Target therapy in oncologia: nuovi farmaci biologici, meccanismo d'azione, efficacia e gestione per il medico di medicina generale

FARMACI BIOLOGICI E IMMUNOLOGICI NEL MELANOMA

Ordine dei Medici Parma 29 Settembre 2015

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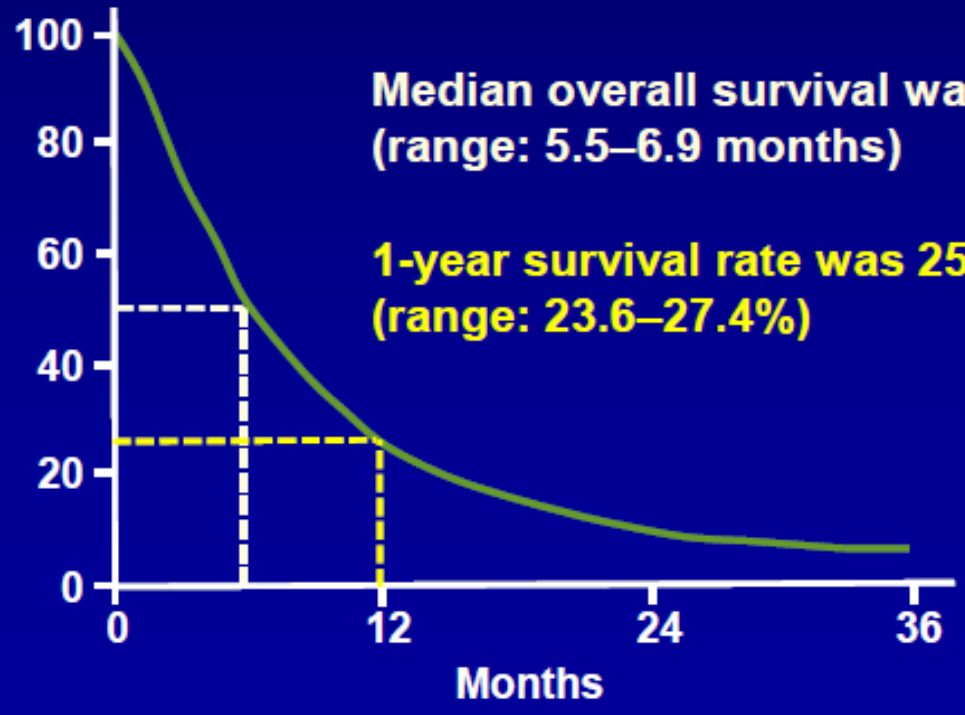
METASTATIC MELANOMA
A NEW ERA

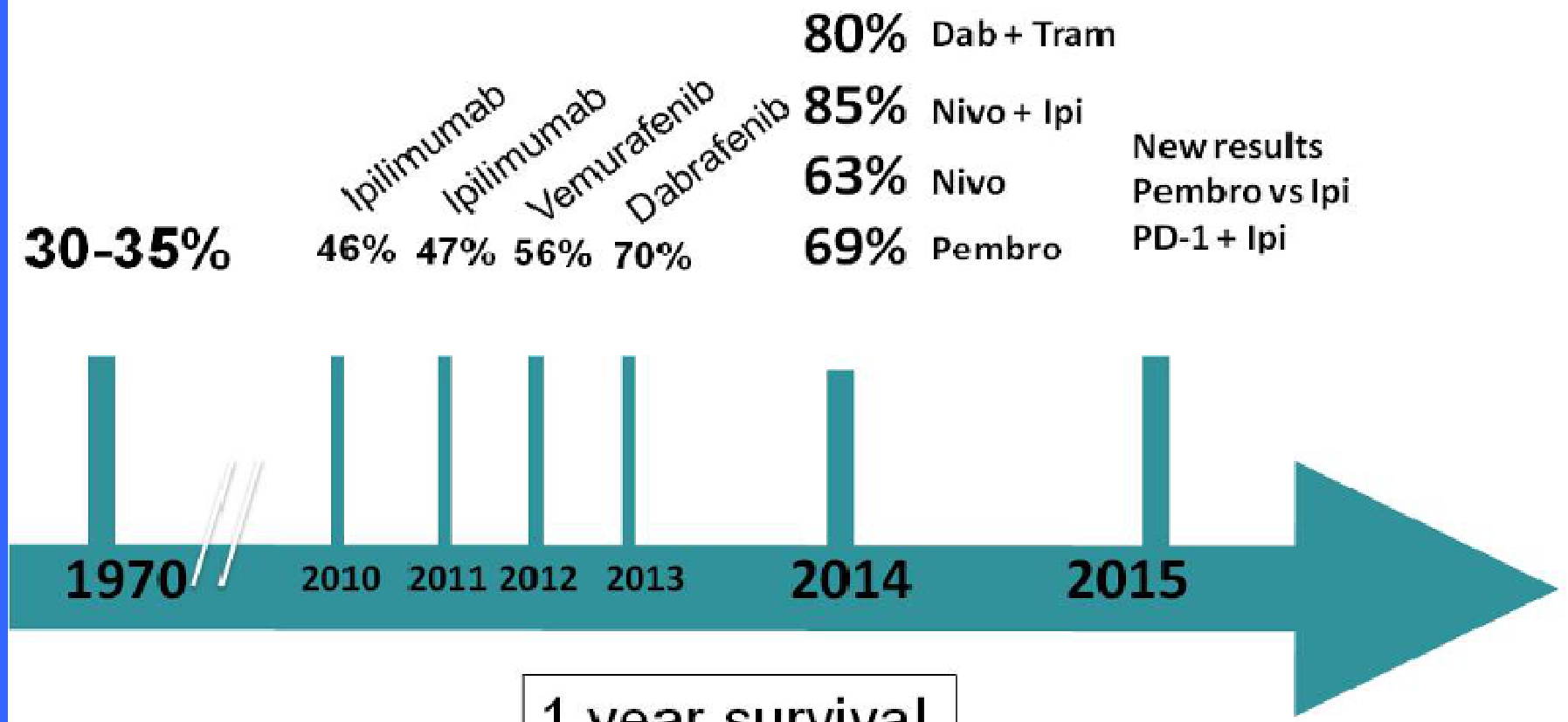
Limited survival outcomes associated with historical treatment options

- Historical data indicate median overall survival for patients with metastatic melanoma of 6 to 9 months
- In a meta-analysis of 42 phase 2 trials in 2,100 patients with metastatic melanoma treated in North America:
  - Prior therapy was not a major covariate of overall survival



Garbe C, et al. *Oncologist* 2011;16:5–24
Kom EL, et al. *J Clin Oncol* 2008;26:527–34

Unprecedented Progress in Treatment of Melanoma



1 year survival

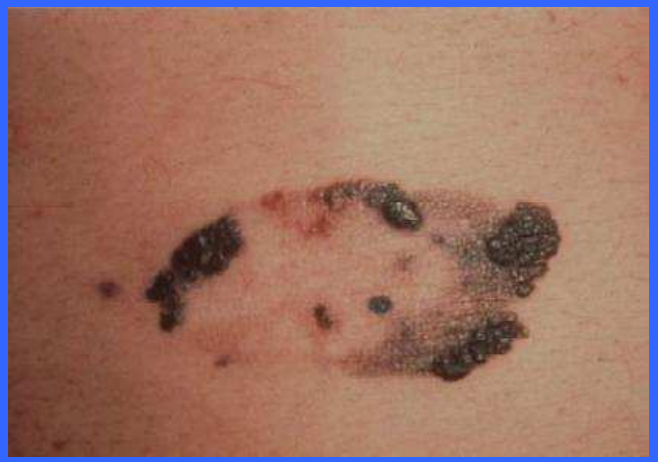
Achieved by clinical trials

Slide courtesy G V Long

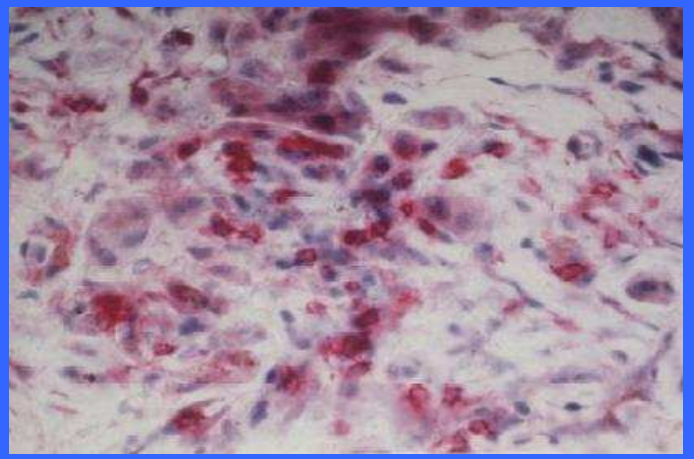
Presented By Lynn Schuchter at 2015 ASCO Annual Meeting

Spontaneous Tumor Regression of Primary Melanomas

- Evidence of regression in 14–50% of primary melanomas
  - Complete spontaneous regression in ~4–15%
- Regressing lesions contain infiltrates of inflammatory cells, providing indirect evidence for an immunological response



Tumor regression



CD8+ infiltrate

Immune Checkpoints

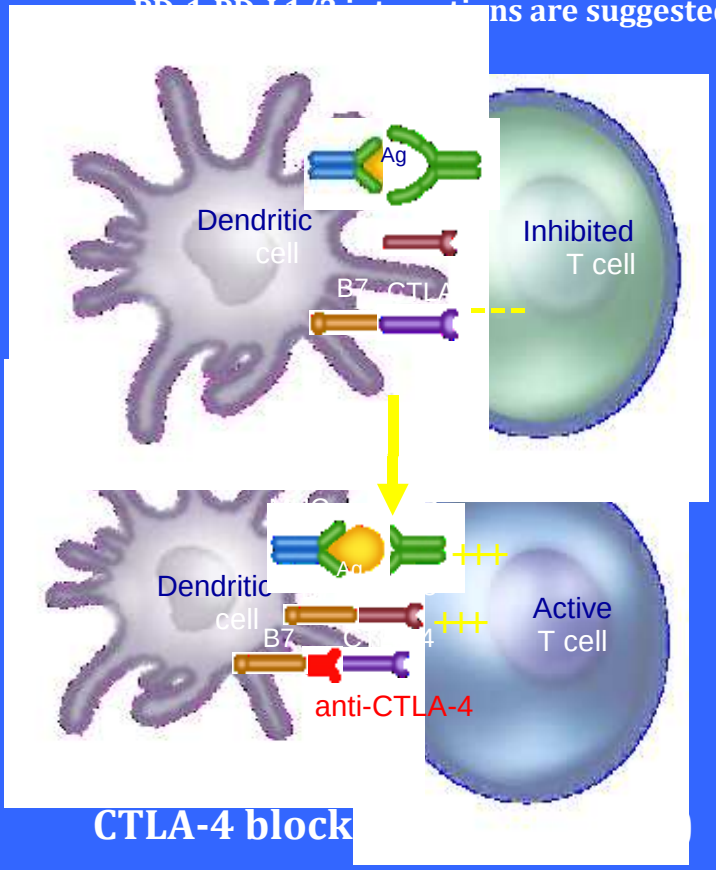
- The amplitude and quality of a T-cell response against cancer is regulated by a balance between costimulatory and inhibitory signals (immune checkpoints).
- PD-1 and CTLA-4 are examples of inhibitory checkpoint receptors expressed on T-cell that can act to inhibit T-cell activity.
- Expression of immune-checkpoint proteins can disrupted by tumors as an important mechanism of immune resistance and immune survillance escape.

CTLA-4 and PD-1 Interactions Occur at Different Anatomic Sites in the Body

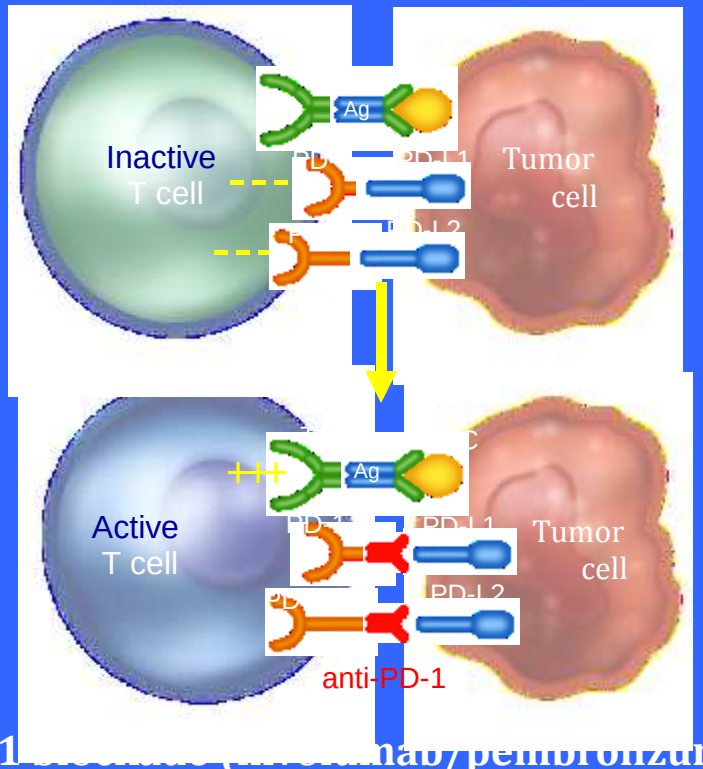
- Reports suggest that expression of the ligands for CTLA-4 and PD-1 differ resulting in spatial differences in where these interactions are occurring in the body1,2

CTLA-4:B7 interactions between T cells and APCs are postulated to occur primarily in the lymph nodes

ns are suggested to occur specifically within peripheral sites



CTLA-4 block



PD-1 b nab/pembrolizumab)

Topalian SL, et al. 2012.

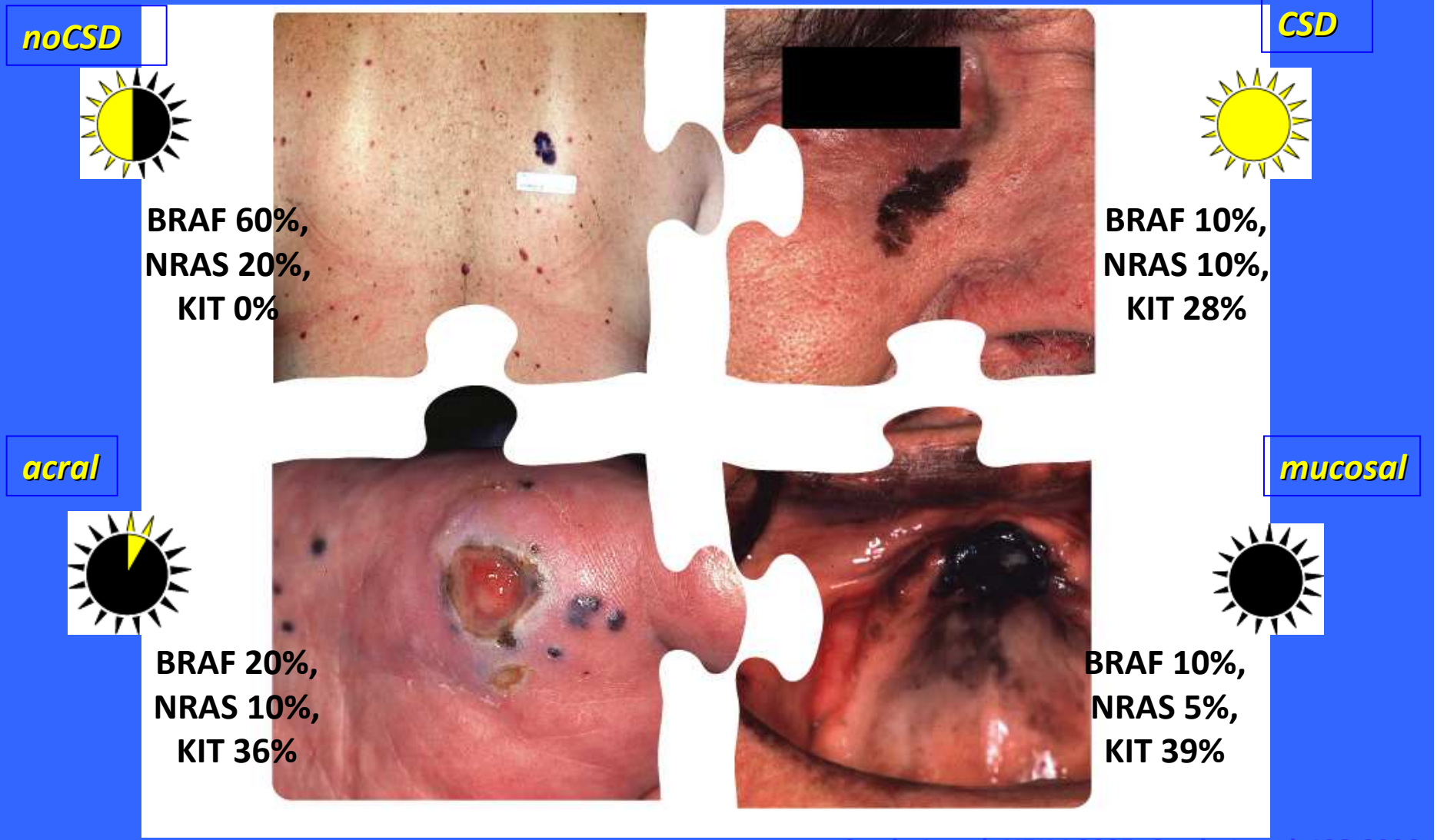
Traditional classification

- Histopathological classification
  - *Superficial spreading melanoma* (SMM)
    most common, around 75%
  - *Nodular melanoma*
    15%, direct vertical growth phase
  - *Acral lentiginous melanoma*
    10%, including glabrous and mucosal
  - *Lentigo maligna melanoma*
    5%, in elderly, chronically sun-exposed area

Prognostic variables

- The only reliable parameters
  - Depth of primary lesion
  - The presence or absence of ulceration
  - Mitoses
  - Lymphocytic infiltration
  - Lymph node metastasis
- The prognostic value of the standard pathological evaluation can be improved by *integration with molecular data*

Molecular classification of melanoma



Curtin J et al. NEJM 2005, Curtin J et al. JCO 2006

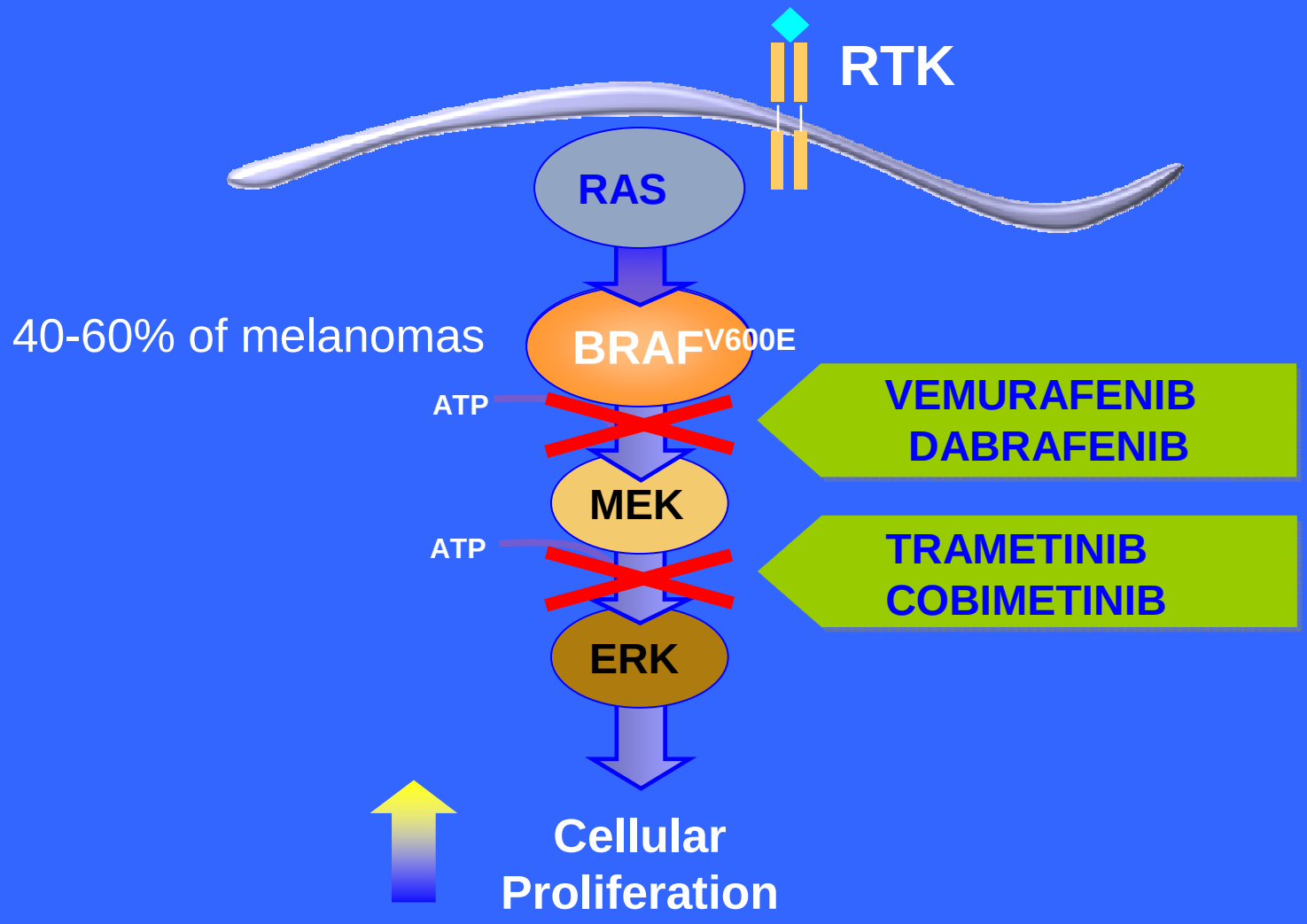
Advanced melanoma: different approaches according to mutational status

BRAF$^{V600E/K}$
c-KIT
^{Q61}*NRAS*

NRAS wt
BRAF wt

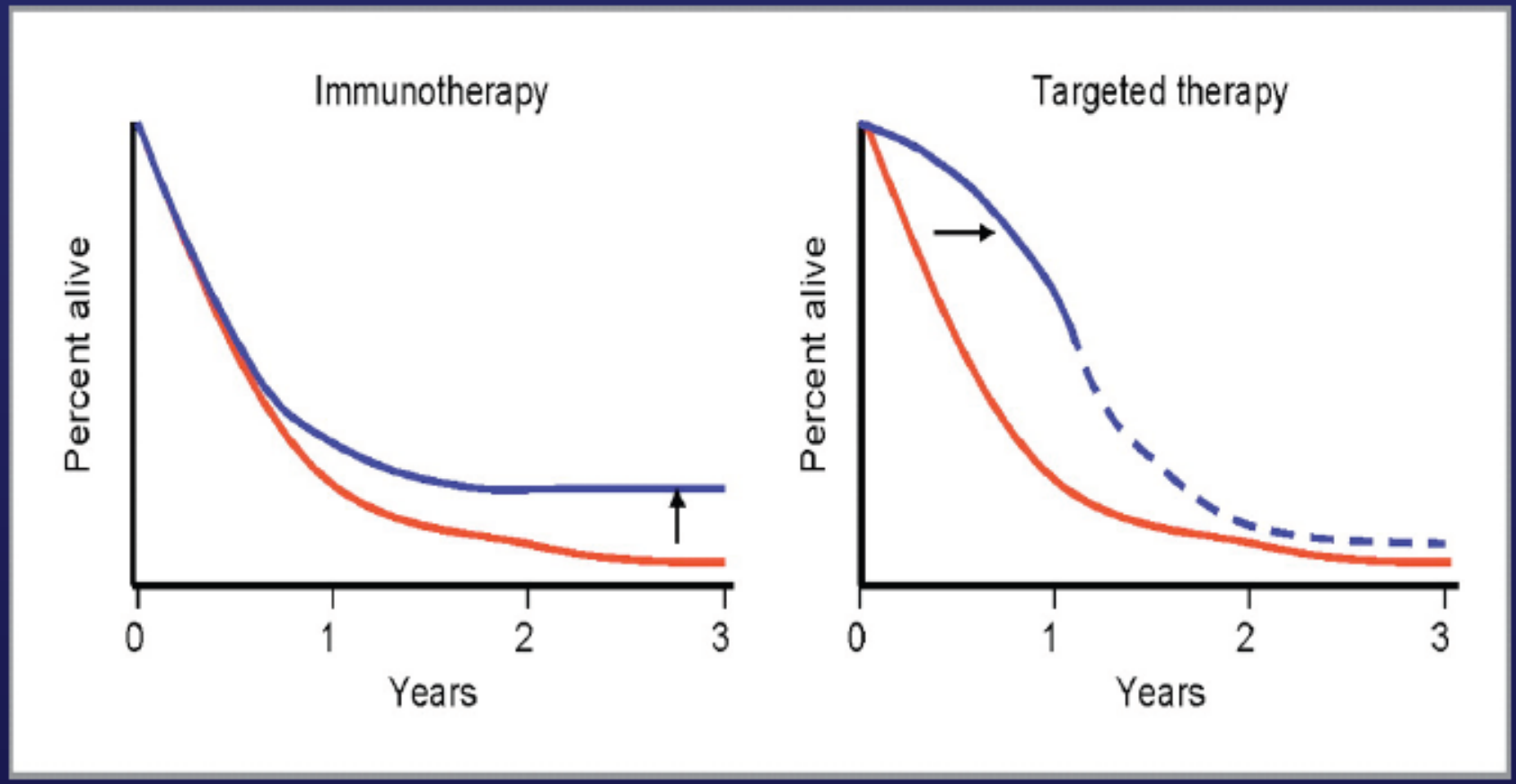
Ascierto P, et al. J Transl Med. 2012 May 2;10(1):83

MAPK PATHWAY: RAS/BRAF



Chapman P. et al Abs LBA4 ASCO 2011

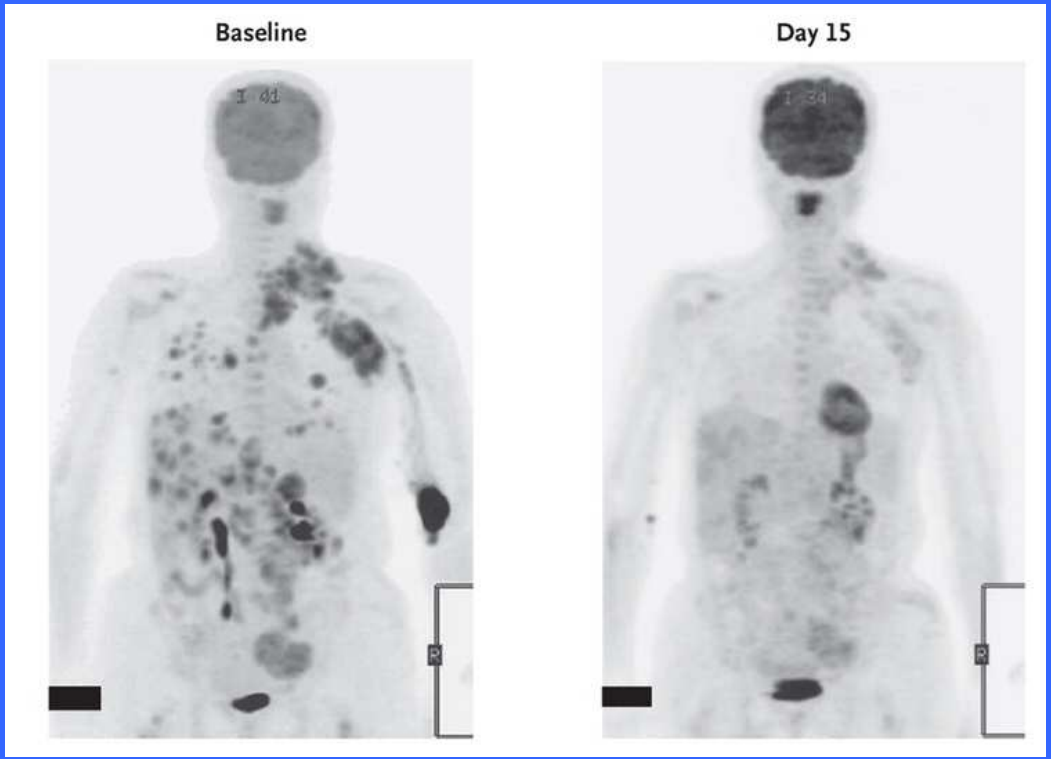
Effects of Immunotherapy and Targeted Therapy on Melanoma survival curves



Ribas A et al. *Clin Cancer Res* 2012;18:336-341

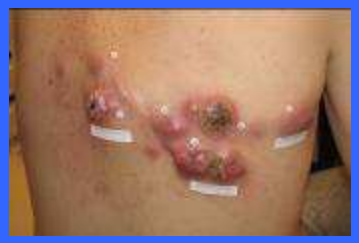
Vemurafenib: Phase I – Early FDG-PET Responses

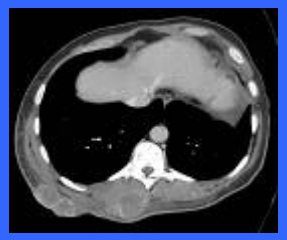
- Patients underwent FDG-PET at baseline and on Day 15 of the first 4 weeks of therapy
- A marked decrease in tumor uptake of FDG was observed at Day 15 after Vemurafenib treatment



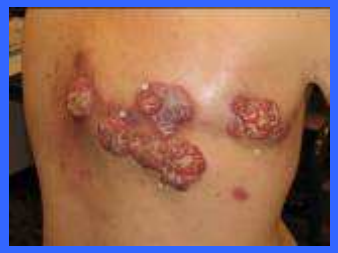
Flaherty KT, *et al. N Engl J Med* 2010;363:809–19.

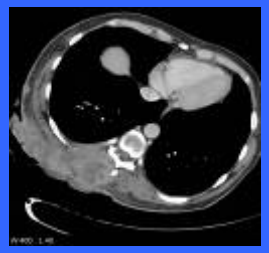
Immunotherapy Response: Patient Example



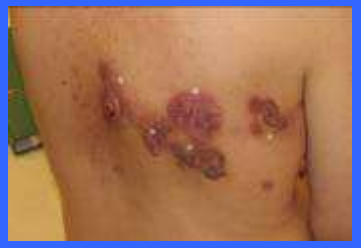


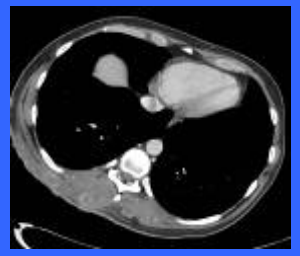
Screening





Week 12
Initial increase in total tumour burden (mWHO PD)

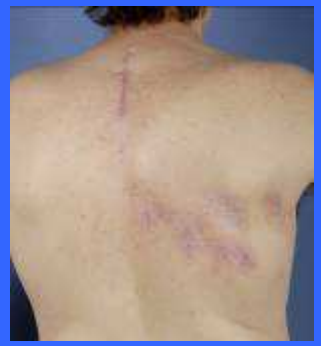


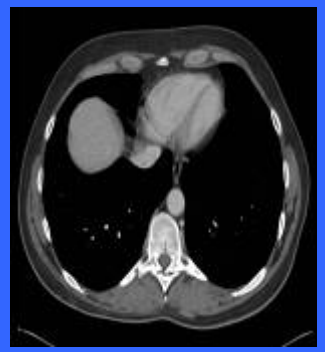


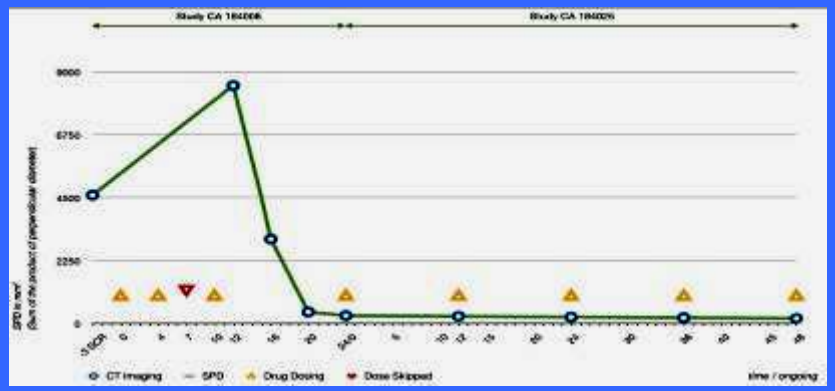
Week 16
Responding

Courtesy of K. Harmankaya, Vienna

Week 96
Durable & ongoing response without signs of IRAEs







Harmankaya et al. Presented at EADO 2009, Vienna, Austria

Le nuove molecole

Farmaci immunoterapici

Ipilimumab
Nivolumab
Pembrolizumab

Farmaci target

Vemurafenib
Dabrafenib
Trametinib
Cobimetinib

Tossicità

Farmaci immunoterapici

Rash e prurito
Colite
Endocrinopatia
Uveite
Tossicità epatica
Polmonite interstiziale

Farmaci target

Tossicità cutanea
Carcinoma spinocellulare
Cheratoacantomi
Artralgia
Febbre

Management della tossicità

Farmaci immunoterapici

Educazione del paziente
Trattamento precoce
Terapia steroidea
Terapia sostitutiva nelle endocrinopatie

Farmaci target

Educazione del paziente
Fotoprotezione
- ✓ Controlli dermatologici
- ✓ Antipiretici

CONCLUSIONI

- **Diverso meccanismo d'azione → diversa tossicità**

<u>diversa gestione degli effetti collaterali</u>

- **Sensibilizzazione del paziente, della famiglia e del curante**

- **Presa in carico multidisciplinare (MMG, oncologo, patologo, dermatologo, radiologo, chirurgo, endocrinologo, gastroenterologo, oculista..)**