4TH International Conference
Traslational Research in Oncology
Forli, November 10, 2016

Cytotoxic T-lymphocyte antigen-4 (CTLA-4)

Luana Calabrò
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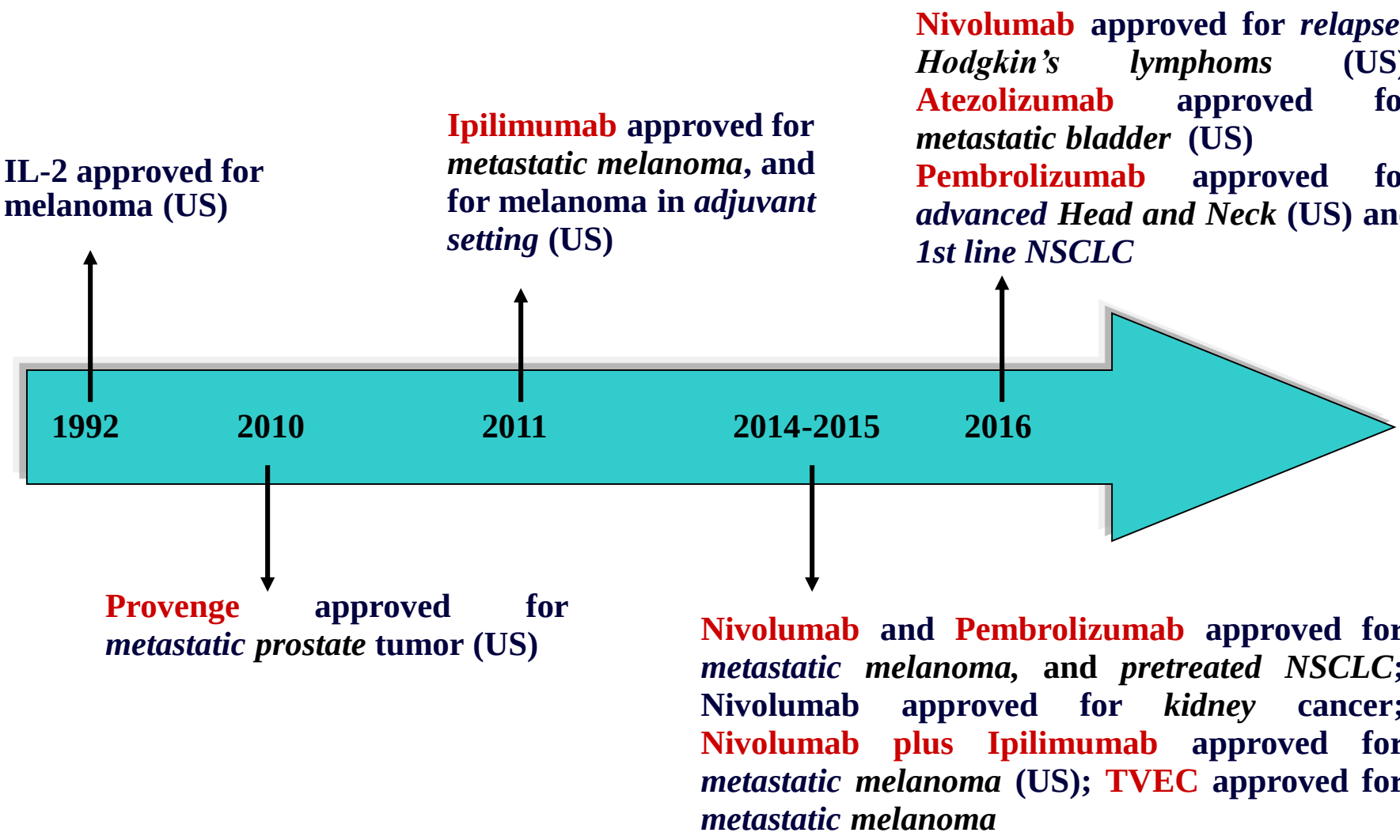
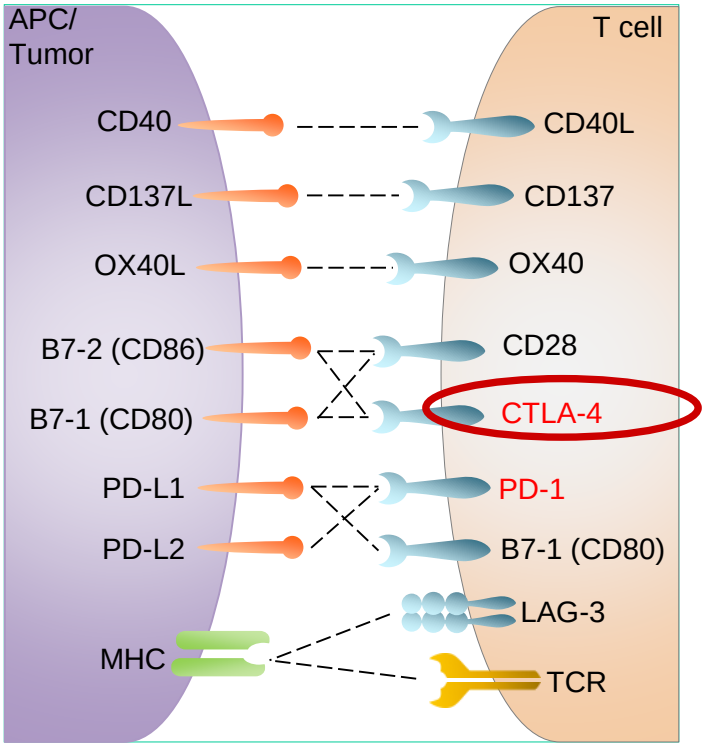
University Hospital of Siena,
Istituto Toscano Tumori
SIENA, ITALY

Exponential evolution of anti-tumor immunotherapy



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.

Releasing the Brakes on Cancer Immunotherapy

Antoni Ribas, M.D., Ph.D.

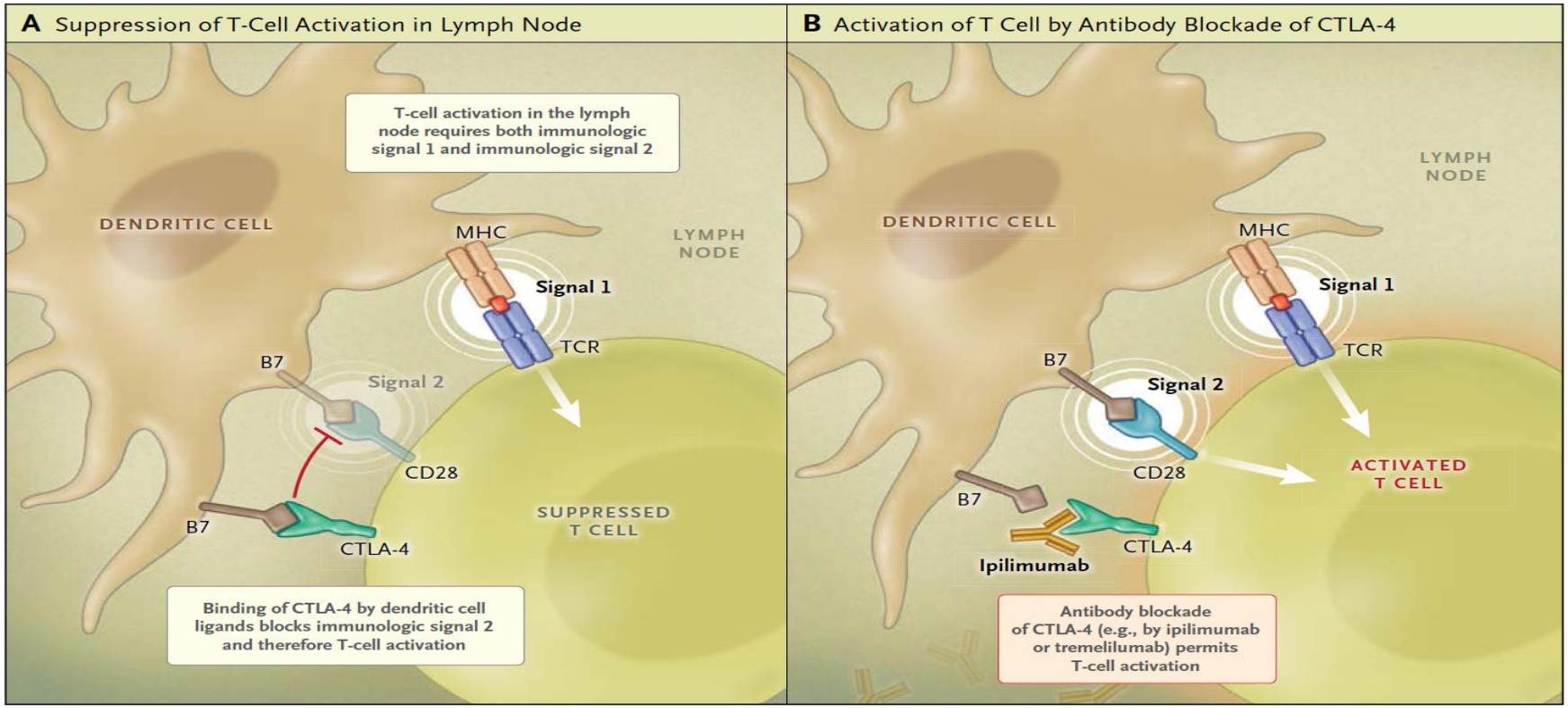


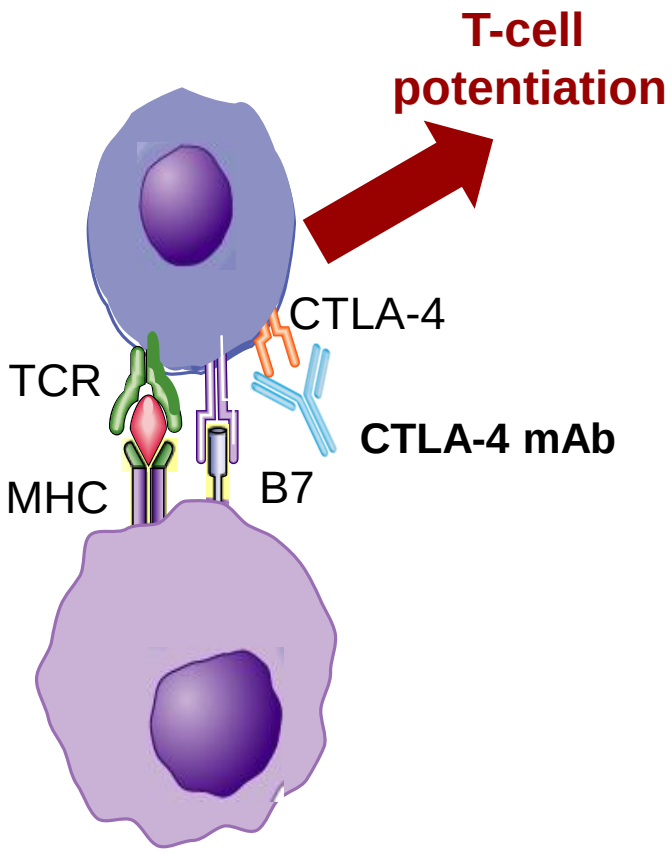
Figure 1. T-cell Activation in the Lymph Node.

Two immunologic signals are required for T-cell activation in the lymph node: stimulation of the T-cell receptor (TCR) by the MHC (immunologic signal 1), and stimulation of CD28 by the B7 costimulatory molecules (immunologic signal 2). However, binding of the B7 costimulatory molecules to CTLA-4 blocks immunologic signal 2, and therefore blocks T-cell activation. Antibody blockade of CTLA-4, for example, by ipilimumab, derepresses signaling by CD28, permitting T-cell activation.

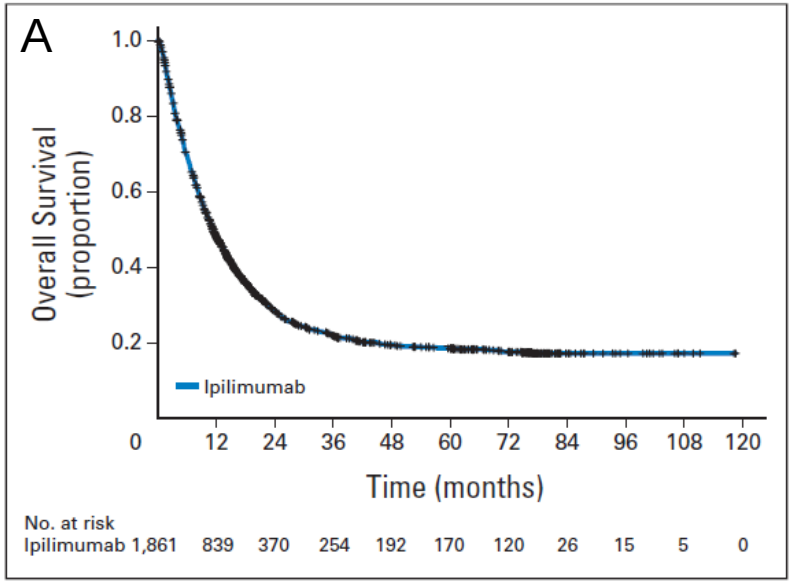
Anti-CTLA-4 mAb in clinical development

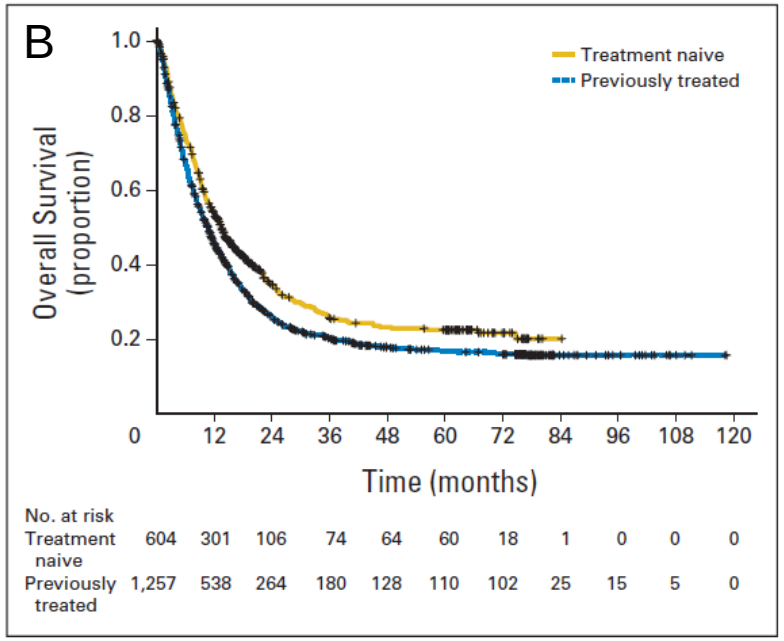
- **Tremelimumab (CP675,206)**
  Pfizer/MedImmune
  IgG2 isotype antibody
  half-life time: 22 days

- **Ipilimumab (MDX-010)**
  BMS/Medarex
  IgG_1 isotype antibody
  half-life time: 12.5 days



Ipilimumab approved in 2011 for unresectable or metastatic melanoma





Two phase 3 trials showed an overall survival benefit with IPI

- At 3 mg/kg alone vs gp100 peptide vaccine in previously treated patients (median OS: 10.1 vs 6.4 mo) (Hodi FS et al. *N Engl J Med*. 2010).
- At 10 mg/kg in combination with DTIC vs DTIC alone in untreated patients (median OS: 11.2 vs 9.1 mo). (Robert C et al. N Engl J Med. 2011).

A) Pooled analysis for 1,861 patients from clinical trials (including two phase 3). Median OS: 11.4 months

B) Including data from the expanded access program (a total of 4,846 patients). Median OS: 9.5 months

(Schadendorf JCO 2015).

In Fig A and B plateau at 22% in the survival curve beginning around year 3.

G3-4 toxicities: 10-15%

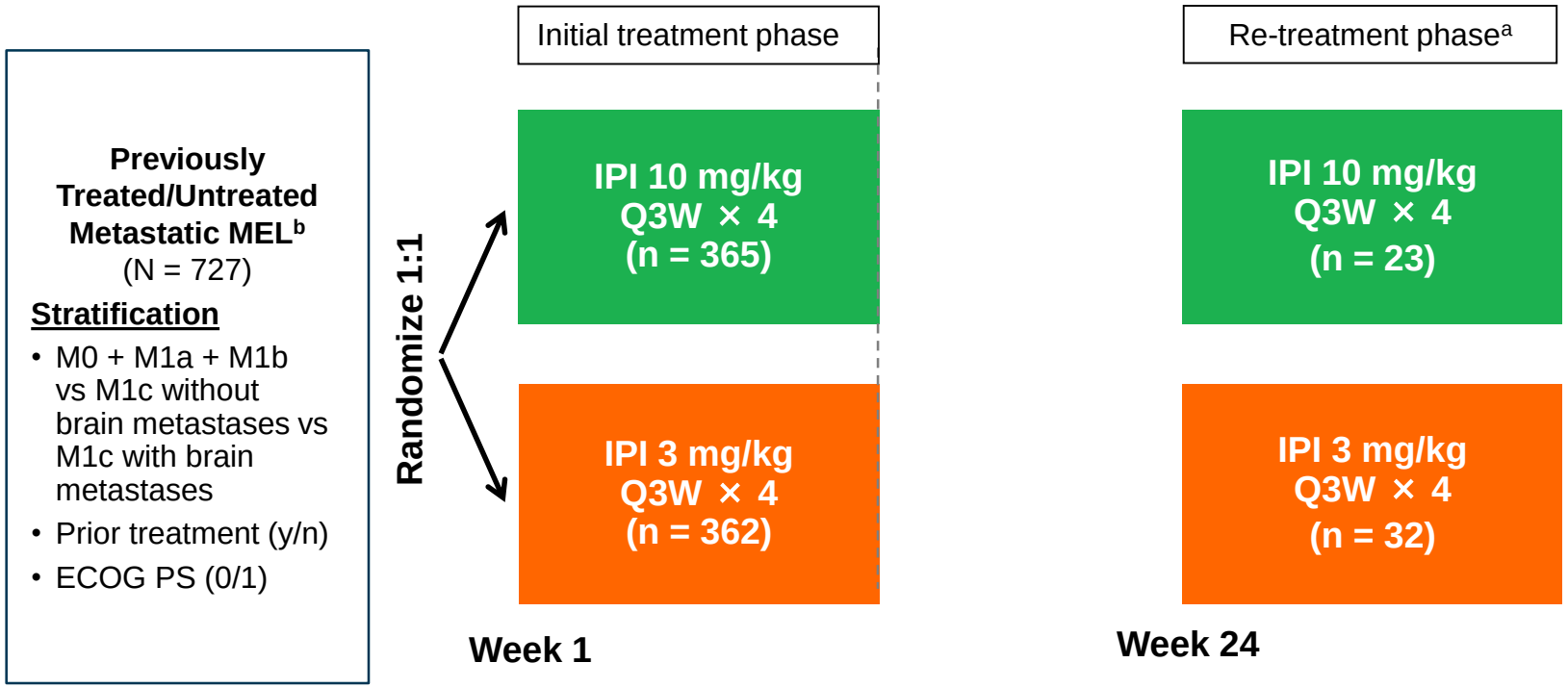
Immune-related adverse events in most cases reversible when managed with immunosuppressive medications such as steroids. (Hodi NEJM 2010)

Overall Survival and Safety Results From a Phase 3 Trial of Ipilimumab at 3 mg/kg vs 10 mg/kg in Patients With Metastatic Melanoma

Ascierto PA,[1] Del Vecchio M,[2] Robert C,[3] Mackiewicz A,[4] Chiarion Sileni V,[5] Arance AM,[6] Schmidt H,[7] Lebbé C,[8] Bastholt L,[9] Hamid O,[10] Rutkowski P,[11] McNeil C,[12] Garbe C,[13] Loquai C,[14] Dreno B,[15] Thomas L,[16] Grob J-J,[17] Hennicken D,[18] Qureshi A,[18] Maio M[19]

[1]Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; [2]Medical Oncology, National Cancer Institute, Milan, Italy; [3]Institute Gustave, Roussy, Villejuif, France; [4]Department of Diagnostics and Cancer Immunology, Greater Poland Cancer Centre, Poznan Medical University, Poznan, Poland; [5]Istituto Oncologico Veneto, Padova, Italy; [6]Hospital Clinic, Barcelona, Spain; [7]Aarhus University Hospital, Aarhus, Denmark; [8]AP-HP Dermatology CIC Departments, Saint-Louis Hospital, INSERM U976, Université Paris Diderot, Paris, France; [9]Odense University Hospital, Odense, Denmark; [10]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [11]Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; [12]Chris O'Brien Lifehouse and Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia and Melanoma Institute Australia, Sydney, New South Wales, Australia; [13]University Hospital Tübingen, Tübingen, Germany; [14]University Medical Center, Mainz, Germany; [15]Department of Oncodermatology, INSERM Research Unit 892, University Hospital, Nantes, France; [16]Department of Dermatology, Centre Hospitalier Lyon Sud, Pierre-Bénite Cedex, France; [17]Aix-Marseille University, APHM Timone, France; [18]Bristol-Myers Squibb, Princeton, NJ, USA; [19]University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy

CA184-169: Study Design

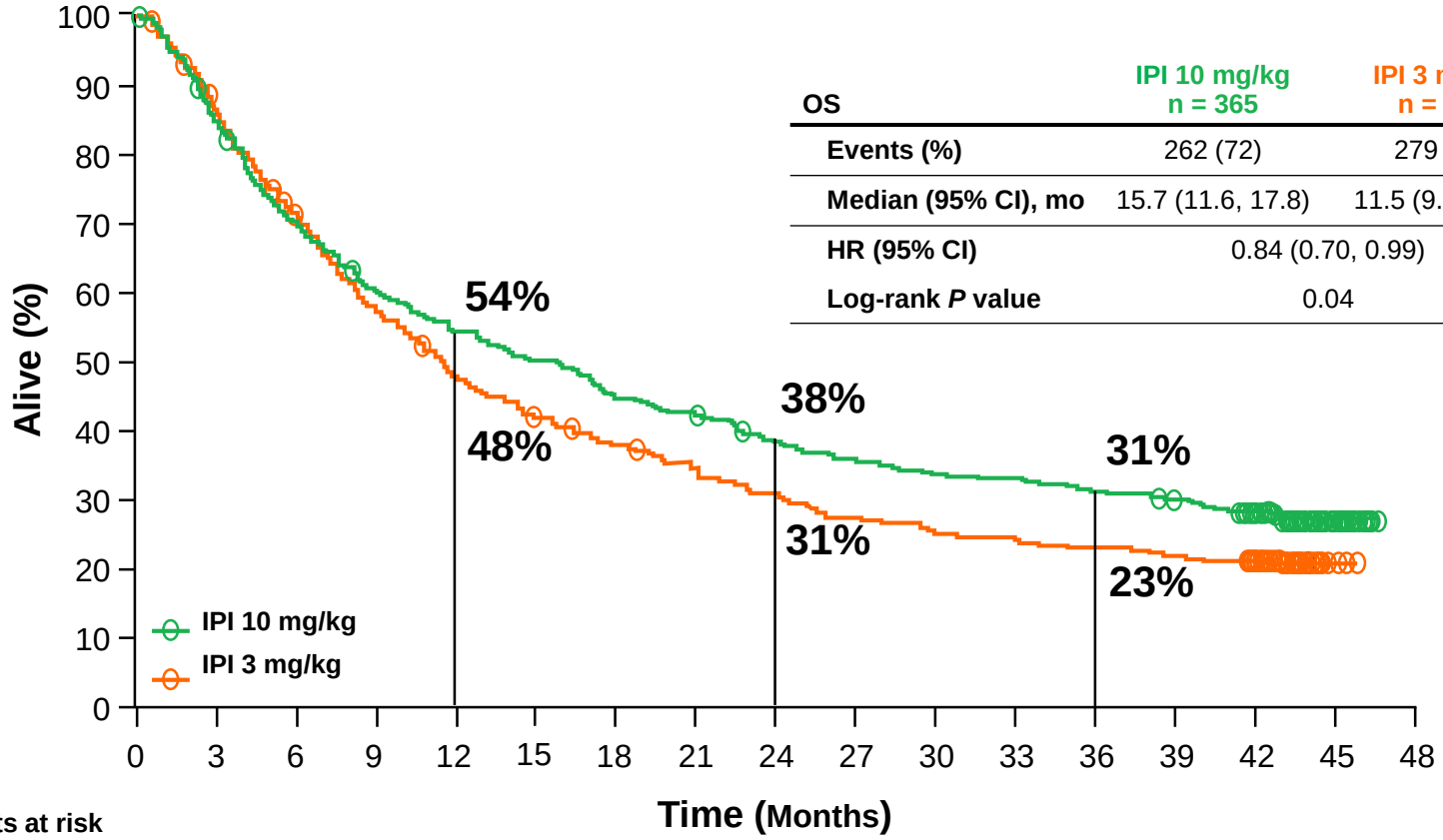


- **Enrollment period:** March 2012 to August 2012
- No crossover allowed between treatment arms

Primary Endopoint: OS
Secondary Endpoint: PFS, ORR, DCR, Safety

[a]After initial response (or stable disease >3 months) and subsequent progressive disease in the absence of intolerable toxicity.
[b]Patients could not be treated with BRAF/PD-1 therapy.
ECOG PS = Eastern Cooperative Oncology Group performance status; Q3W = every 3 weeks.

OS: Randomized Patients



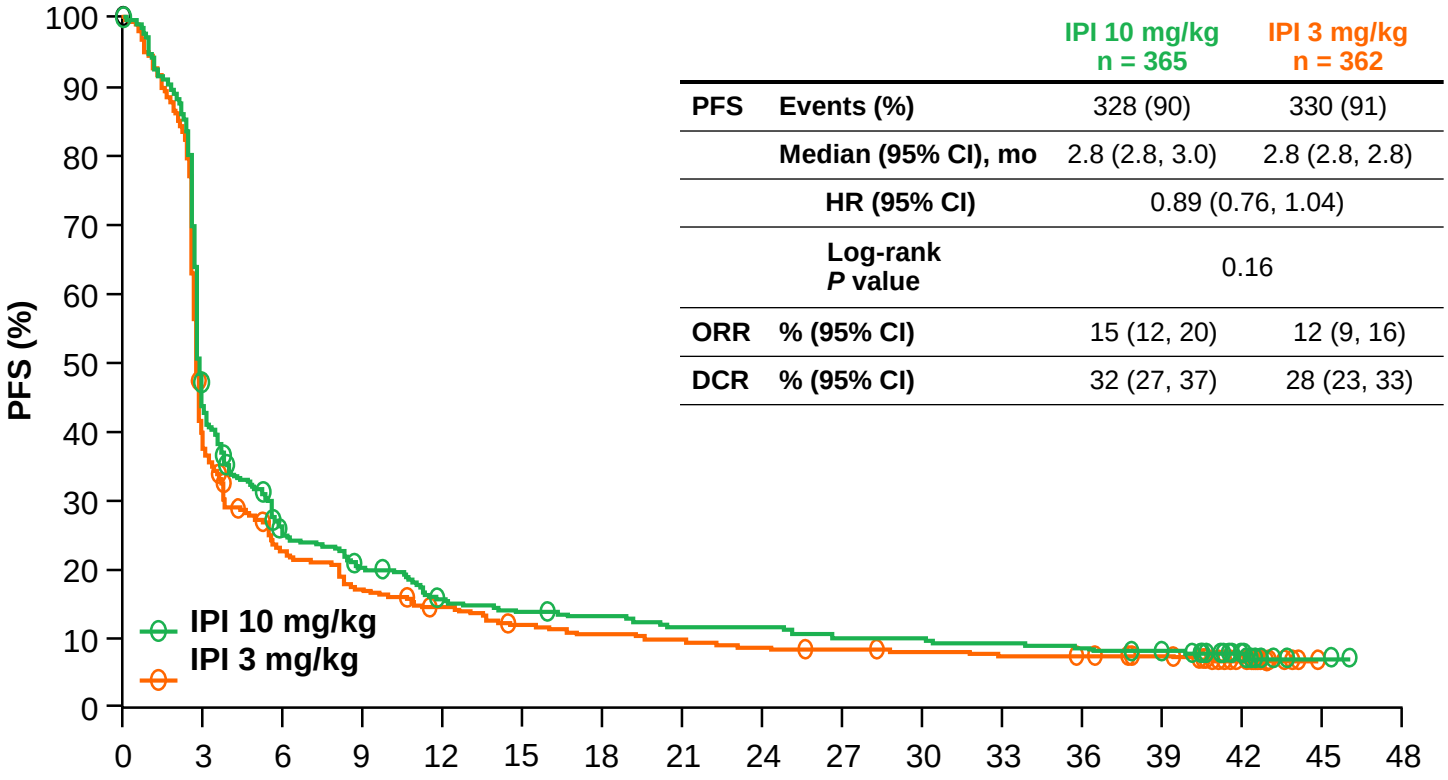
OS	IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
Events (%)	262 (72)	279 (77)
Median (95% CI), mo	15.7 (11.6, 17.8)	11.5 (9.9, 13.3)
HR (95% CI)	0.84 (0.70, 0.99)	
Log-rank *P* value	0.04	

Number of patients at risk

IPI 10 mg/kg	365	306	253	217	196	181	161	151	137	126	120	118	111	105	94	16	0
IPI 3 mg/kg	362	310	253	205	168	146	131	118	107	95	87	83	80	76	71	8	0

Minimum OS follow-up: ~43 mo

PFS, ORR, DCR by mWHO: Randomized Patients



		IPI 10 mg/kg n = 365	IPI 3 mg/kg n = 362
PFS	**Events (%)**	328 (90)	330 (91)
	Median (95% CI), mo	2.8 (2.8, 3.0)	2.8 (2.8, 2.8)
	HR (95% CI)	0.89 (0.76, 1.04)	
	Log-rank *P* value	0.16	
ORR	**% (95% CI)**	15 (12, 20)	12 (9, 16)
DCR	**% (95% CI)**	32 (27, 37)	28 (23, 33)

Number of patients at risk

IPI 10 mg/kg	365	160	89	69	52	46	43	38	38	33	33	31	29	23	11	2	0
IPI 3 mg/kg	362	138	79	60	49	39	35	32	29	27	25	23	22	19	8	0	0

Safety Summary: Treated Patients

AEs during initial treatment phase	IPI 10 mg/kg n = 364		IPI 3 mg/kg n = 362	
	Any grade	Grades 3-5	Any grade	Grades 3-5
AEs, %	95	59	93	52
Treatment-related AEs, %	79	34	63	19
Serious AEs, %	64	53	51	43
AEs leading to discontinuation, %	31	26	19	16
Immune-related AEs, %	74	30	54	14

- During the entire study period, study-drug toxicity led to death in
  - 4 patients (1%) in the 10 mg/kg arm:
    - Diarrhea leading to general deterioration, fulminant colitis, multi-organ failure, bowel perforation
- 2 patients (<1%) in the 3 mg/kg arm:
  - Multifocal colon perforation, myocardial infarction from complications of diarrhea and colitis

Ipilimumab vs Placebo After Complete Resection of Stage III Melanoma: Final Overall Survival Results From the EORTC 18071 Randomized, Double-Blind, Phase 3 Trial

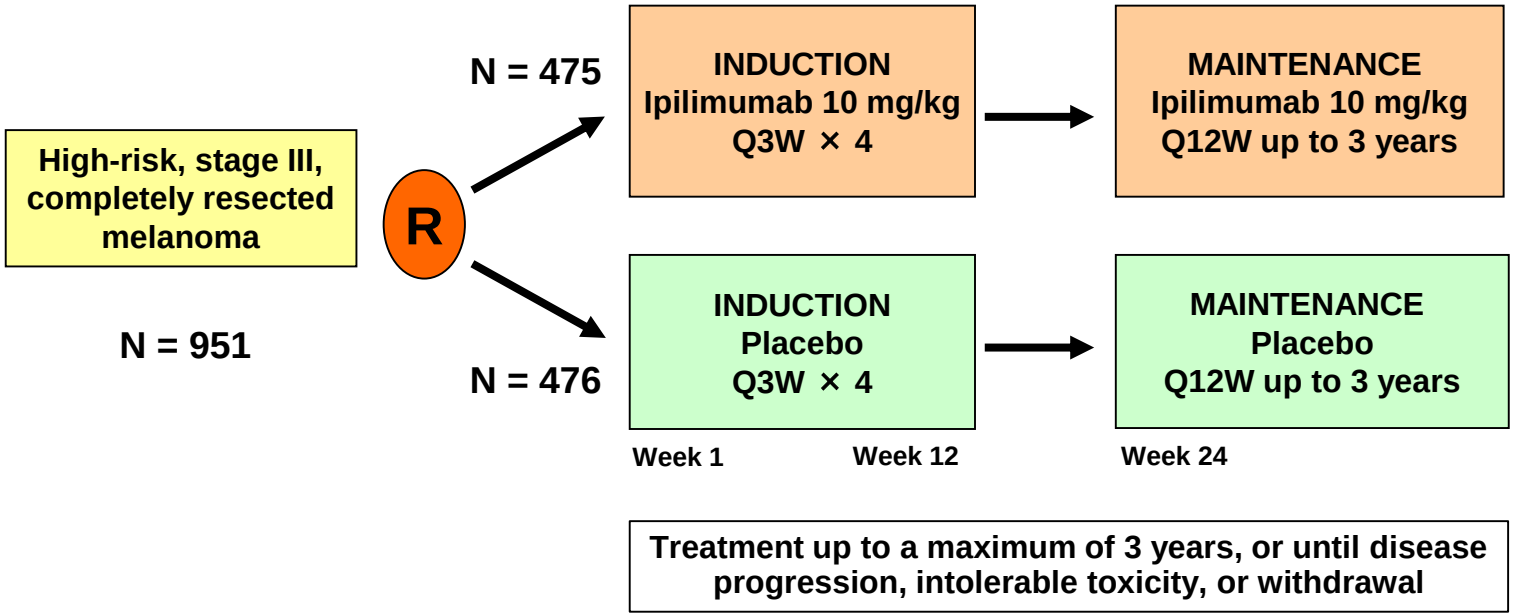
Alexander MM Eggermont,[1] Vanna Chiarion Sileni,[2] Jean-Jacques Grob,[3] Reinhard Dummer,[4] Jedd D Wolchok,[5] Henrik Schmidt,[6] Omid Hamid,[7] Caroline Robert,[1] Paolo A Ascierto,[8] Jon M Richards,[9] Céleste Lebbé,[10] Virginia Ferraresi,[11] Michael Smylie,[12] Jeffrey S Weber,[13,*] Corina Taitt,[14] Veerle de Pril,[14] Gaetan de Schaetzen,[15] Stefan Suciu,[15] Alessandro Testori[16]

[1]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; [2]Oncology Institute of Veneto–Istituto di Ricovero e Cura a Carattere Scientifico, Padua, Italy; [3]Aix-Marseille University, Hôpital de La Timone, Marseille, France; [4]University of Zürich Hospital, Zürich, Switzerland; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Aarhus University Hospital, Aarhus, Denmark; [7]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [8]Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy; [9]Oncology Specialists S.C., Park Ridge, IL, USA; [10]Department of Dermatology and Centred'Investigation Clinique, U-976 Hôpital Saint Louis, Université Paris Diderot, Paris, France; [11]Istituti Fisioterapici Ospitalieri, Rome, Italy; [12]Cross Cancer Institute, Edmonton, Alberta, Canada; [13]H Lee Moffitt Cancer Center, Tampa, FL, USA; [14]Bristol-Myers Squibb, Princeton, NJ, USA; [15]EORTC Headquarters, Brussels, Belgium; [16]European Institute of Oncology, Milan, Italy.
*Current affiliation: Perlmutter Cancer Center at NYU-Langone Medical Center, New York, NY, USA

Abstract Number LBA 3070

EORTC 18071/CA184-029: Study Design

Randomized, double-blind, phase 3 study evaluating the efficacy and safety of ipilimumab in the adjuvant setting for high-risk melanoma



Stratification factors

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries, and Australia)

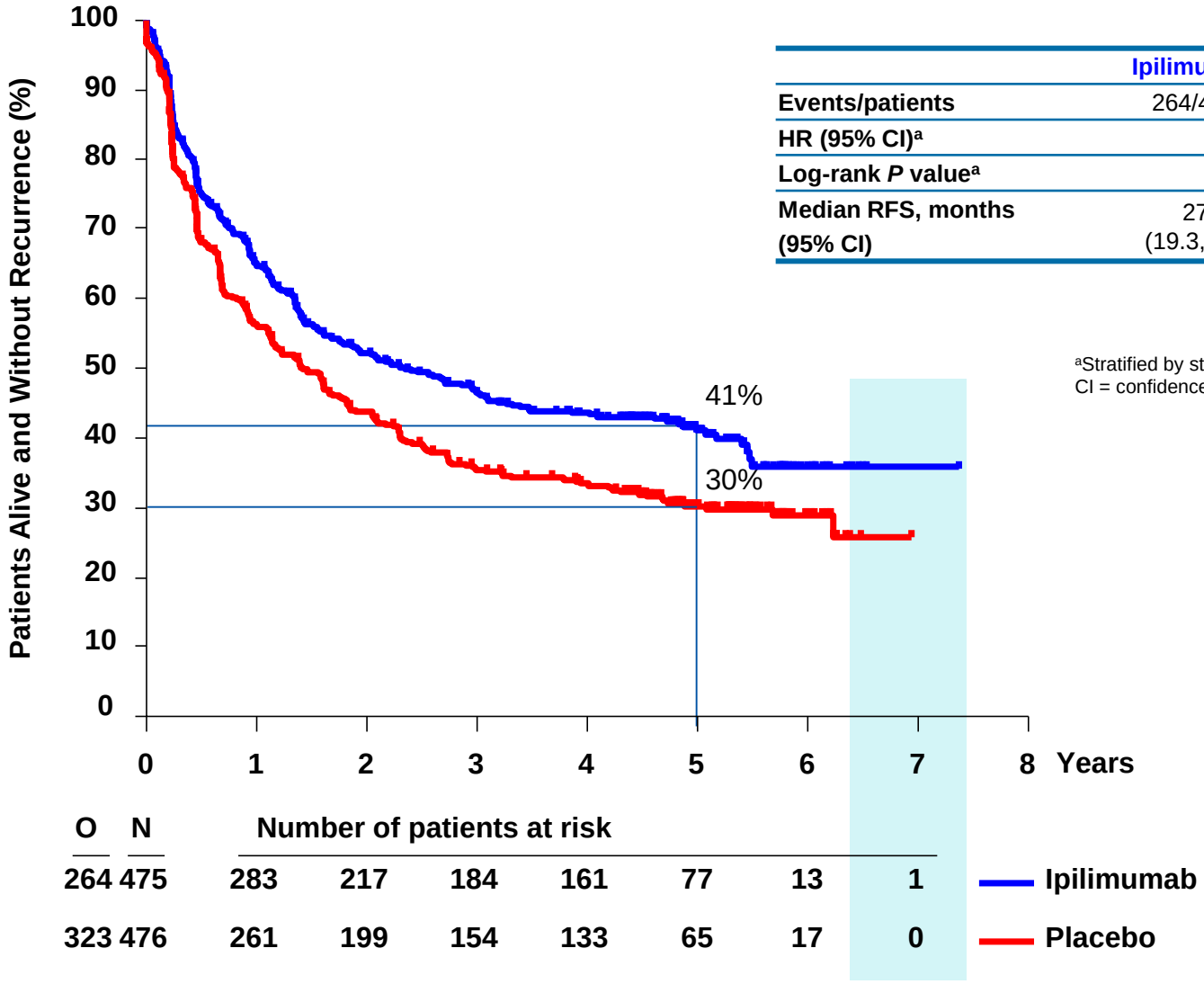
Enrollment Period: June 2008 to July 2011

Primary endpoint: RFS

Secondary endpoints: OS, DMFS, Safety

Q3W = every 3 weeks; Q12W = every 12 weeks; R = randomization.

RFS (Per IRC)

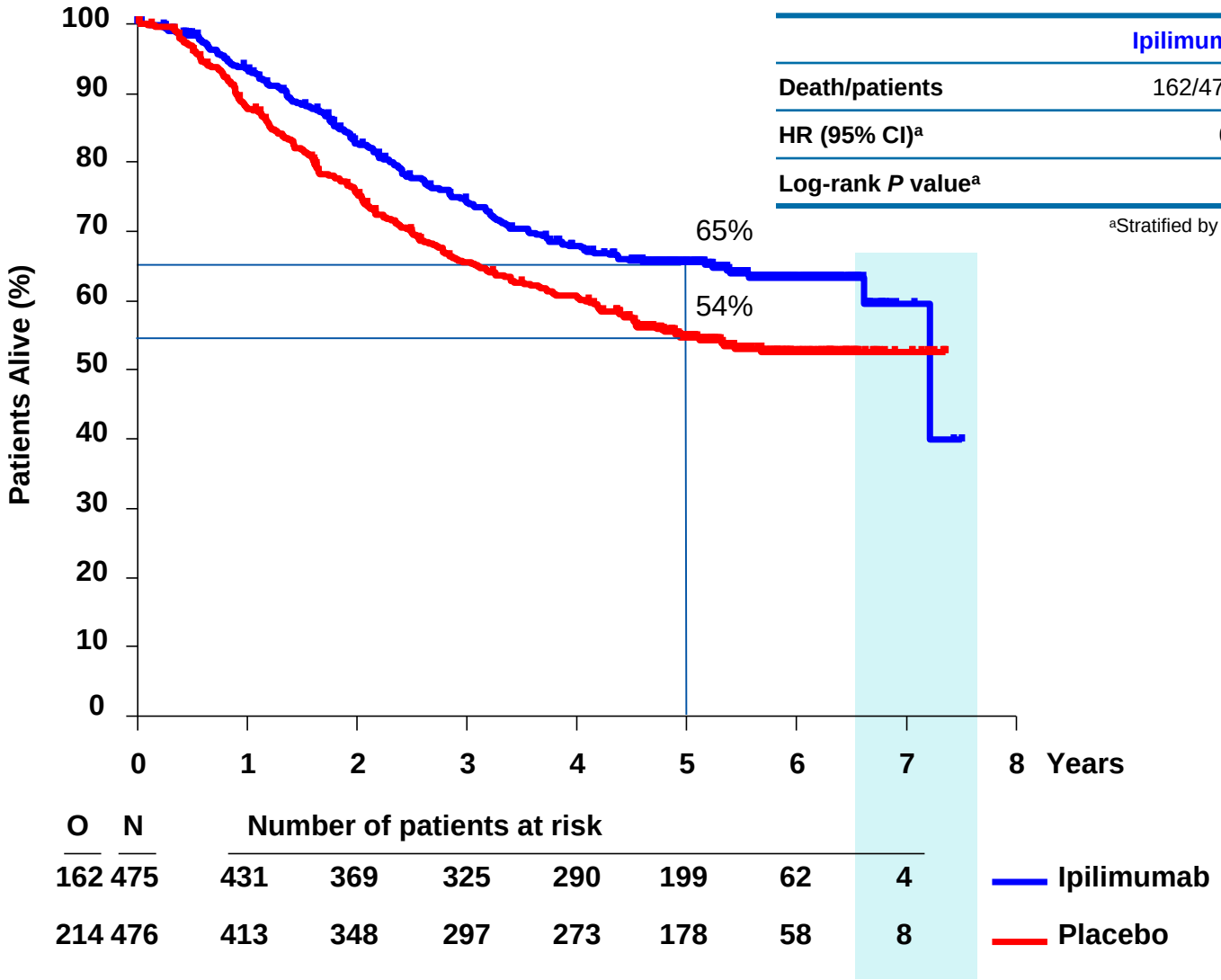


	Ipilimumab	Placebo
Events/patients	264/475	323/476
HR (95% CI)[a]	0.76 (0.64, 0.89)	
Log-rank *P* value[a]	0.0008	
Median RFS, months (95% CI)	27.6 (19.3, 37.2)	17.1 (13.6, 21.6)

[a]Stratified by stage provided at randomization.
CI = confidence interval.

Eggermont A, et al, ESMO 2016

OS



	Ipilimumab	Placebo
Death/patients	162/475	214/476
HR (95% CI)[a]	0.72 (0.58, 0.88)	
Log-rank *P* value[a]	0.001	

[a]Stratified by stage provided at randomization.

Eggermont A, et al, ESMO 2016

FDA News Release

FDA approves Yervoy to reduce the risk of melanoma returning after surgery

For Immediate Release October 28, 2015

Release

Español

Today the U.S. Food and Drug Administration expanded the approved use of Yervoy (ipilimumab) to include a new use as adjuvant therapy for patients with

Inquiries

Media

Sarah Peddicord
301-796-2805

Consumers

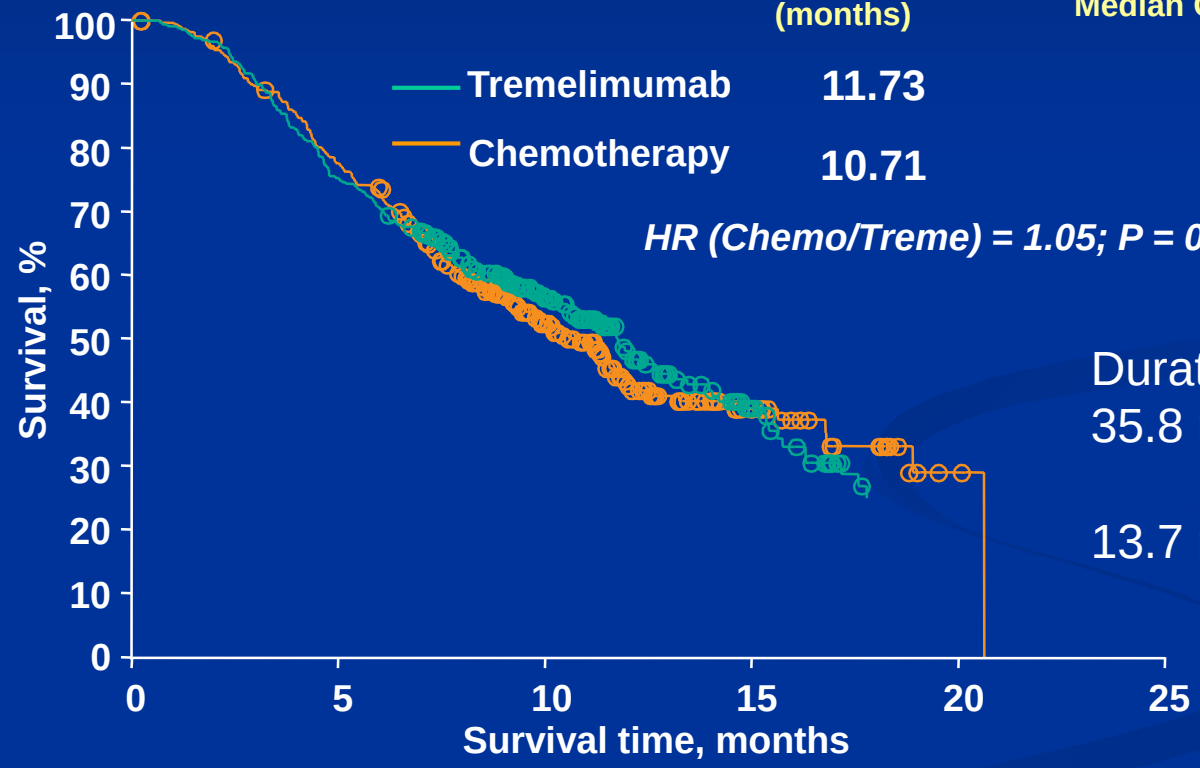
888-INFO-FDA

Spotlight

- FDA: Office of Hematology and Oncology Products
- FDA: Approved Drugs:

Front-line Trial of Tremelimumab Versus DTIC or TMZ

Kaplan-Meier Estimate of Overall Survival (OS): 655 pts

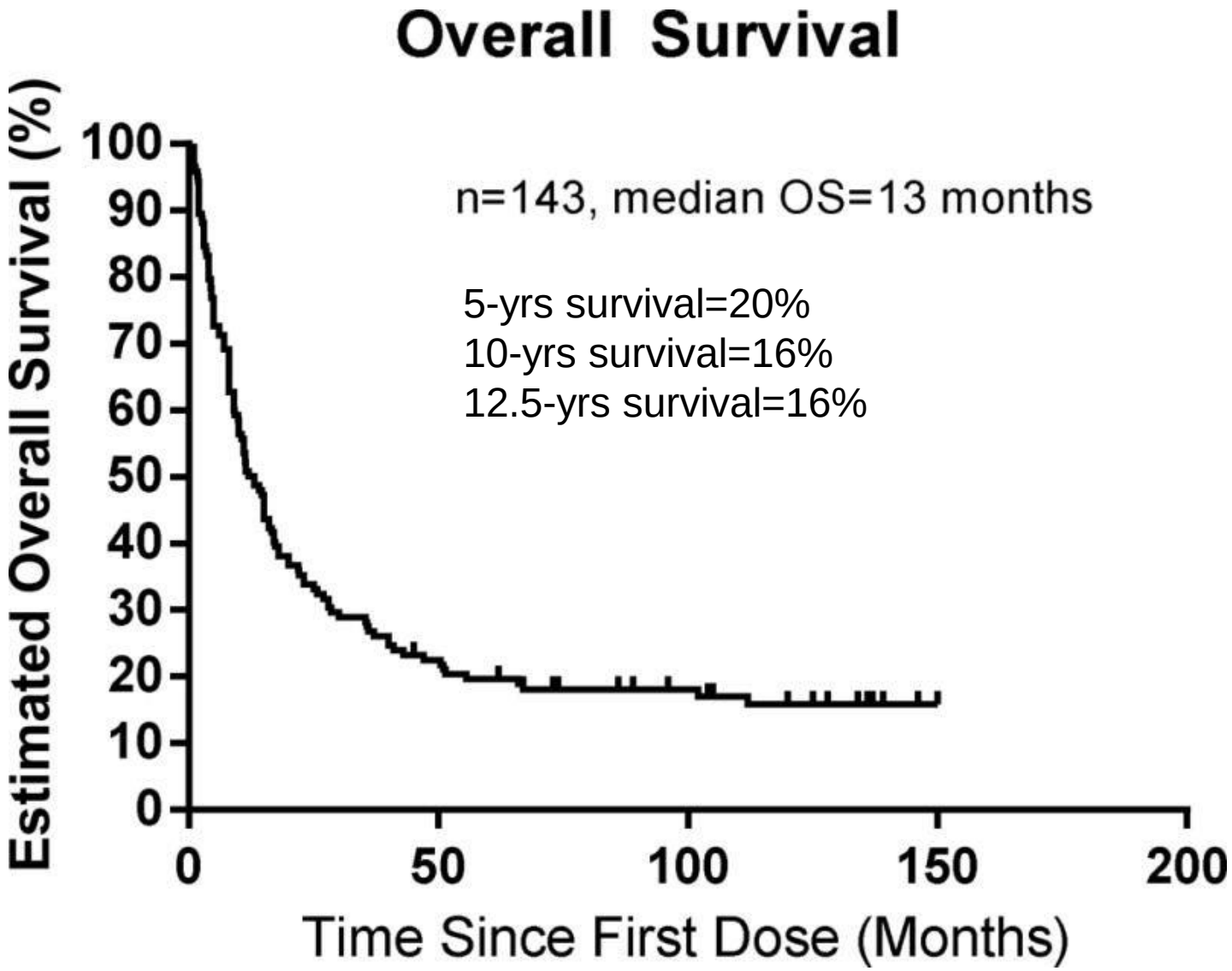


	Median Survival (months)	95% CI for Median OS	Prob. Est. of PFS at 6 months
Tremelimumab	11.73		0.241
Chemotherapy	10.71		0.216
	HR (Chemo/Treme) = 1.05; P = 0.679)		*(P = 0.4506)*

Duration of ORR:
35.8 months w treme
vs
13.7 months w CT

Patients at risk					
Tremelimumab	328	245	129	34	3
Chemotherapy	327	248	114	27	1

Long-term survival with tremelimumab: analysis from 4 phase I/II studies



Eroglu Z et al, Eur J Cancer, 2015

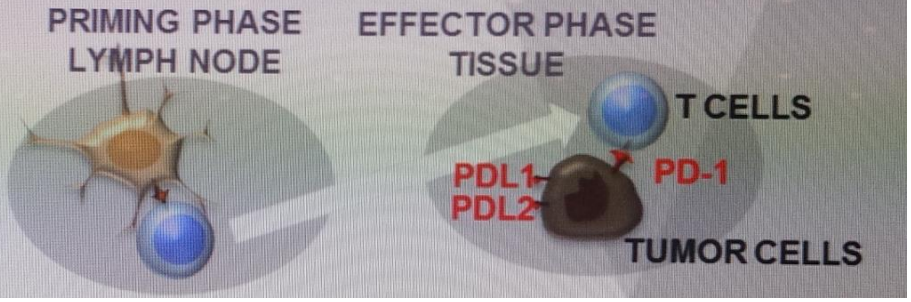
KEY LESSONS FROM ANTI-CTLA-4 mAb

- Objective response or stabilization of disease can be long-lasting, can improve over time without further treatment, and can be associated with a favourable survival (hallmark of cancer immunotherapy);
- Different kinetic of response can be observed with immunotherapeutic agents thus changing the paradigm *“progression of disease = uneffective treatment” ;*
- Standard response criteria cannot capture all response patterns, and novel criteria for immunotherapy have to be utilized
- Confirmation of progression of disease is strongly recommended to avoid early discontinuation of therapy in patients with delayed responses or false progression of disease (Increased volume of lesions may be due to lymphocytic infiltrate);
- Reinduction can results in further disease control in patients who progress after activity to induction therapy

OLD PARADIGM: TARGETING TUMORS CELLS

CHEMOTHERAPY
TARGETED THERAPY
EBR

NEW PARADIGM: TARGETING IMMUNITY→NEW PATTERNS

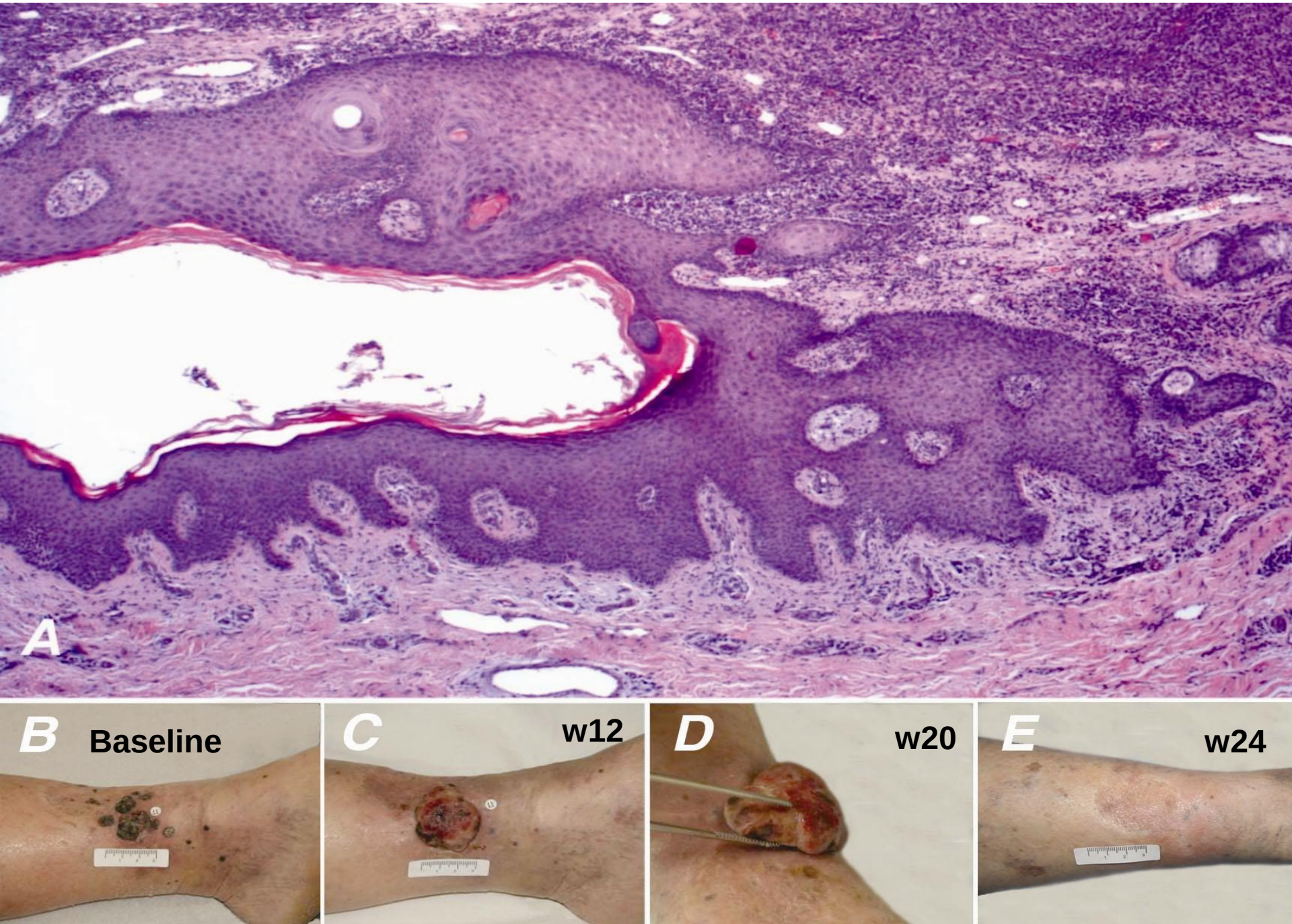


PARADIGM SHIFT

- The target is immunity and not tumor cells
- A transitory increase in tumor size or FDG-uptake might be observed even in case of a response

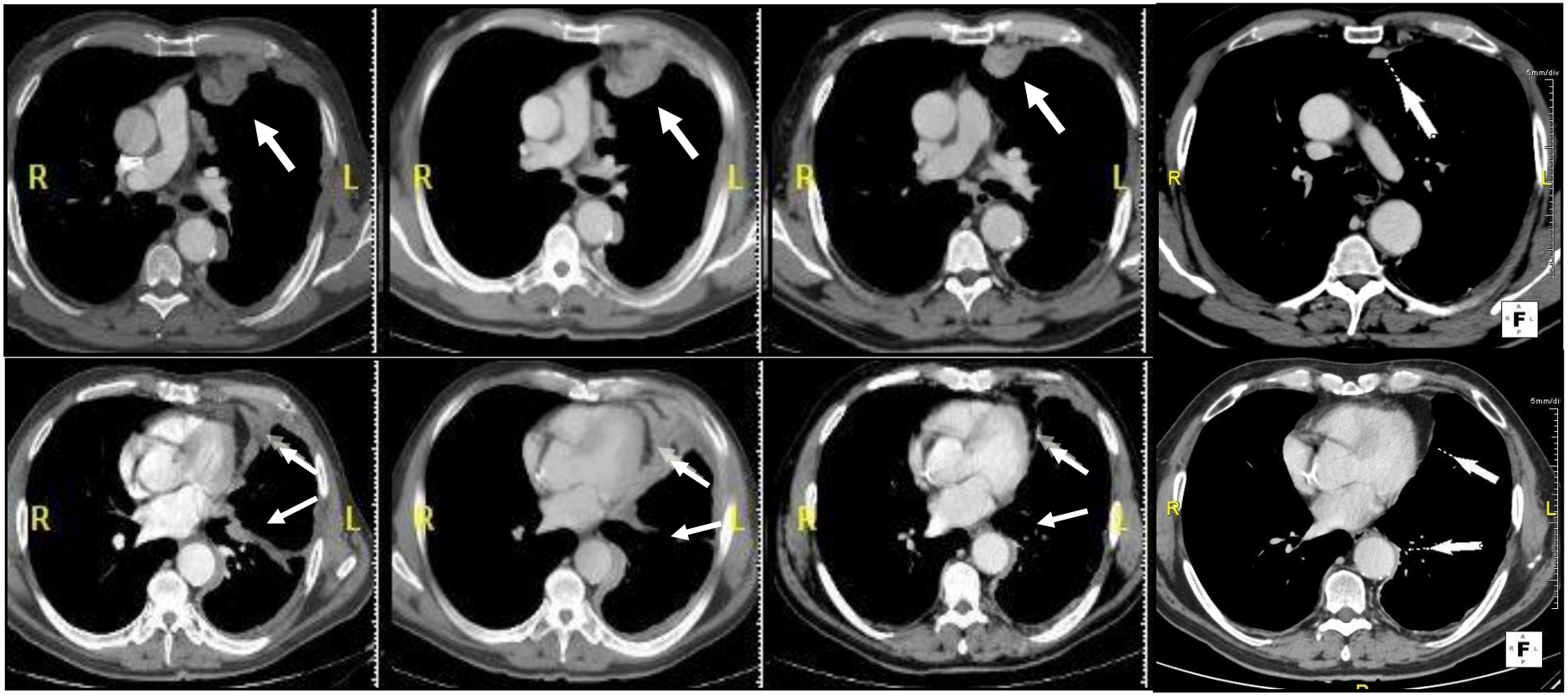
→ DELAYED RESPONSE
→ IMMUNE-INFILTRATION
→ PSEUDO-PROGRESSION

F, 76 yrs, cutaneous metastatic melanoma, PD after 1st line w DTIC+IFN+Thy→IPILIMUMAB



Pleural mesotelioma

Baseline | **PD** after 2nd dose | **PR** after 4th dose | **PR** after 7th dose



Survival 52 months, received 8 cycles (last one in Aug 2012)

Calabrò et al, OncoImmunology 2014

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- Different kinetic of response can be observed with immunotherapeutic agents thus changing the paradigm *“progression of disease = uneffective treatment” ;*
- Standard response criteria cannot capture all response patterns, and novel criteria for immunotherapy have to be utilized (*immune-related Response criteria*)
- Confirmation of progression of disease is strongly recommended to avoid early discontinuation of therapy in patients with delayed responses or false progression of disease (Increased volume of lesions may be due to lymphocytic infiltrate);
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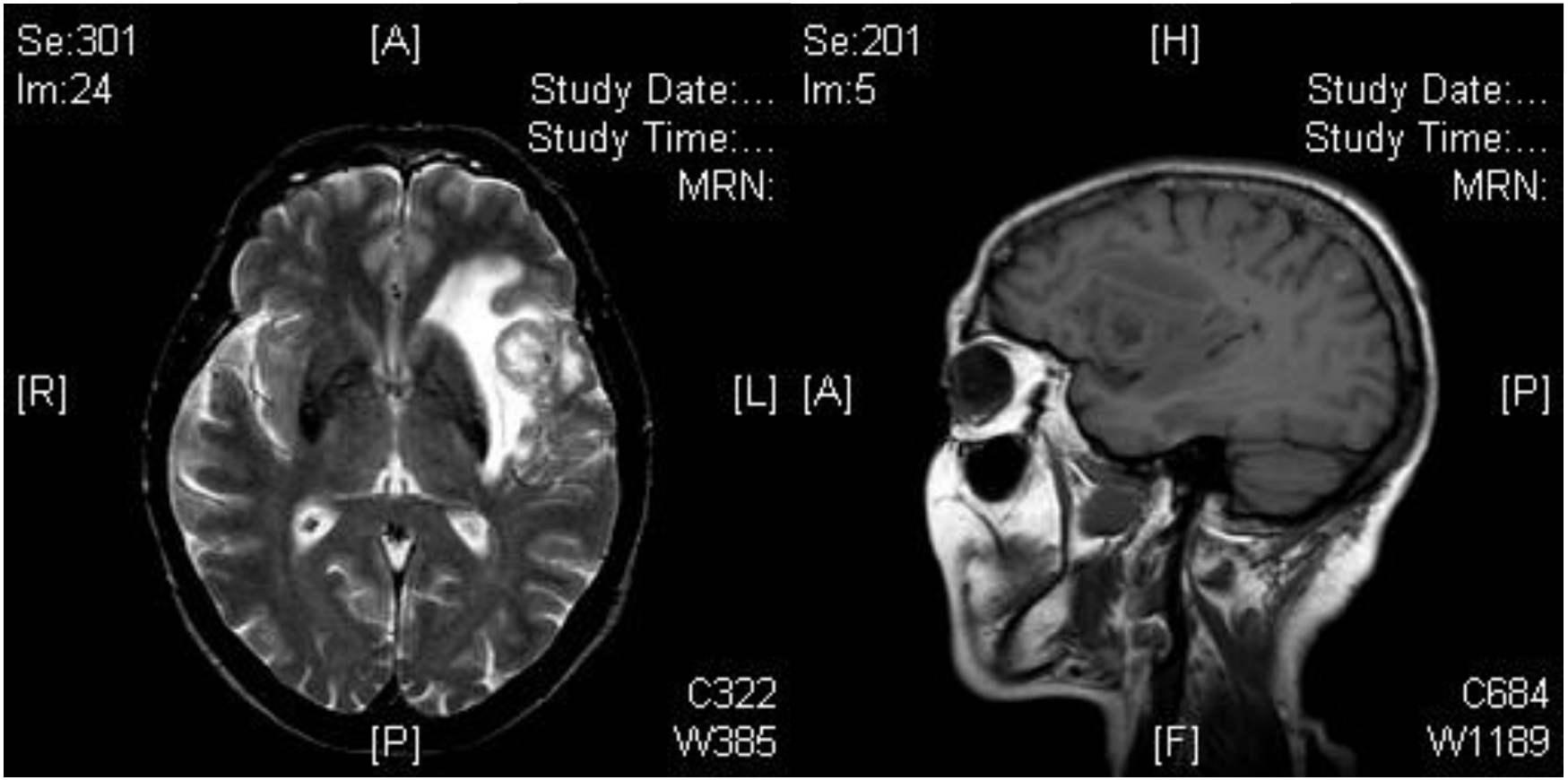
Effect in the CNS?



CTLA-4 blockade in MBM

IPILIMUMAB *Margolin K, Lancet Oncol 2012*	N	DCR	OS (m)	PSF (m)
Asymptomatic	51	24%	7.0	1.5
Symptomatic	21	10%	4.0	1.2
IPILIMUMAB + FTM NIBIT M1 *Di Giacomo AM, ESMO 2013*	**N**	**DCR**	**OS (m)**	**PSF (m)**
Asymptomatic	20	50%	12.7	3.4

NIBIT
Network Italiano per la Bioterapia dei Tumori

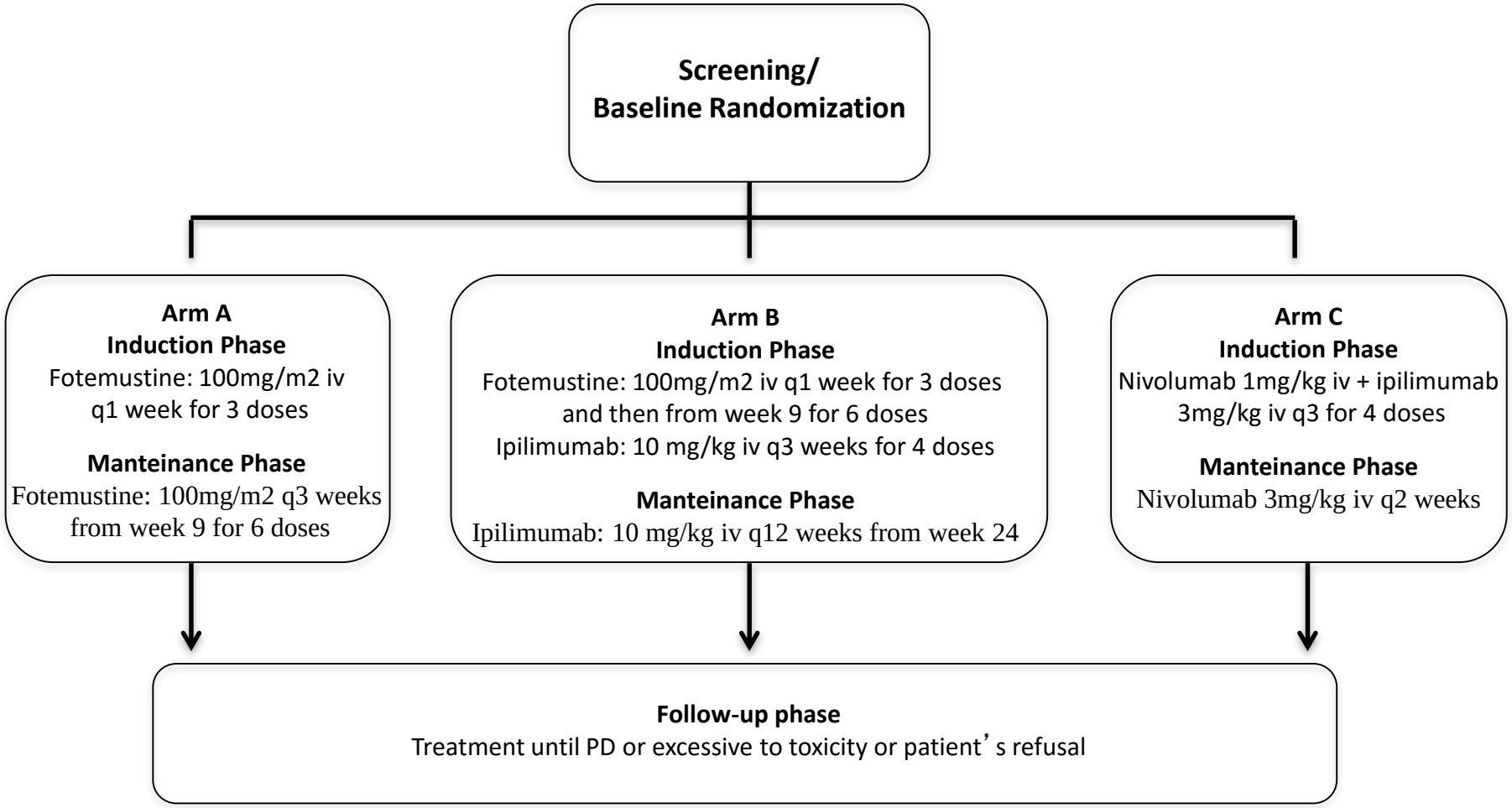
NIBIT - M1
3-years survival update

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)

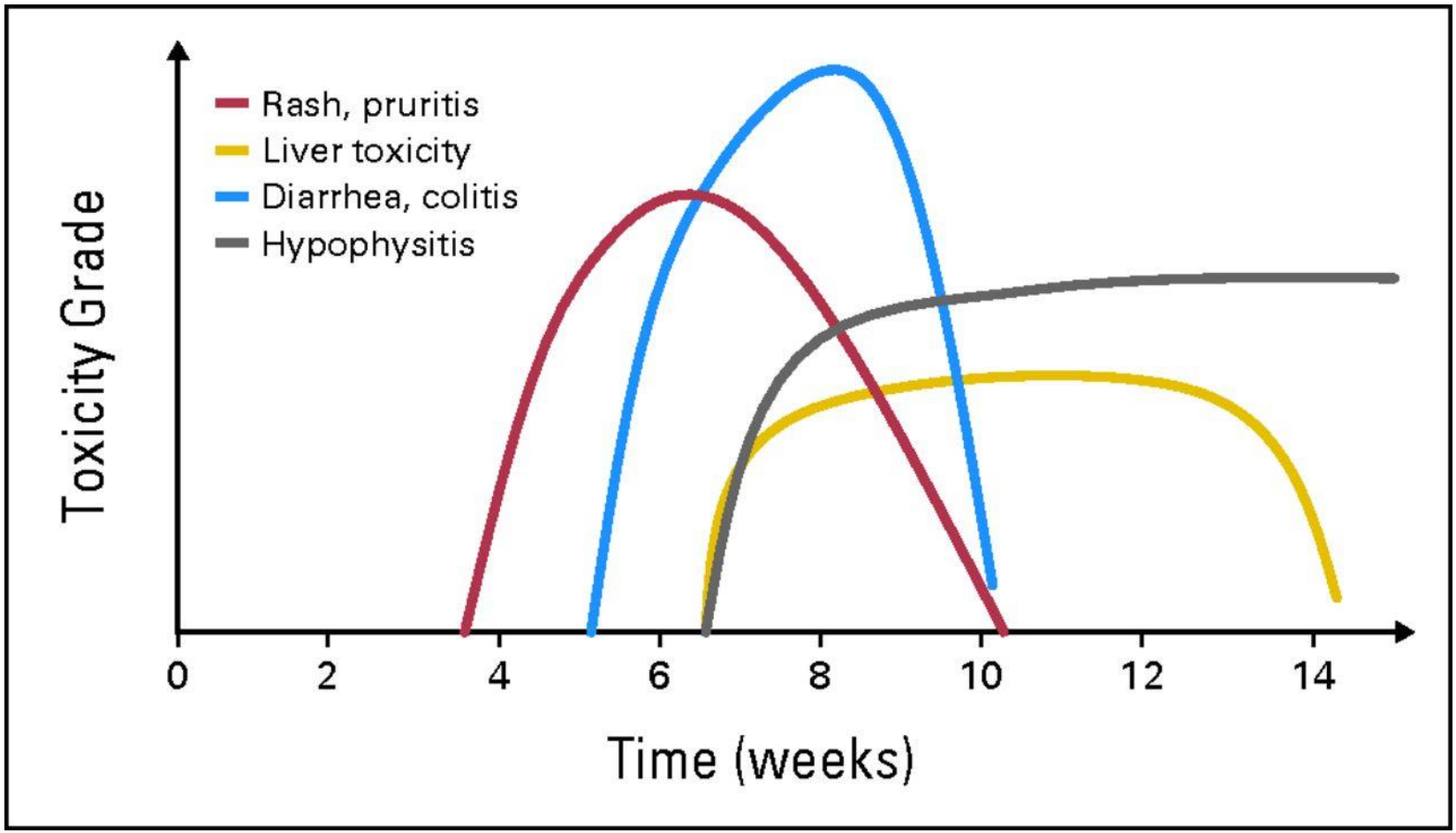
Di Giacomo AM et al., Annals Oncol 2015

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

The NIBIT-M2 study design



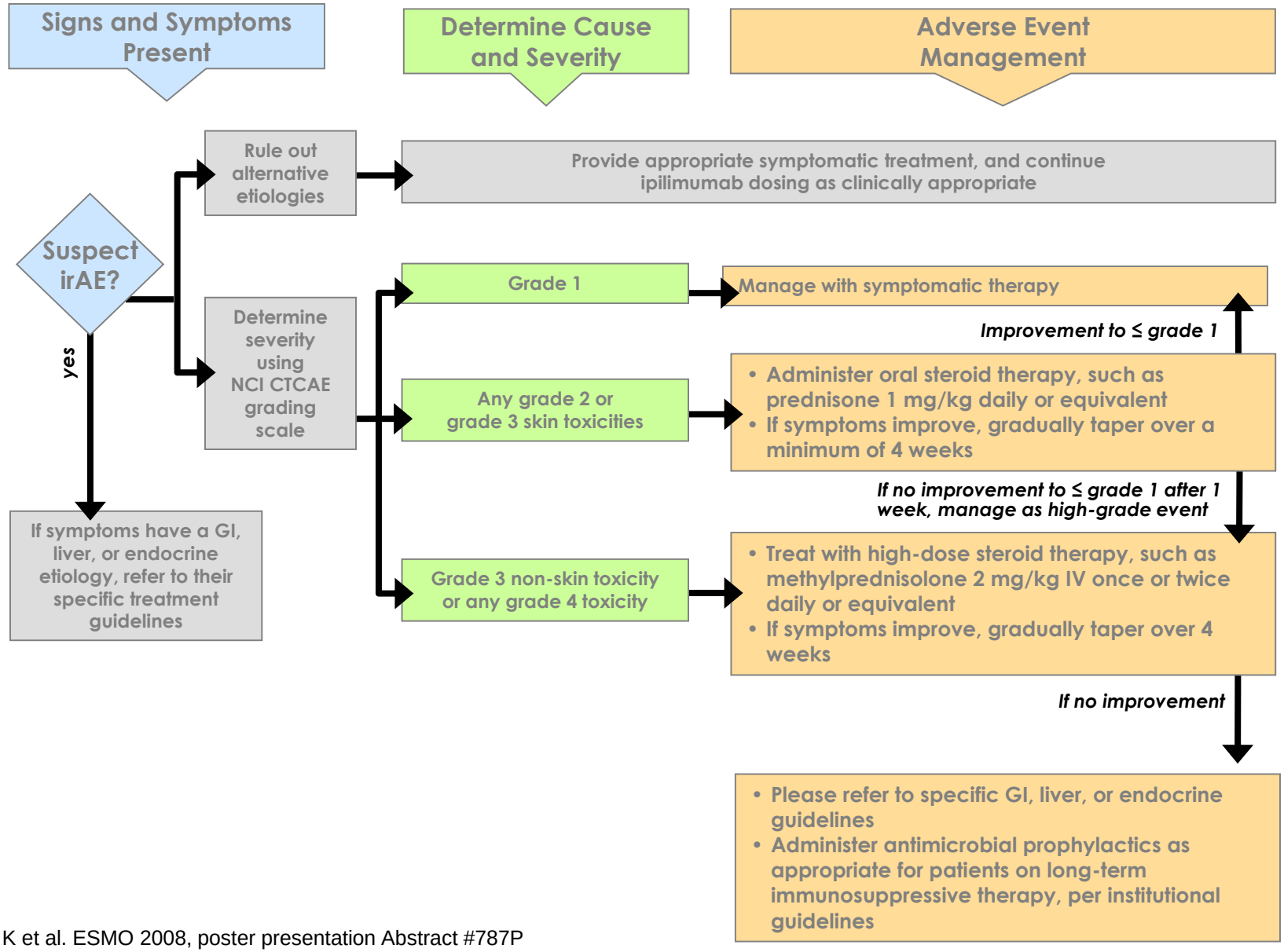
Kinetics of appearance of immune-related adverse event



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

JOURNAL OF CLINICAL ONCOLOGY

General Management Guidelines for irAEs



Chin K et al. ESMO 2008, poster presentation Abstract #787P

Prospectives

- *New combinations*
- *New indications*

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

- Anti-PD-1/PD-L1 or other immune checkpoint
- Vaccines
- Cytokines
- Tumor microenvironment modulating agents
- Selected chemotherapeutic agents
- Targeted therapies
- Epigenetic therapies

Epigenetic immuno-sequencing

COMBOS

Improve host's immune system activity

HOST

Check-point mAb

Modulate tumor immunogenicity and immune recognition

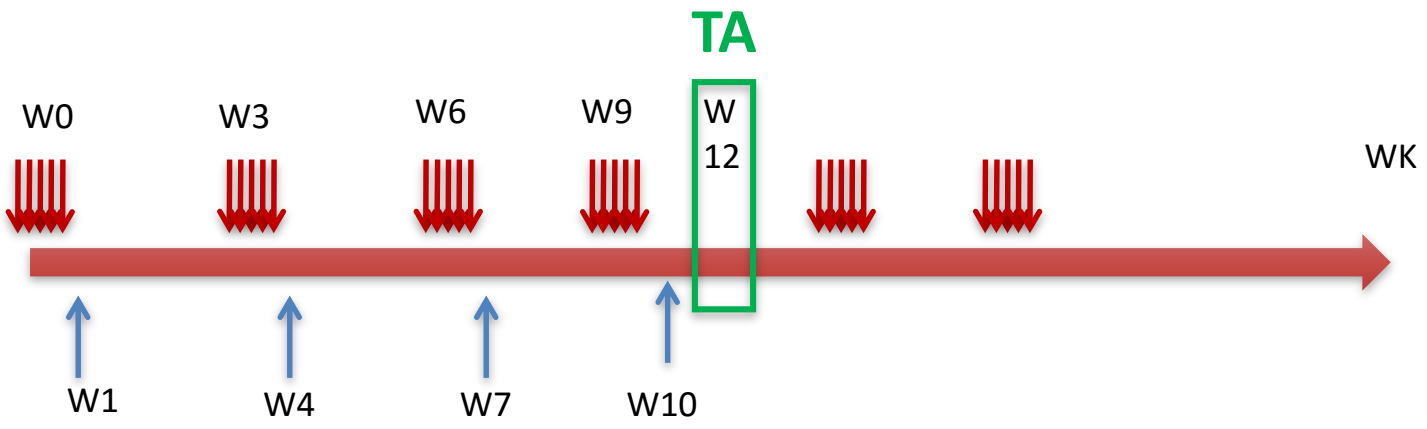
TUMOR

Epigenetic drugs

Epigenetic immuno-sequencing: the NIBIT-M4 Study

(NCT02608437)

SGI-110
5 days q21



Ipilimumab
4 x q21

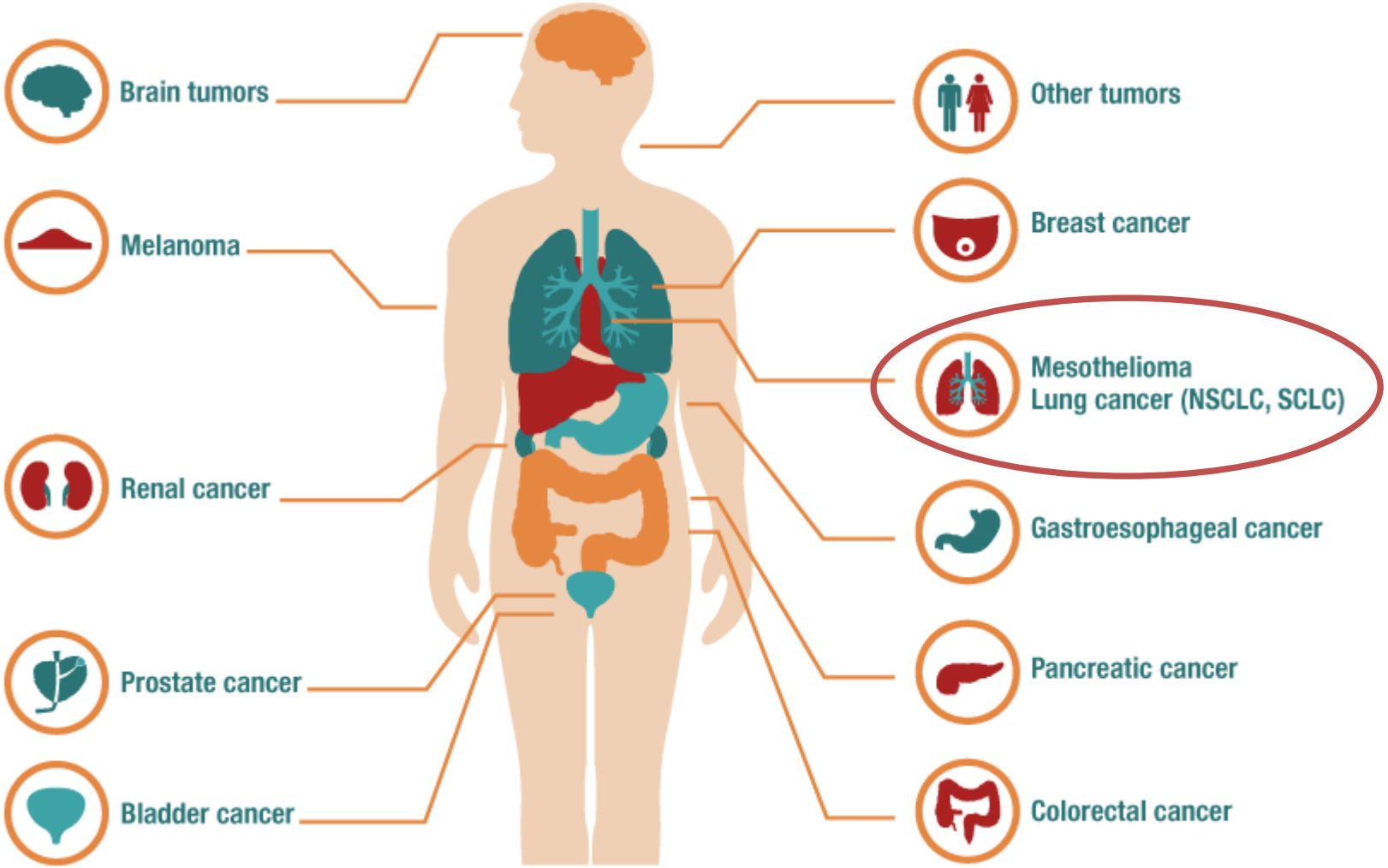
FPFV October 12, 2015

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

Prospectives

- *New combinations*
- *New indications*

Immunotherapy in solid tumors with immunomodulating antibodies



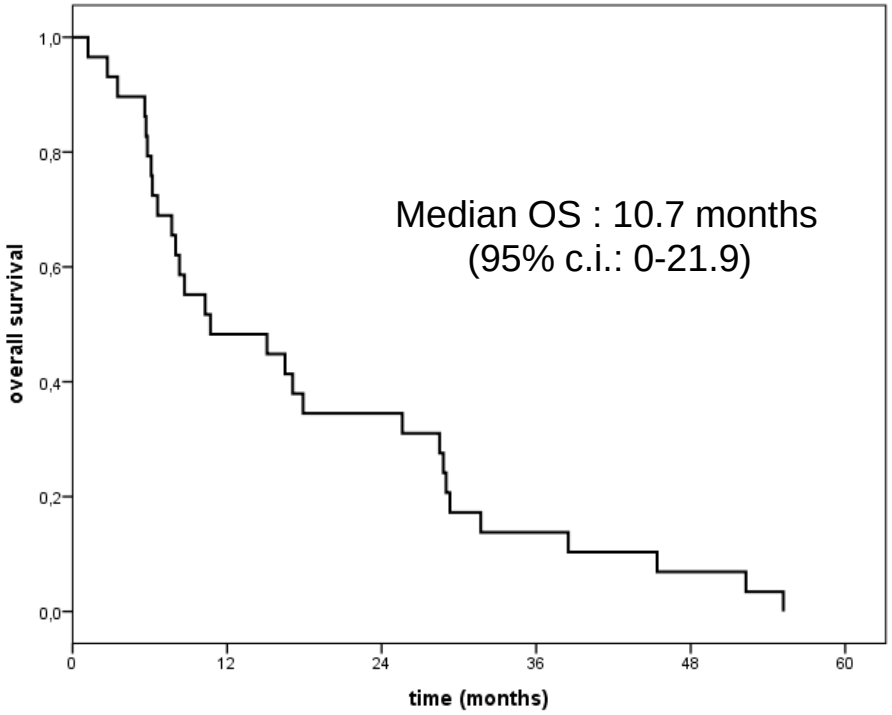
www.ImmunOncologia.it

Anti-CTLA-4 Tremelimumab studies in Mesothelioma

Study	Schedule	Phase/ setting	ORR	DCR	mOS	1-yr OS	Reference
MESOT-TREM-2008 (IST study)	15mg/Kg Q90 days	II 2nd line	7%	31%	10.7 months	48.3%	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	48.3%	Calabrò et al, Lancet Resp Med 2015

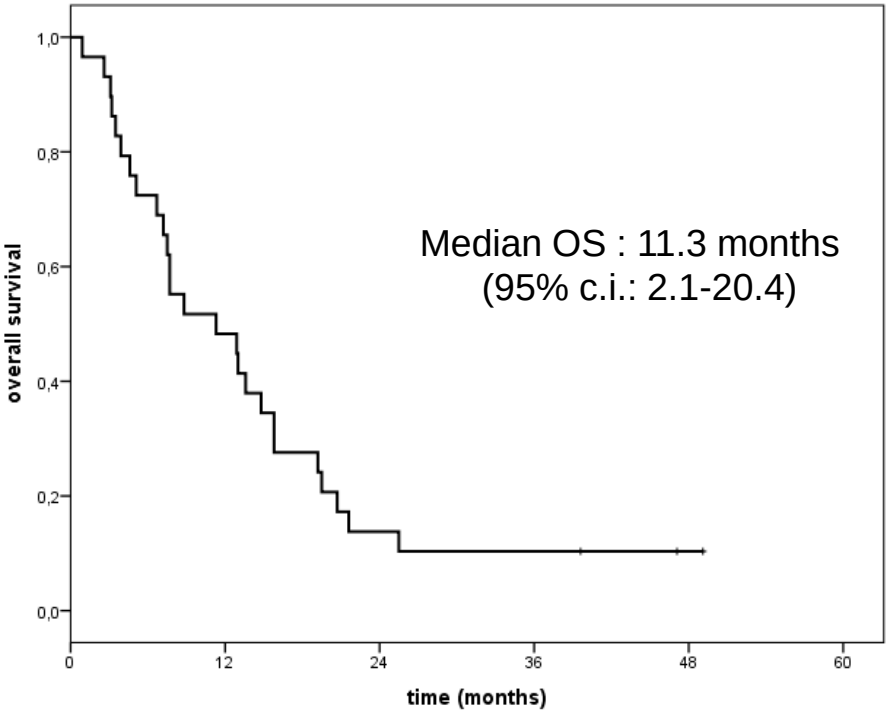
Long-term survival in MESOT-TREM studies

Mesot-trem-2008



Time points	12 months	24 months	36 months	48 months
% Pts alive	48.3	34.5	17.2	6.9

Mesot-trem-2012



Time points	12 months	24 months	36 months	48 months
% Pt salive	48.3	13.8	10.3	10.3

Calabrò et al, unpublished data

DETERMINE Study Design

Global, Randomized, Double-Blind, Placebo-Controlled, Phase 2b Trial

N=571

- Pleural/peritoneal MM
- ECOG PS 0–1
- 1–2 prior regimens (including a platinum)
- Measurable disease

2:1 randomization

Stratification:

- Pleural vs. peritoneal
- 2nd vs. 3rd line
- EORTC low vs. high risk

Tremelimumab i.v.
10 mg/kg q4w x 7 doses, then q12w
n=382

Placebo i.v.
n=189

Primary endpoint: Overall survival (OS)

Key secondary endpoints: 18-month OS, PFS, overall response rate and duration, disease control rate (DCR), durable DCR, safety

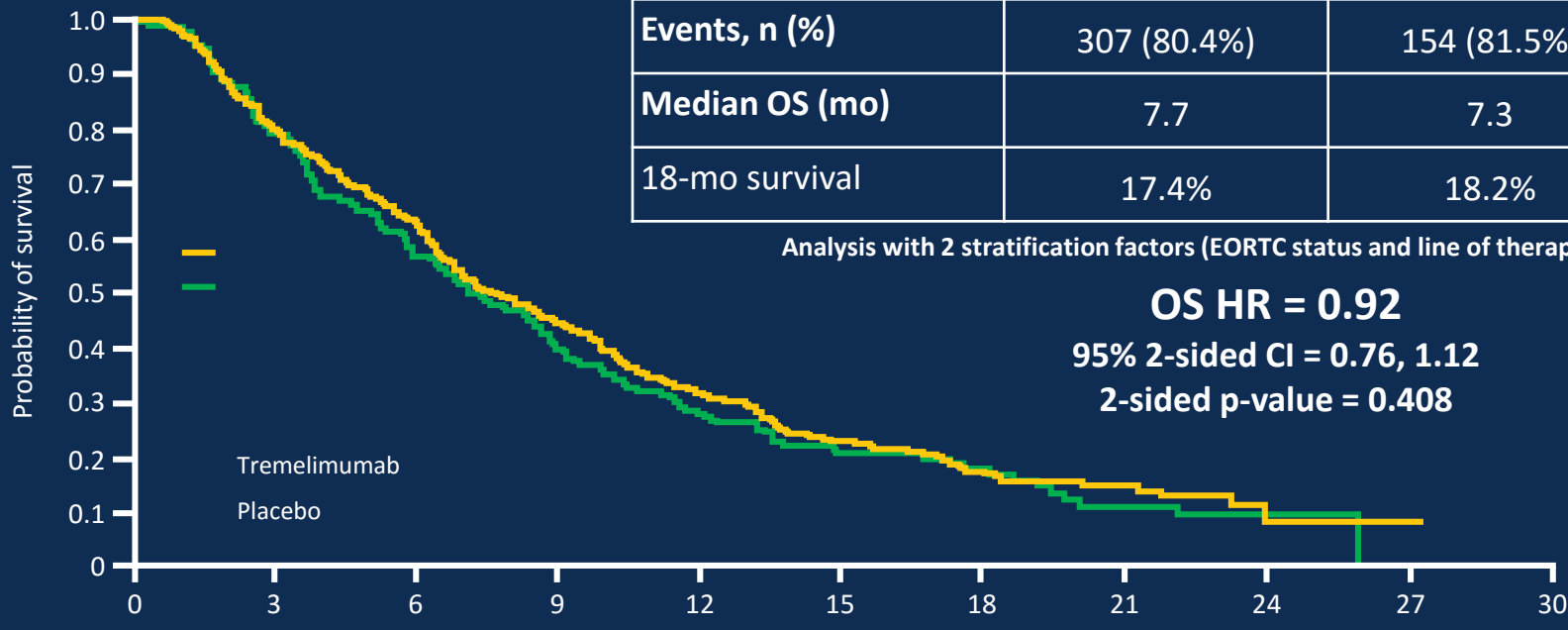
Statistics: 90% power to detect an overall HR of 0.71 (increase in median OS from 7 to 9.3 mo) using a 2-sided 0.05 level test

ECOG PS, Eastern cooperative oncology group performance status; EORTC, European organisation for research and treatment of cancer; HR, hazard ratio.

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-CTLA-4 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)

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

DSMB Approval

AIFA Approval
- 01 Oct 2015

SIV
- 22 Oct 2015

FPFV
- 30 Oct 2015

10 th subject enrolled
- 10 Dec 2015

ClinicalTrials.gov Id: NCT02588131

Efficacy

Best response per immune-related (ir) response criteria at w12

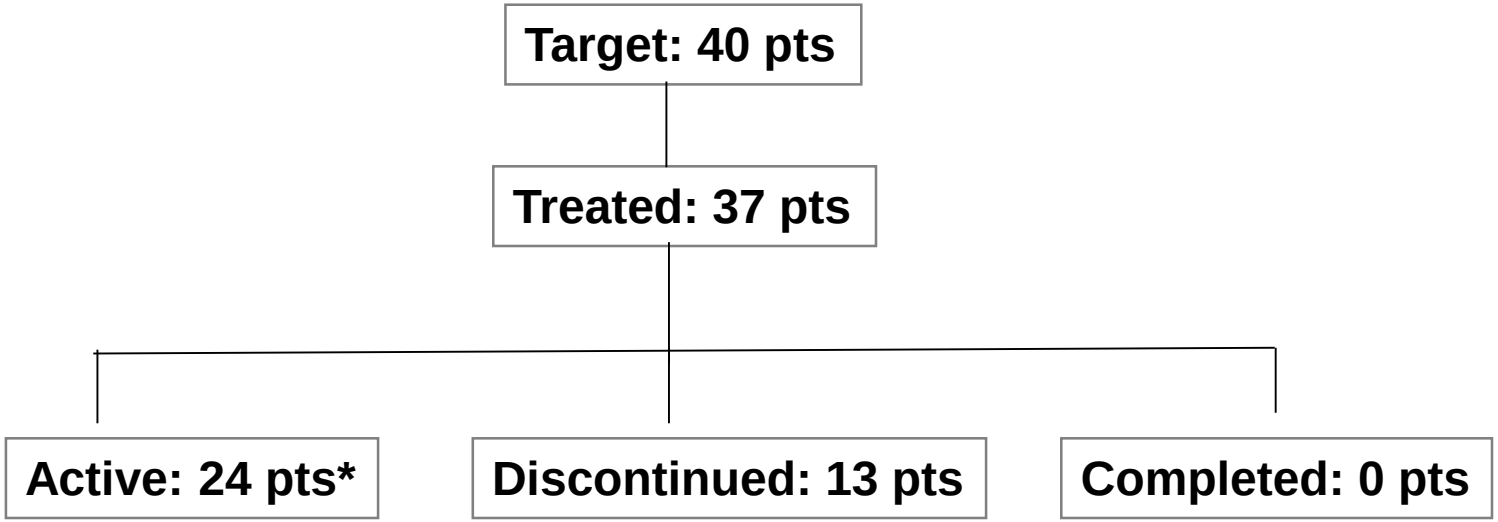
Tumor response*	Patients (N=10)
ir-CR	0
ir-PR	4 (40%, CI: 5-86)
ir-SD	4 (40%, CI: 5-86)
ir-PD	2 (20%, CI: 2-56)*
Ir-DCR	8 (80%, CI: 44-97)

* Modified RECIST for pleural MM, and RECIST 1.1 for peritoneal MM

Calabrò L et al, IMIG 2016

NIBIT-MESO-1 study

Enrollment status as of Oct 10, 2016



*4 pts in re-treatment phase

A Phase III, Randomized, Open Label Trial of Nivolumab in Combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in Unresectable Malignant Pleural Mesothelioma (CA209-273)

Patients

- Unresectable untreated pleural mesothelioma
- Available tumor sample
- PS 0-1

R

Ipilimumab 1 mg/kg Q6 weeks + Nivolumab 3 mg/kg Q2 weeks (up to progression/toxicity*)

Cisplatin 75mg/m2 or Carboplatin AUC 5 + Pemetrexed 500 mg/m2 in 21 day cycles for up to six cycles

Endpoints

Co-primary

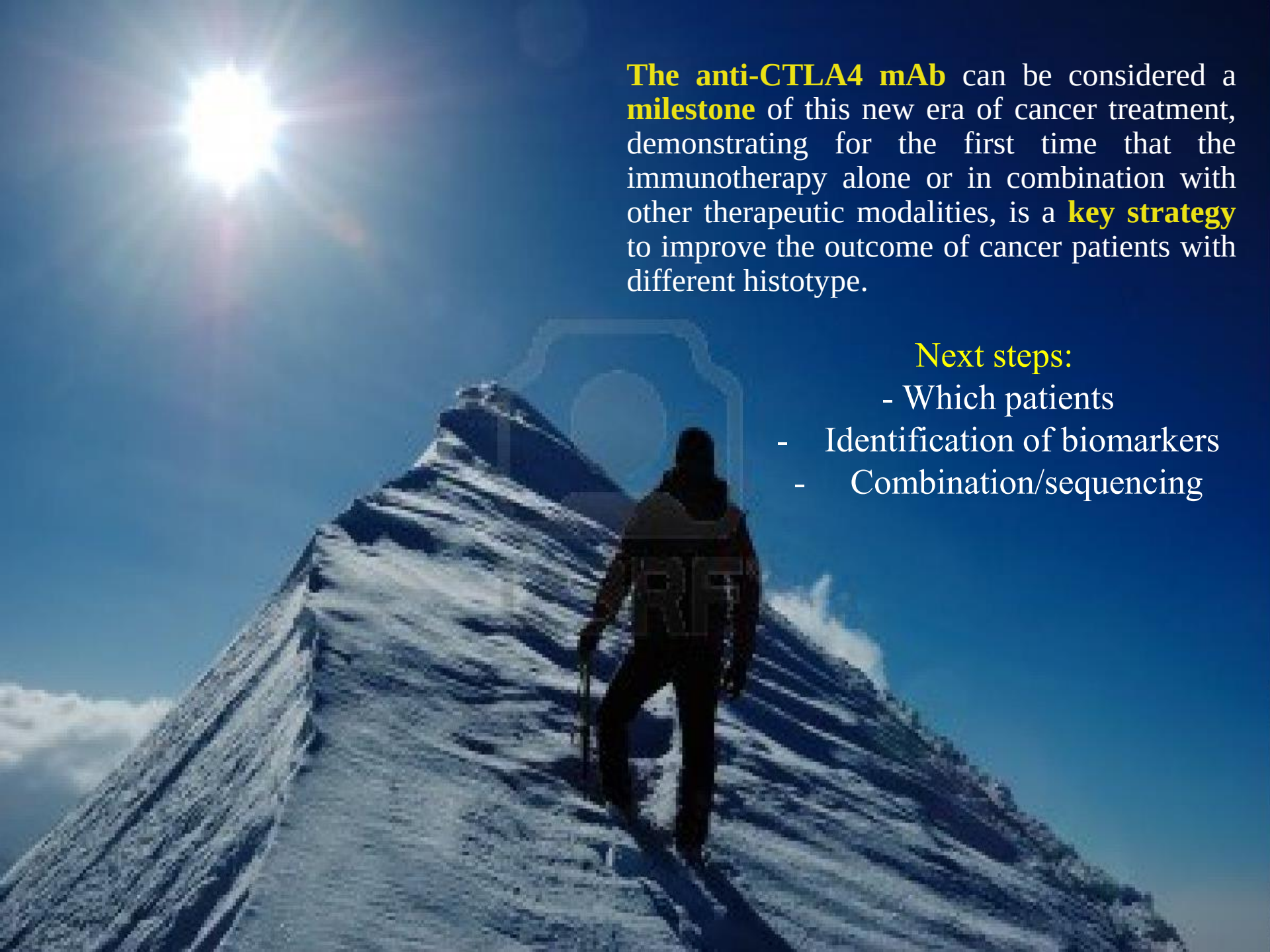
- PFS
- OS

Stratification Factors

Histology (epithelioid vs sarcomatoid or mixed histology subtypes)

Gender

* Treatment beyond initial investigator assessed progression according to m-RECIST specific to mesothelioma, will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.



The anti-CTLA4 mAb can be considered a **milestone** of this new era of cancer treatment, demonstrating for the first time that the immunotherapy alone or in combination with other therapeutic modalities, is a **key strategy** to improve the outcome of cancer patients with different histotype.

Next steps:

- Which patients
- Identification of biomarkers
- Combination/sequencing

Medical Oncology and Immunotherapy, University Hospital of Siena

AIRC

FONDAZIONE NIBIT
Network Italiano per la Bioterapia dei Tumori

AstraZeneca

MedImmune

HARRY J. LLOYD CHARITABLE TRUST

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