MADRID 2014 ESMO congress

Educational Session: Adjuvant treatment of melanoma

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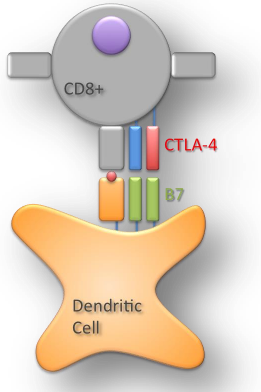
Disclosure Slide

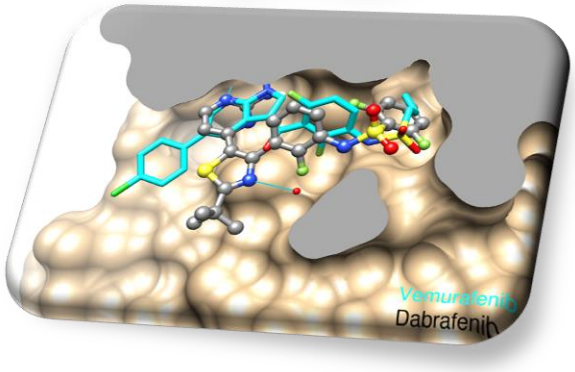
- OM is an occasional consultant for BMS, Roche and GSK
- OM has received honoraria from BMS, Roche and GSK to participate in advisory boards and to speak at sponsored meetings
- OM declares no conflicts of interest

Treatment landscape in stage IV melanoma: a rapidly evolving field

- Major breakthroughs in stage IV melanoma
  - Immunotherapies
    - Checkpoint blockades



  - Targeted therapies
    - MAPK inhibitors

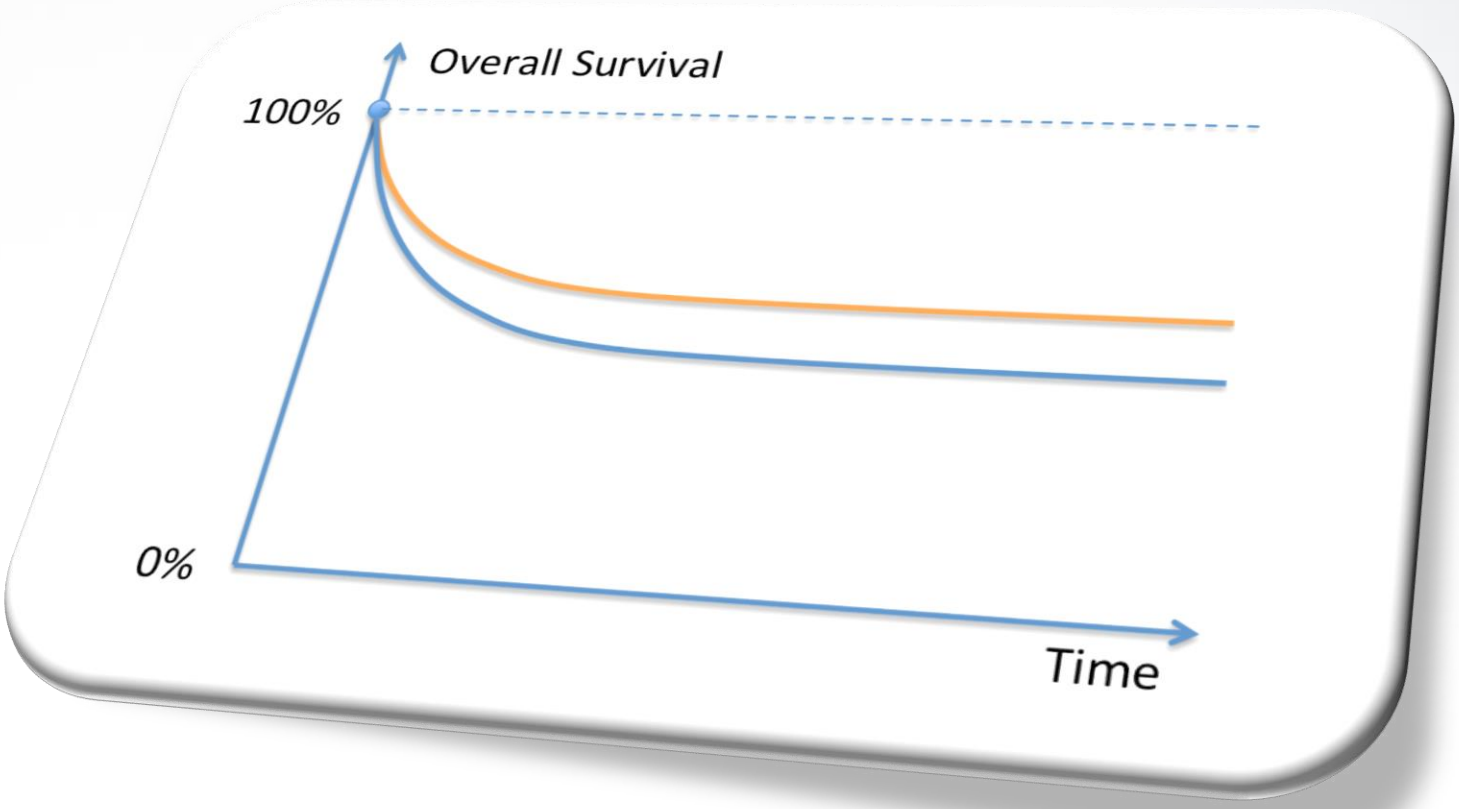


- … are now entering the field of **adjuvant therapies**

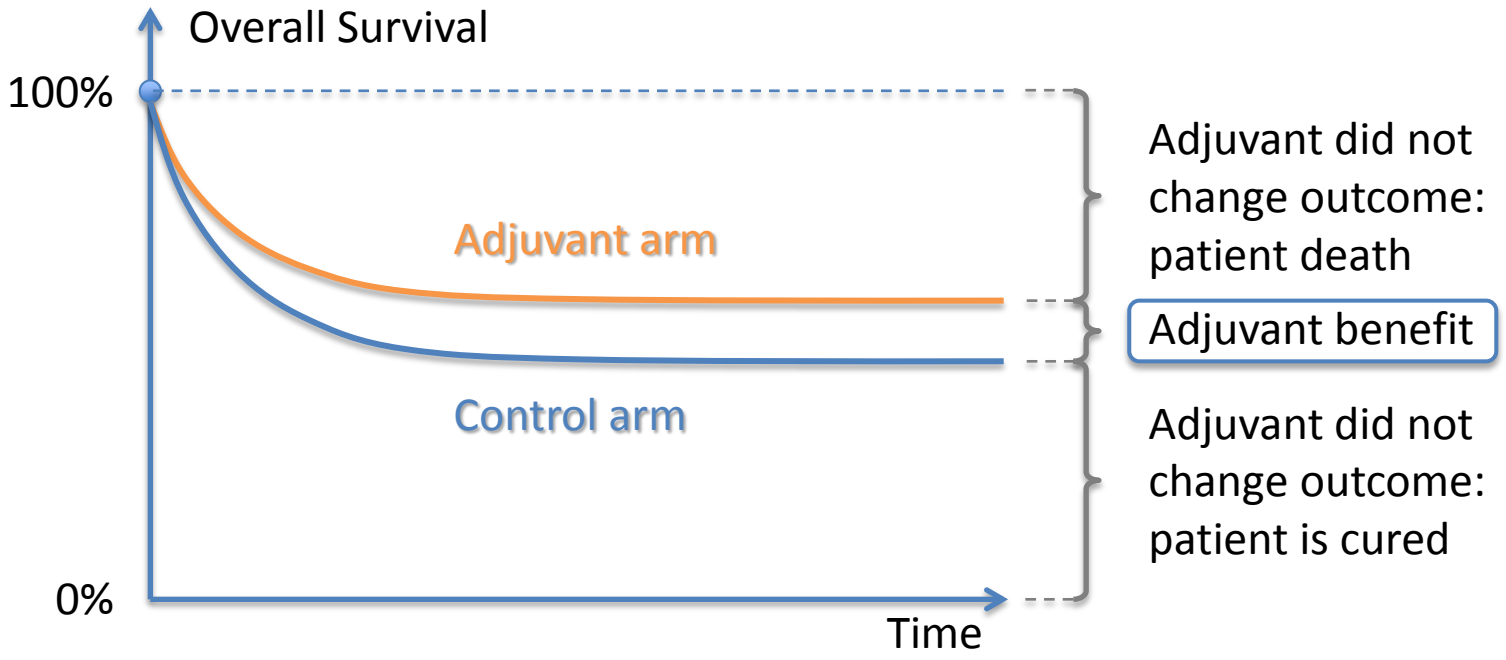
Learning objectives

- Introduction
  - Statistical considerations: cost/benefit ratio in the adjuvant setting
  - Biological aspects: residual disease, cancer stem cells (CSCs)
- Unsuccessful adjuvant approaches so far: chemotherapy, vaccines
- **Interferon**
- **Checkpoint blockades**
  - CTLA-4 blockades: MoA, adjuvant trial results
  - PD-1 blockades: MoA, planned adjuvant trials
- **Targeted therapies**
  - BRAF inhibitors: MoA, planned adjuvant trials
  - BRAF and MEK double inhibition: MoA, planned adjuvant trials
- Conclusion and outlook

Introduction: cost / benefit ratio in the adjuvant setting



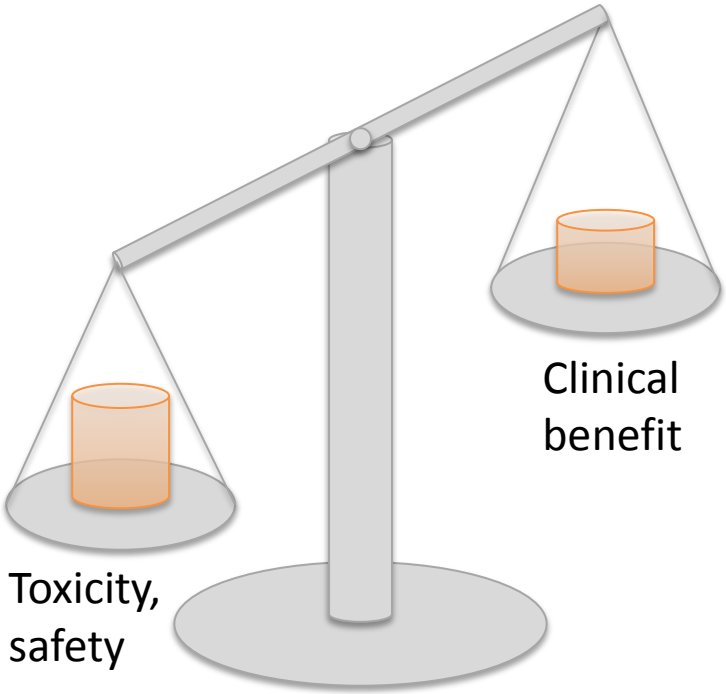
Introduction: Benefit of adjuvant therapy



In typical adjuvant trials, this results in a large number of **patients needed to treat**:

- Adjuvant Interferon - Cochrane Review (Mocellin 2013):
  - 35 participants in order to prevent 1 death
  - 97% of patients exposed for no benefit

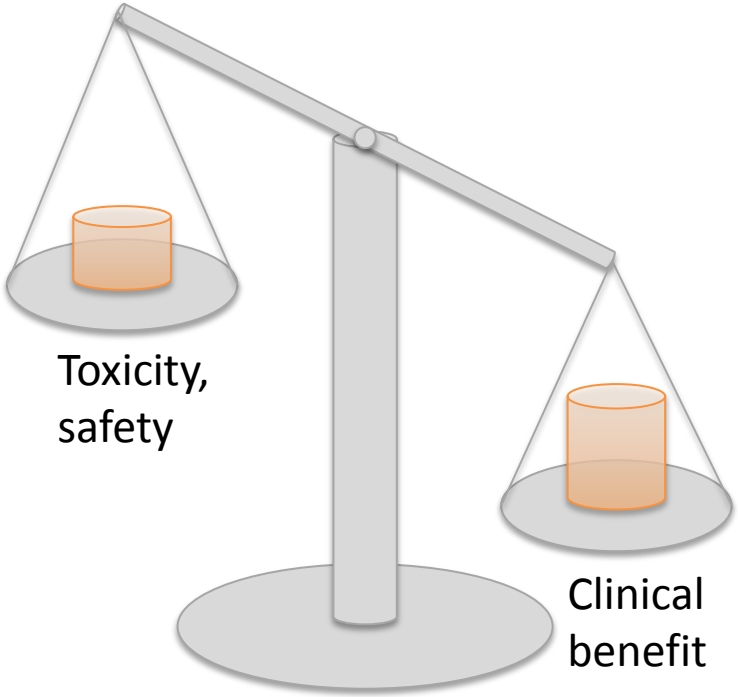
Adjuvant treatment of melanoma: weighting benefit vs. toxicity



Metastatic setting

Due to poor outcome in stage IV

- Higher toxicity and AE might be acceptable



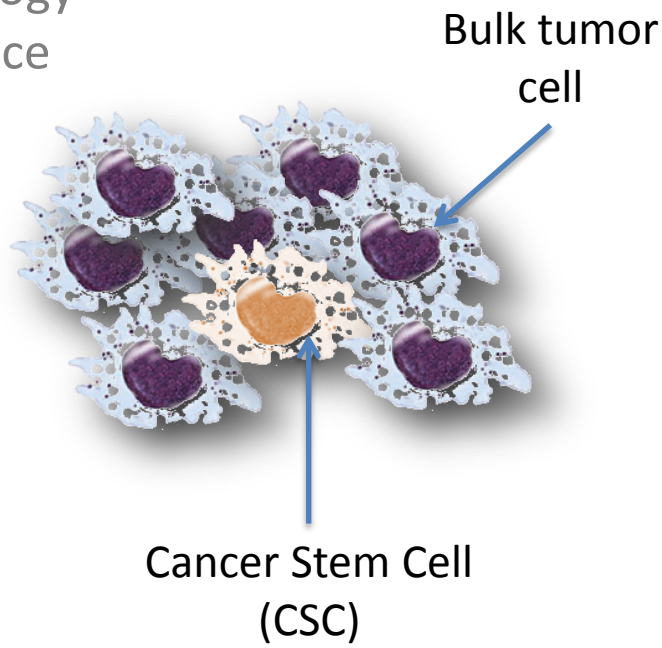
Adjuvant setting

Since a large fraction of patients are already cured by surgery

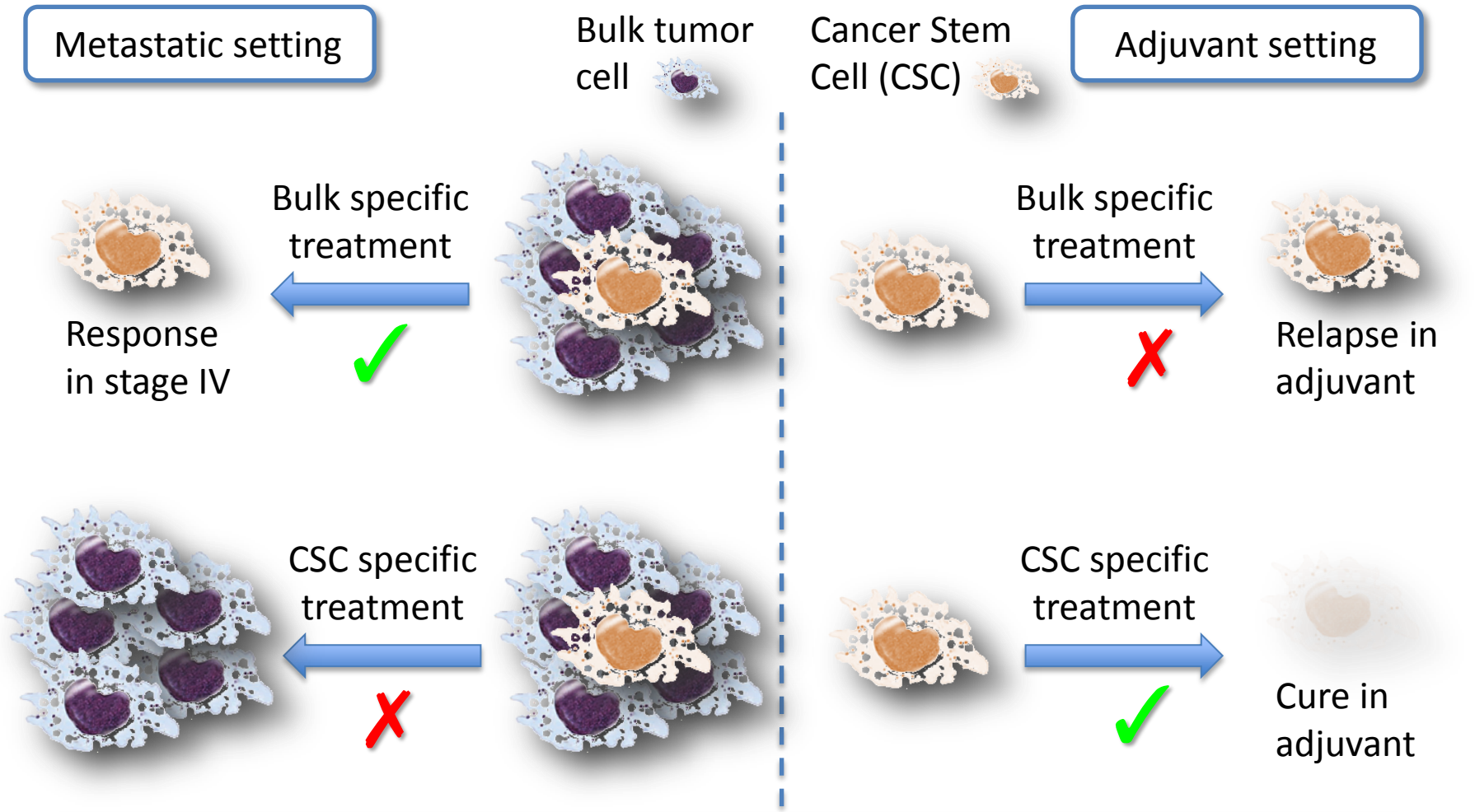
- Toxicity and safety are a major concern

Introduction: biological considerations

- Adjuvant therapy aims at eradicating residual, microscopic disease at the origin of relapses in order to increase the fraction of patients cured by surgery
- The required biological steps at play might differ significantly from the metastatic setting where tumor bulk response is pursued
- Cancer stem cells (CSCs) have a different biology compared to bulk and are drivers of recurrence
  - Lower proliferation rate
  - Different antigen expression
  - Higher resistance to apoptosis
- CSCs are, therefore, more resistant to apoptotic stress (chemo/radiotherapy)
- Their resistance to immune interventions is being intensively investigated
- For an illustration in breast cancer, see Liu & Wicha, *JCO* 2010

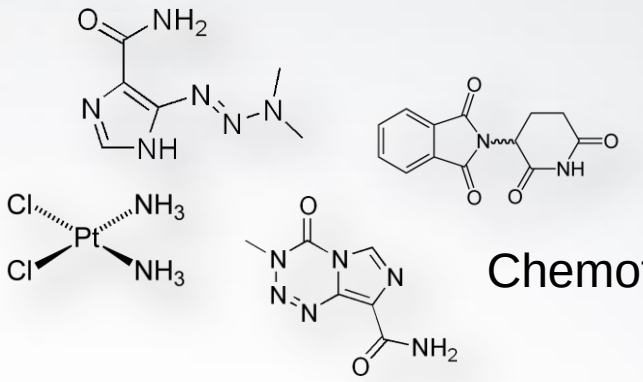


Introduction: biological considerations

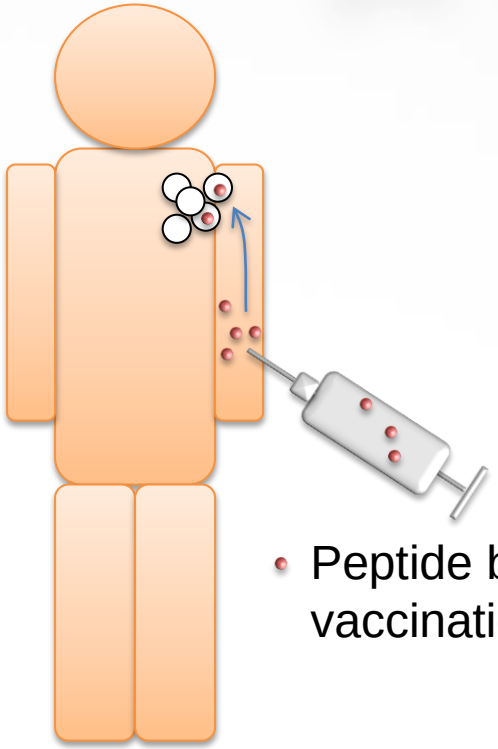


"Whether known efficacy of the agent in metastatic melanoma is an absolute requirement for successful adjuvant therapy remains to be defined"
Sondak & Gibney, *Lancet Oncol* 2014.

Summary of some so far unsuccessful strategies in the adjuvant setting



Chemotherapy

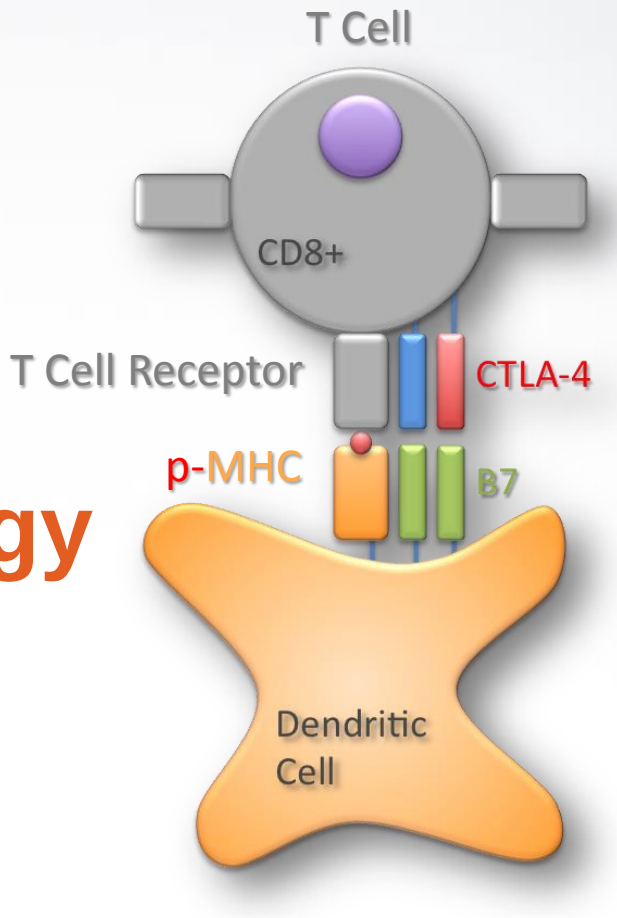


- Peptide based vaccination

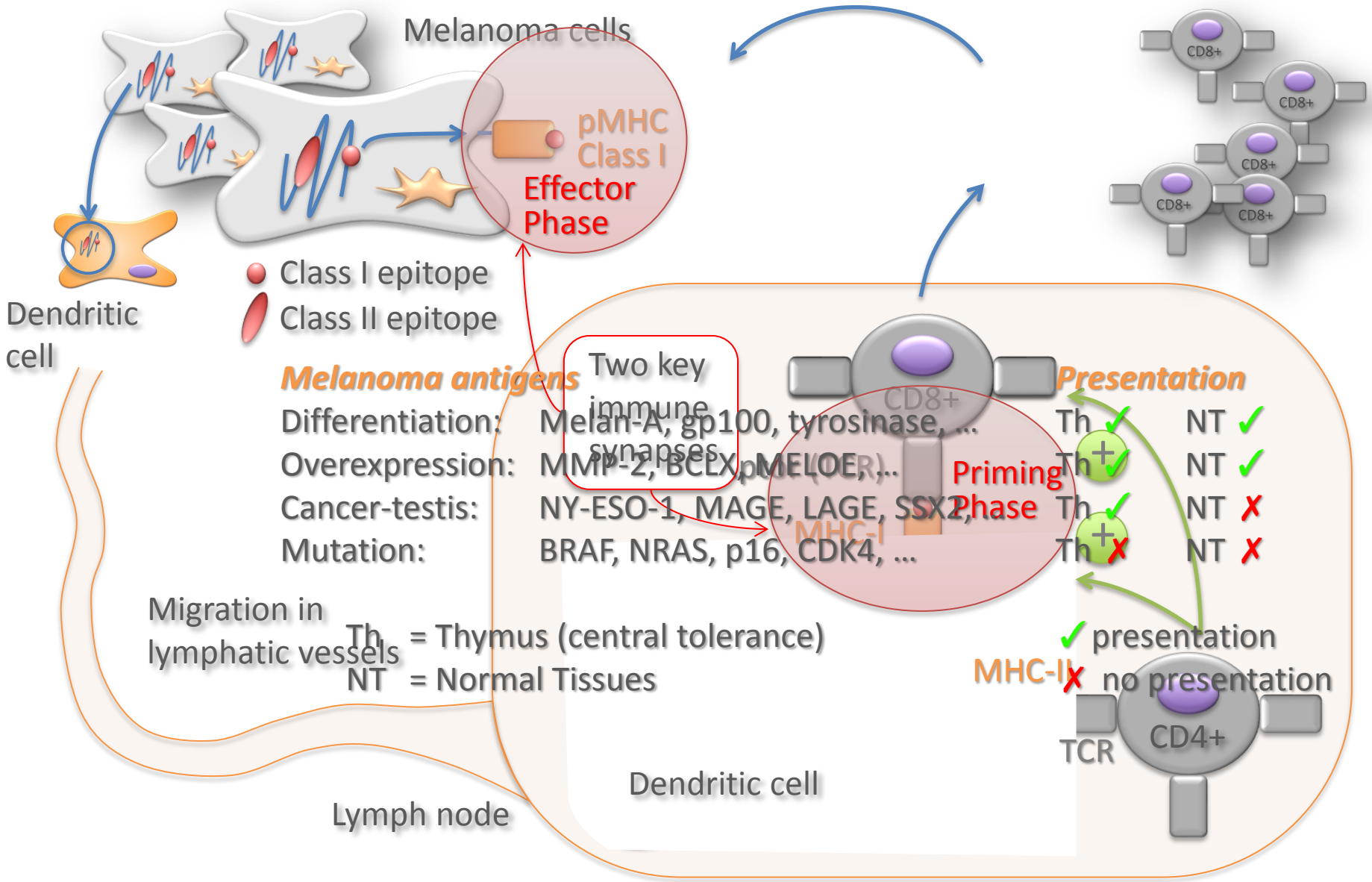
Strategies that did not show benefits in the adjuvant setting

- More than 25 randomized trials have been conducted in stage II/III melanoma in order to evaluate adjuvant therapies, such as
  - Chemotherapy:
    - Many are small, underpowered, non-conclusive studies
  - BCG and Corynebacterium parvum:
    - 20 RCT, all negative but 2 small trials (40 and 73 pts)
  - Levamisole
    - 5 RCT, 1 positive, 4 negative
- Most show negative results with some occasional but non-repeatable positive findings
- Some strategies yielded to *detrimental* outcomes:
  - Canvaxin (allogeneic tumor cell-based vaccine): 2 large RCT in 2006
  - GMK (ganglioside): 1 RCT (EORTC 18961)
  - Interferon-γ: 1 RCT (SWOG)
- Peptide based vaccinations: will be discussed separately

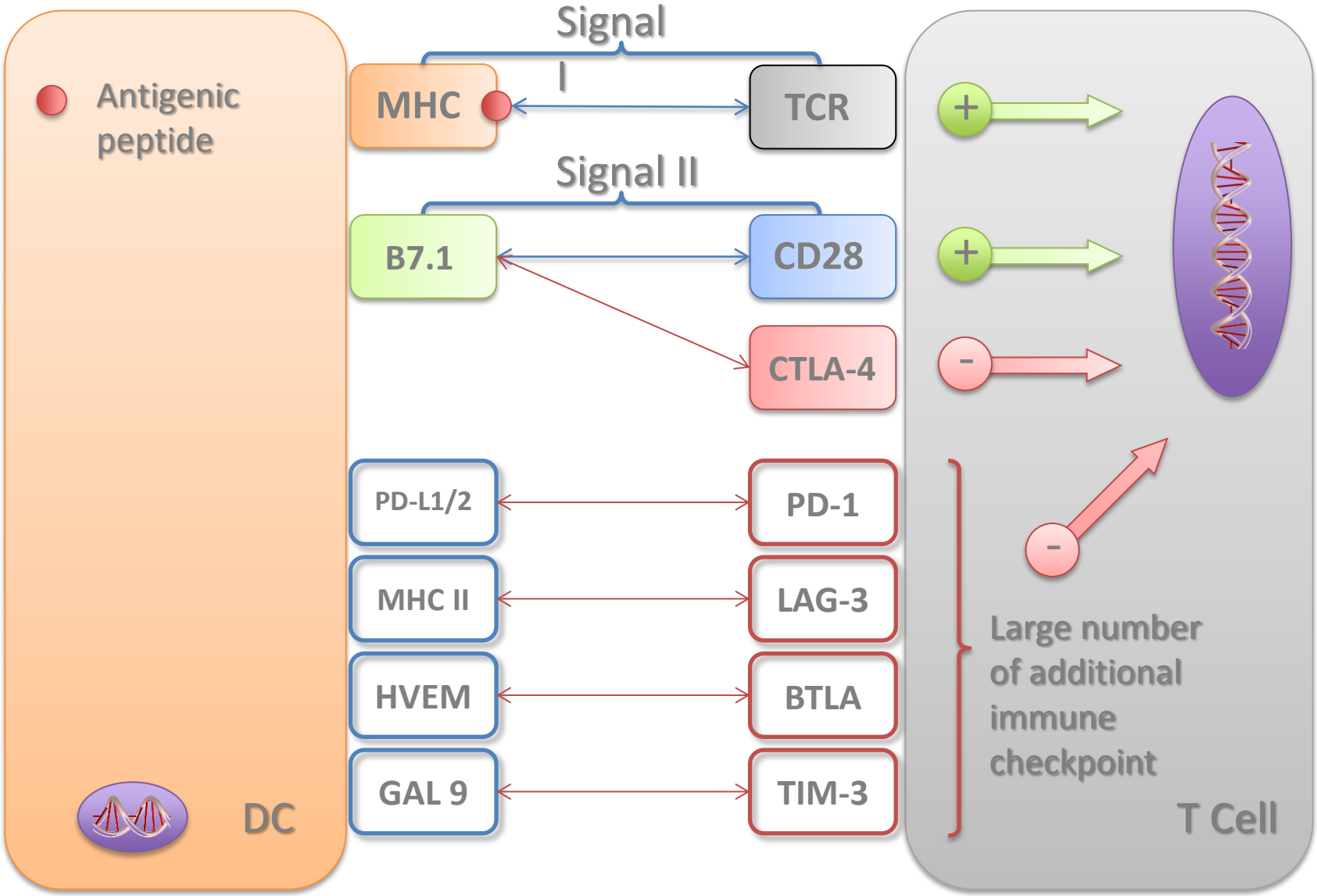
Molecular basis of tumor immunology



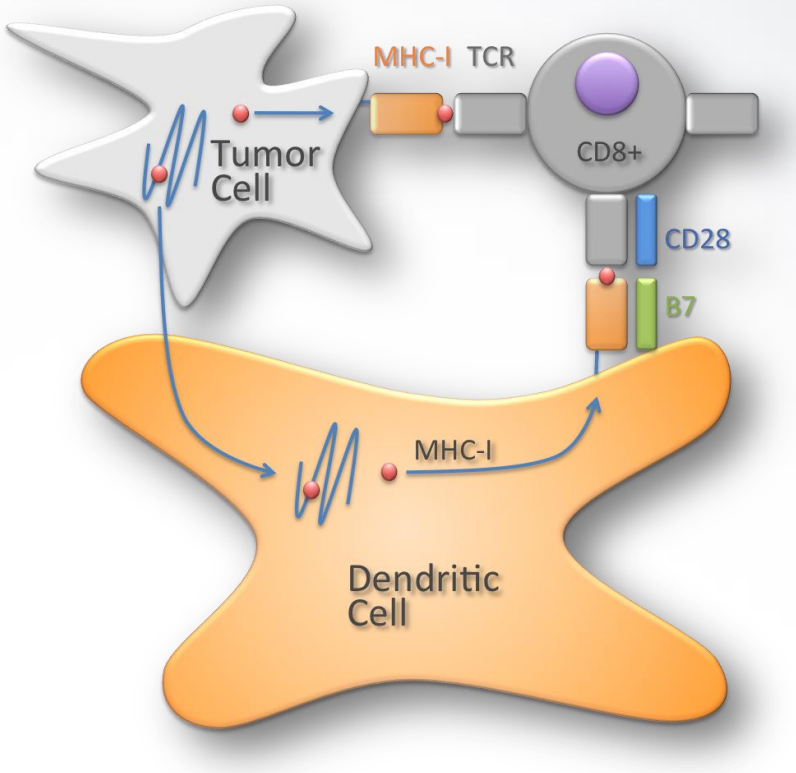
Molecular basis of melanoma immunology



T cell activation & the immune synapse

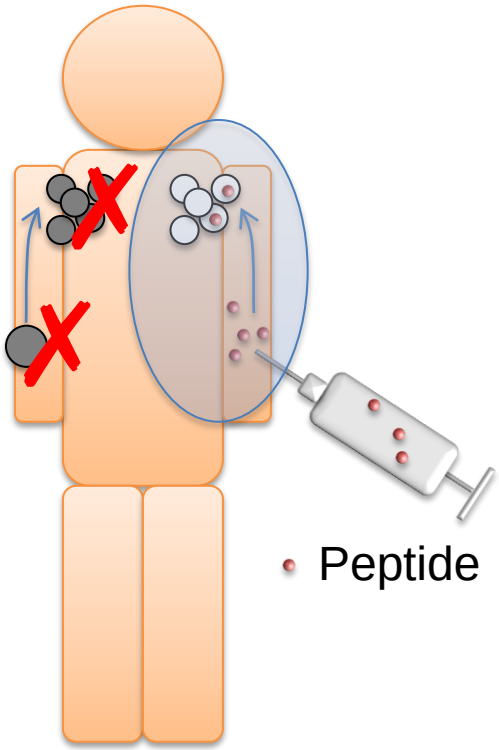


Peptide-based immunotherapies



Principles of peptide-based immunotherapy

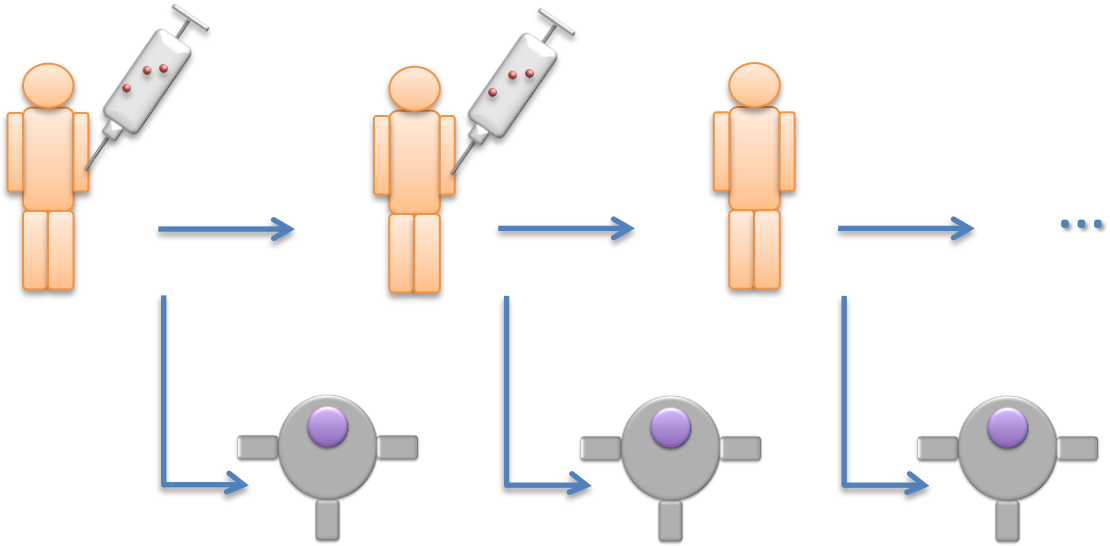
Resected stage II-III patient

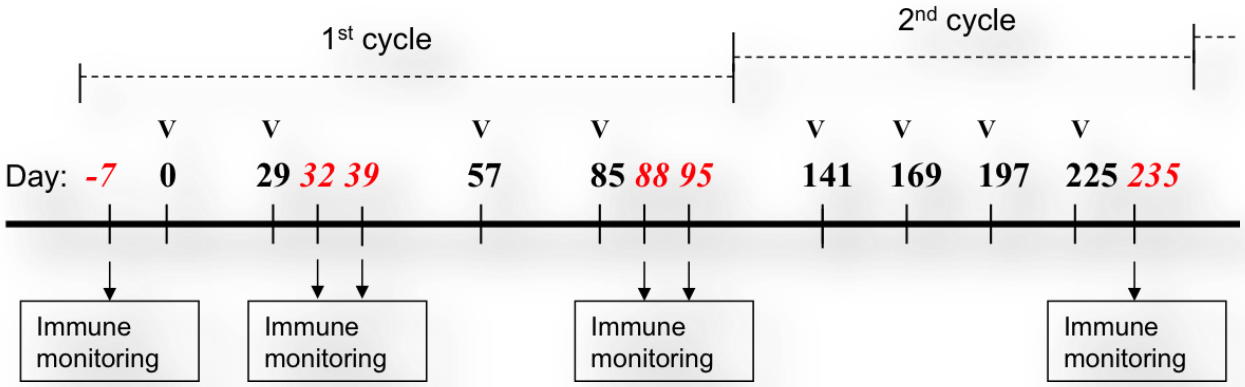


Peptide

Primary melanoma

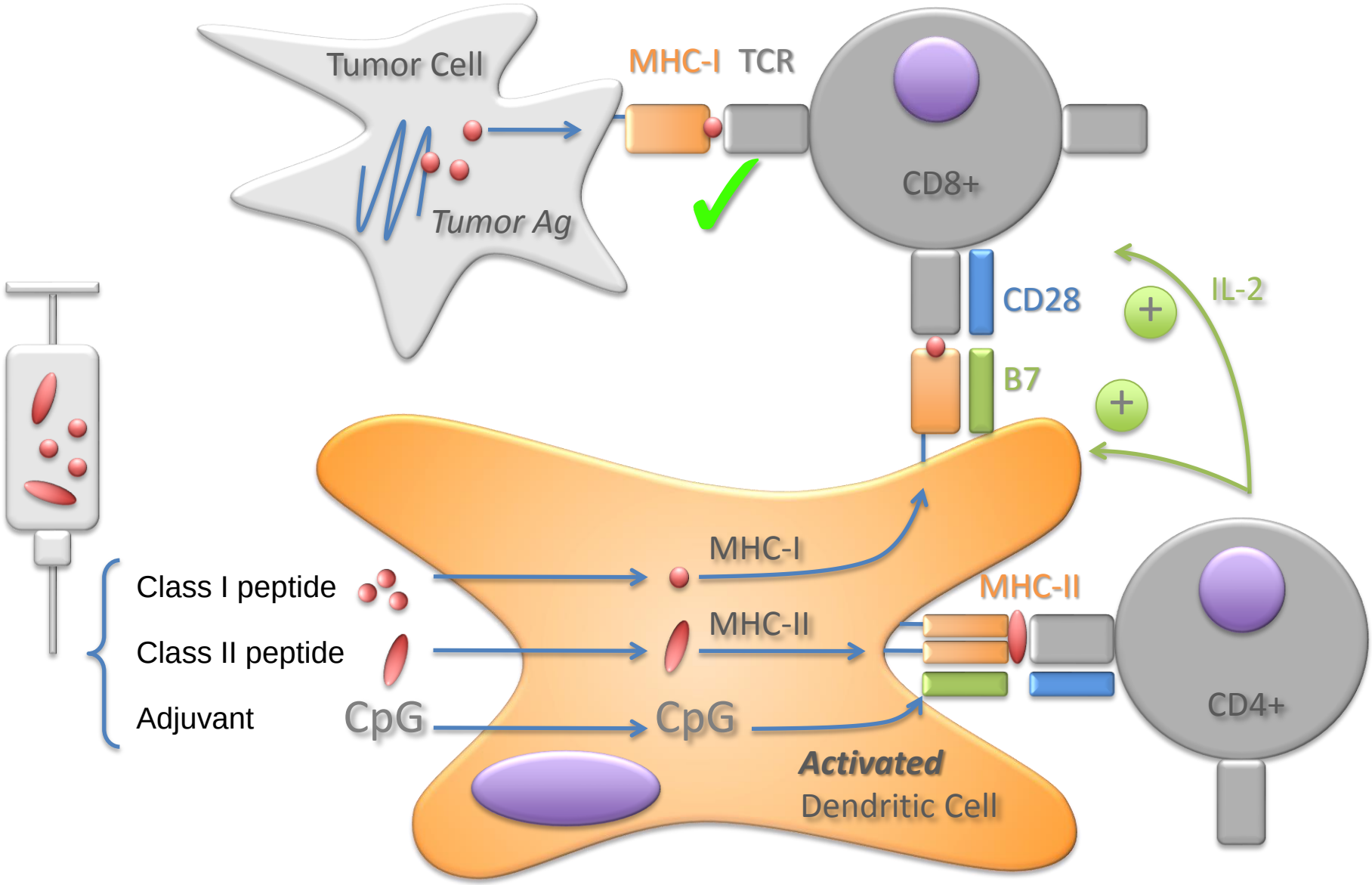
Lymph node metastasis



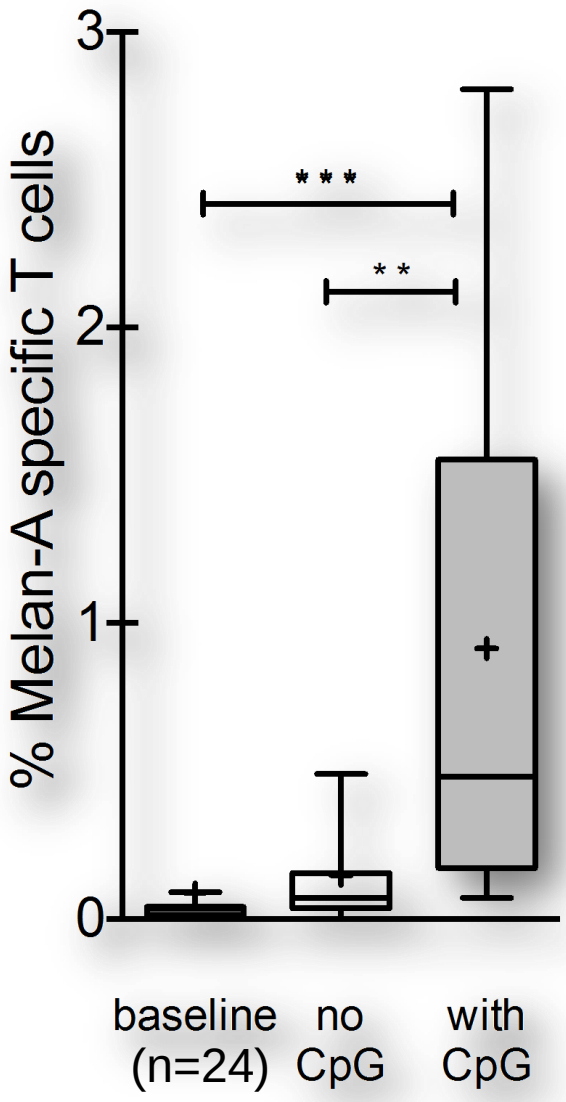


LUD 01-003: ClinicalTrials.gov, NCT00112242

Peptide-based vaccination *with* CpG



LUD 00-018 phase I clinical trial: NCT00112229



Baumgaertner, & al
Vaccination-induced functional competence of circulating human tumor-specific CD8 T-cells.
International Journal of Cancer (2012)

Phase III validation: GSK Derma Trial

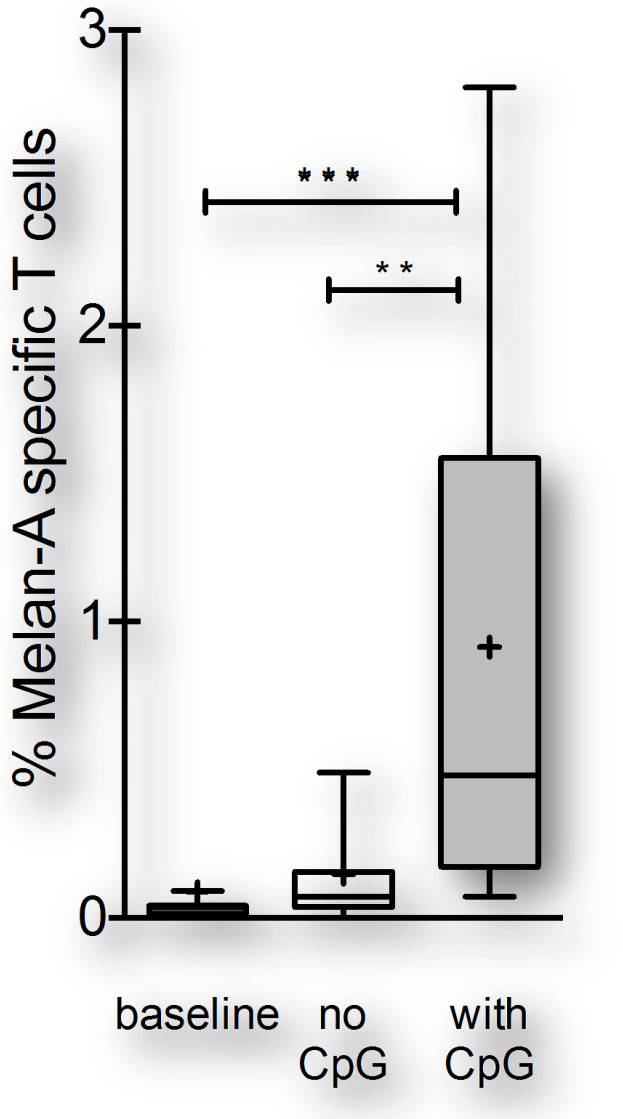
1349 completely resected stage III, MAGE-A3 + melanoma patients

2014 Update: Following the MAGRIT announcement, GSK is continuing to evaluate in the DERMA phase III whether a gene signature can identify a sub-population of melanoma patients that would benefit from the same investigational MAGE-A3 cancer immunotherapeutic. This follows the read-out of the first co-primary endpoint in September 2013, of DFS in the overall MAGE-A3 positive population, which was not met. Work is progressing on the mathematical model (the gene signature classifier) to allow assessment of DFS in the gene signature population, the second co-primary endpoint in the DERMA trial. Outcome is expected in 2015.

Accrual:	Completed, first analysis planned for October 2016 (DFS)

Peptide based vaccination: where to go?

- Peptide vaccines are able to generate large populations of specific effector T cell (Speiser, *PNAS* 2011)
- … but have not yet delivered on their promise!
- **Possible solutions**:
  - Use of long peptides requiring professional APC
  - Combinations therapies with checkpoint blockades
    - NCT01176474, J. Weber, multipeptide vaccine + nivolumab +/- ipilimumab
  - Combination with other immune modulations
    - Adoptive cell transfer, …



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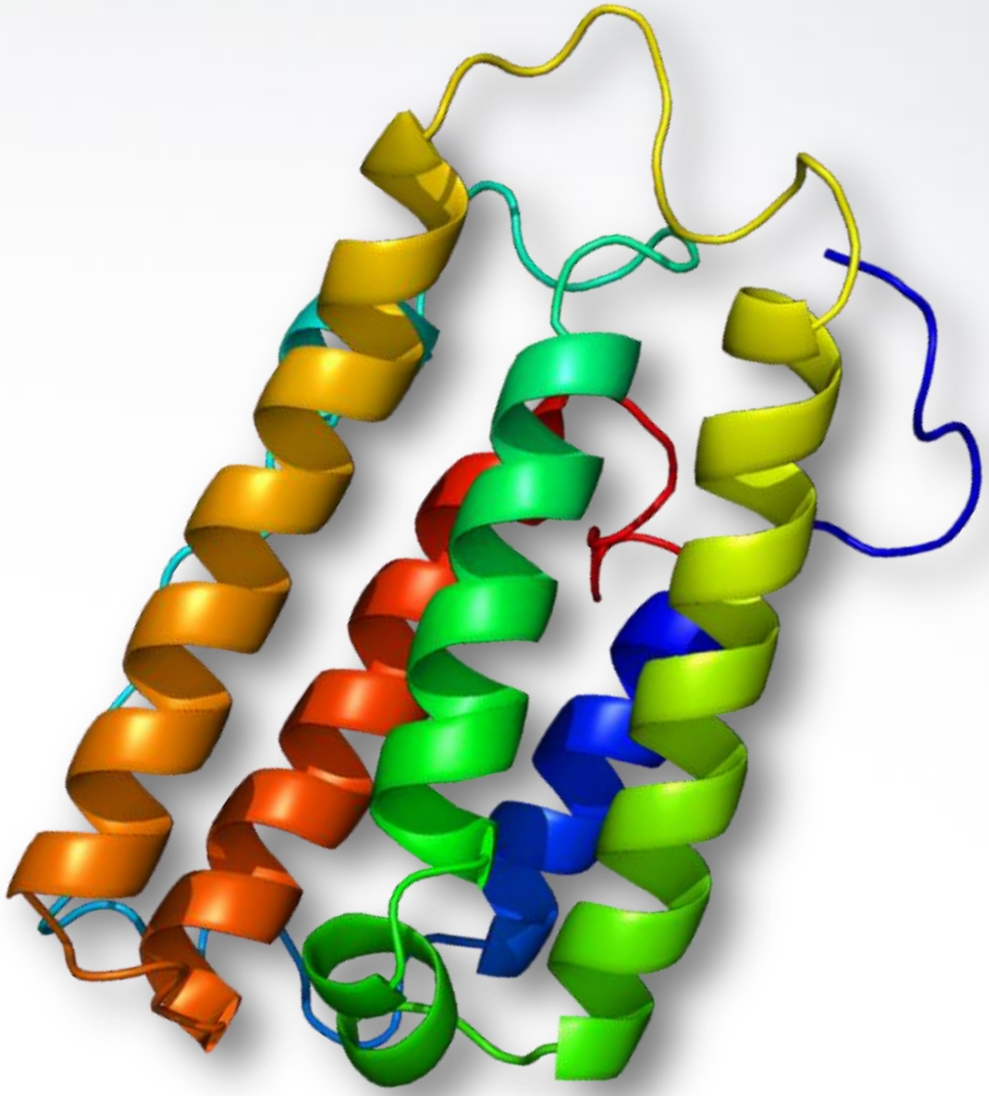
Immune modulations: INF-α2b



Interferon α2b: Mechanisms of action

- Complex MoA involving blocking the cell cycle machinery and by stimulating the immune response, not fully elucidated
  - **Cellular signaling:**
    - INF bind to INF-Receptor 1 & 2 and trigger TYK2 and JAK1+2 / STAT
  - **Immune effects:**
    - Activation of DC (Santini, *J Exp Med* 2000)
    - Up regulation of MHC and Ag presentation (Cresswell, *Traffic* 2000)
    - Increased CD3 and CD11c cell infiltrates (Moshow & al, JCO 2006)
  - **Other effects:**
    - Direct APo2L/TRAIL mediated apoptotic effect (Chawla-Sarkar, *Apoptosis* 2003)
    - Antiangiogenic by direct endothelial cell inhibition (Folkman, *Nature Rev. Drug Discovery* 2007)
- For reviews:
  - Borden & al. *Nature Review Drug Discovery*, 2007
  - S. Pasquali & al., *Current Medicinal Chemistry*, 2010

High dose INFα: Overview of adjuvant trials

Trial	Size	Stage	Treatment schedule	DFS		OS	
				HR	p	HR	p
ECOG 1697 Agarwala 2011 (stopped at 3rd interim analysis)	1150 Pts.	II, III	INFα2b 20 MU/m^2, d1-5 x4w, IV	0.91	NS	1.01	NS
ECOG 1690 Kirkwood 2000	405 Pts.	IIB, III	INFα2b 20 MU/m^2, d1-5 x4w, IV + 10 MU/m^2, 3x/w x48w, SC	0.88	0.054	1.07	0.99
ECOG 1684 Kirkwood 1996	287 Pts.	IIB, III	INFα2b 20 MU/m^2, d1-5 x4w, IV + 10 MU/m^2, 3x/w x48w, SC	0.56	0.0046	0.68	0.046
NCTCG Creagan 1995	262 Pts.	II-III	INFα2a 20 MU/m^2, 3x/w x3m, IM	0.77	0.19	0.88	0.40
SUNBELT, McMasters 2008	218 Pts.	III-Sn+	INFα2b 20 MU/m^2, d1-5 x4w, IV + 10 MU/m^2, 3x/w x48w, SC	0.82	0.46	1.03	0.90

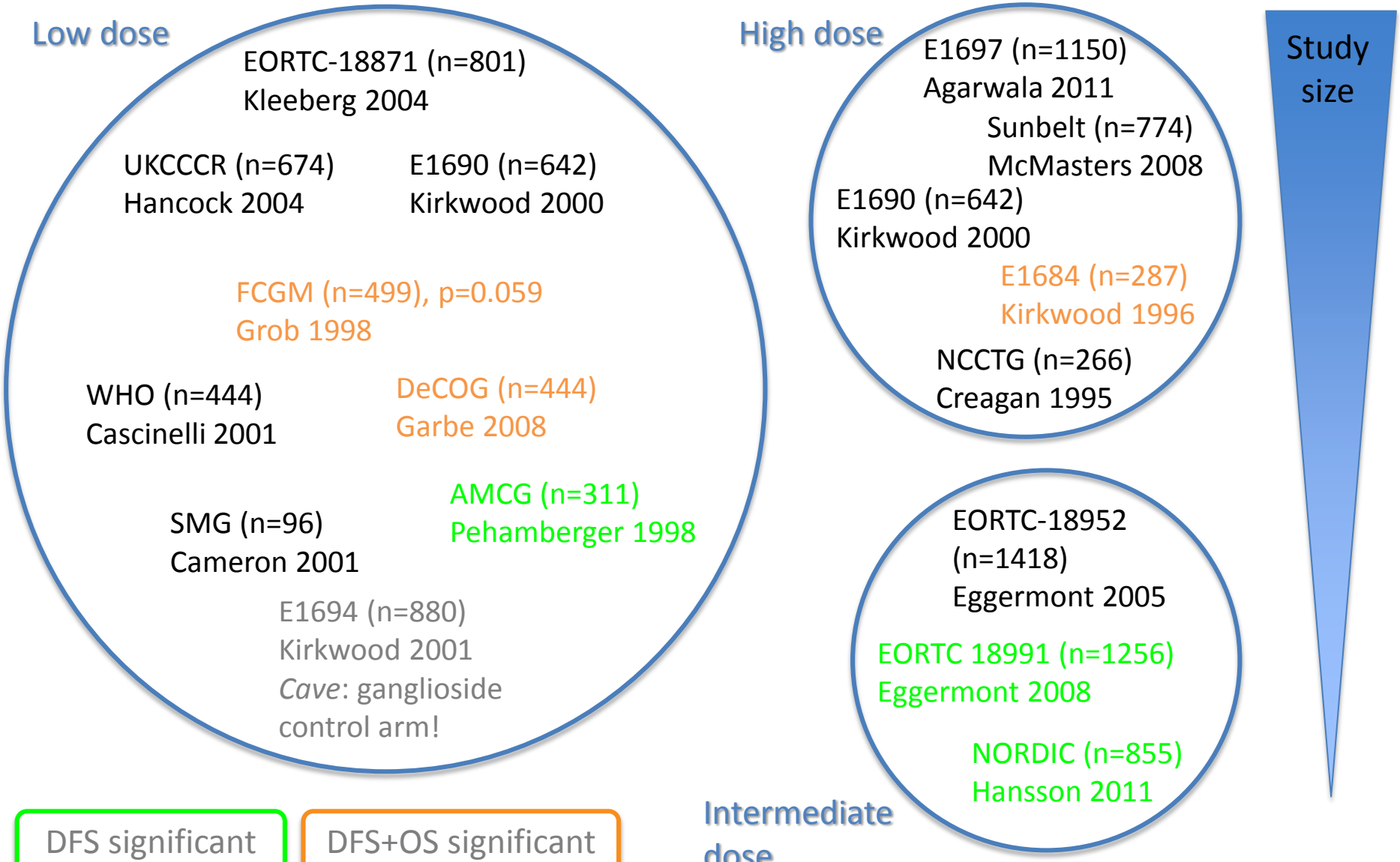
Intermediate dose INFα: Overview of trials

Trial	Size	Stage	Treatment schedule	DFS		OS	
				HR	p	HR	p
EORTC 18952 Eggermont 2005	1418 Pts.	IIB-III	INFα2b 10 MU, d1-5 x4w, SC + 10 MU, 3x/w x12m, SC or 10 MU, 3x/w x24m, SC	0.81	0.12	0.88	0.40
NORDIC, Hansson 2011	855 Pts.	IIB-III	INFα2b 10 MU, d1-5 x4w, SC + 10 MU, 3x/w x12m, SC or 10 MU, 3x/w x24m, SC	0.83	0.05	0.88	0.47
EORTC 18991 Eggermont 2008	1256 Pts.	III	PEG-INFα2b 180 MU/w, x8w, SC + 30-90 MU/w, 5 years, SC	0.82	0.012	0.98	0.98

Low dose INFα: Overview of adjuvant trials

Trial	Size	Stage	Treatment schedule	DFS		OS	
				HR	p	HR	p
EORTC 18871 Kleeberg 2004	830 Pts.	II-III	INFα2b 1 MU, 3x/w, x 12 m	0.96	> 0.50	0.96	> 0.70
UKCCCR Hancock 2004	674 Pts.	IIB, III	INFα2a 3 MU, 3x/w, x 24 m	0.94	0.60	0.91	0.30
ECOG 1690 Kirkwood 2000	642 Pts.	IIB,III	INFα2b 3 MU, 3x/w, x 24 m	0.90	0.17	0.93	0.81
FCGM Grob 1998	499 Pts.	II	INFα2a 3 MU, 3x/w, x 18 m	0.75	0.035	0.72	0.059 (!)
DeCOG Garbe 2008	444 Pts.	III	INFα2a 3 MU, 3x/w, x 24 m	0.69	0.018	0.62	0.0045
WHO Cascinelli 2001	444 Pts.	III	INFα2a 3 MU, 3x/w, x 36 m	0.95	0.50	0.96	> 0.50
AMCG Pehamberger 1998	311 Pts.	II	INFα2a, 3 MU daily, x3w + 3 MU, 3x/w, x12 m	0.62	0.02	0.83	NS
SMG Cameron 2001	96 Pts.	IIB, III	INFα2b 3 MU, 3x/w, x 6 m	0.72	NS at > 2 years	0.81	> 0.20

INF-α: Trial overview



Adjuvant interferon: 2013 Cochrane review

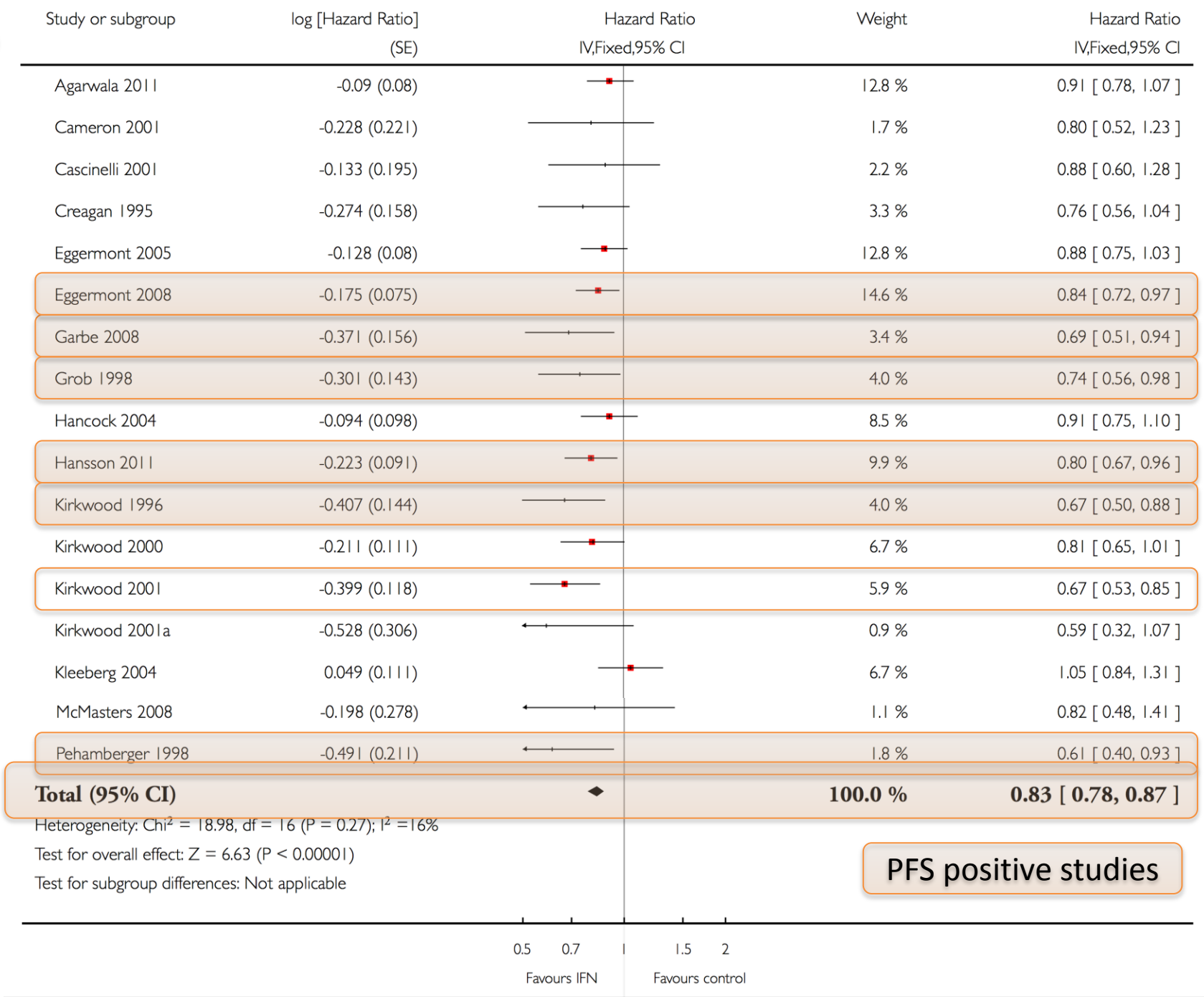
THE COCHRANE COLLABORATION®

Mocellin, S., Lens, M. B., Pasquali, S., Pilati, P., & Chiarion-Sileni, V.

Interferon alpha for the adjuvant treatment of cutaneous melanoma. The Cochrane Database of Systematic Reviews

2013

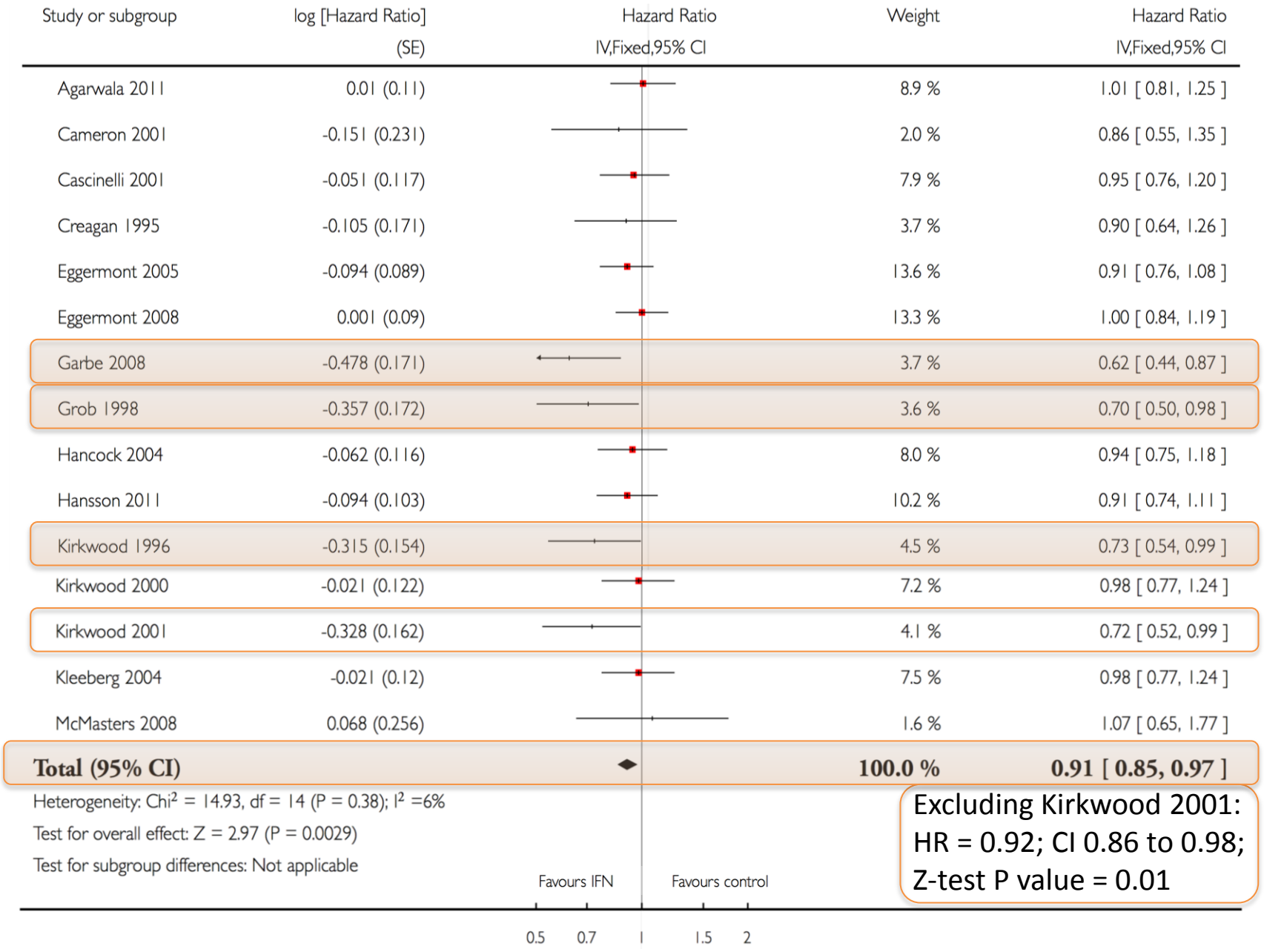
DFS



PFS positive studies

Overall survival data

OS positive studies



Excluding Kirkwood 2001:
HR = 0.92; CI 0.86 to 0.98;
Z-test P value = 0.01

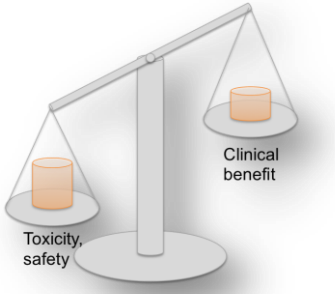
Toxicity data (All numbers in %, INF=interferon, HD=High Dose, LD=Low Dose, m=month)

Trial	Arm	Fever		Fatigue		Myalgia		Arthralgia		Anorexia		Dizziness		Headache		Mood	
		G3	G4	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4	G3	G4
Grob 1998	INF	< 1	0									0		1		< 1	< 1
Kirkwood 2000	HD			23	1	16	1									8	1
	LD			3	0	8	1									2	0
Kirkwood 2001	INF			21	0.3	4	0									9	1
Hancock 2004	INF	1	0	7	0											3	0
Eggermont 2005	13m	6	1	14	1	7	1	6	1	6	1	4	1	5	1	10	2
	25m	8	1	12	1	2	1	2	1	6	1	4	1	5	1	9	1
Garbe 2008	0	0														2	0.8
Eggermont 2008	PEG INF	4	1	15	1	4	1							4	1	6	1
Hansson 2011	13m	1	0.4	10		5		3		4				4		5	1
	25m	1	0	11		5		5		4				3		2	0

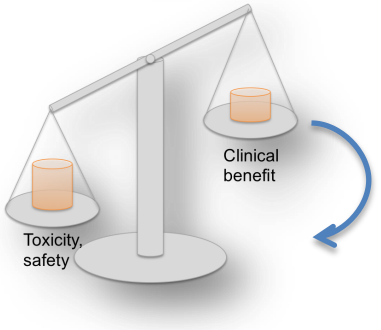
Interferon α2b: Conclusion

- Consistent improvement of PFS and, to a lesser extend, OS with a modest effect
- PFS: no optimal treatment schedule emerged as being superior between, high dose, low dose or intermediate dose
- OS: no association between outcome and dose or treatment duration.
- Important toxicity

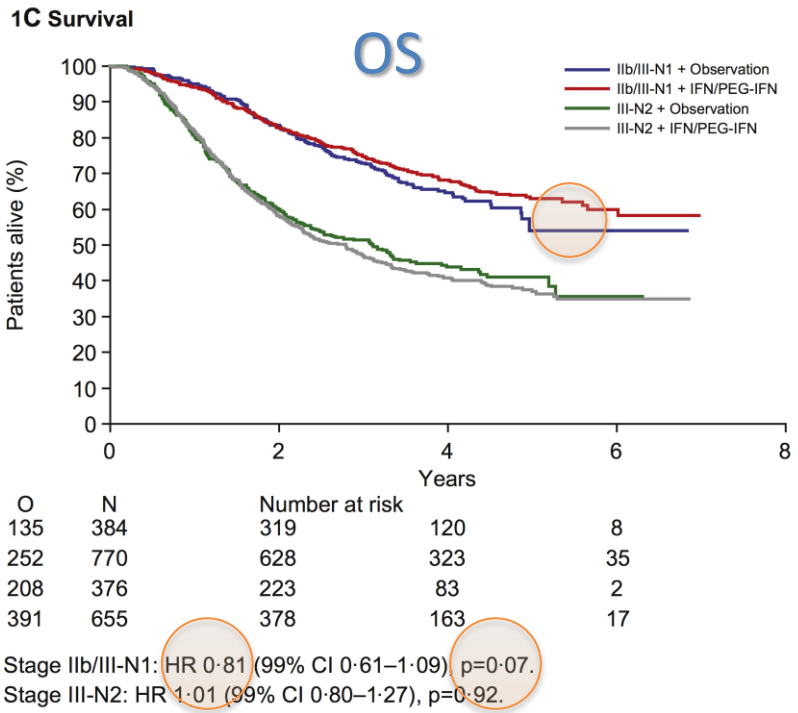
- Does the clinical benefit justify the toxicity?
  - No international consensus
  - Guidelines are diverging

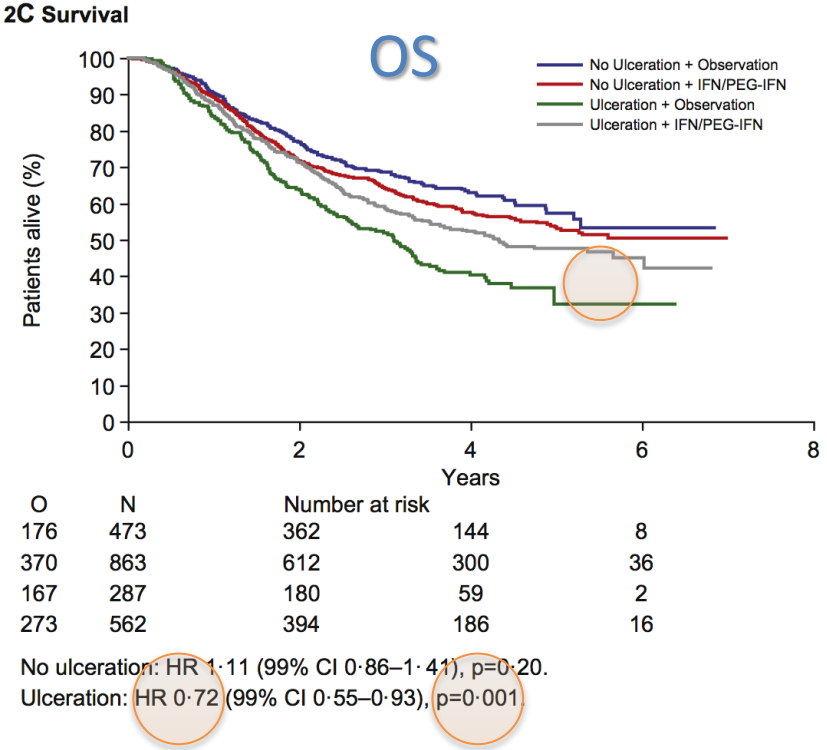


- What are the options to move forward?
  - Better selection of patient population
    - searching for a predictive biomarker…

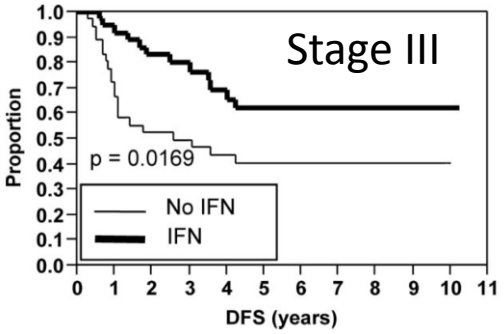


EORTC 18952 and 18991 meta-analysis suggests stage and ulceration as a predictive biomarker for adjuvant INF





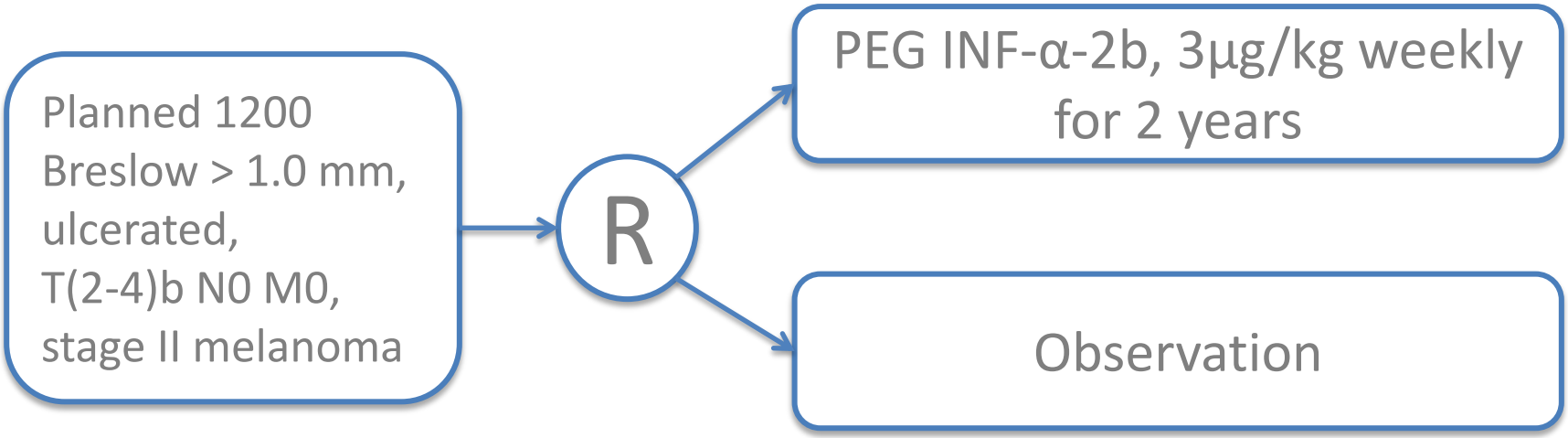
- Confirmation of the impact of ulceration on DFS for stage III (SN+) melanoma in the Sunbelt Trial [1]



[1] McMaster &al., *Ann. Surg.* 2010;

EORTC 18081 (NCT01502696)

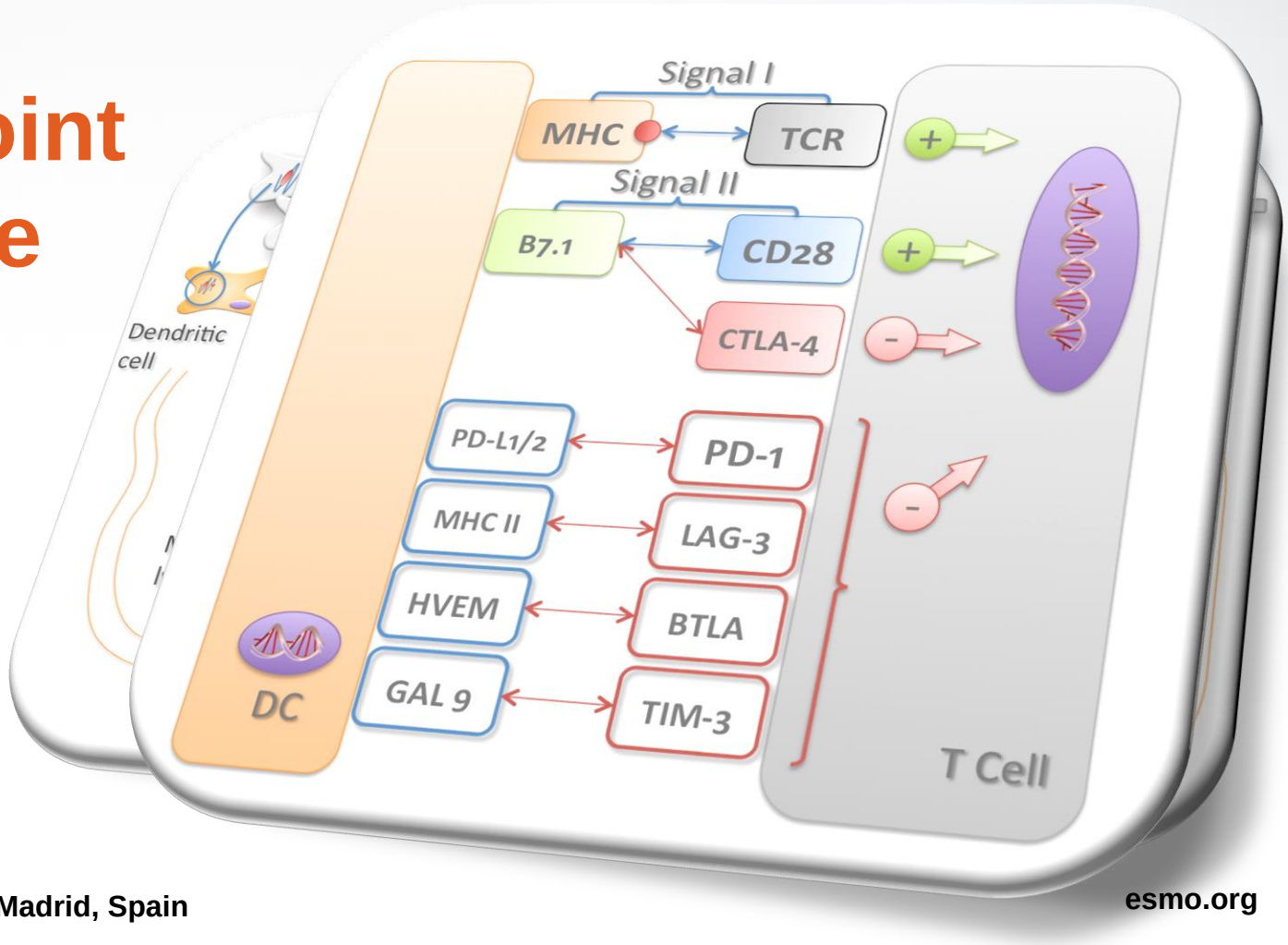
- **Trial design:**



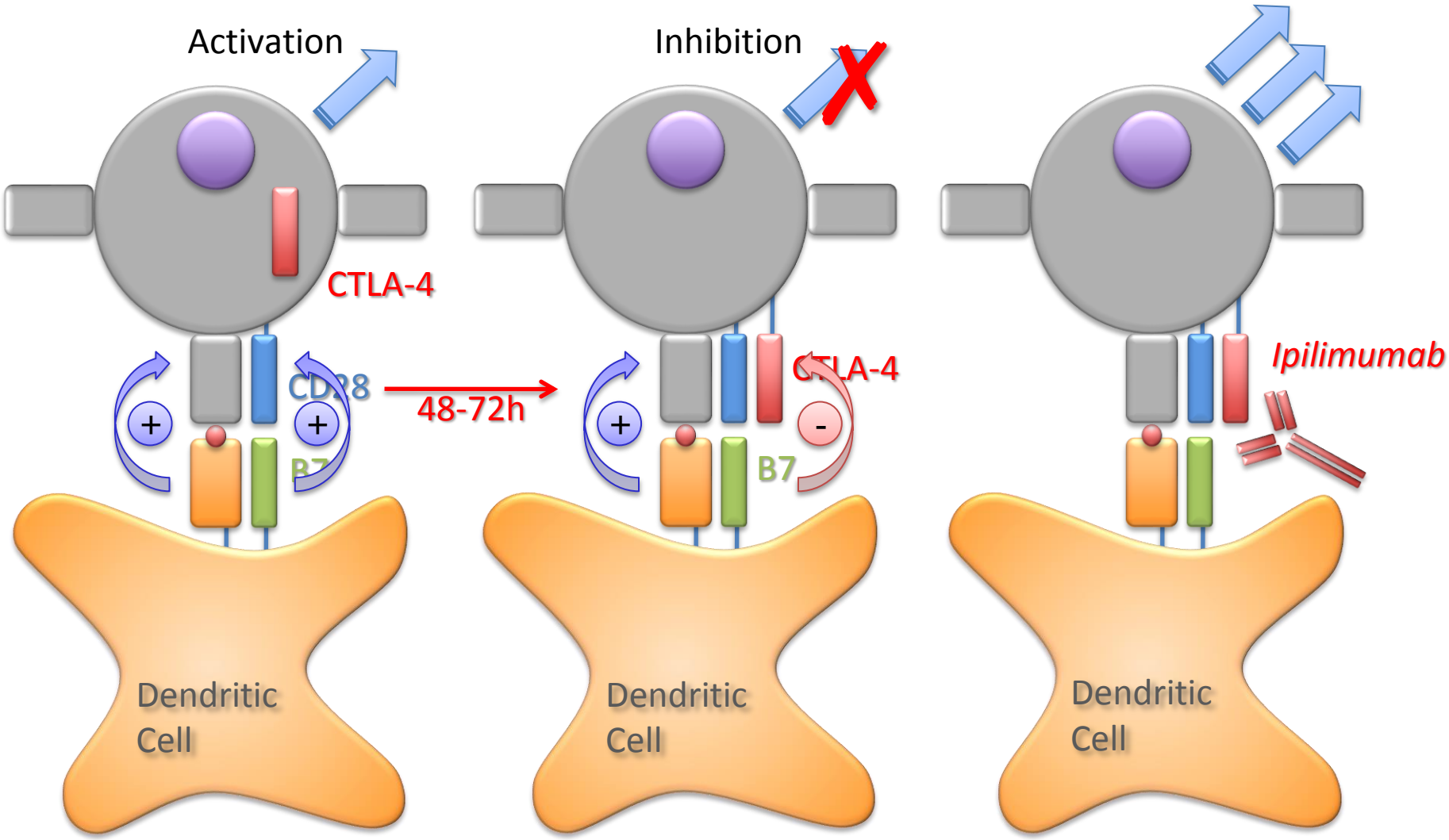
- **Endpoints:**
  - Primary endpoint:
    - RFS
  - Secondary endpoint:
    - AEs, OS, DMFS, QoL

- **Results:**
  - primary endpoint data:
    April 2020

Immune modulations: CTLA-4 checkpoint blockade

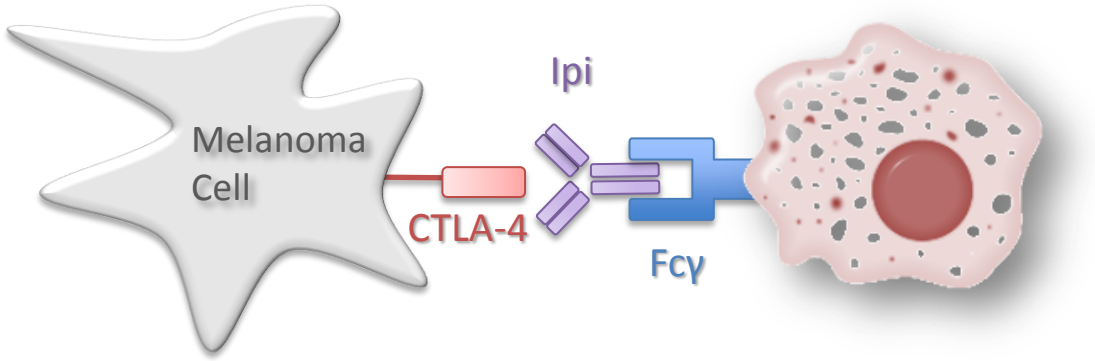


Role of CTLA-4 in T cell activation

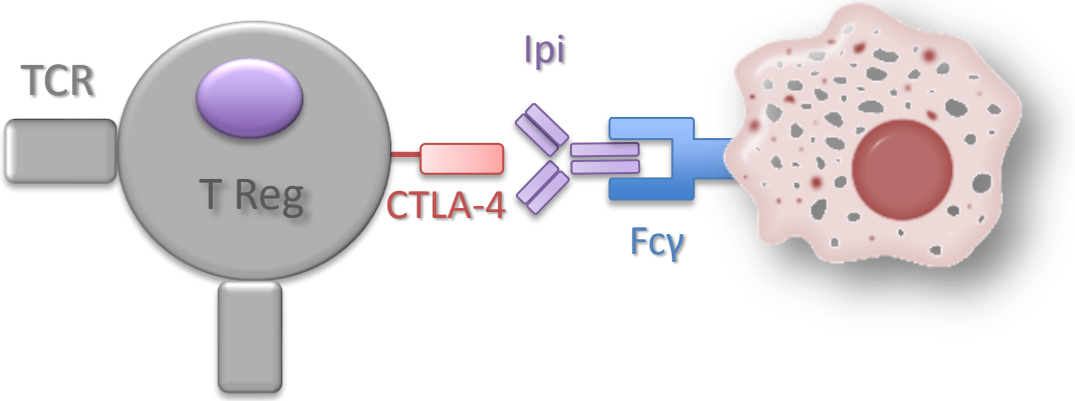


Other biological mechanisms of action (MoA)

- CTLA-4 is expressed at the surface of melanoma cells and ipilimumab can mediate ADCC
  - Laurent & al. *J. Transl. Med.* 2013



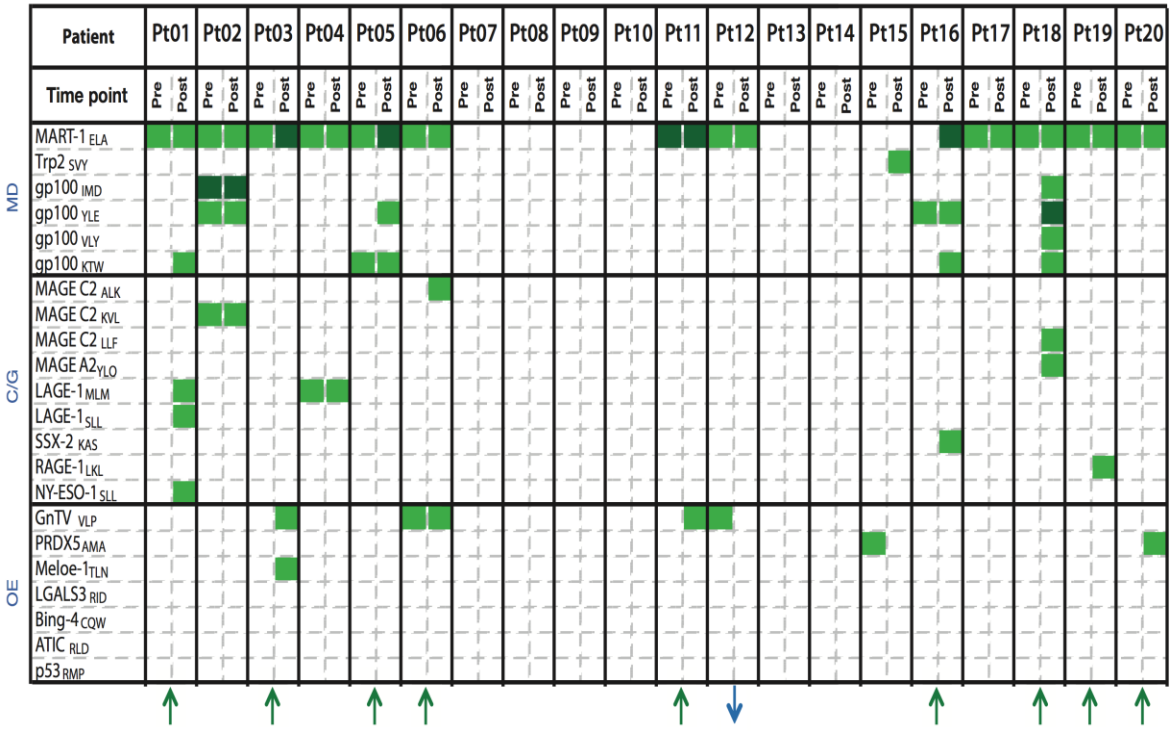
- Similar Fc-γ dependent T-Reg depletion by ADCC that increase the Teff / Treg ratio
  - Simpson & al. *J. Exp. Med.* 2013



- These MoA might have an important role in the adjuvant setting

Impact of ipilimumab on existing / new antigenic specificities

- Systematic blood collections of patients treated by ipilimumab in our institution and at NKI (Amsterdam), pre- , during and post-treatment
- Large scale analysis of antigenic specificities (Ton Schumacher)
  - UV–induced peptide exchange and (pMHC) combinatorial coding
  - Screening of 145 melanoma epitopes



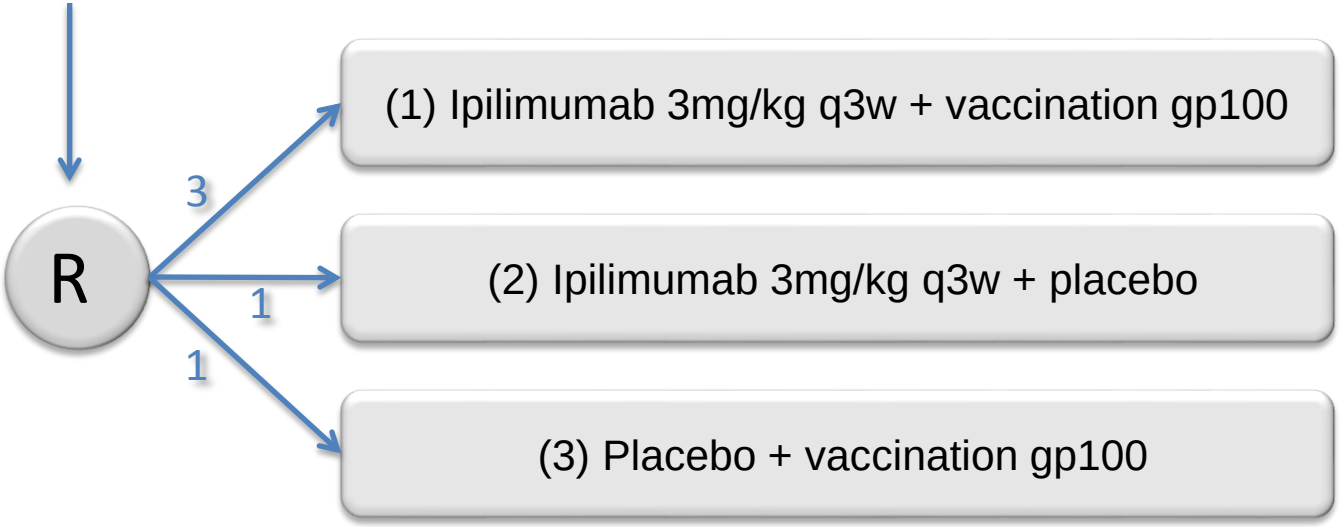
Conclusion:

- Pre-existing response remained unaltered
- Appearance of new antigenic specificities
- Confirms the clinical role in T cell priming

Kvisborg, *Science Transl. Med.* 2014

Design of BMS 020 Phase III study

676 HLA A2+ patients with stage III or IV non operable melanoma, 2nd line



Methodology:

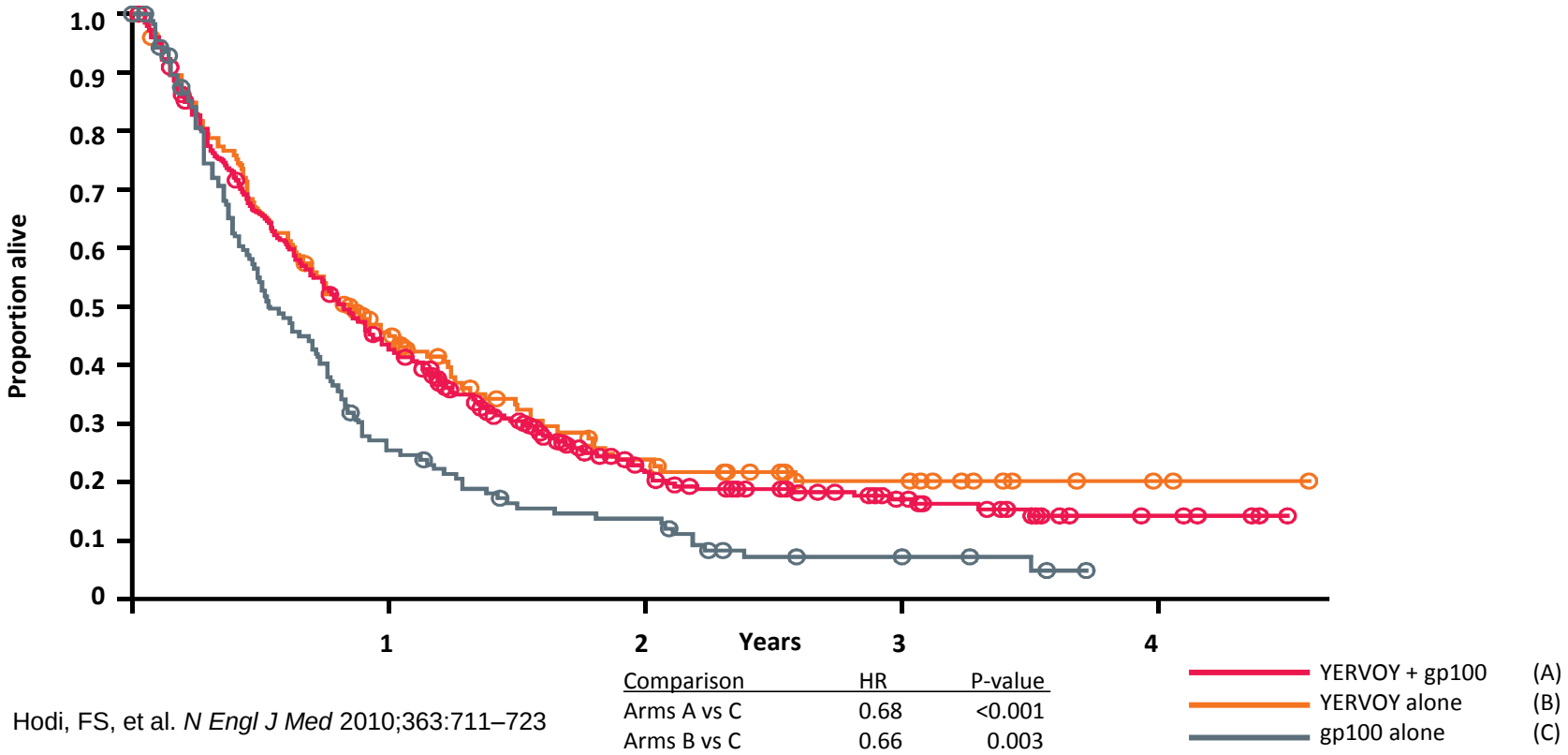
Primary endpoint: Overall survival (OS)

Secondary endpoint: PFS, response rate

Hodi & al, NEJM, 2010

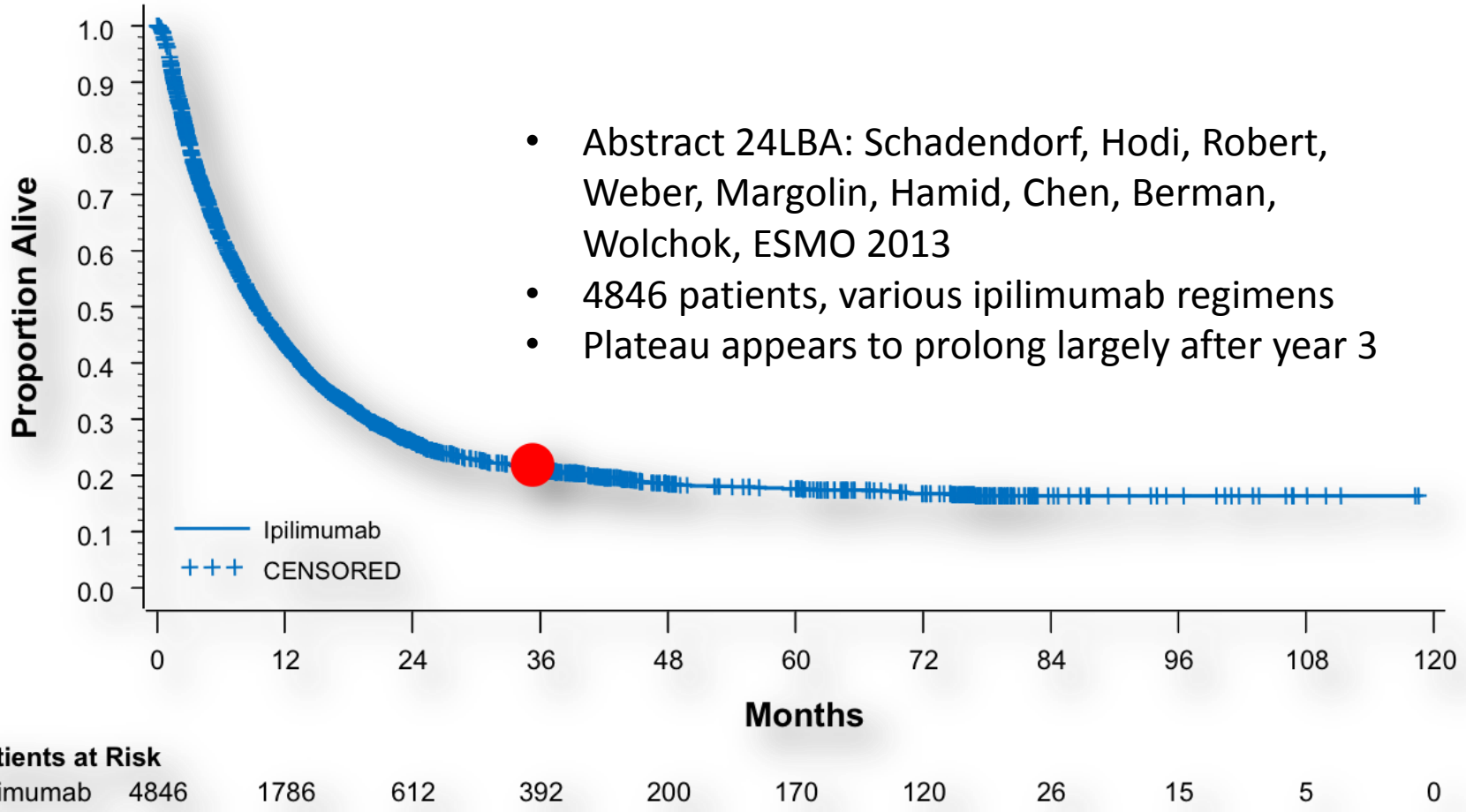
Improved OS with Ipilimumab (> 4.5 y FU)

Survival Rate	YERVOY + gp100 N=403 (95% CI)	YERVOY + placebo N=137 (95% CI)	gp100 + placebo N=136 (95% CI)
1 year	44% (0.39,0.49)	46% (0.37,0.54)	25% (0.18,0.33)
2 year	22% (0.17,0.26)	24% (0.16,0.32)	14% (0.08,0.2)



Hodi, FS, et al. *N Engl J Med* 2010;363:711–723

Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma



- Abstract 24LBA: Schadendorf, Hodi, Robert, Weber, Margolin, Hamid, Chen, Berman, Wolchok, ESMO 2013
- 4846 patients, various ipilimumab regimens
- Plateau appears to prolong largely after year 3

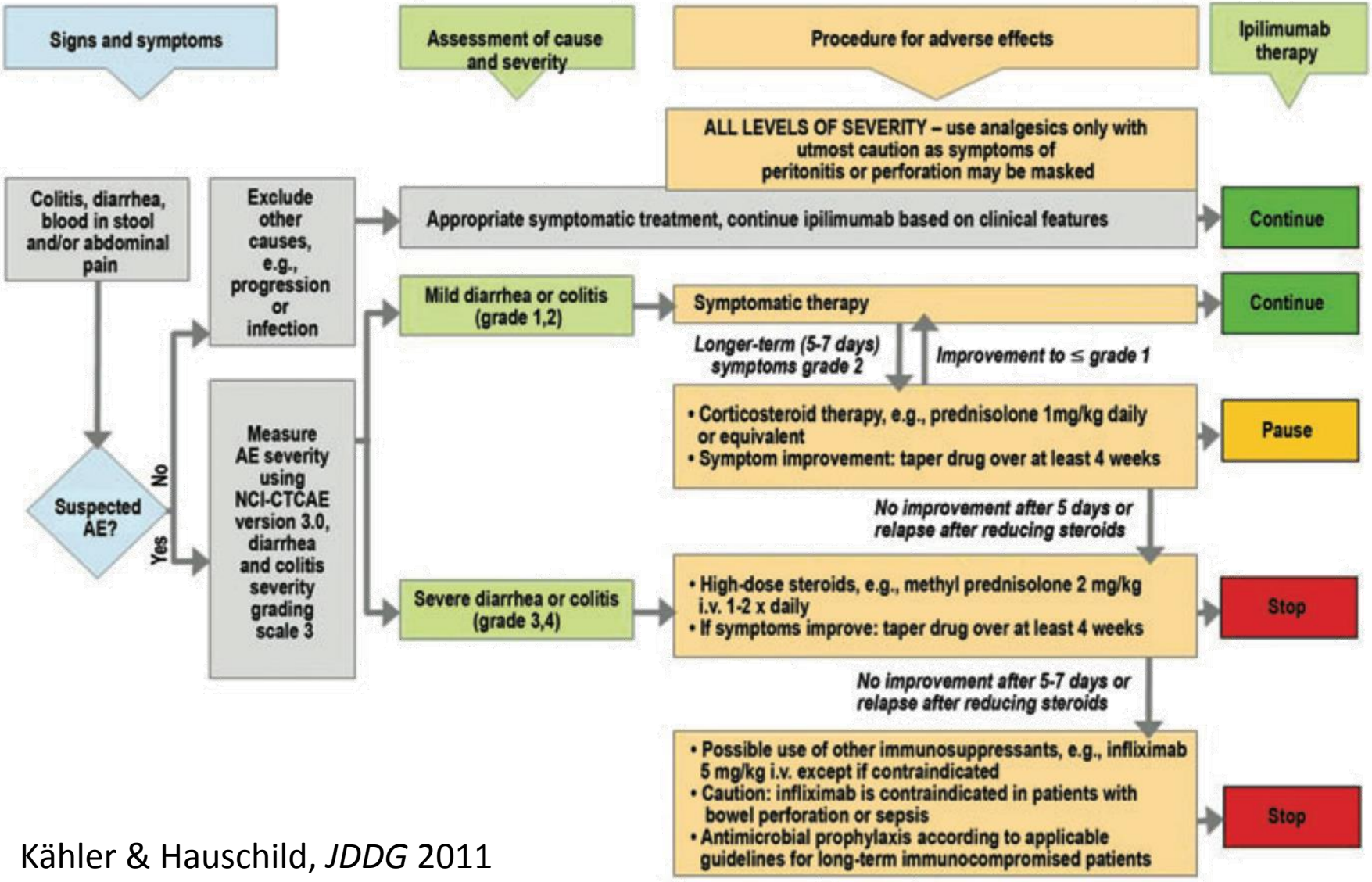
Hodi & al, *ESMO*, 2013

irAE associated with ipilimumab (Hodi & al. *NEJM*, 2010)

Table 3. Adverse Events in the Safety Population.*

Adverse Event	Ipilimumab plus gp100 (N=380)			Ipilimumab Alone (N=131)			gp100 Alone (N=132)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)								
Any event	374 (98.4)	147 (38.7)	26 (6.8)	127 (96.9)	49 (37.4)	11 (8.4)	128 (97.0)	54 (40.9)	8 (6.1)
Any drug-related event	338 (88.9)	62 (16.3)	4 (1.1)	105 (80.2)	25 (19.1)	5 (3.8)	104 (78.8)	15 (11.4)	0
Gastrointestinal disorders									
Diarrhea	146 (38.4)	16 (4.2)	1 (0.3)	43 (32.8)	7 (5.3)	0	26 (19.7)	1 (0.8)	0
Nausea	129 (33.9)	5 (1.3)	1 (0.3)	46 (35.1)	3 (2.3)	0	52 (39.4)	3 (2.3)	0
Constipation	81 (21.3)	3 (0.8)	0	27 (20.6)	3 (2.3)	0	34 (25.8)	1 (0.8)	0
Vomiting	75 (19.7)	6 (1.6)	1 (0.3)	31 (23.7)	3 (2.3)	0	29 (22.0)	3 (2.3)	0
Abdominal pain	67 (17.6)	6 (1.6)	0	20 (15.3)	2 (1.5)	0	22 (16.7)	6 (4.5)	1 (0.8)
Other									
Fatigue	137 (36.1)	19 (5.0)	0	55 (42.0)	9 (6.9)	0	41 (31.1)	4 (3.0)	0
Decreased appetite	88 (23.2)	5 (1.3)	1 (0.3)	35 (26.7)	2 (1.5)	0	29 (22.0)	3 (2.3)	1 (0.8)
Pyrexia	78 (20.5)	2 (0.5)	0	16 (12.2)	0	0	23 (17.4)	2 (1.5)	0
Headache	65 (17.1)	4 (1.1)	0	19 (14.5)	3 (2.3)	0	19 (14.4)	3 (2.3)	0
Cough	55 (14.5)	1 (0.3)	0	21 (16.0)	0	0	18 (13.6)	0	0
Dyspnea	46 (12.1)	12 (3.2)	2 (0.5)	19 (14.5)	4 (3.1)	1 (0.8)	25 (18.9)	6 (4.5)	0
Anemia	41 (10.8)	11 (2.9)	0	15 (11.5)	4 (3.1)	0	23 (17.4)	11 (8.3)	0
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)	42 (31.8)	4 (3.0)	0
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0	22 (16.7)	0	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0	14 (10.6)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0	6 (4.5)	0	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0	1 (0.8)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0	19 (14.4)	1 (0.8)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0	18 (13.6)	1 (0.8)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0	1 (0.8)	0	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)	2 (1.5)	0	0
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)	0	0	0
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0	0	0	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	0	0	0

Example: guidelines for managing GI irAE



Kähler & Hauschild, *JDDG* 2011

Ipilimumab Versus Placebo After Complete Resection of Stage III Melanoma: Initial Efficacy and Safety Results from the EORTC 18071 Phase III Trial

Eggermont AM,[1] Chiarion-Sileni V,[2] Grob JJ,[3] Dummer R,[4] Wolchok JD,[5] Schmidt H,[6] Hamid O,[7] Robert C,[8] Ascierto PA,[9] Richards JM,[10] Lebbé C,[11] Ferraresi V,[12] Smylie M,[13] Weber JS,[14] Maio M,[15] Konto C,[16] Karra Gurunath R,[17] de Pril V,[18] Suciu S,[17] Testori A[19]

[1]Cancer Institute Gustave Roussy, Villejuif, France; [2]IOV-IRCCS, Melanoma Oncology Unit, Padova, Italy; [3]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]Institut Gustave Roussy, Villejuif, France; [9]Istitute Nazionale Tumori Fondazione "G. Pascale", Naples, Italy; [10]Oncology Specialists S.C., Park Ridge, IL, USA; [11]Hôpital Saint-Louis, Paris, France; [12]Istituti Fisioterapici Ospitalieri, Rome, Italy; [13]Cross Cancer Institute, Edmonton, Alberta, Canada; [14]H Lee Moffitt Cancer Center , Tampa, FL, USA; [15]University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [16]Bristol-Myers Squibb, Wallingford, CT, USA; [17]EORTC Headquarters, Brussels, Belgium; [18]Bristol-Myers Squibb, Braine-l'Alleud, Belgium; [19]European Institute of Oncology, Milan, Italy.

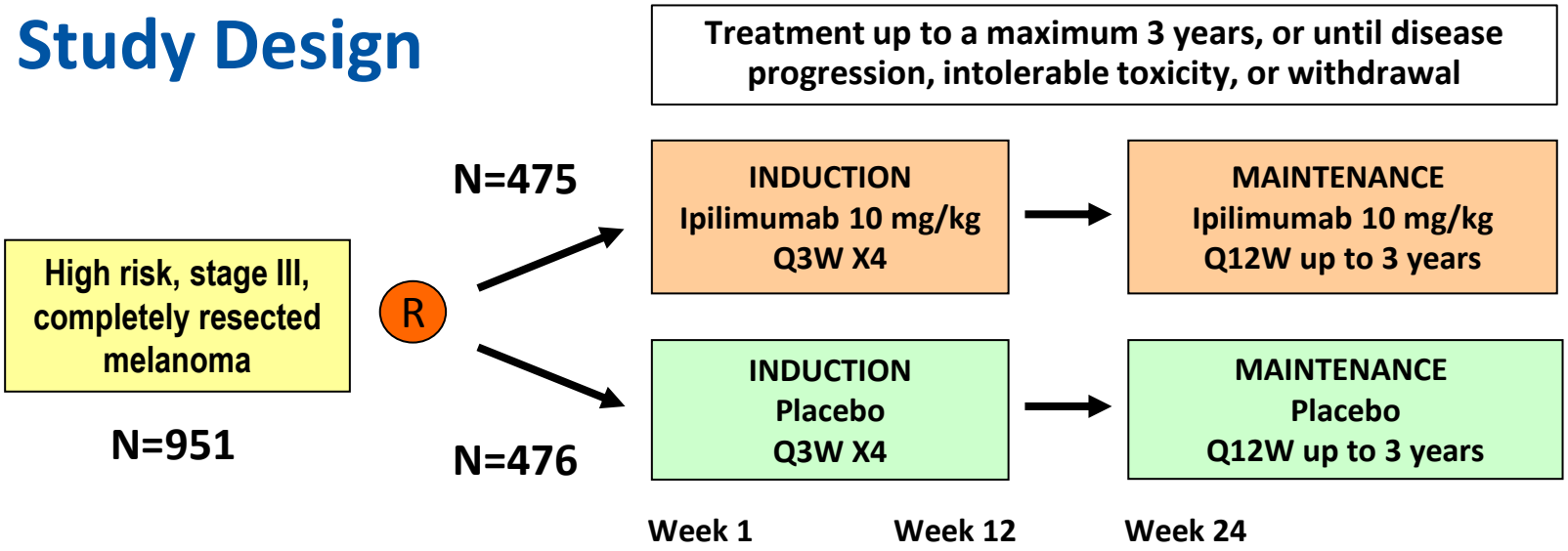
Abstract Number LBA9008

EORTC

Presented by A. Eggermont, ASCO 2014

The future of cancer therapy

EORTC 18071: Study Design



Primary endpoint:

- RFS by independent review committee: time to local, regional, distant metastasis or death

Secondary endpoints:

- OS, distant metastasis-free survival, AE profile, health related QoL

Stratification factors:

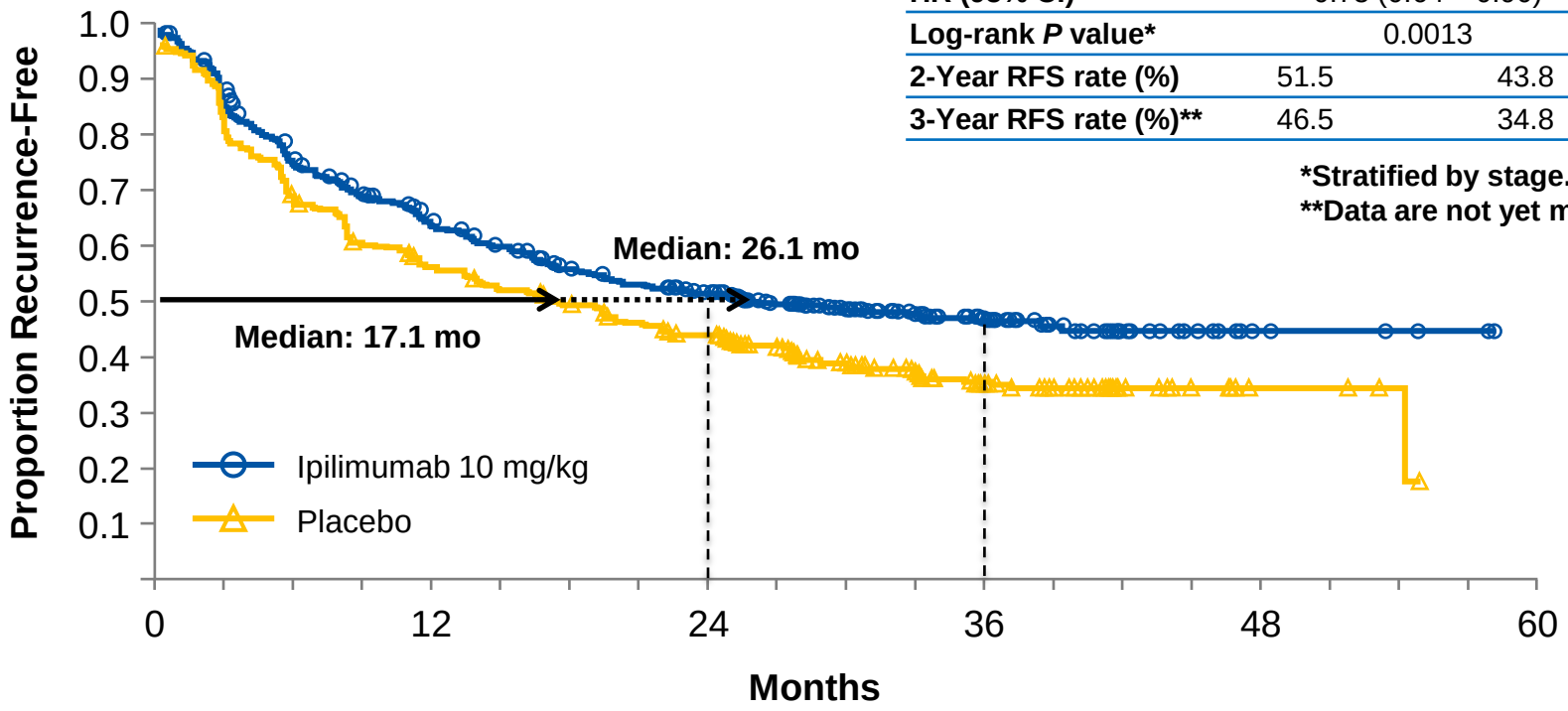
- Stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIc ≥4 nodes)
- Regions (North America, European countries and Australia)

Primary Endpoint: Recurrence-free Survival

(2.7 years /56% of overall patients reached an RFS event)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
Median RFS, mo	26.1	17.1
HR (95% CI)	0.75 (0.64 – 0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

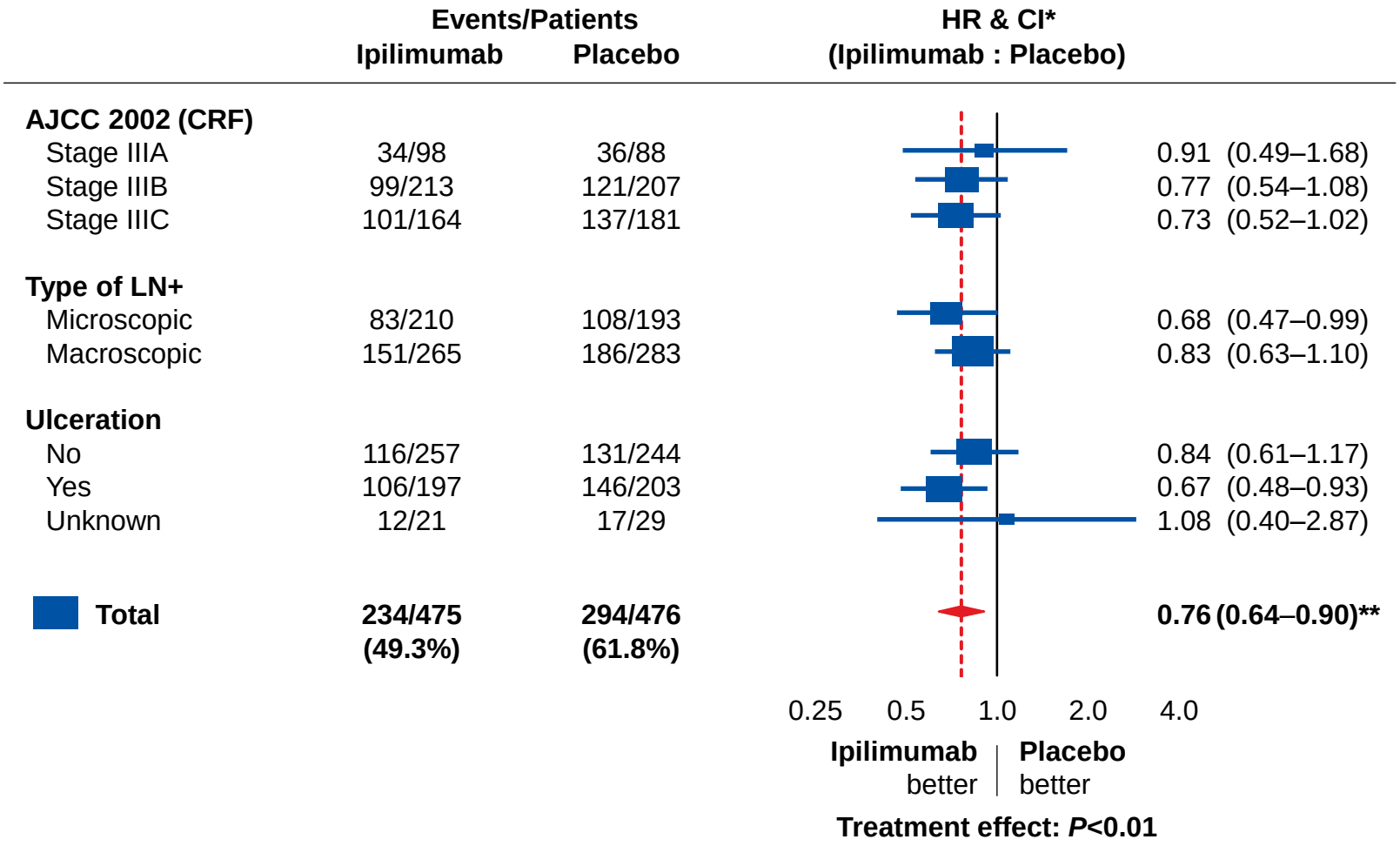
***Stratified by stage.**
****Data are not yet mature.**



Patients at Risk

Ipilimumab	475	276	205	67	5	0
Placebo	476	260	193	62	4	0

Recurrence-free Survival: Prespecified Subgroups



*95% CI for total, 99% CI elsewhere.
**RFS stratified by disease stage as per CRF.

Safety: Immune-related Adverse Events

	% Patients			
	Ipilimumab (n = 471)		Placebo (n =474)	
	All grades	Grade 3-4	All grades	Grade 3-4
Any IrAE	90.4	42.0	38.6	2.5
Dermatologic	63.3	4.5	20.9	0
Rash	34.4	1.3	11.0	0
Gastrointestinal	46.3	15.9	17.7	0.8
Diarrhea	41.4	9.6	16.7	0.4
Colitis*	15.9	7.6	1.3	0.2
Endocrine	37.6	8.5	6.5	0
Hypophysitis	18.3	5.1	0.4	0
Hypothyroidism	8.9	0.2	0.8	0
Hepatic	25.1	10.6	4.4	0.2
LFT increase	19.7	5.3	4.0	0
Neurologic	4.5	1.9	1.9	0
Other	23.6	7.9	4.4	1.7

*GI perforations: ipilimumab, 6 related (1.3%); placebo, 3 unrelated (0.6%).

Deaths Related to Study Drug

- Five patients (1.1%) died due to drug-related adverse events in the ipilimumab group:
  - 3 patients with colitis (2 with GI perforations)
  - 1 patient with myocarditis
  - 1 patient with Guillain-Barré syndrome
- No deaths related to study drug were reported in the placebo group

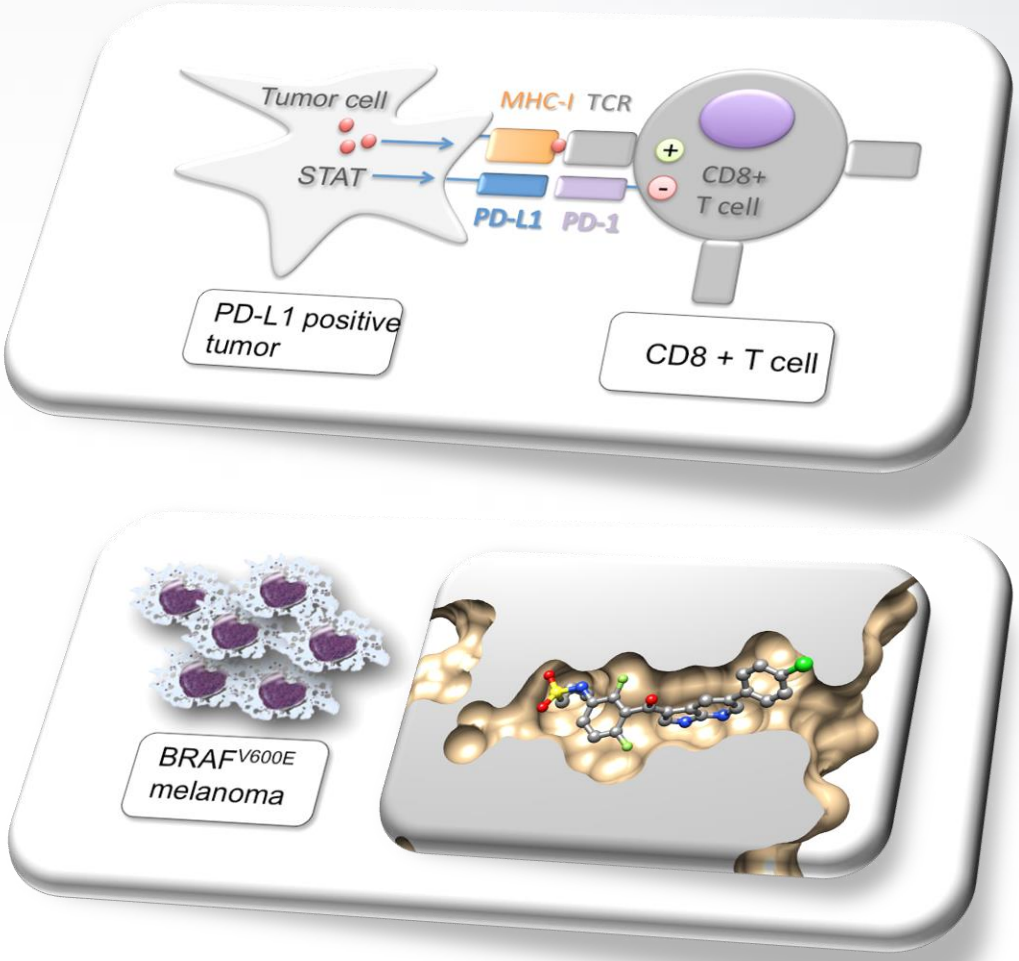
Summary/Conclusions

- Study EORTC18071/CA184-029 met its primary endpoint of a significant improvement in RFS with 10 mg/kg ipilimumab vs placebo
  - Median RFS ipilimumab 26.1 mo vs placebo 17.1 mo; HR (95%CI)=0.75 (0.64–0.90), *P*=0.0013
- Results from prespecified subgroup and sensitivity analyses show a consistent pattern with HRs favoring ipilimumab relative to placebo
- Data remain blinded for OS and DMFS and will be reported at future congresses
- Safety profile is generally consistent with that observed in advanced melanoma, although the incidence of some irAEs (e.g., endocrinopathies) were higher in this study
  - Most irAEs were managed and resolved with established treatment algorithms
- Ongoing second phase III study in adjuvant setting (E1609), evaluating ipilimumab at 3 or 10 mg/kg vs high-dose IFN

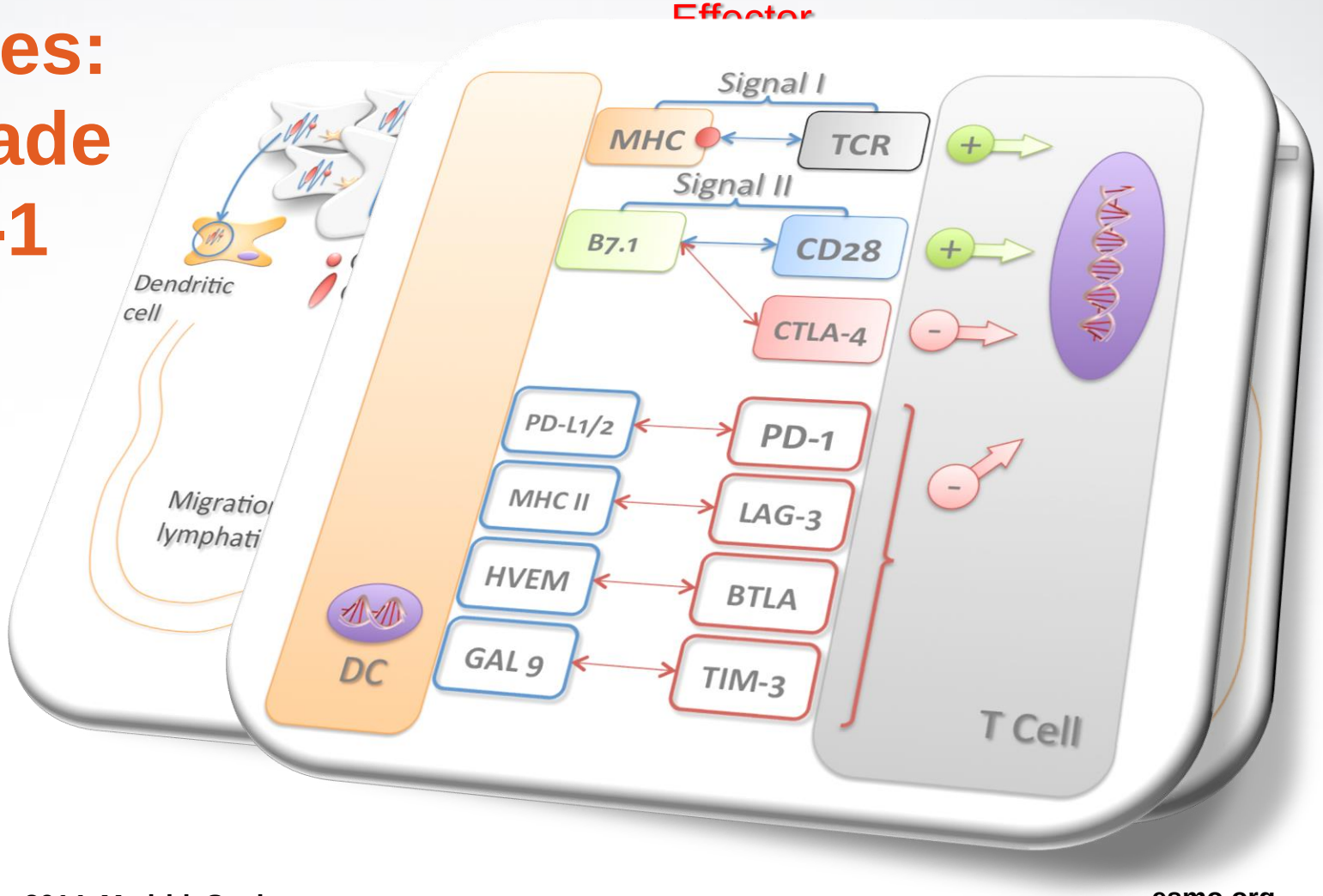
Ongoing key adjuvant trials in melanoma

- PD-1 blockade

- MAPK inhibition

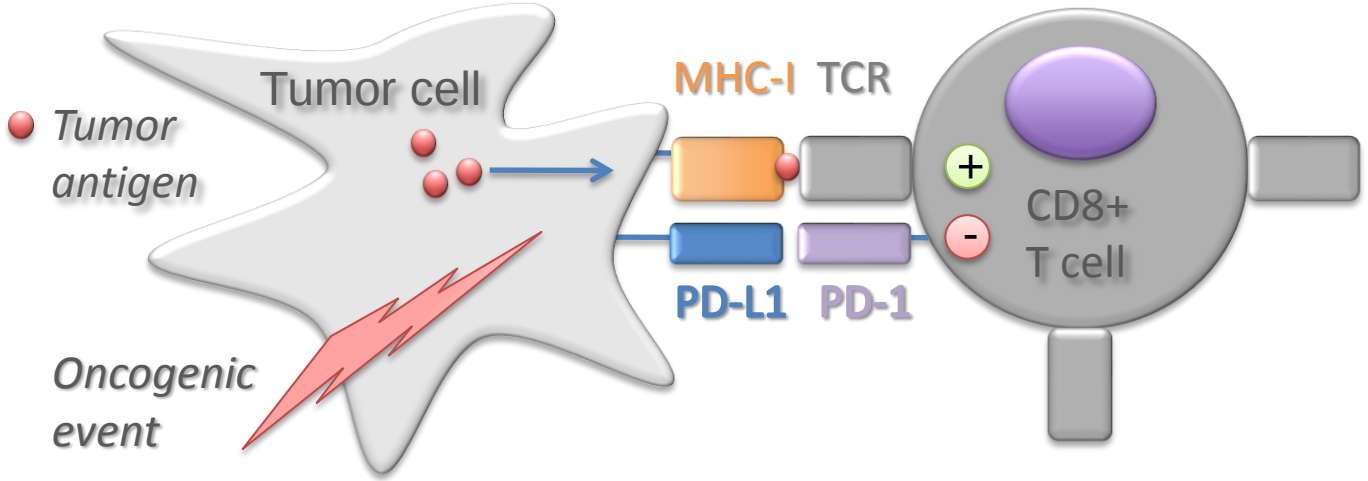


Counteracting immune escapes: blockade of PD-1

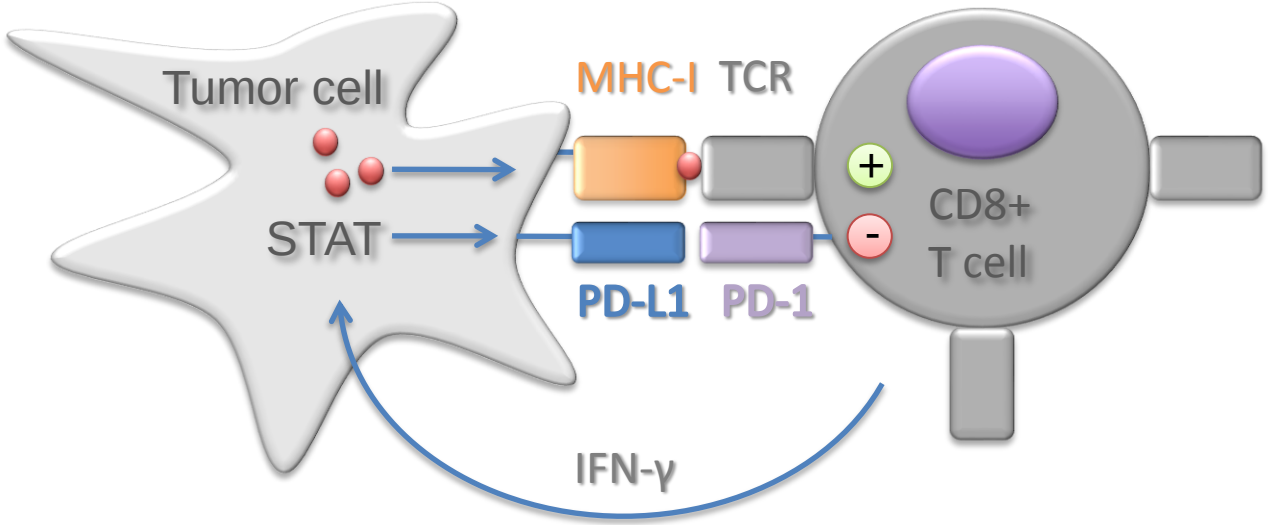


Biology of PD-L1 expression

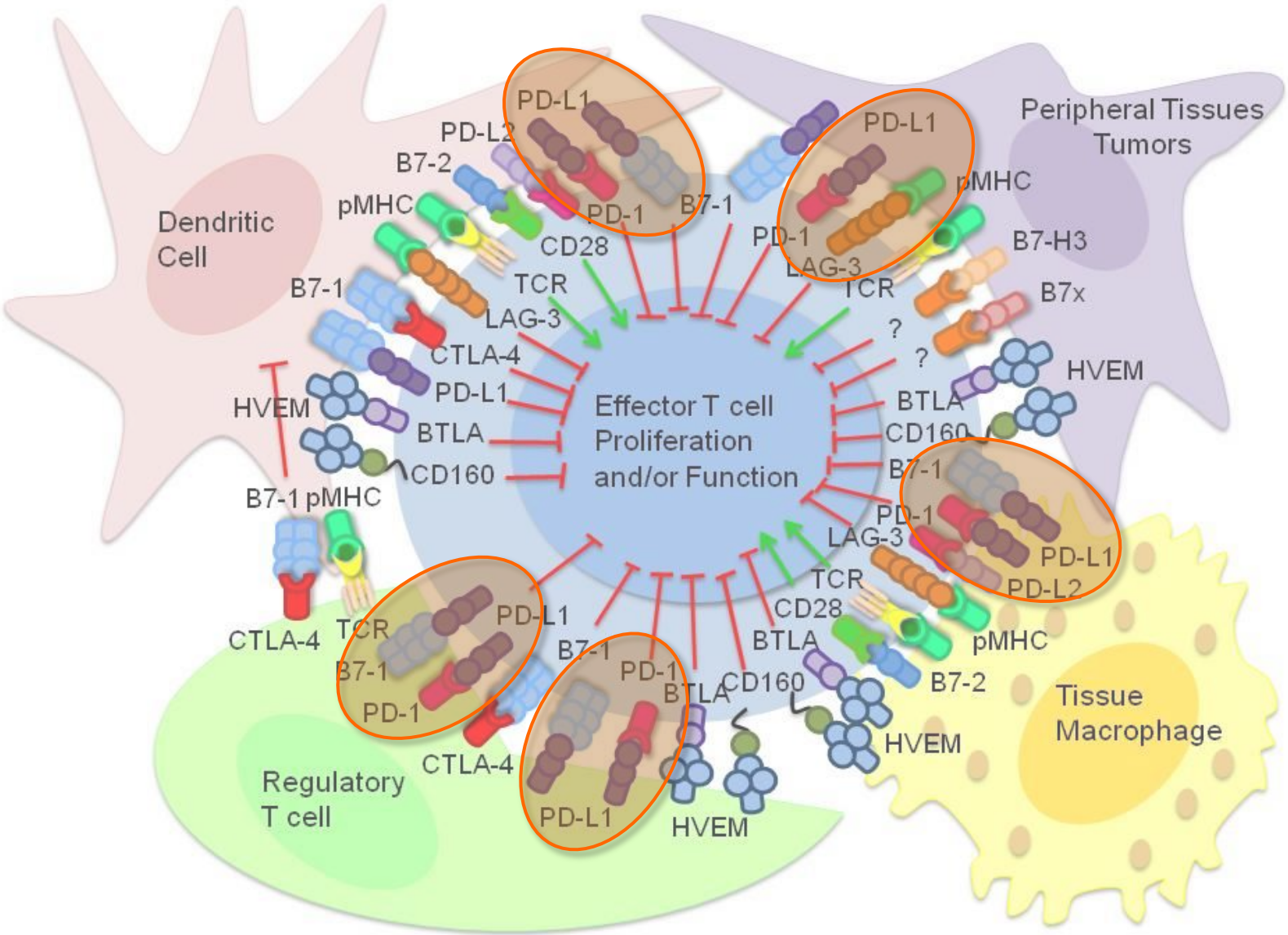
1 Oncogenic origin



2 Induced by chronic inflammation



Complex role of the PD-1/PD-L1 axis



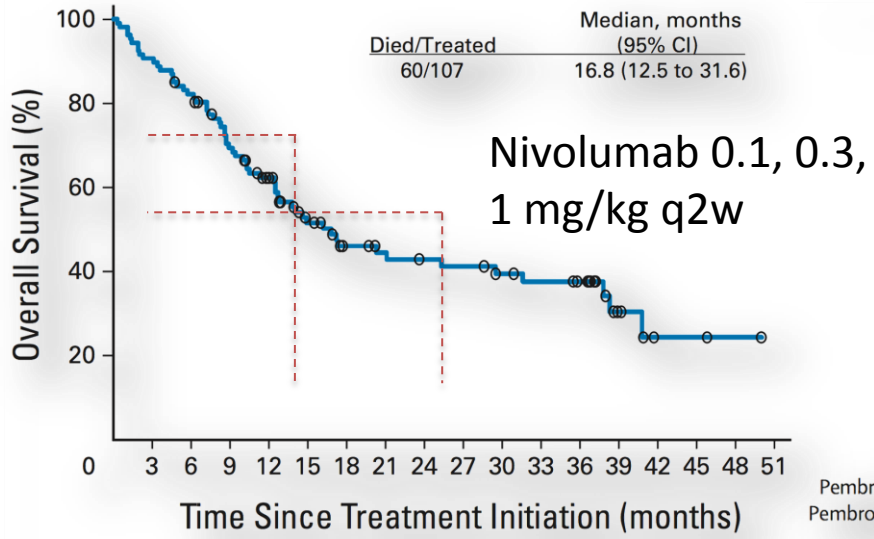
PD-1 / PD-L1 Interactions

Image from J. Allison

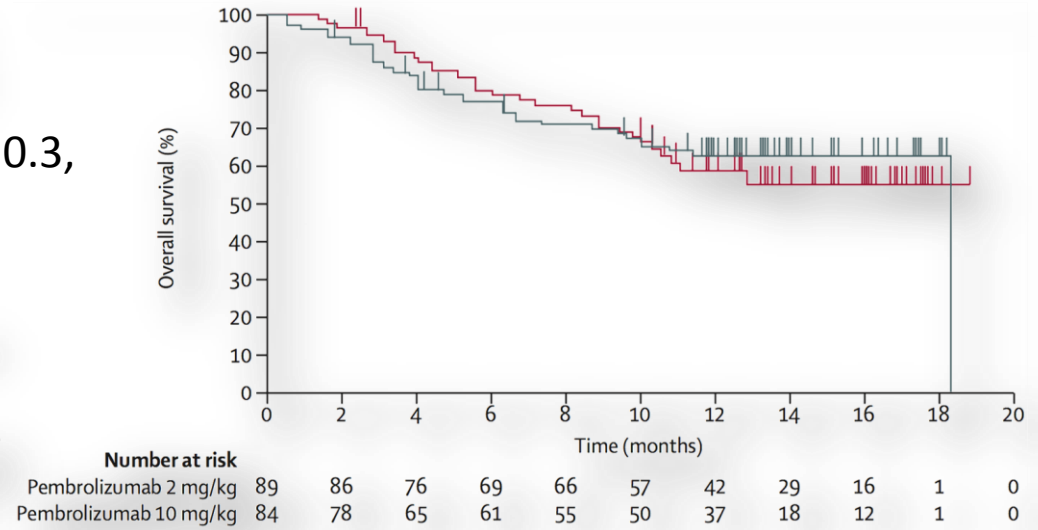
Overall survival (not randomized)

NA: Not Available,
NR: Not Relevant

Treatment Option	Response rate	1 year OS rate	2 year OS rate
Historical control: M1c (Balch, *JCO* 2009)	NR	33%	19%
CTLA-4 blockade (Hodi, *NEJM* 2010; Wolchok, *Ann Oncol* 2013)	11%	46%	24%
PD-1 blockade (pembrolizumab) (Ribas, ASCO 2014 & Kefford, ASCO 2014)	34%	69%	(60%)
PD-1 blockade (nivolumab) (Topalian, *JCO* 2014)	31%	62%	43%



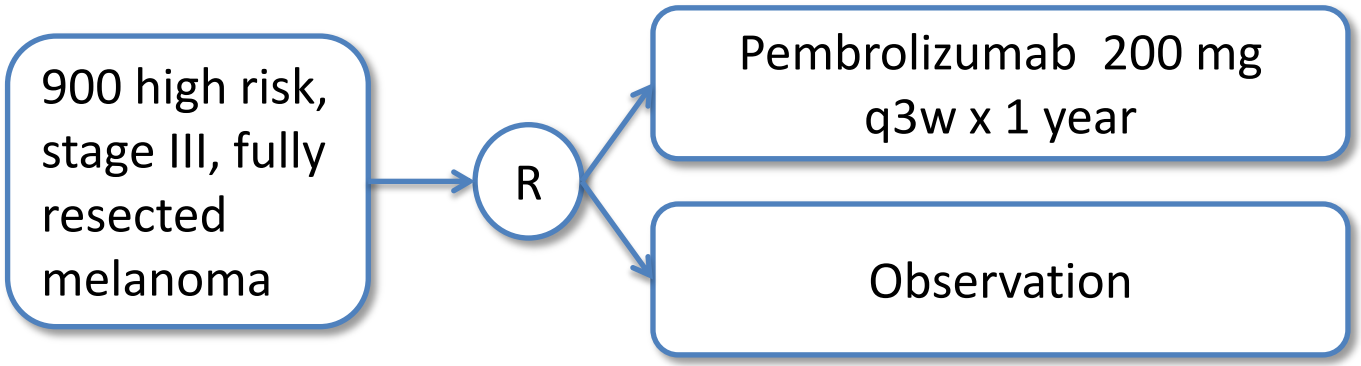
Topalian, *JCO* 2014



Robert, *Lancet* 2014

PD-1 blockade: Adjuvant trials

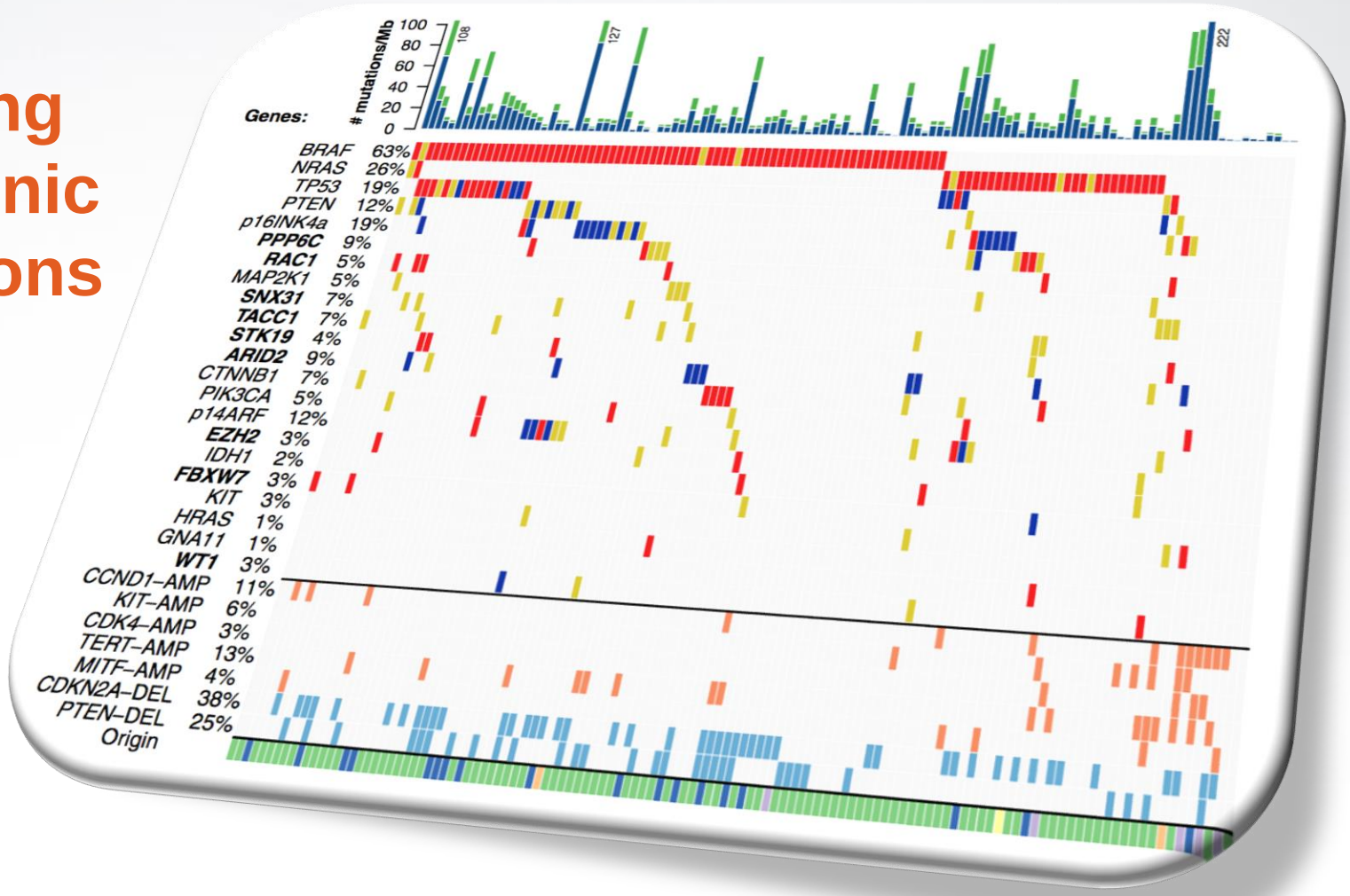
- Following the success of PD-1 blockade in the metastatic setting, these molecules are now moved into the adjuvant with randomized phase III
- **EORTC 1325:** "Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group"



Endpoints:

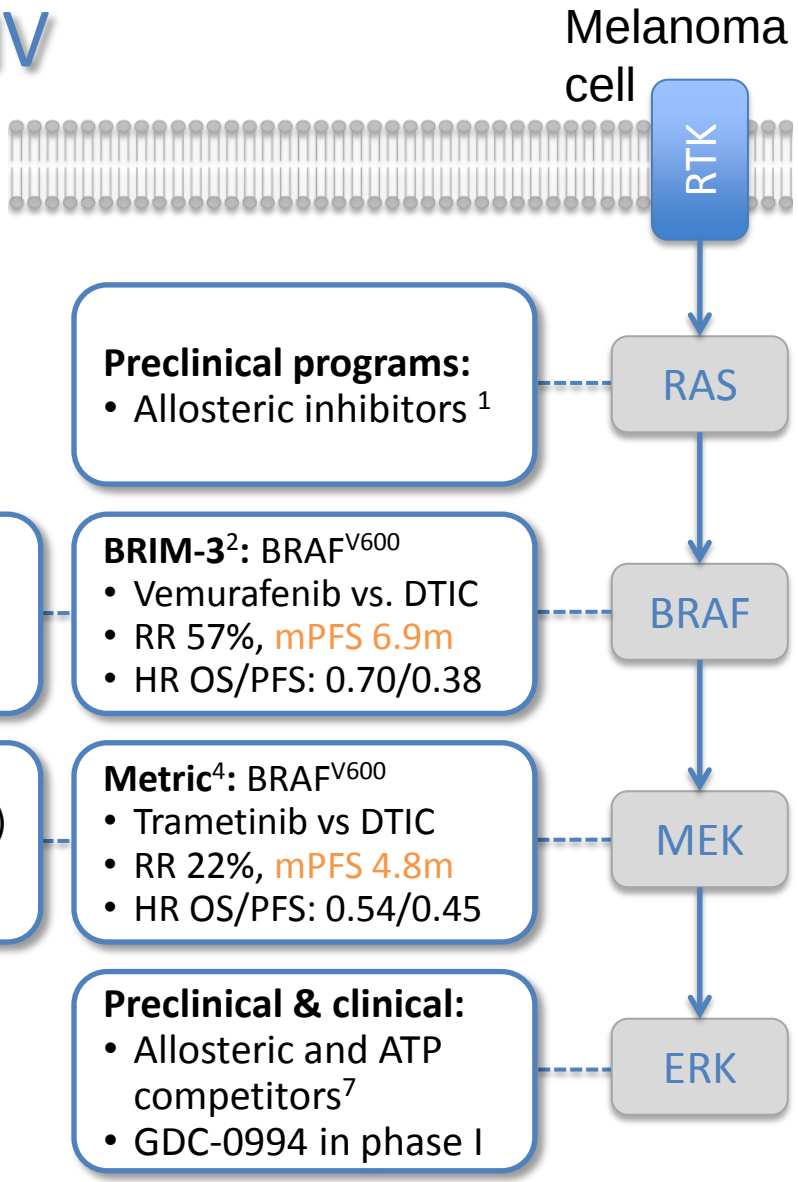
- **Primary:** RFS
- **Secondary:** RFS for PD-L1 high, overall survival, distant metastasis-free survival (DMFS)

Targeting oncogenic alterations of the tumor cells



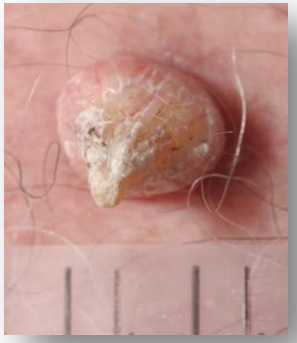
Hodis & al. *Cell* 2012

Targeted therapies in stage IV melanoma: main trials



[1] Ostrem, *Nature* 2013; [2] McArthur, *Lancet Oncol* 2014; [3] Hauschild, *Lancet* 2012; [4] Flaherty, NEJM 2012; [5] Ascierto, *Lancet Oncol* 2013; [6] Long, ASCO 2014; [7] Wong, *Molecular Cancer* 2014, NA: Not Available

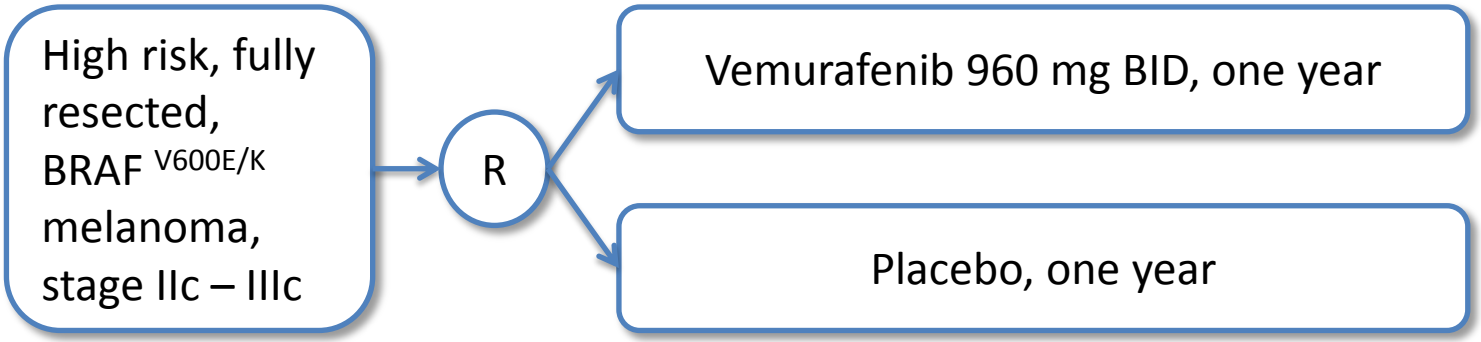
BRAF WT and BRAF^{V600E} signaling



- Papilloma
- KA
- cuSCC
- Melanoma
- Rash
- …

Adjuvant trials with BRAF inhibitors

- Vemurafenib is currently being tested in the adjuvant setting in a phase III trial: BRIM-8 / NCT01667419



Duration*:* 1 year (all arms)

Endpoints:

- ***Primary*:** DFS
- ***Secondary*:** OS, DMFS, safety (SCC!), QoL, pharmacokinetics

BRAF WT and BRAF^{V600E} signaling

Normal cell

RTK

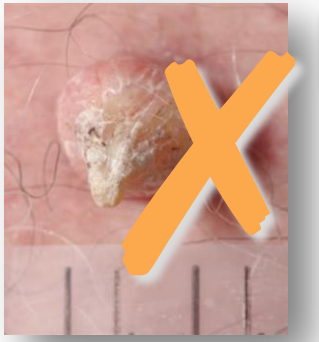
RAS

WT BRAF

MEK

ERK

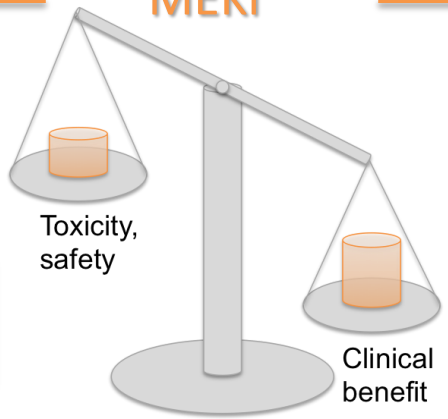
Cell survival & proliferation



- Papilloma
- KA
- Melanoma
- cuSCC
- Rash
- …

BRAFi

MEKi



Melanoma cell

RTK

RAS

BRAF V600E

MEK

ERK

Cell survival & proliferation

Resistances:
- BRAF splice variant
- NRAS, MEK mutations
- COT…

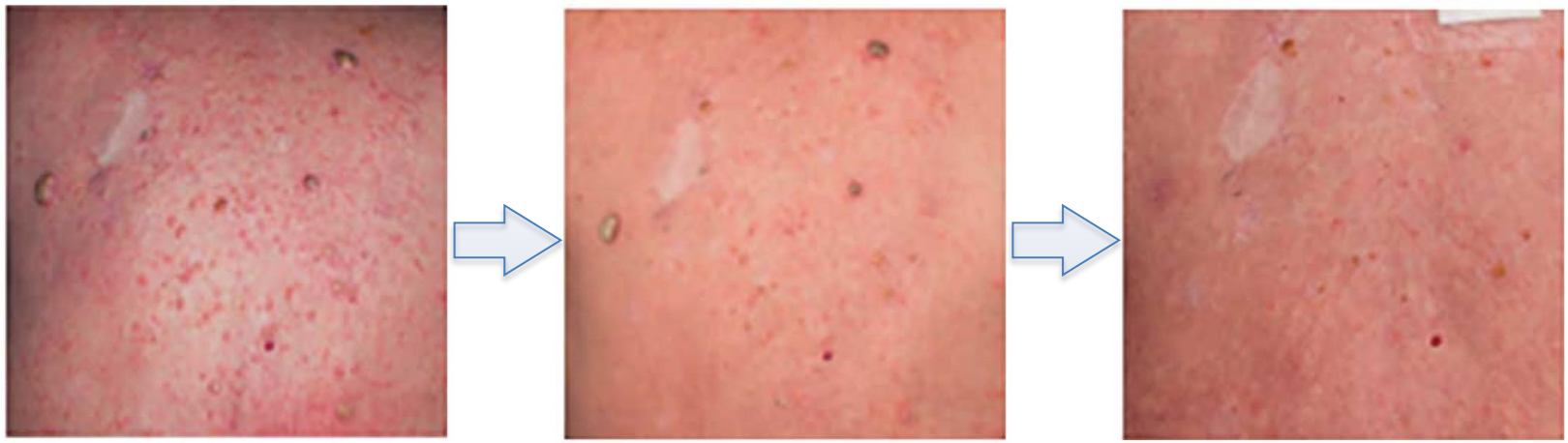
Impact of MEK inhibitors on KA & cuSCC

- The incidence of 2nd cutaneous lesion is reduced with BRAFi + MEKi

BRAFi related cuAE	D Alone (%)	D + T (%)
cuSCC + KA	9	2
Hyperkeratosis	32	3
Skin papilloma	21	1
New primary melanoma	1	< 1
Non-cutaneous malignancy	1	< 1

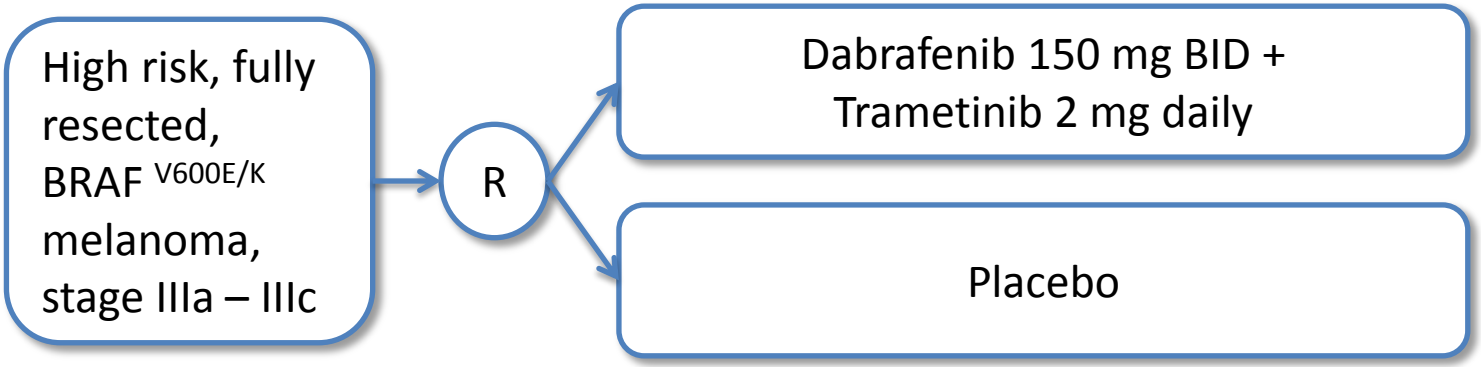
COMBI-d,
Long, ASCO 2014

- Pre-existing BRAF inhibitor induced lesion can also be cleared by the addition of a MEK inhibitor:
  Peters, *Melanoma Res* 2014 & Robert, *Melanoma Res* 2014 (Editorial)



Adjuvant trials with BRAF + MEK inhibitors

- Combination of dabrafenib + trametinib is currently being evaluated in the adjuvant setting: **Combi-AD** / NCT01682083



Duration*:* 1 year (all arms)

Endpoints:

- ***Primary*:** RFS
- ***Secondary*:** OS, DMFS, safety (SCC!), freedom from relapse

Results: Data for primary endpoint expected 07/2015

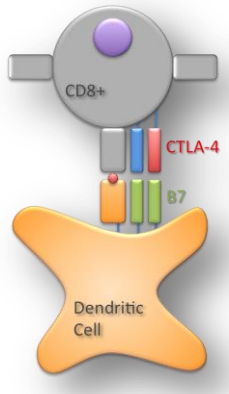
Conclusion

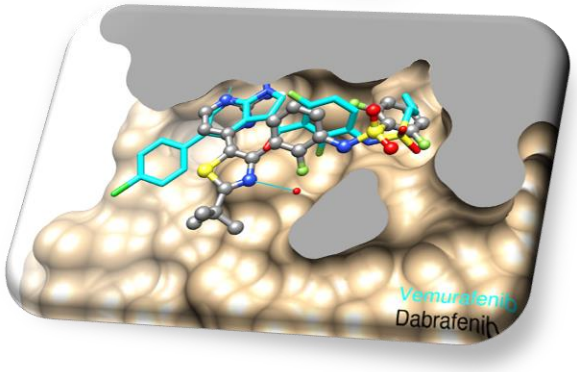
- A new era is starting in the adjuvant setting!

- **Clinical recommendations:**
  - Inclusion in ongoing / upcoming clinical trials!

    - Checkpoint blockade
      - CTLA-4 blockade
      - PD-1 blockade

    - MAPK inhibition
      - BRAF inhibitors
      - BRAF + MEK inhibitors





Thank you
for your attention!