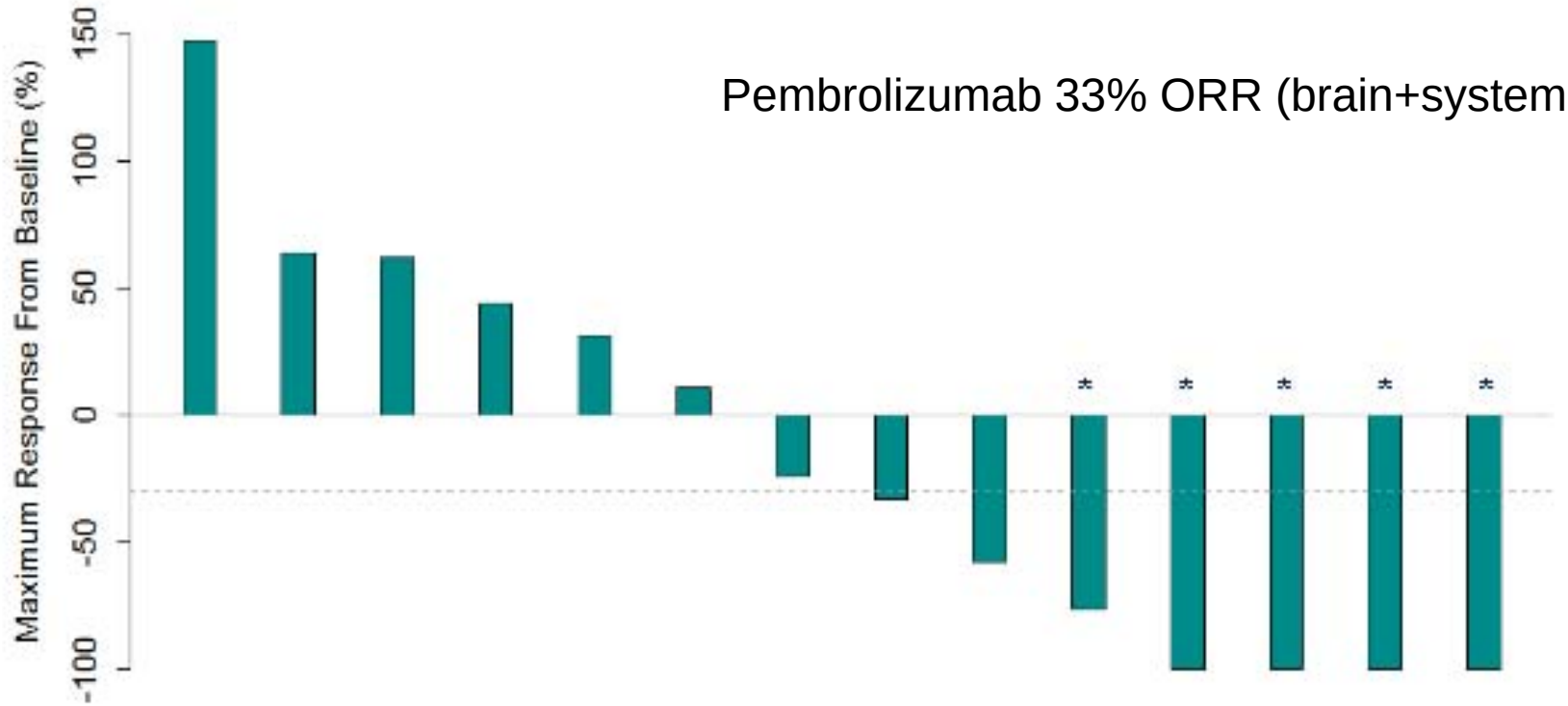
KENILWORTH, N.J., June 16, 2016 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, KEYTRUDA was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients

Jun 16, 2016

Effect in the CNS?



Best Brain Metastasis Response by mRECIST



Pembrolizumab 33% ORR (brain+systemic)

Note: 4 patients were unevaluable in the brain due to rapid systemic progression

* Confirmed brain metastasis response

Nivolumab Expanded Access Program in Italy

Preliminary data in squamous histology in brain Mets+

	EAP squamous		Checkmate 017-nivo arm	
	N	%	N	%
Total patients	36		9	-
Evaluable for response	27	100	-	-
Overall response rate	6	22.2	-	-
Complete response	0	0	-	-
Partial response	6	22.2	-	-
Stable Disease	4	14.8	-	-
Progressive disease	17	63.0	-	-

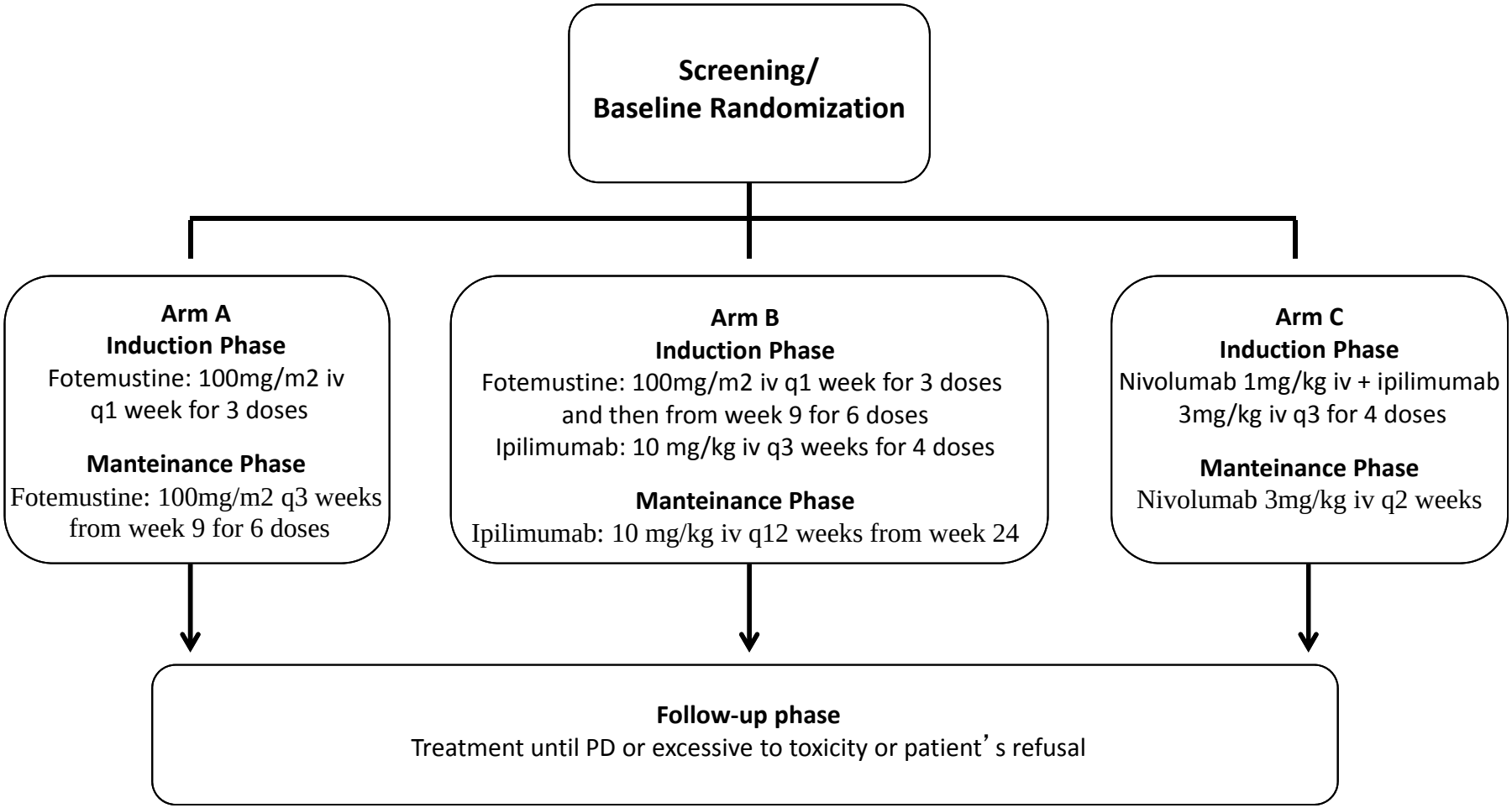
NIBIT - M1
3-years survival update

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


FONDAZIONE
NIBIT
Network Italiano per la Bioterapia dei Tumori

The NIBIT-M2 study design

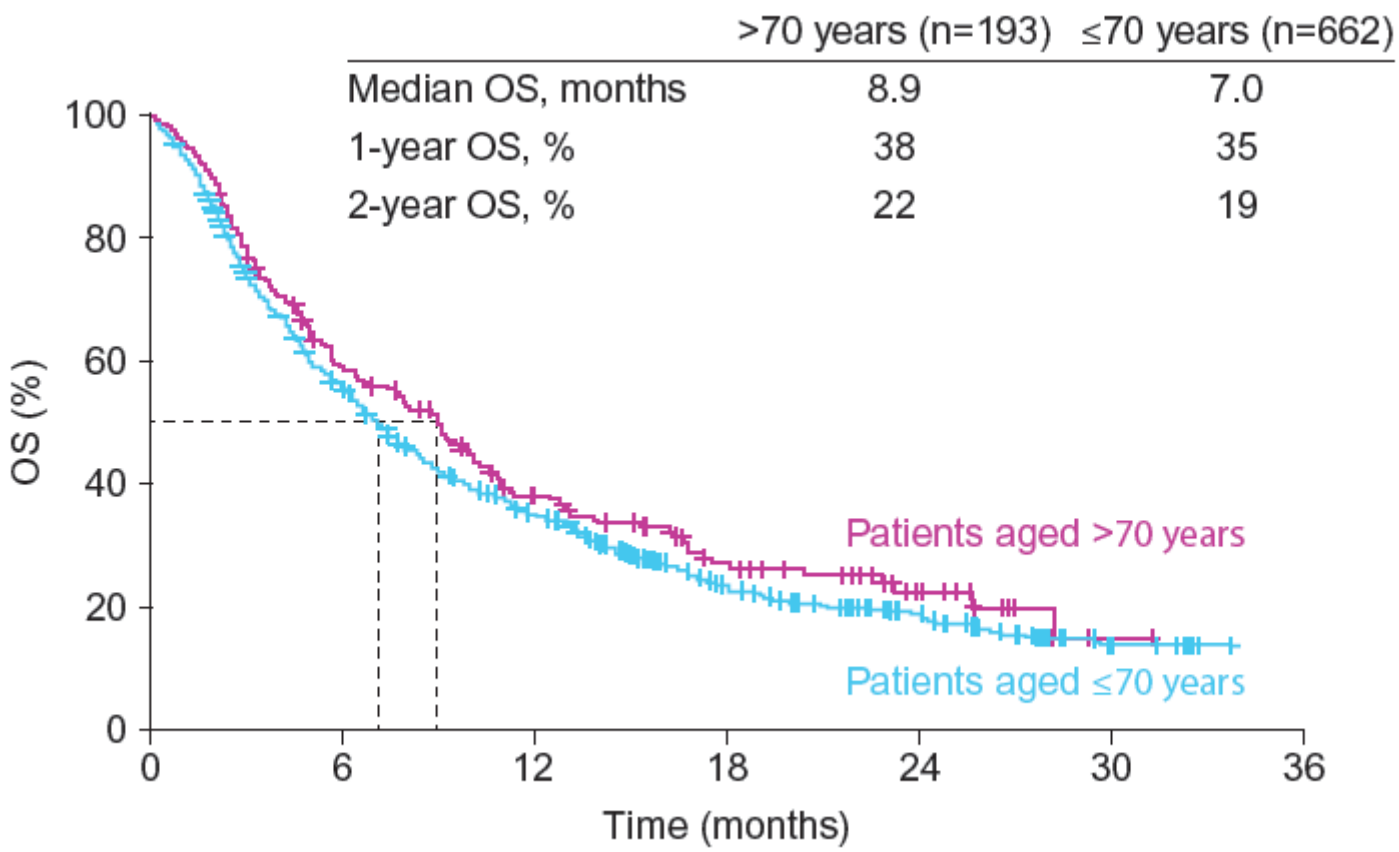


Nivolumab Expanded Access Program in Italy

Preliminary data in squamous histology in elderly

	EAP squamous		Checkmate 017-nivo arm	
	N	%	N	%
Total patients age ≥75	69		11	
Evaluable for response	47	100	-	-
Overall response rate	7	14.9	-	-
Complete response	0	0	-	-
Partial response	7	14.9	-	-
Stable Disease	10	21.3	-	-
Progressive disease	30	63.8	-	-

Elderly Patients (>70 years): OS



Maio et al. European Ipilimumab EAP, Italian Cohort of Patients.

Anti-CTLA-4 Tremelimumab studies in Mesothelioma

Study	Schedule	Phase/ setting	ORR	DCR	mOS	2-yr OS	Reference
MESOT-TREM-2008 (IST study)	15mg/Kg Q90 days	II 2nd line	7%	31%	10.7 months	36%	Calabrò et al, Lancet Oncol 2013
MESOT-TREM-2012 (IST study)	10mg/kg Q4W x 6 doses, then Q12W	II 2nd line	14%	52%	11.3 months	NA	Calabrò et al, Lancet Resp Med 2015

DETERMINE: Overall Survival (ITT Population)

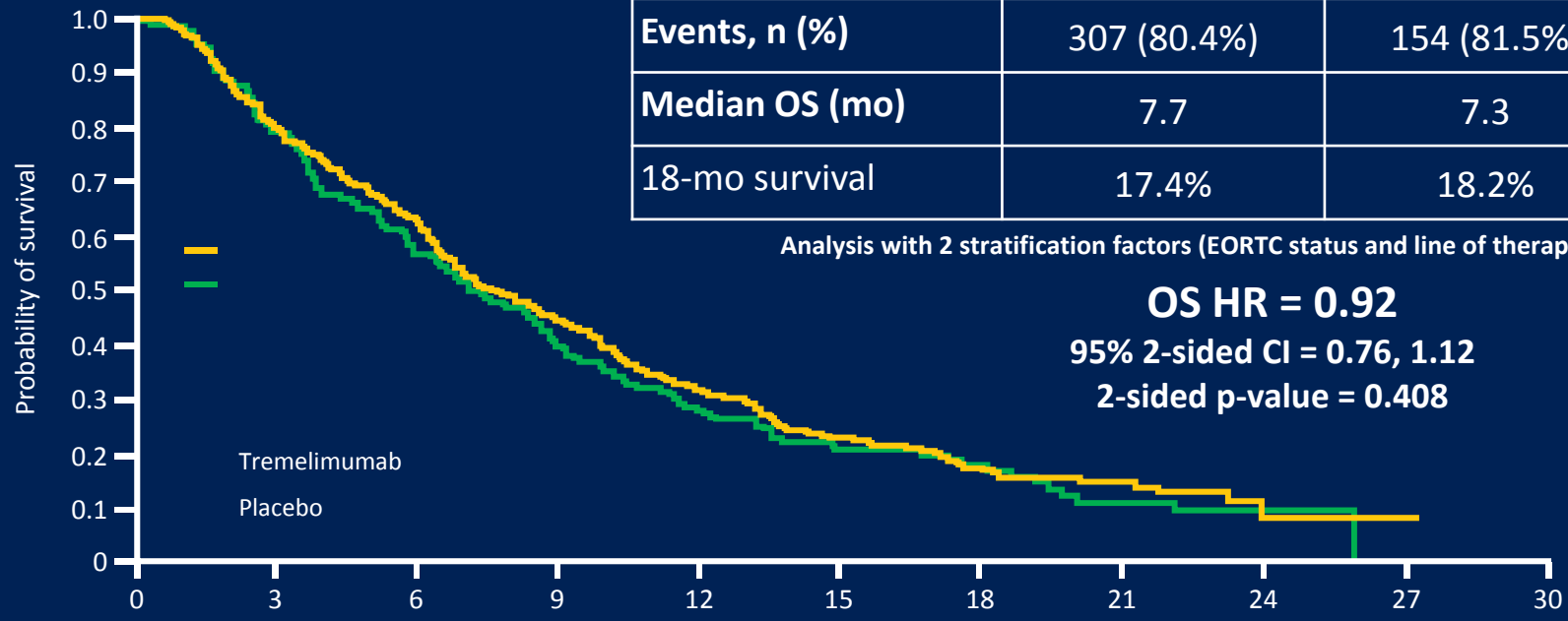
	Tremelimumab	Placebo
n	382	189
Events, n (%)	307 (80.4%)	154 (81.5%)
Median OS (mo)	7.7	7.3
18-mo survival	17.4%	18.2%

Analysis with 2 stratification factors (EORTC status and line of therapy)[a]

OS HR = 0.92

95% 2-sided CI = 0.76, 1.12

2-sided p-value = 0.408



Number of patients at risk:

Tremelimumab	382	300	232	163	116	69	36	16	3	1	0
Placebo	189	147	103	70	48	32	17	8	2	0	0

[a]p-value for OS derived from stratified Log-rank test; HR and its CI derived from stratified Cox regression. HR<1 implies a lower risk of death with tremelimumab.

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

A single arm, phase II clinical study of anti-CTLA4 tremelimumab combined with the anti-PD-L1 monoclonal antibody Durvalumab in patients with unresectable malignant mesothelioma:

NIBIT-MESO-1 study

Clincal Cancer Gov Id NCT02588131

Patients (n=40)

- **Refused 1st-line CT**
- **Refractory/relapsed to 1st- line CT**
- **No autoimmune diseases**
- **ECOG PS 0 or 1**
- **Life expectancy >12 weeks**

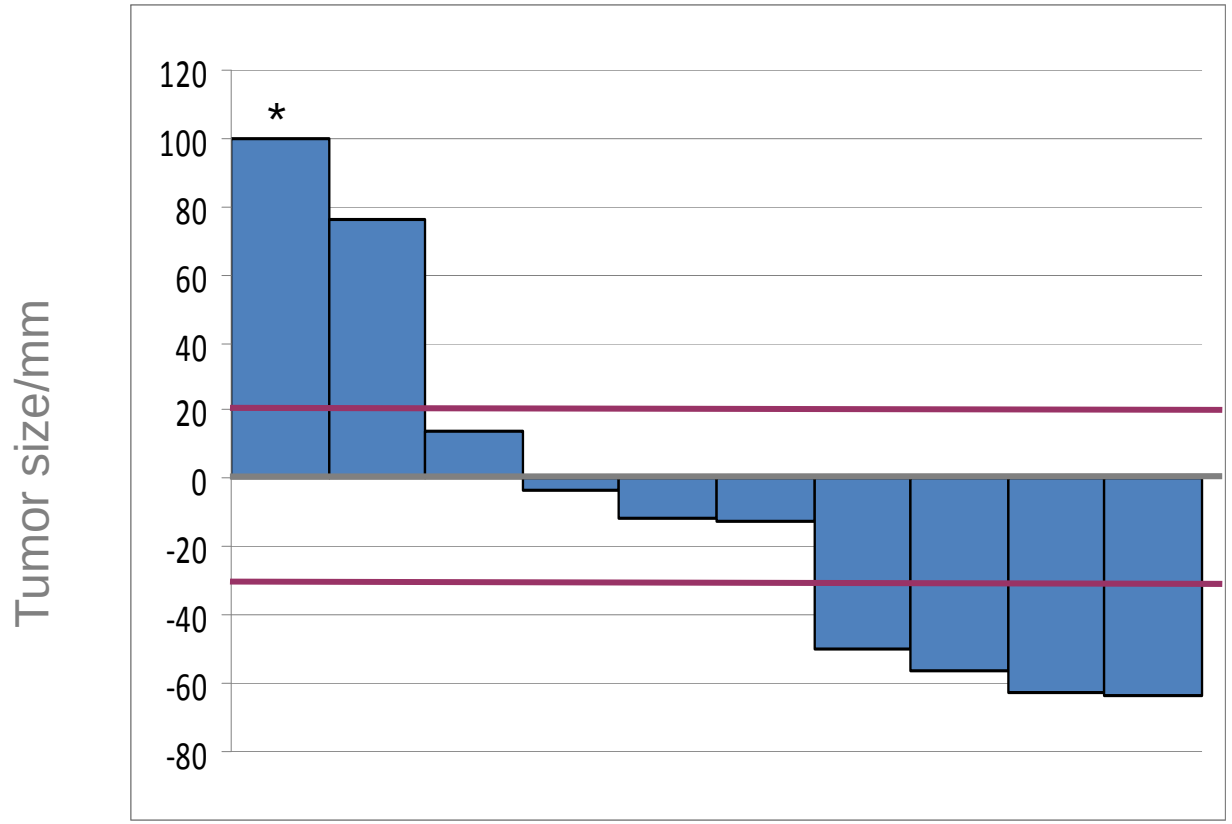
→

Tremelimumab
1mg/Kg iv, Q4 wks, x 4 doses
+
Durvalumab
20mg/Kg, Q4 wks, x 13 doses

Status: Recruiting (FPFV: 30 Oct 2015)

Efficacy

Unconfirmed tumor responses
(at first TA w12**)**



*One pt with clinical PD (no radiological assessement at W12)

Calabrò L et al, unpublished

A-BRAVE-TRIAL

ADJUVANT TREATMENT FOR HIGH-RISK TRIPLE NEGATIVE BREAST CANCER PATIENTS WITH THE ANTI-PD-L1 ANTIBODY AVELUMAB: A Phase III randomized trial

EUDRACT: 2016-000189-45

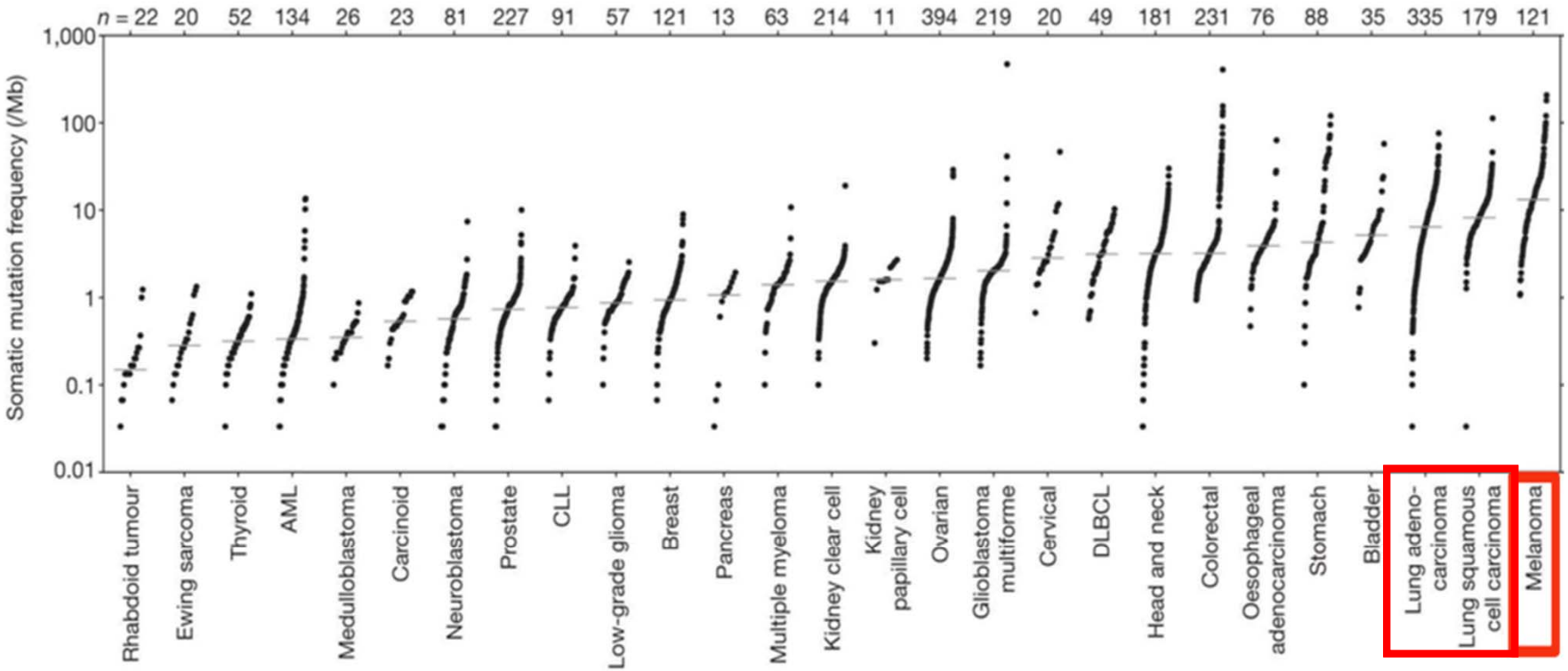
Co-primary endpoints: DFS in all-comers and DFS in PD-L1+ patients

Study centers: Multicentric study (about 40 Italian Institution)

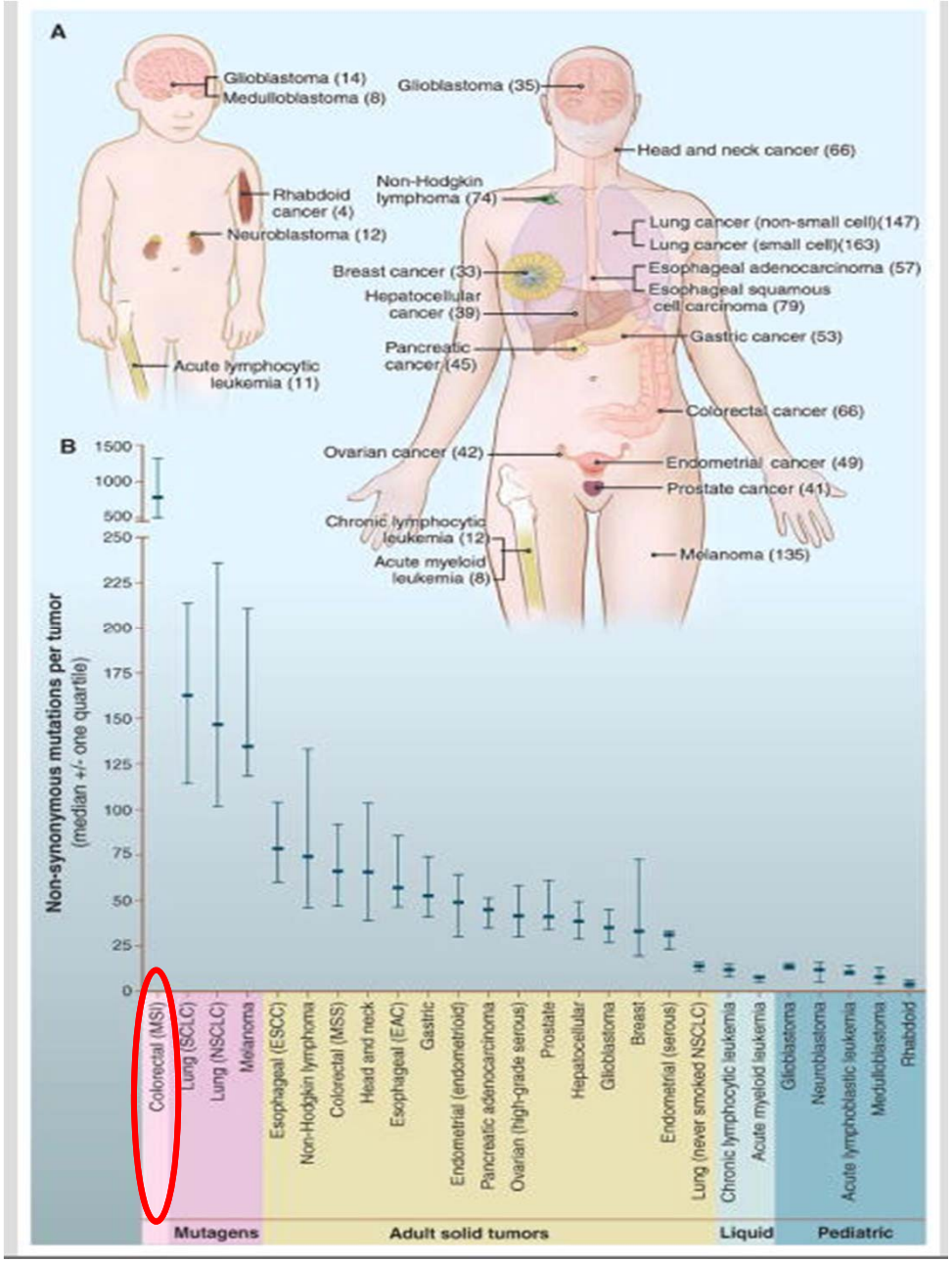
Sponsor: Università di Padova

Principal Investigator: Prof. Pierfranco Conte

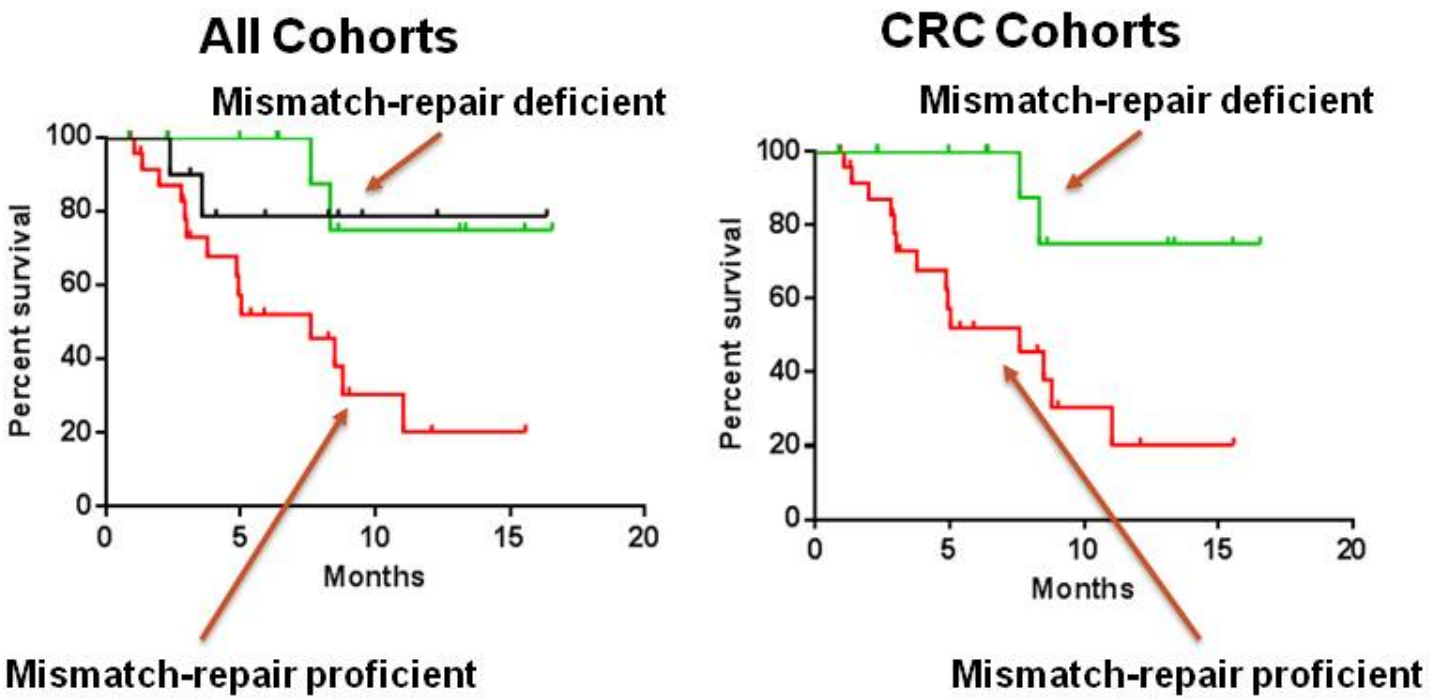
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs



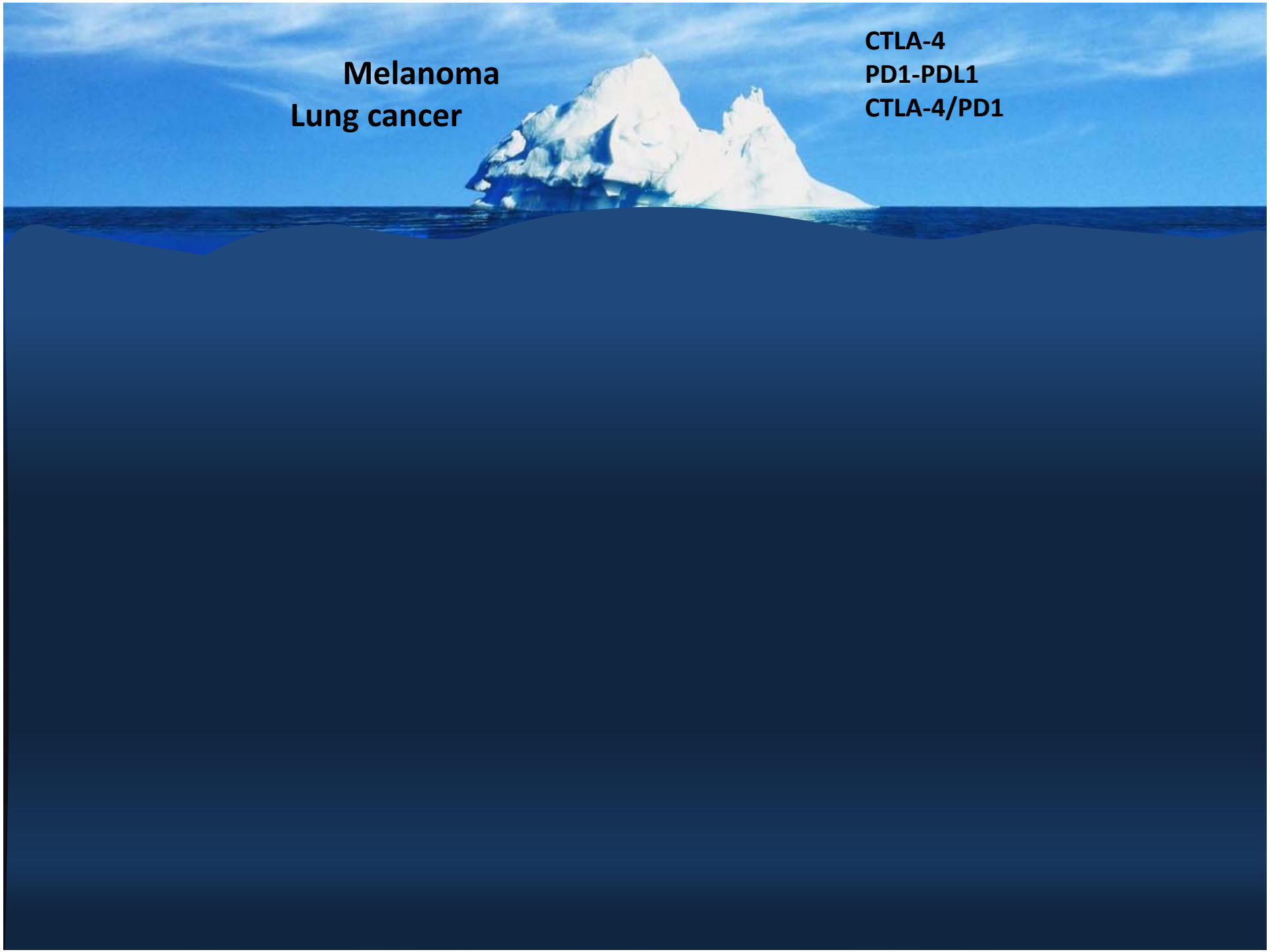
Lawrence et al, Nature 2013


A
Glioblastoma (14)
Medulloblastoma (8)
Rhabdoid cancer (4)
Neuroblastoma (12)
Acute lymphocytic leukemia (11)
Glioblastoma (35)
Head and neck cancer (66)
Non-Hodgkin lymphoma (74)
Lung cancer (non-small cell)(147)
Lung cancer (small cell)(163)
Breast cancer (33)
Esophageal adenocarcinoma (57)
Esophageal squamous cell carcinoma (79)
Hepatocellular cancer (39)
Gastric cancer (53)
Pancreatic cancer (45)
Colorectal cancer (66)
Ovarian cancer (42)
Endometrial cancer (49)
Prostate cancer (41)
Chronic lymphocytic leukemia (12)
Acute myeloid leukemia (8)
Melanoma (135)
B
Non-synonymous mutations per tumor
(median +/- one quartile)
1500
1000
500
250
225
200
175
150
125
100
75
50
25
0
Colorectal (MSI)
Lung (SCLC)
Lung (NSCLC)
Melanoma
Esophageal (ESCC)
Non-Hodgkin lymphoma
Colorectal (MSS)
Head and neck
Esophageal (EAC)
Gastric
Endometrial (endometrioid)
Pancreatic adenocarcinoma
Ovarian (high-grade serous)
Prostate
Hepatocellular
Glioblastoma
Breast
Endometrial (serous)
Lung (never smoked NSCLC)
Chronic lymphocytic leukemia
Acute myeloid leukemia
Glioblastoma
Neuroblastoma
Acute lymphoblastic leukemia
Medulloblastoma
Rhabdoid
Mutagens
Adult solid tumors
Liquid
Pediatric

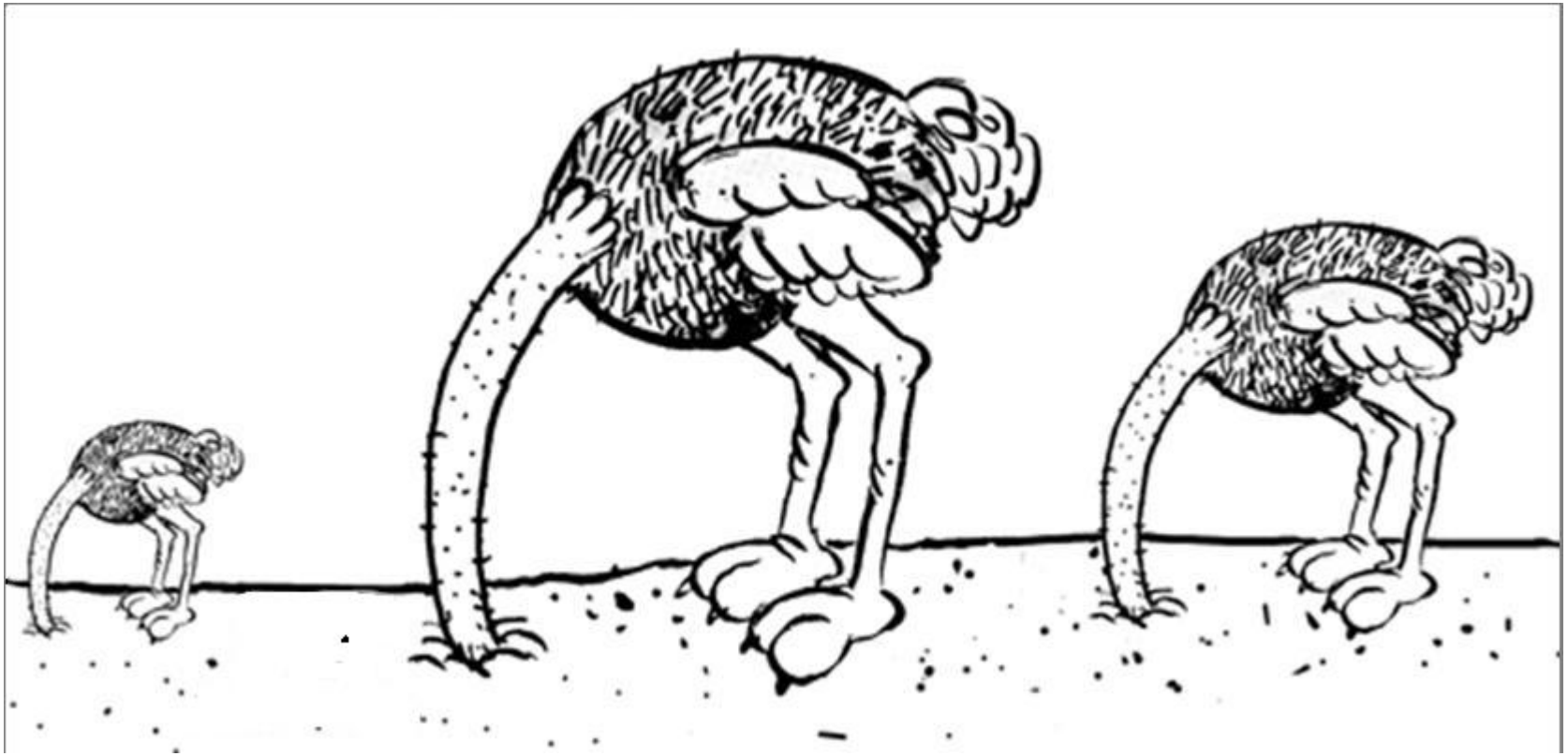
Overall Survival



Presented By Dung Le at 2015 ASCO Annual Meeting


Melanoma
Lung cancer
CTLA-4
PD1-PDL1
CTLA-4/PD1

Immunotherapy of lung cancer ……?!?

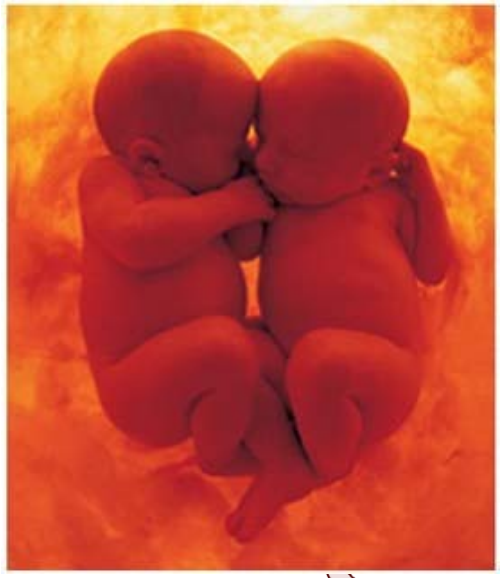


Medical Oncology and Immunotherapy, University Hospital of Siena

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

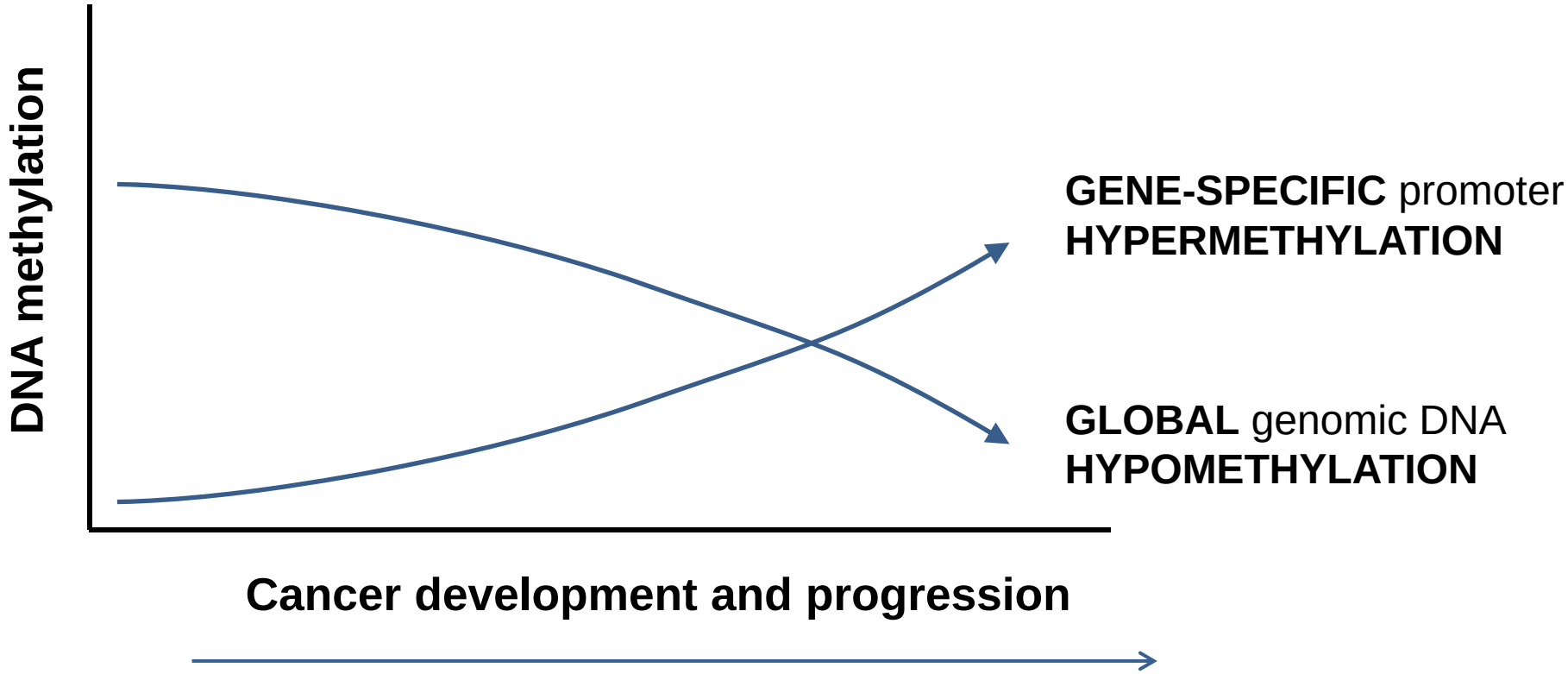
- Vaccines
- Cytokines
- Tumor microenvironment modulating agents
- Selected chemotherapeutic agents
- Targeted therapies
- Epigenetic therapies

EPIGENETICS

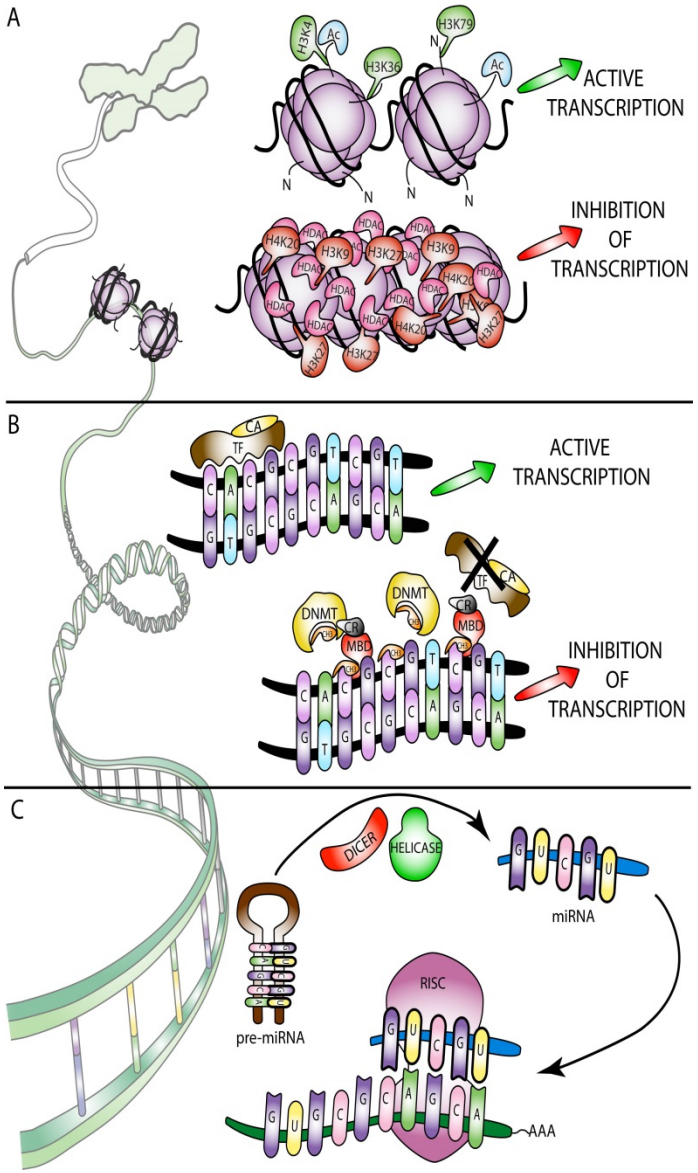


Heritable changes in gene expression
<u>not based</u>
on modifications of the DNA sequence

EPIGENETICS AND CANCER



EPIGENETIC MODIFICATIONS



Histone modifications

DNA methylation

MicroRNA gene silencing

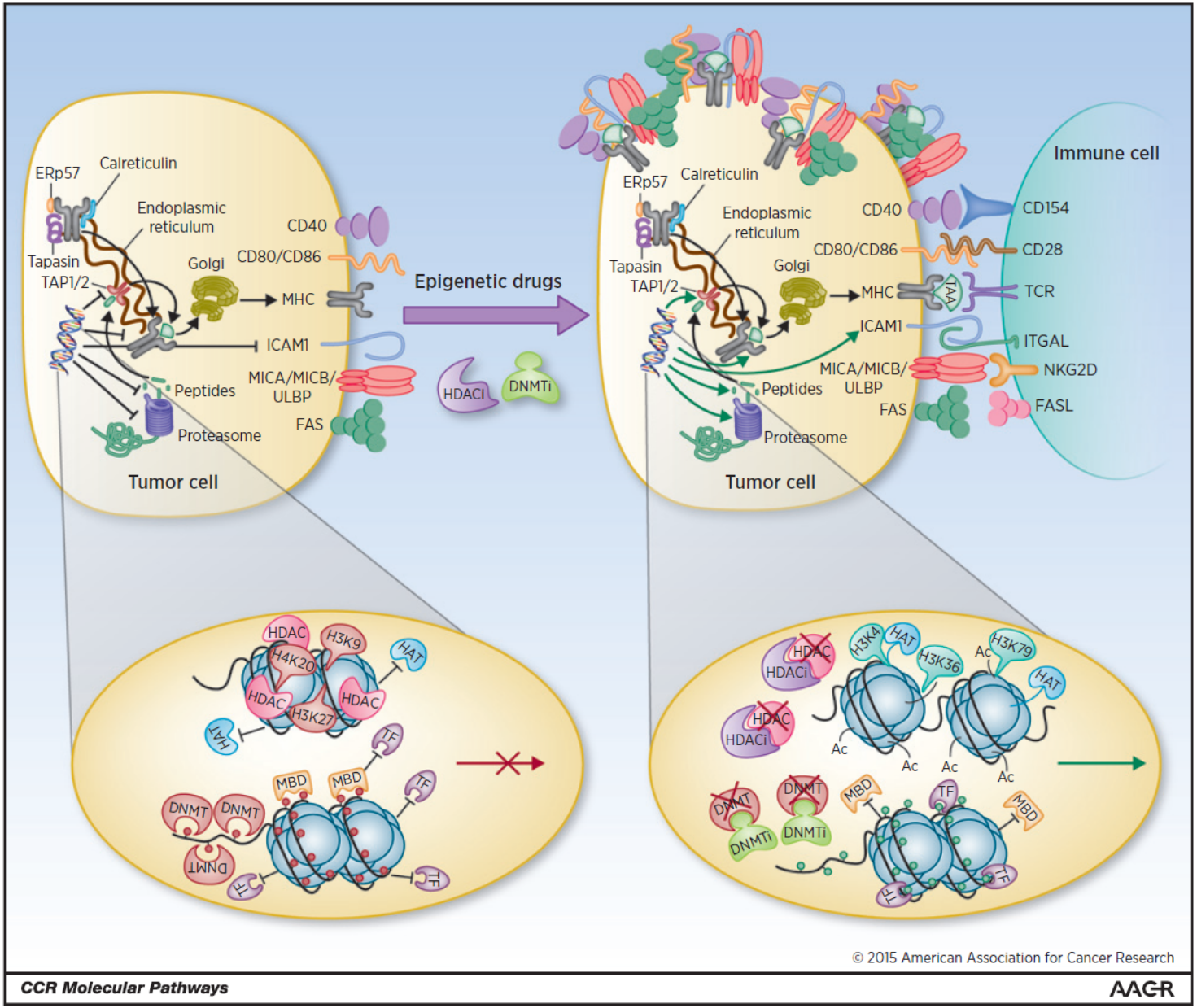
PHARMACOLOGICALLY REVERSIBLE

HDAC inhibitors (HDACi)

DNMTs inhibitors (DNMTi)

Maio et al, unpublished

Epigenetic Immunomodulation of Cancer cell

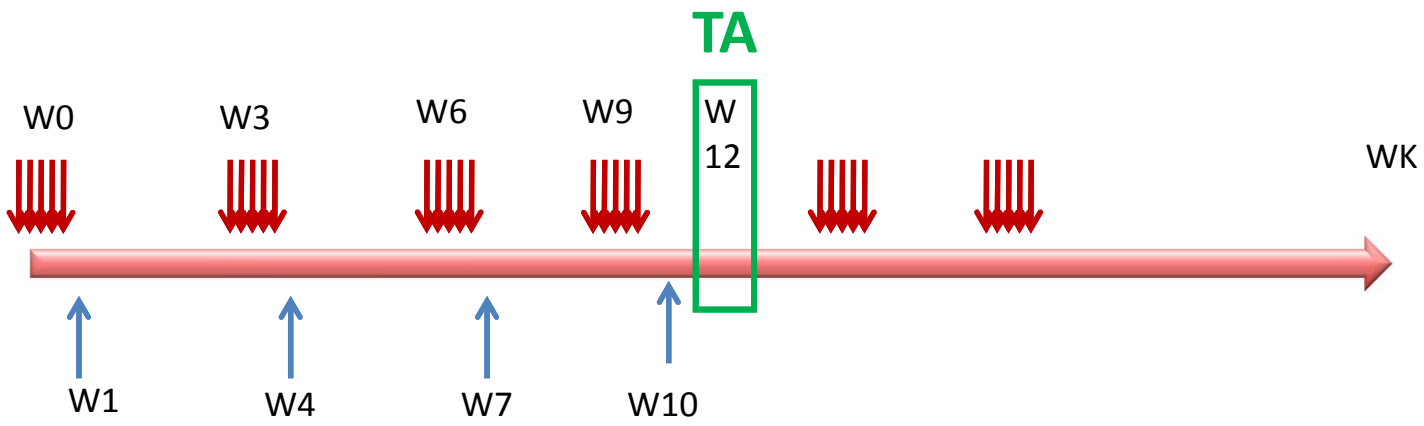


Maio M. *et al.*, CCR 2015

Epigenetic immuno-sequencing: the NIBIT-M4 Study

(NCT02608437)

SGI-110
5 days q21



Ipilimumab
4 x q21

FPFV October 12, 2015

A.M. Di Giacomo et al. *Semin Oncol*, 2015

Take two:

Combining immunotherapy with epigenetic drugs to tackle cancer

By Karen Weintraub

In 2010, six individuals with advanced lung cancer all received bad news. Early preclinical studies in mice had suggested that a drug called azacitidine might work in combination with an experimental medication called entinostat to treat their non-small cell lung cancer (NSCLC). But none of these six people enrolled in the subsequent clinical trial saw any significant tumor shrinkage. Hoping to buy the patients a little more time, Julie Brahmer, the group's oncologist at Johns Hopkins' Sidney Kimmel Cancer Center, gave them an immunotherapy drug called nivolumab. When it works, this drug unchecks the immune system to fight cancer.

Among people with NSCLC participating in other studies, fewer than half of those on nivolumab—a checkpoint inhibitor that targets a cell surface protein known as PD-1—survived six months without cancer progression. Brahmer and her colleagues expected similar results in her trial: perhaps three of the six would survive for at least six months, and maybe one for longer than a year (*N. Engl. J. Med.* 366, 2443–2454, 2012). Yet five survived past the initial six months—and four years later, two are still alive. A third person, who died of complications from previous treatment, showed no evidence of cancer recurrence at the time of death, according to Brahmer (*Cancer Discov.* 1, OF1–OF10, 2011).

Given the small size of the group, the possibility that the success could be due simply to chance can not be ruled out. But azacitidine and entinostat, which alter the epigenome, may have primed the patients' immune systems to respond to the checkpoint inhibitor. The experiment was the first to suggest that pairing these drugs could radically improve patient outcomes.

The idea of combining different therapeutic agents to fight cancer is not new. Immunotherapeutic agents such as checkpoint inhibitors are being tested and used in combination with other treatment methods, such as chemotherapy and radiation, and in October 2015, the US Food and Drug Administration (FDA) approved for the first time a combination immunotherapy—nivolumab and another checkpoint inhibitor known as ipilimumab—for the treatment of melanoma. These combinations have proved more effective than using one drug alone, which supports the idea that cancer is more likely to yield if hit from multiple directions at once (*N. Engl. J. Med.* 373, 23–34, 2015).

Epigenetic therapies such as azacitidine and entinostat might offer another approach to rendering combinations more effective, and the next few years will see this idea put to the test. Shored up by a growing body of translational research that hints at tremendous potential, at least seven trials in the US, and more in Canada and Europe, are underway to test combinations of immune checkpoints and epigenetic therapies in solid tumors. A trial in people with melanoma started in October 2015 in Siena, Italy. At Johns

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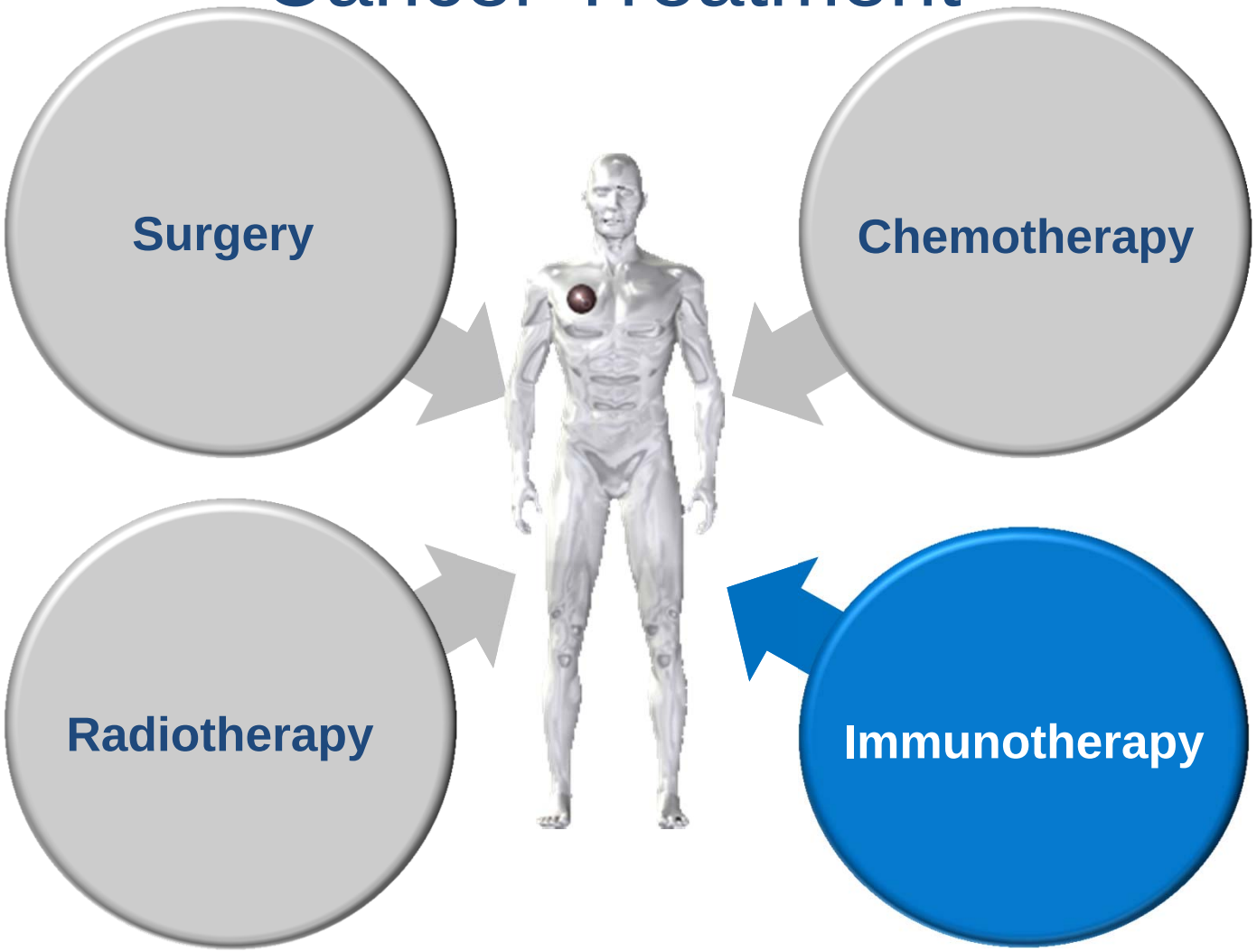

Melanoma as a tool for cancer research

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