CITADELLE CHATEAU ROUGE SAINTE ROSALIE

VOTRE SANTÉ, NOTRE MÉTIER

# Mélanome métastatique thérapies ciblées/immunothérapie

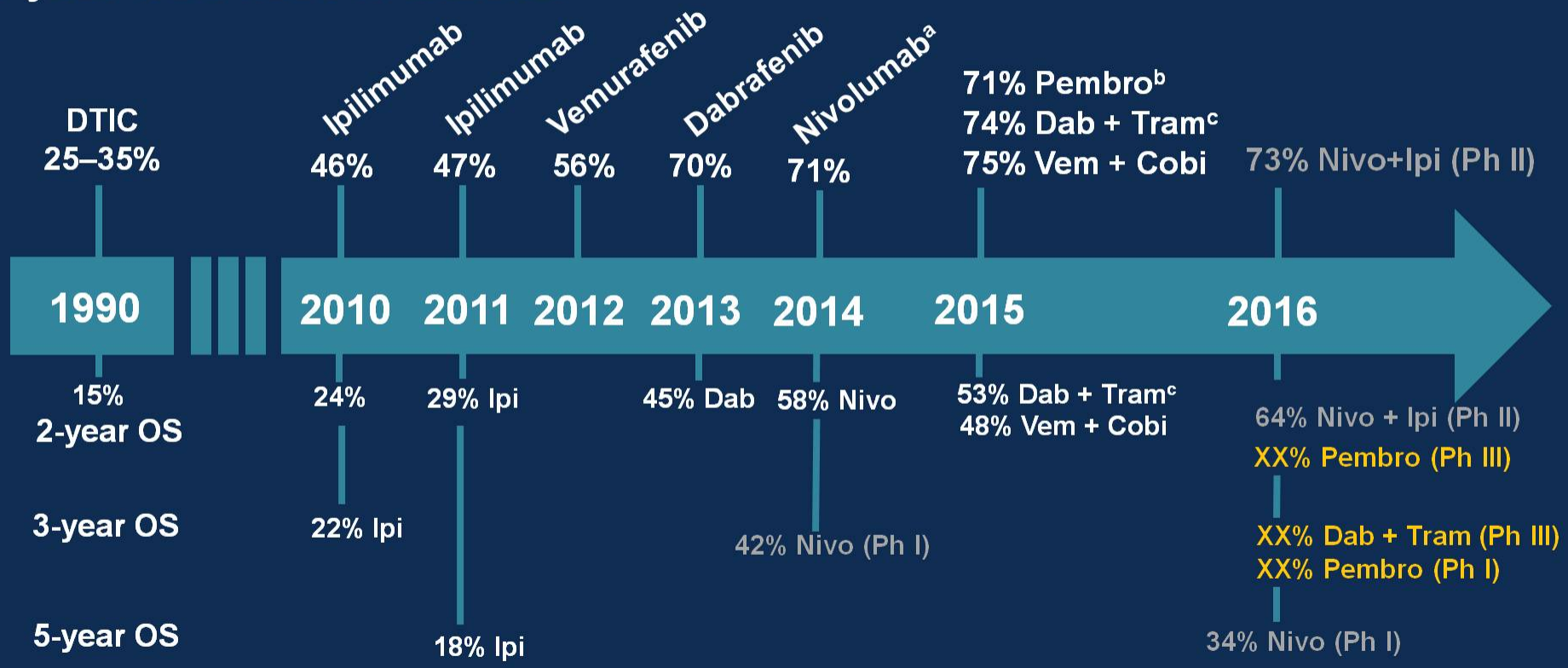
Dr Jean Paul Salmon Pr Guy Jerusalem

CHR Liège, le 09 mars 2017

VOTRE SANTÉ, NOTRE MÉTIER

# Overall Survival Metastatic Melanoma

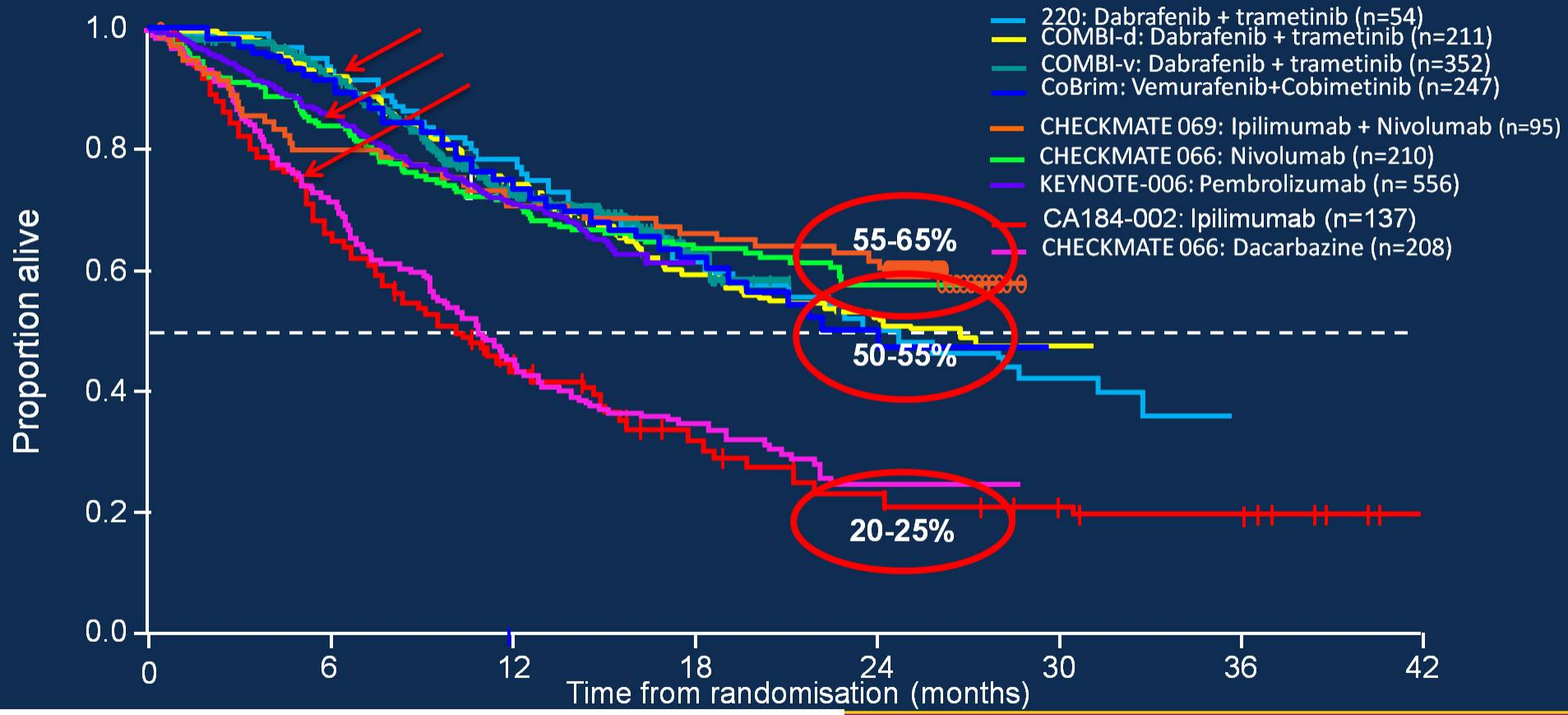
## 1-year OS Phase III Studies




a BRAF wt only; b Pooled pembrolizumab Q2W and Q3W 10mg/kg; c Pooled Dab + Tram data; Cobi=cobimetinib; Dab=dabrafenib; Ipi=ipilimumab; Nivo=nivolumab; Pembro=pembrolizumab; Tram=trametinib; Vem=vemurafenib.

Presented by Georgina V. Long

# Overall Survival in Melanoma



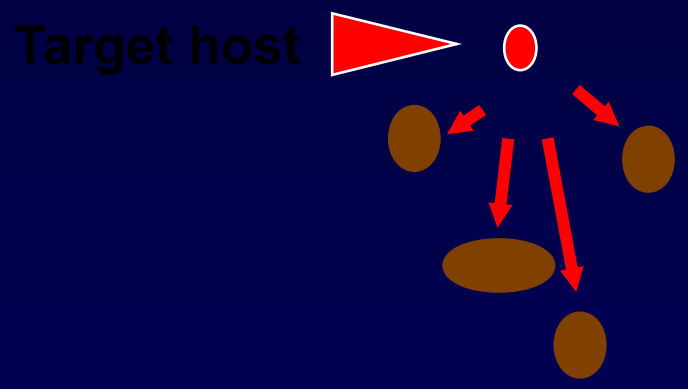

1. Hodi FS, *et al. N Engl J Med* 2010; 2. Long GV, *et al JCO* 2016; . 3. Long GV, *et al. Lancet* 2015;
4. Robert C, *et al. N Engl J Med* 2015; 372:2521-2532; 5. Robert C, *et al. N Engl J Med* 2015;
6. Robert C, *et al. N Engl J Med* 2015; 7. Atkinson V et al SMR 2015; 8. Padstow AACR 2016

Presented by Georgina V. Long

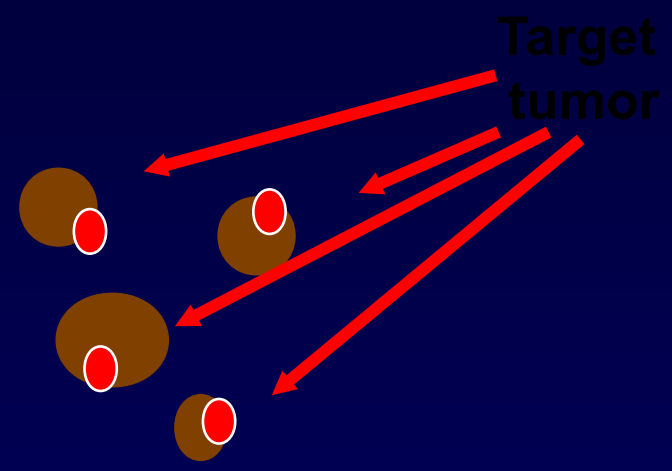
Presented By Georgina Long at 2016 ASCO Annual Meeting

# Two Paradigms for Advancing the Therapy of Metastatic Melanoma

Immunotherapy




Targeted Therapy




Ribas A.

# Les traitements ciblés

Klik om het opmaakprofiel van de modelondertitel te bewerken

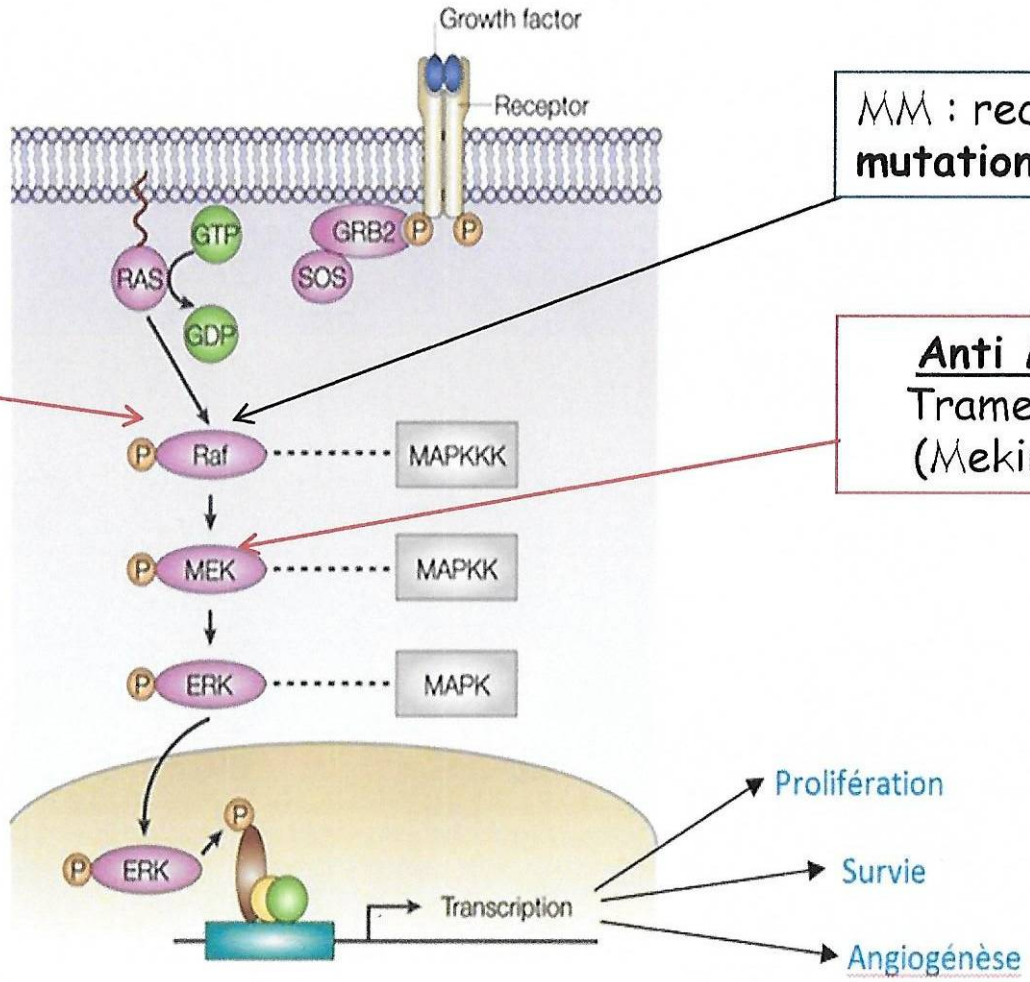
# ÉRAPIES CIBLÉES ANTI BRAF ET ANTI MEK

anisme d'action : Voie RAS / MAP kinases

i BRAF
urafenib
oraf ®)
orafenib
inlar ®)

MM : recherche
**mutation BRAF V600E**

**Anti MEK**
Trametinib
(Mekinist)



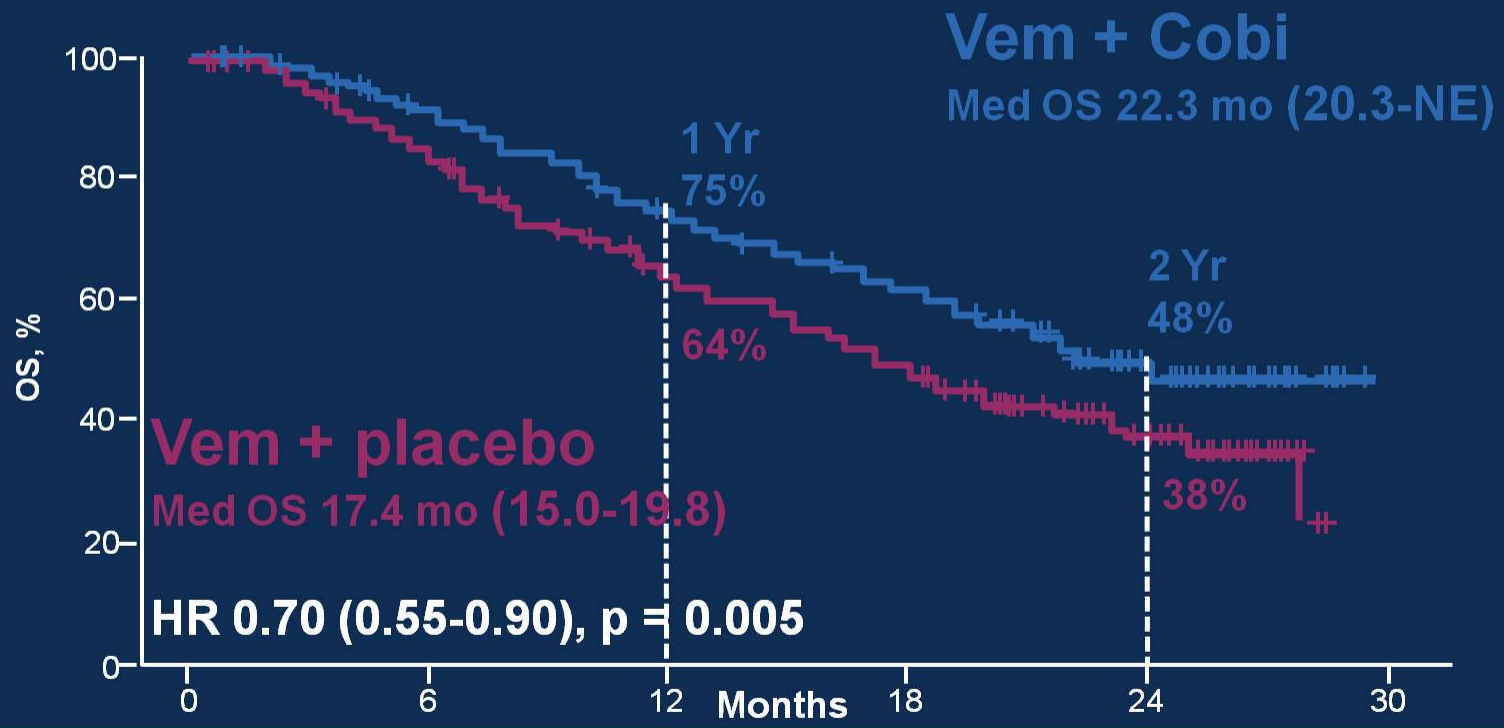
# Effets secondaires

- Cutanés:
  - induction de tumeurs cutanées malignes (kératoacanthomes, carcinomes épidermoïdes, nvx mélanomes)
  - anomalies / prolifération kératinocytaire (papillomes, syndromes main-pied, éruptions type kératose pilaire ou dyskératose acantholytique, kystes induits…
  - réactions de photosensibilité

# Effets secondaires (2)

- Arthralgies
- Asthénie
- Pyrexie sous dabrafenib
- Digestifs: nausées, pancréatite, hépatite
- Oculaires sous cobimetinib
- Cardiologiques (QT, FE, HTA)
- Hématologiques
- Pulmonaires (pneumonie interstitielle)

# coBRIM: Overall Survival

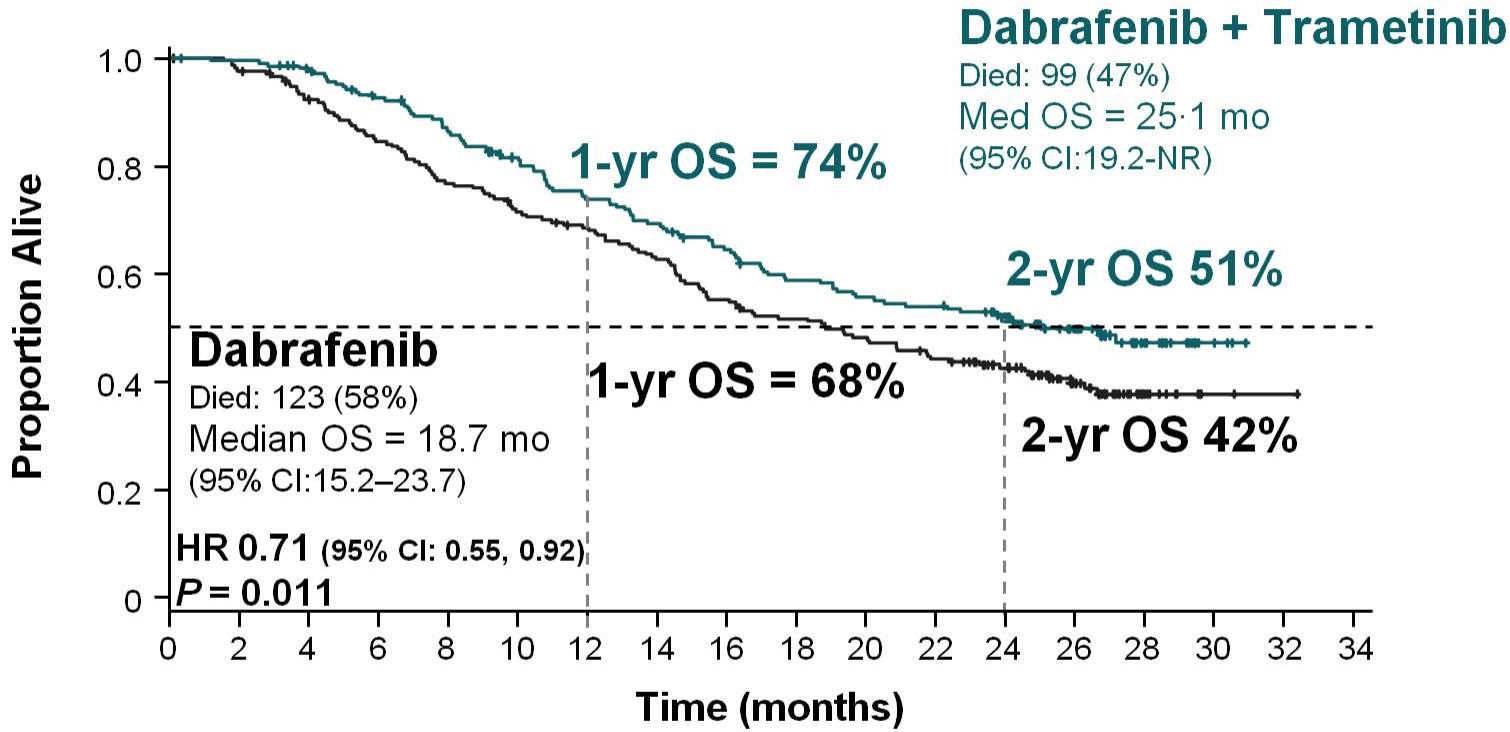






Data cutoff, August 28, 2015.; Median F/u 18.5 mo
Atkinson V et al SMR 2015

# COMBI-d: Overall Survival



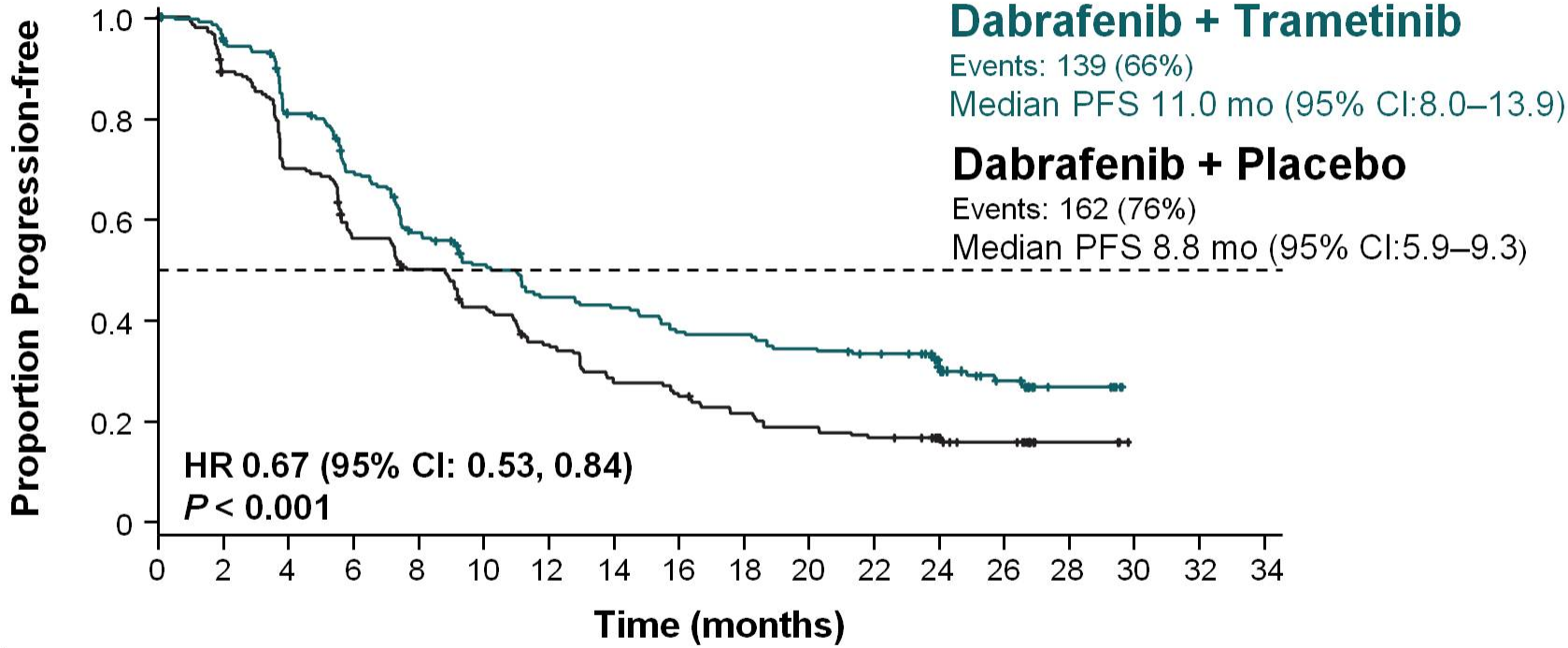

| Number at risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabrafenib + trametinib | 211 | 208 | 200 | 187 | 174 | 159 | 144 | 135 | 124 | 112 | 106 | 103 | 88 | 53 | 21 | 3 | 0 | 0 |
| Dabrafenib + placebo | 212 | 206 | 191 | 175 | 159 | 147 | 138 | 127 | 111 | 104 | 95 | 88 | 70 | 42 | 10 | 2 | 1 | 0 |

Dabrafenib+Trametinib med follow up 20 mo (range 0-30 mo); Dabrafenib med follow up 16 mo (range 0-32 mo).



Long GV, et al. *Lancet* epub 31 May 2015.

# COMBI-d: Progression-free Survival



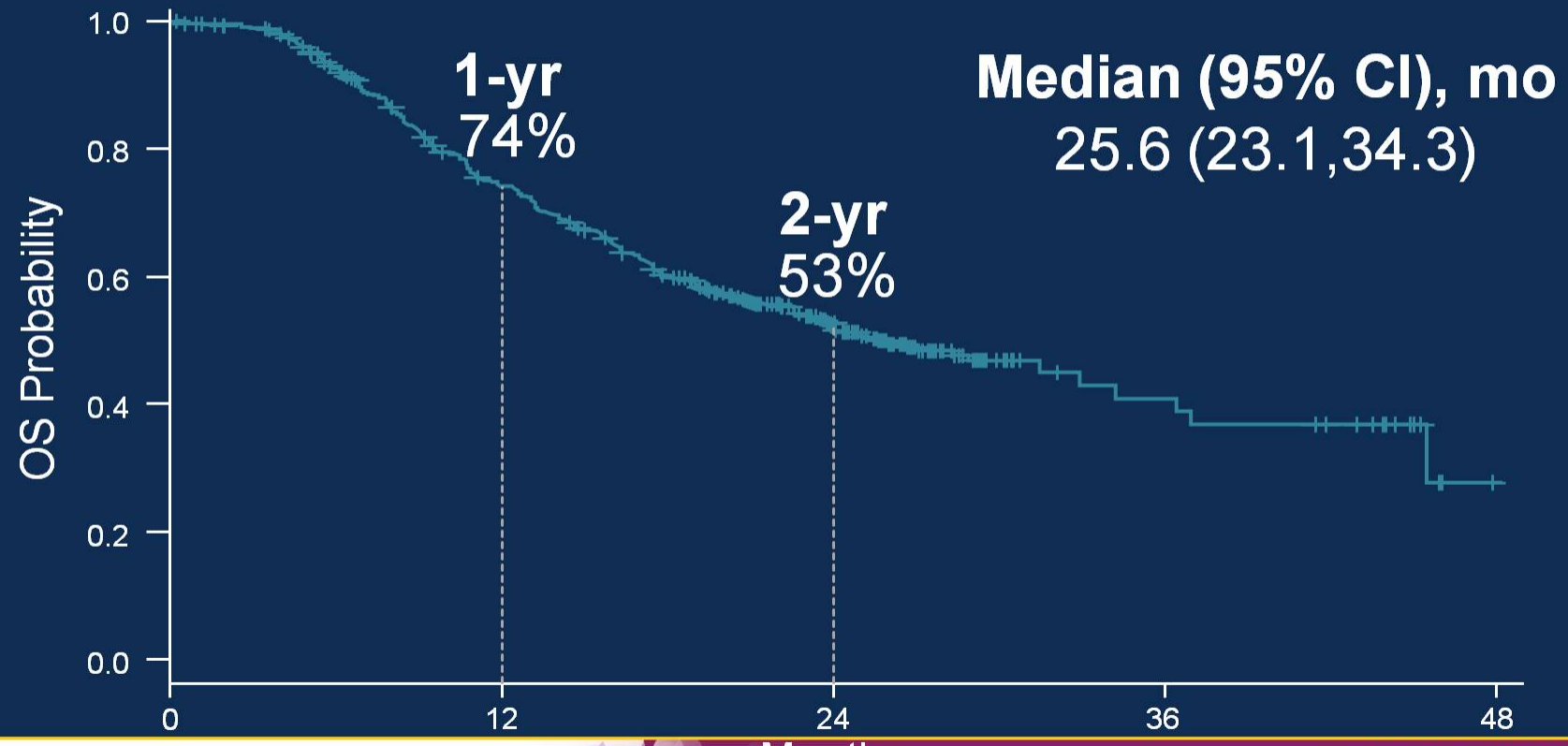

| Number at risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabrafenib + trametinib | 211 | 196 | 164 | 137 | 125 | 96 | 84 | 80 | 71 | 70 | 65 | 61 | 38 | 26 | 6 | 0 | 0 | 0 |
| Dabrafenib + placebo | 212 | 177 | 139 | 109 | 96 | 81 | 65 | 52 | 47 | 40 | 35 | 31 | 19 | 16 | 4 | 0 | 0 | 0 |



Long GV, et al. *Lancet* epub 31 May 2015.

# Pooled Overall Survival: Dabrafenib + Trametinib

## Three Randomised Trials (N = 617)







1. Long GV, *et al JCO* 2016; 34:871;
2. Long GV, et al. *Lancet*. 2015;386:444-45;
3. Robert C, et al. ECC. 2015;[abstract 3301].

# RECIST RESPONSE: BRAFi + MEKi

| BRAFi+MEKi | ORR | CR | DoR | Med PFS | Med OS |
|---|---|---|---|---|---|
| COMBI-d | 69% | 16% | 12.9mo | 11.0mo | 25.1mo |
| COMBI-v | 66% | 17% | 13.8mo | 11.4mo | 25.6mo |
| COBRIM | 70% | 16% | 12.98mo | 12.25mo | NR |
| Encoraf + Binimet* | 75% | 13% | - | 11.3mo | - |

* Phase 1 and all doses.

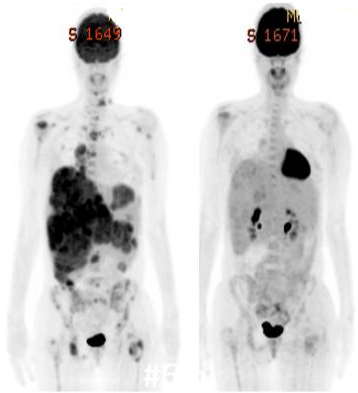
**No other therapy in melanoma has shown a better ORR**

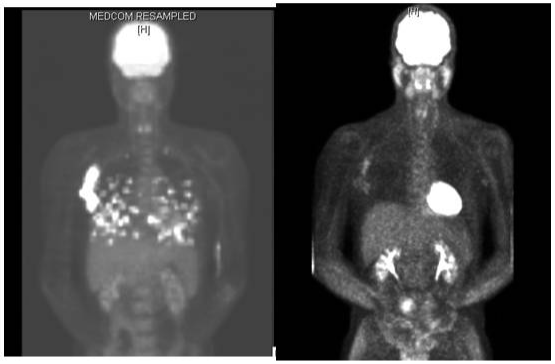


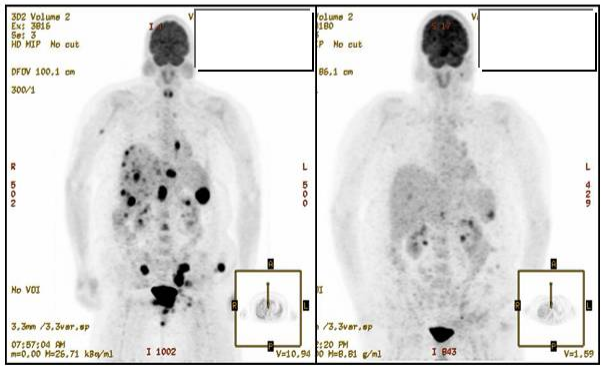


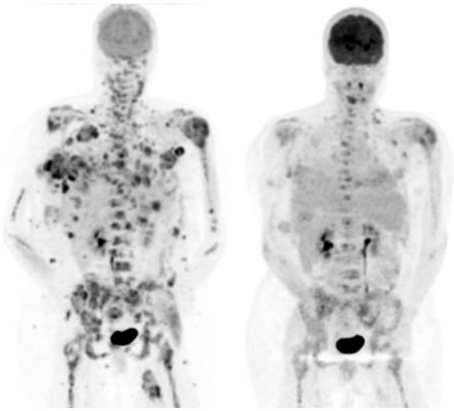
Long GV et al Lancet 2015; Robert et al ECC 2015; Larkin ASCO 2015; Sullivan ASCO 2015

# PET Scans at Baseline and Day 15 on vemurafenib



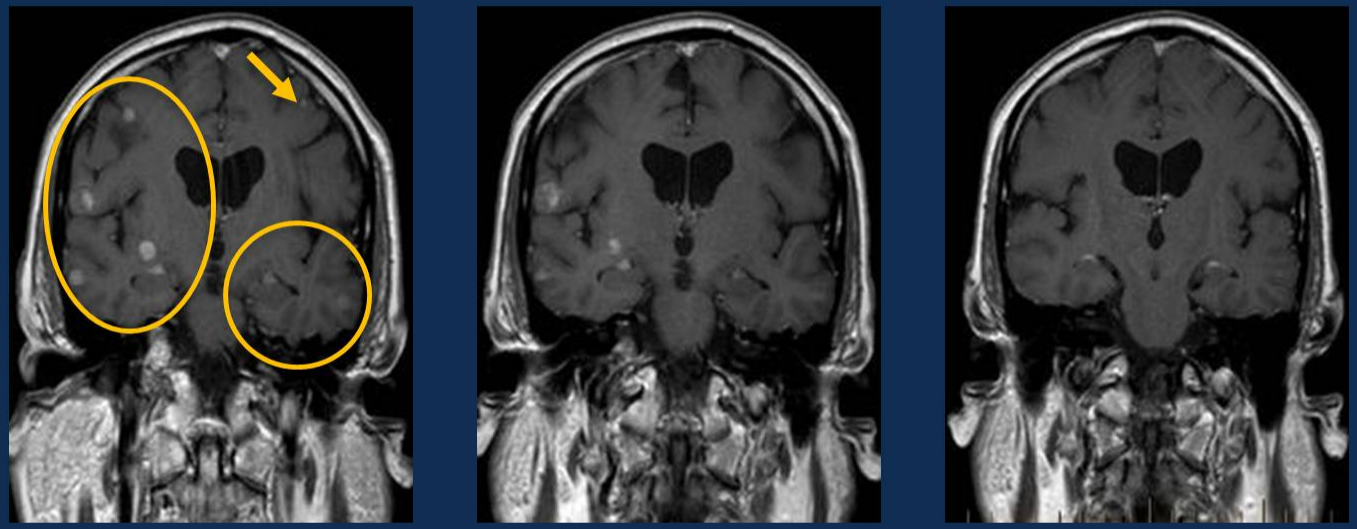





Flaherty KT et al. ASCO 2009

# BRAF Inhibitor: Response in Brain



Baseline | Week 4 | Week 10

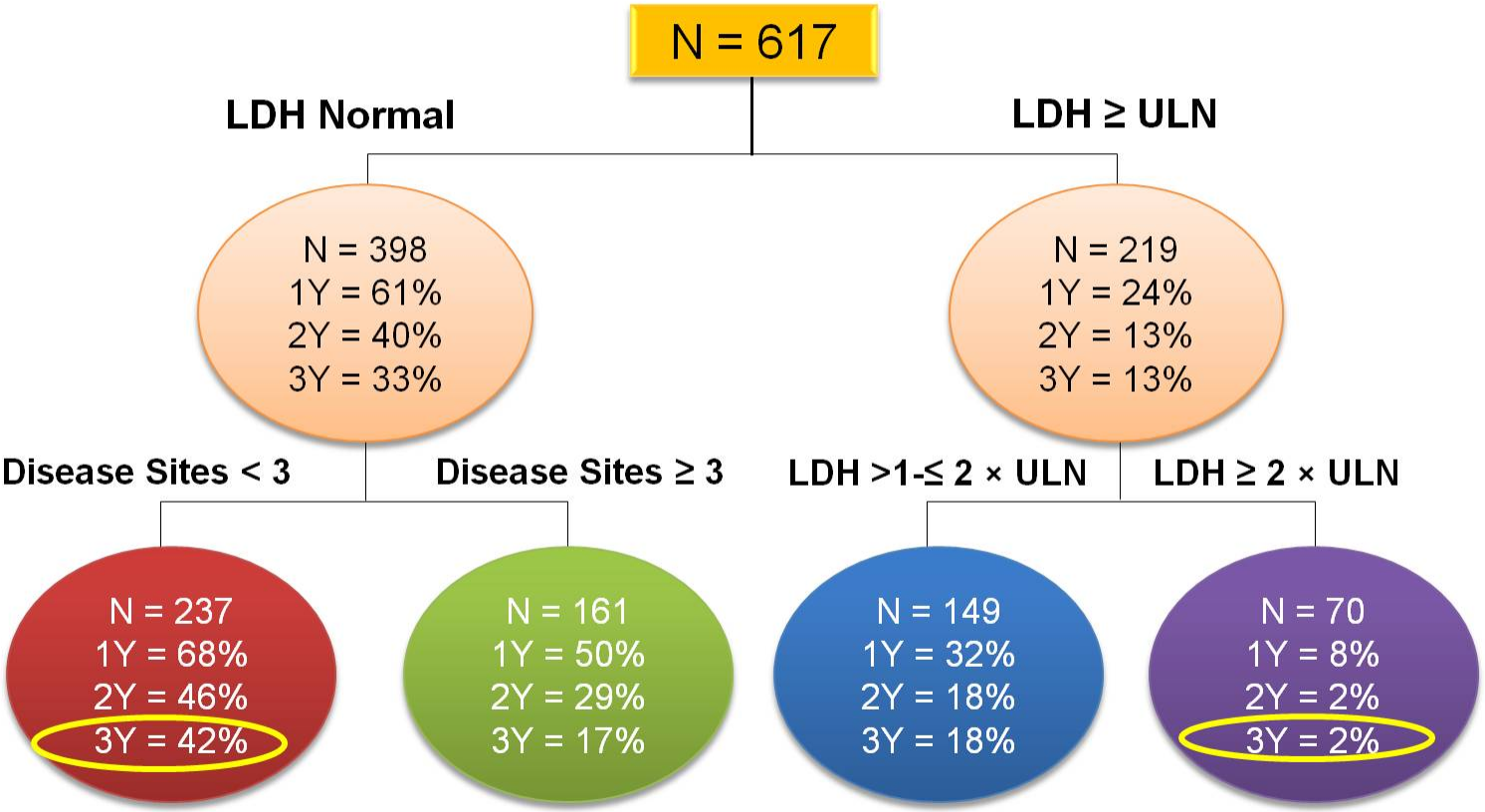
**Dabrafenib**




Presented by Georgina V. Long

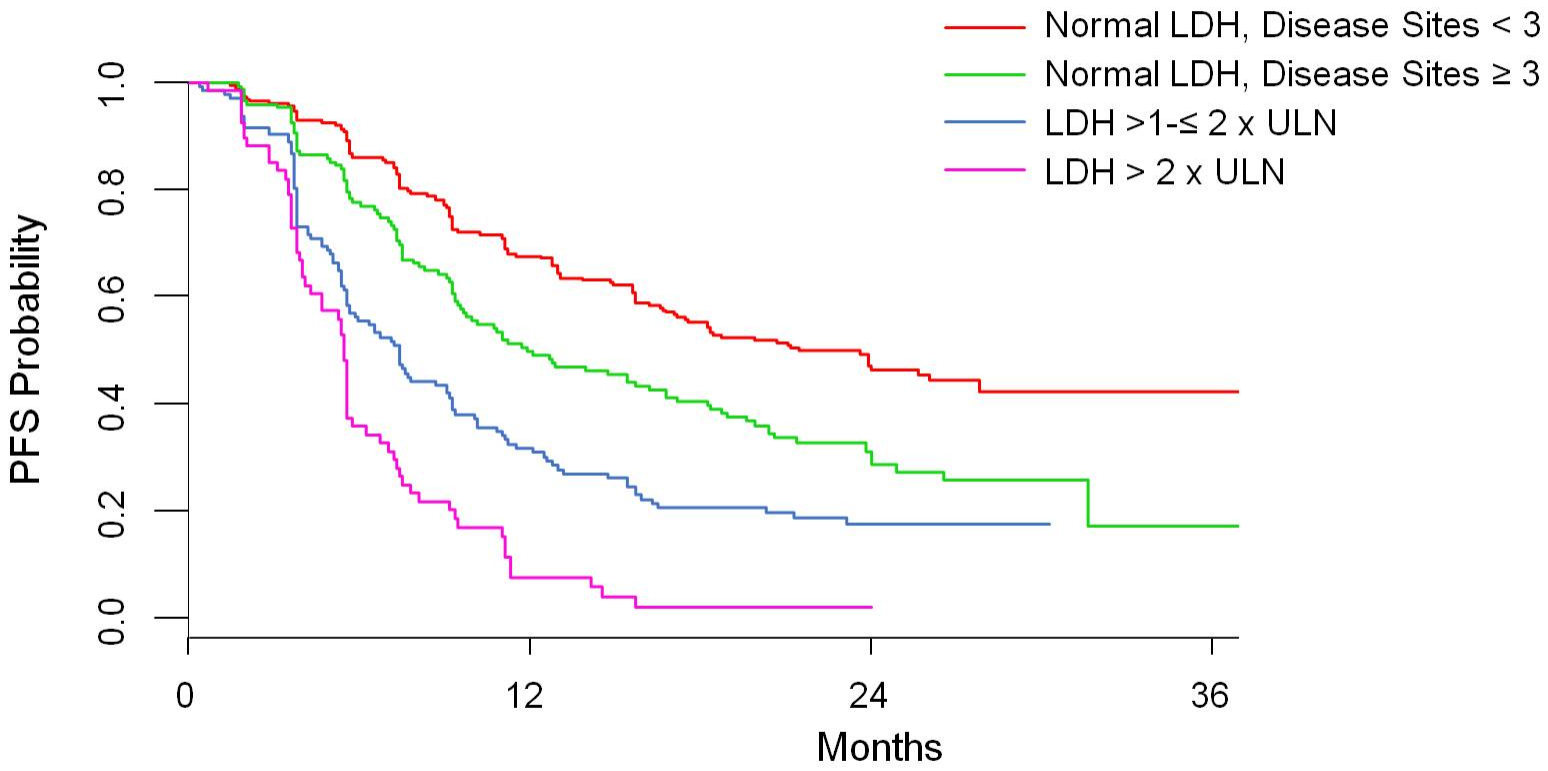
Long GV et al. *Lancet Onc.* 2012.
Falchook-Long. *Lancet.* 2012.

# Four Baseline Factors Influenced PFS[a]



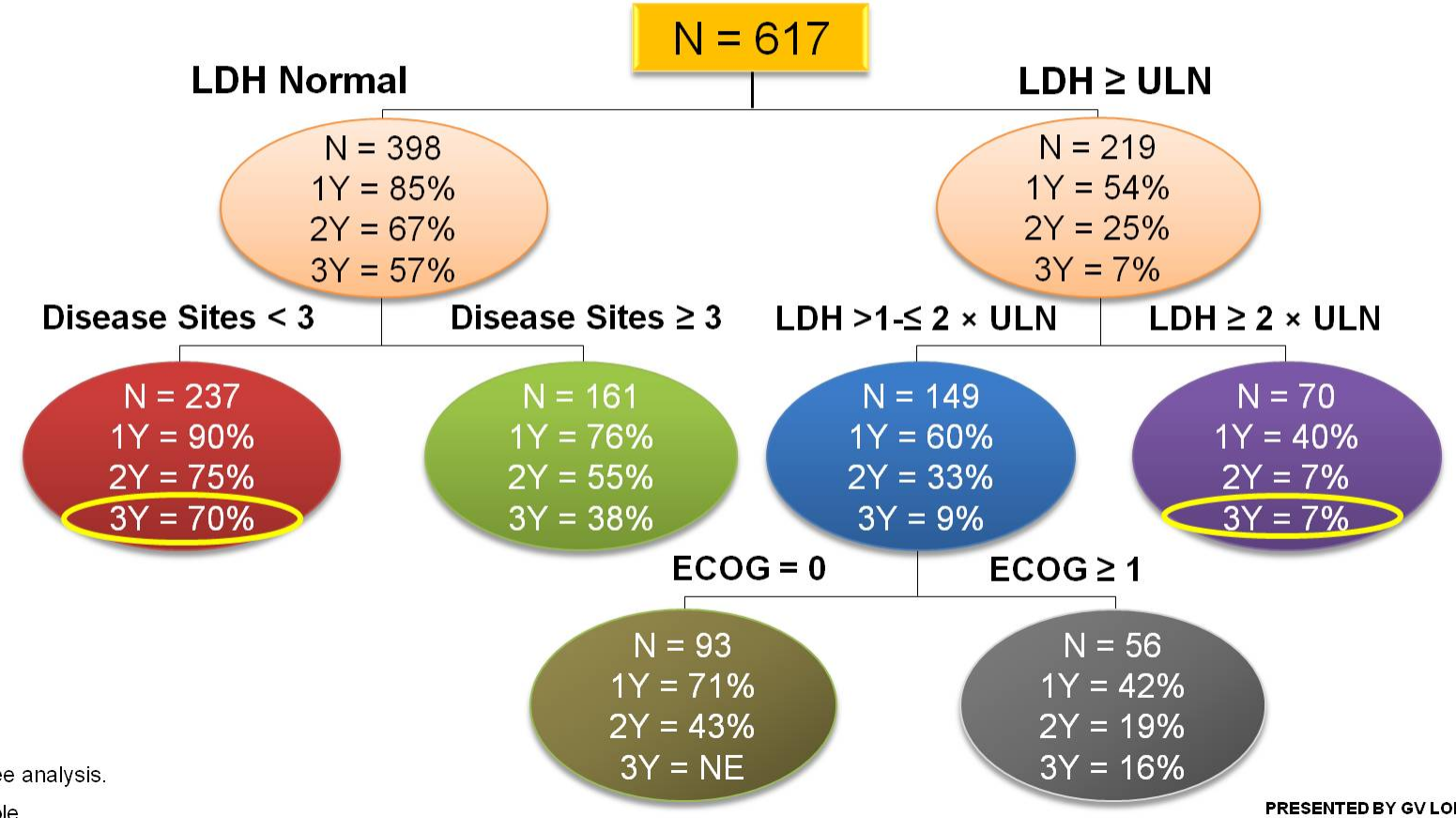

[a] Regression tree analysis.

# PFS by LDH and Number of Disease Sites[a]




[a] Factors identified by the regression tree analysis.

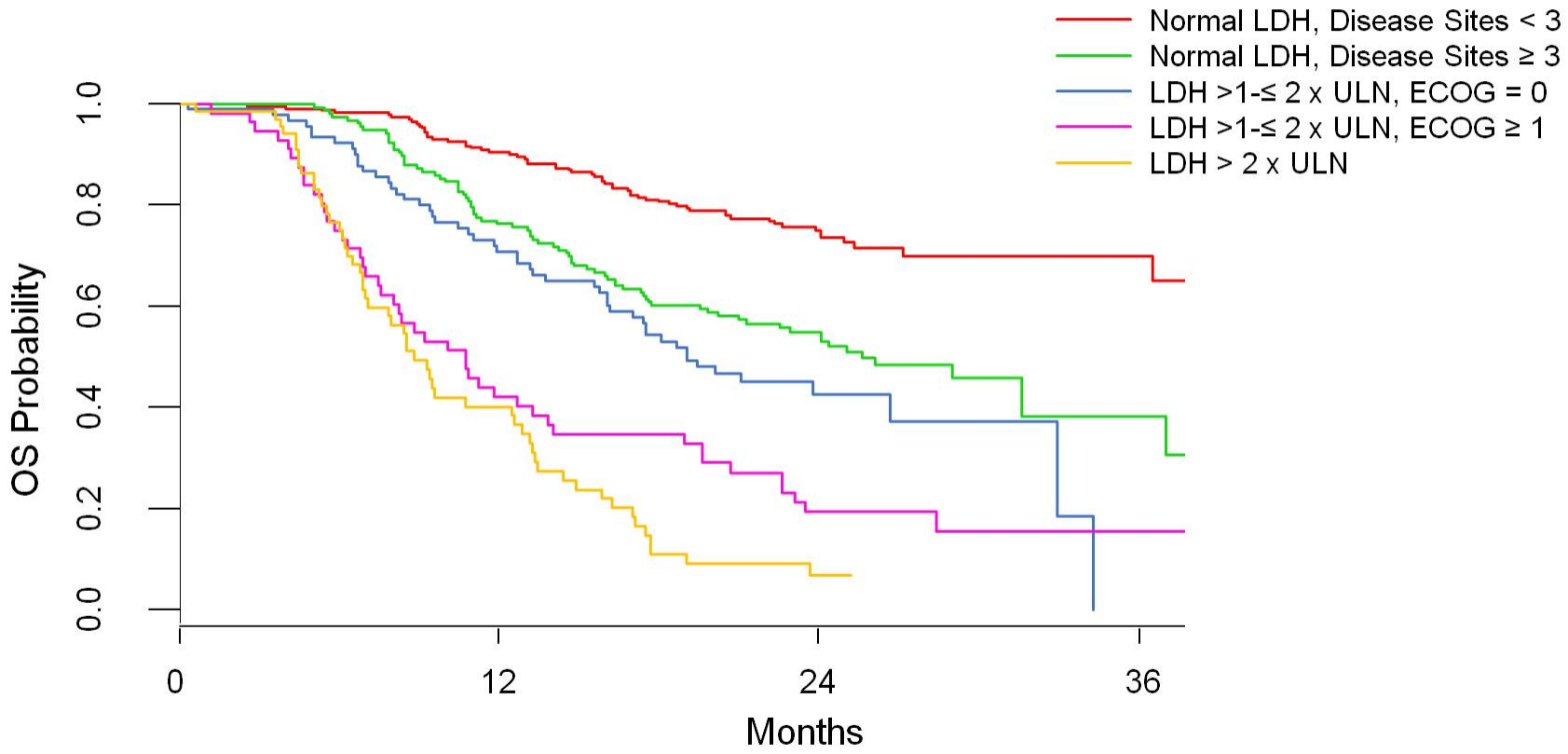
# Five Baseline Factors Influenced OS[a]




[a] Regression tree analysis.

NE, not estimable.

# OS by LDH, Number of Disease Sites, and ECOG[a]




[a] Factors identified by the regression tree analysis.

# Conclusions:

- **Les combinaisons anti BRAF + anti MEK permettent un contrôle précoce de la maladie**

- **Les thérapies ciblées produisent la réponse la plus durable dans les tumeurs les moins évolutives / les moins hétérogènes**

- ***Besoin d'identifier un groupe dont le pronostic serait meilleur sous anti BRAF/anti MEK en première intention***

- **L'immunothérapie reste une option après les traitements anti BRAF/anti MEK**

# L’immunothérapie

Klik om het opmaakprofiel van de modelondertitel te bewerken

2 - Is There Space for Immunotherapy - Soria.pdf - Adobe Reader

Fichier Edition Affichage Fenêtre Aide

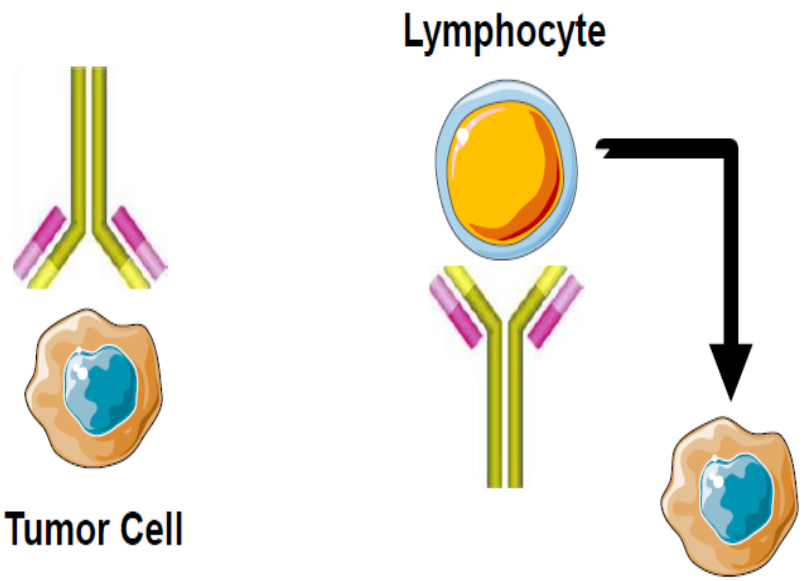
10 / 22 75,6% Outils Commentaire

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

UNIVERSITÉ PARIS SUD

# Paradigm Shift in Cancer Therapy

| Historic Paradigm: Targeting Tumor Cells | New Paradigm: Targeting Immune Cells |
| --- | --- |




Courtesy A Marabelle

FR 10:01 17/12/2015

Soria, Prime

2 - Is There Space for Immunotherapy - Soria.pdf - Adobe Reader

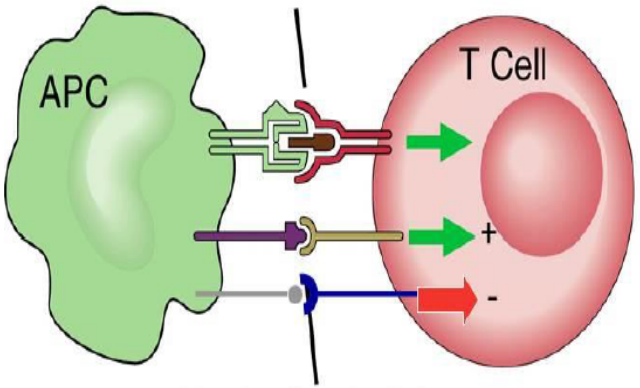
Fichier Edition Affichage Fenêtre Aide

13 / 22 75,6% Outils Commentaire

# What Is an Immune Checkpoint?

## T-cell activation

Signal 1: Antigen recognition




Signal 2: Co-stimulation

- **There are positive and negative second signals**

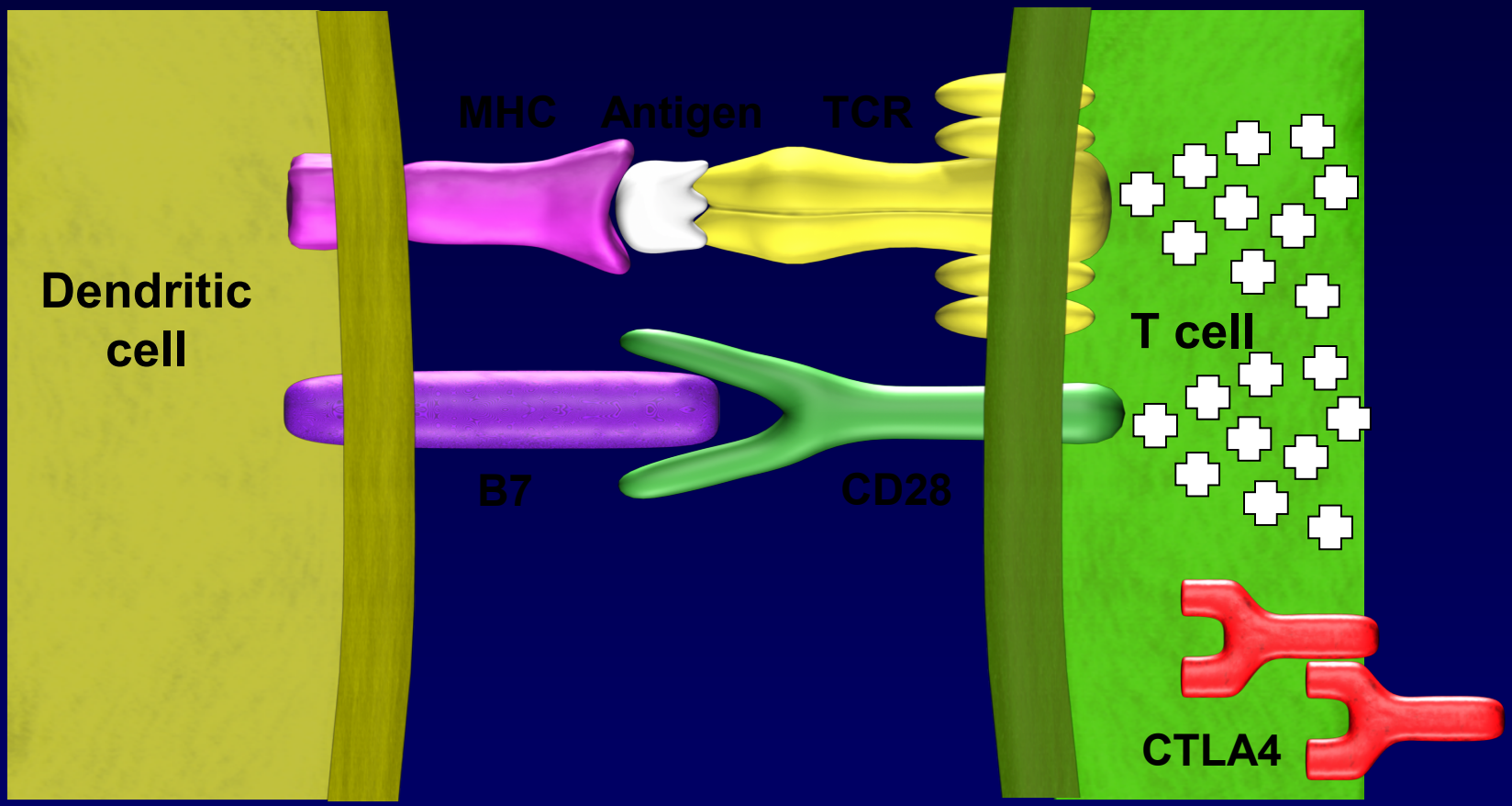
➔ ***But the concept is not limited to T cells (NK cells, macrophages)***

**Sharpe A. Presented at: 2013 American Society of Clinical Oncology Annual Meeting; May 31 - June 3, 2013: Chicago, Illinois.**

FR 10:06 17/12/2015

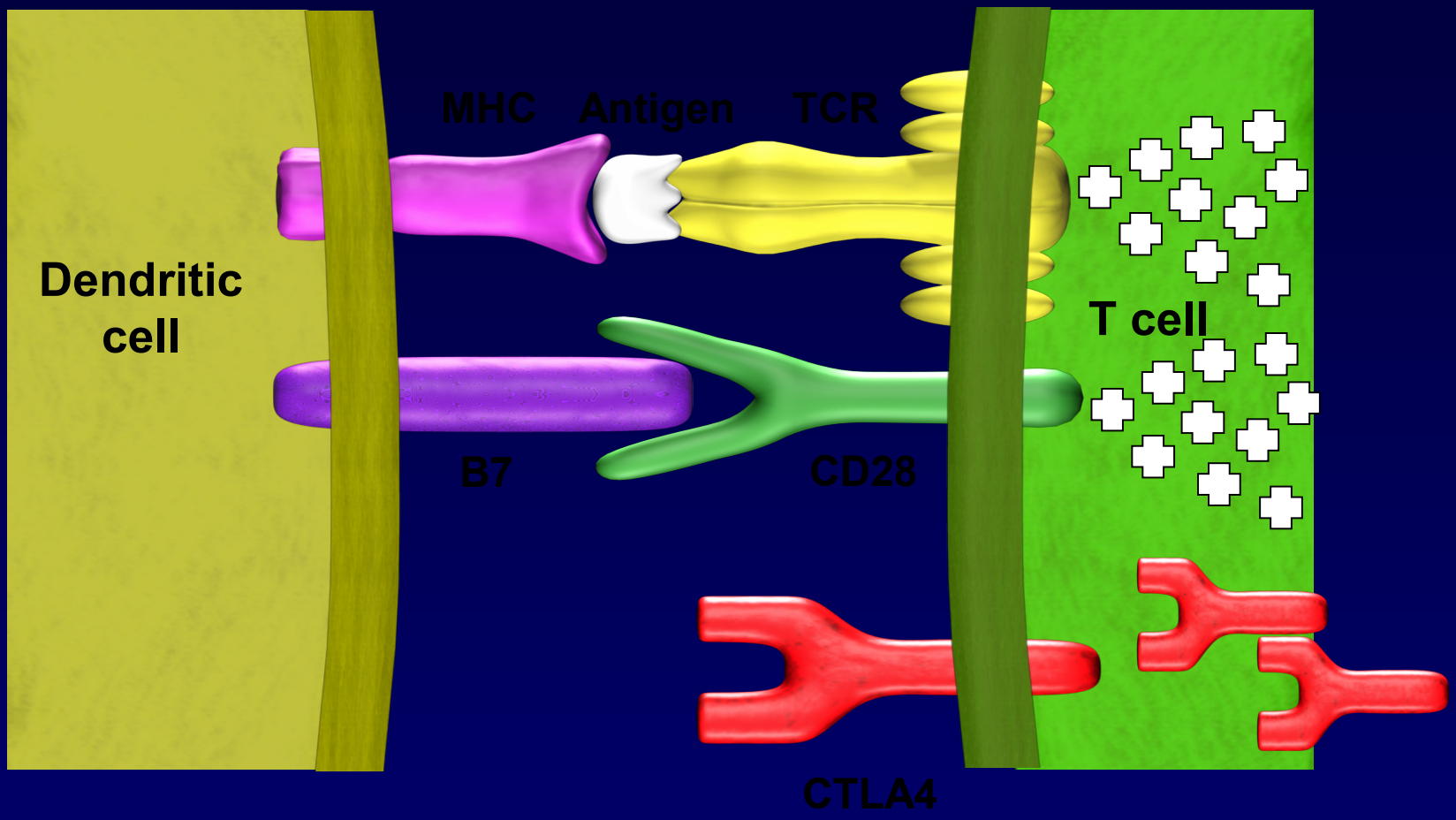
Soria, Prime Oncology, Chicago, 2015

# T Cell Activation by TCR and Co-stimulation Through CD28



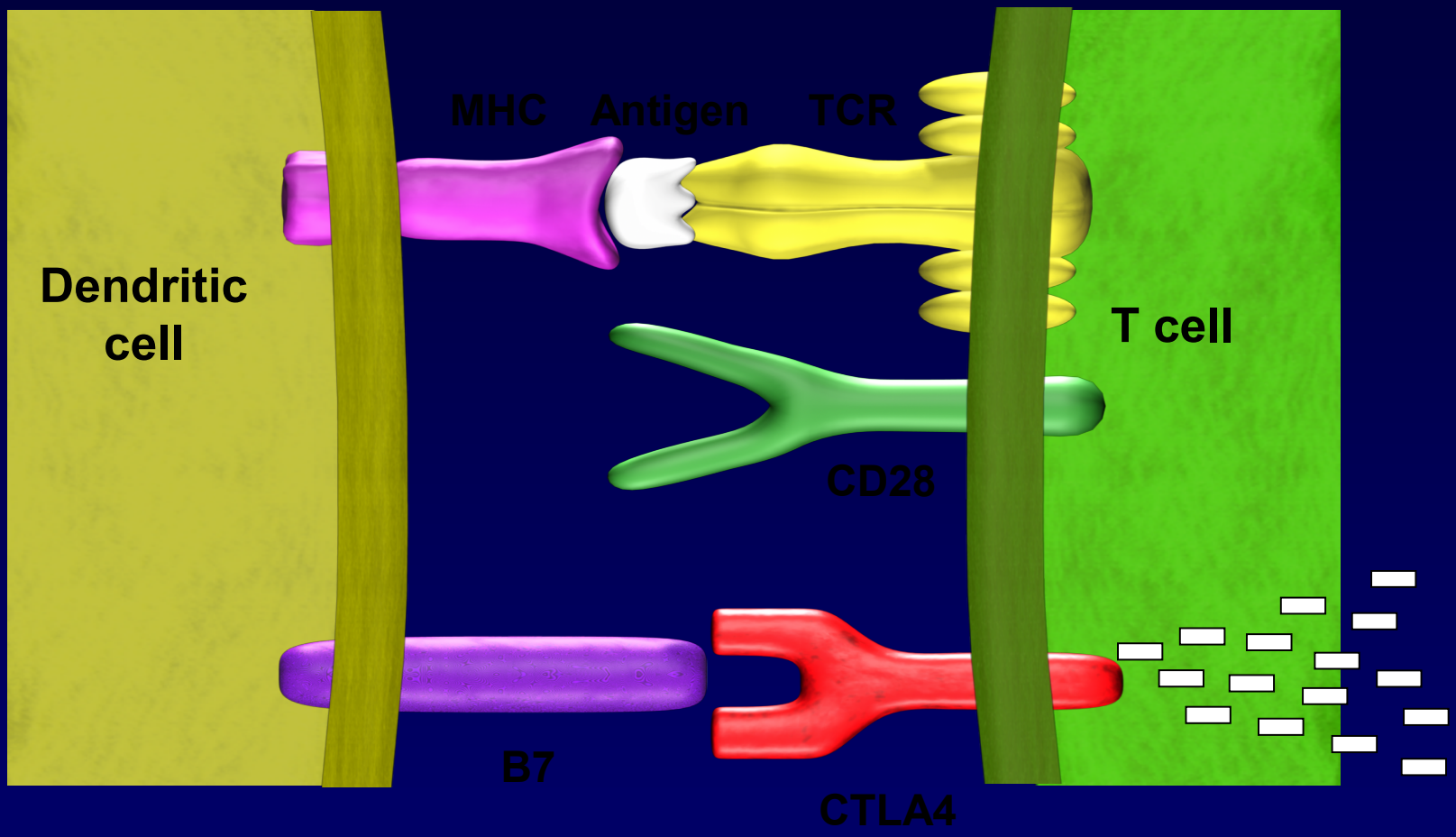

Byun T.

# CTLA4 Receptors Are Up-Regulated Following T-Cell Activation



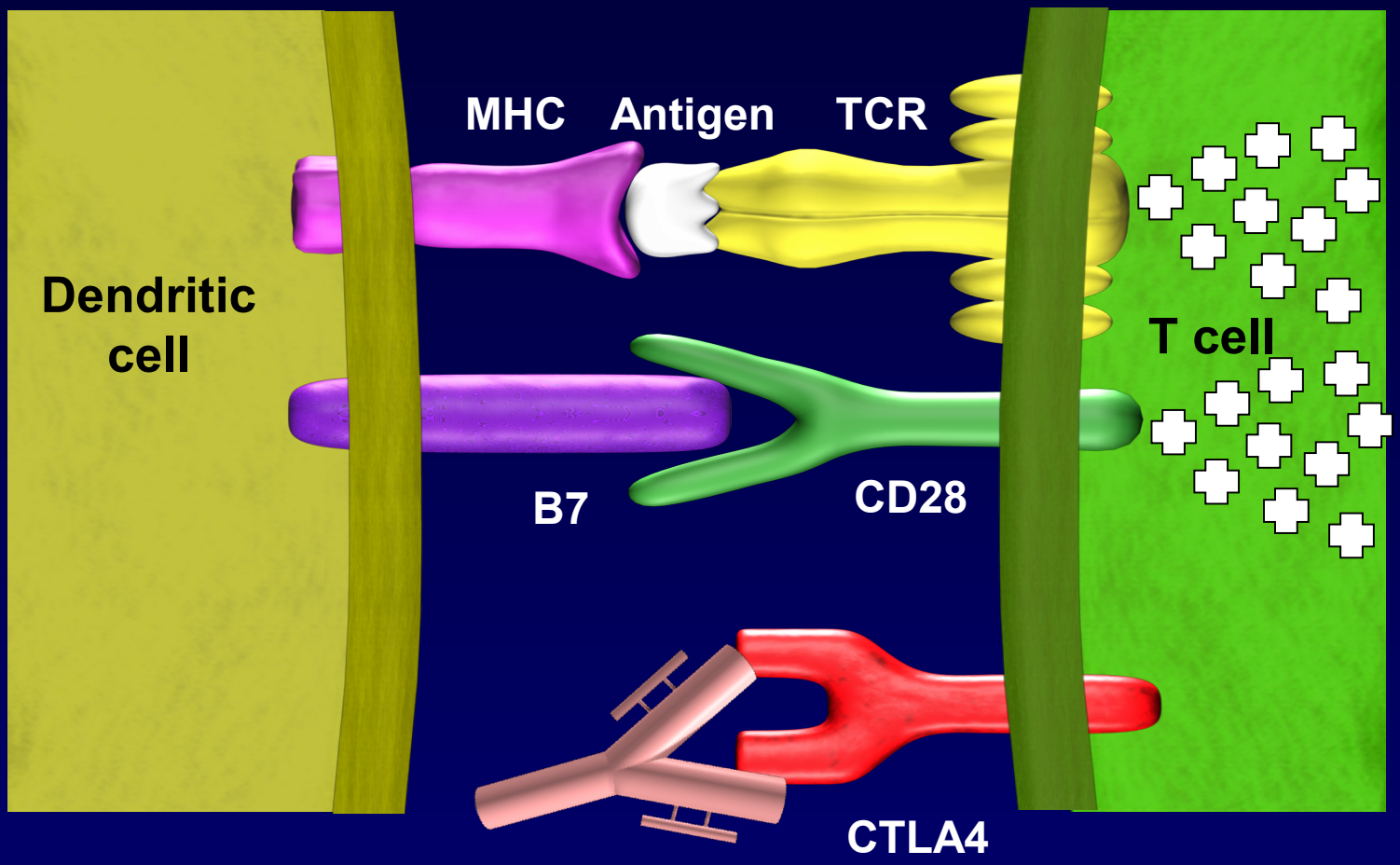

Byun T.

# CTLA4 Negatively Modulates T-Cell Activation




Byun T.

# Blocking Antibodies to CTLA4 Allow Positive Signaling from Costimulatory Molecules to T Cells



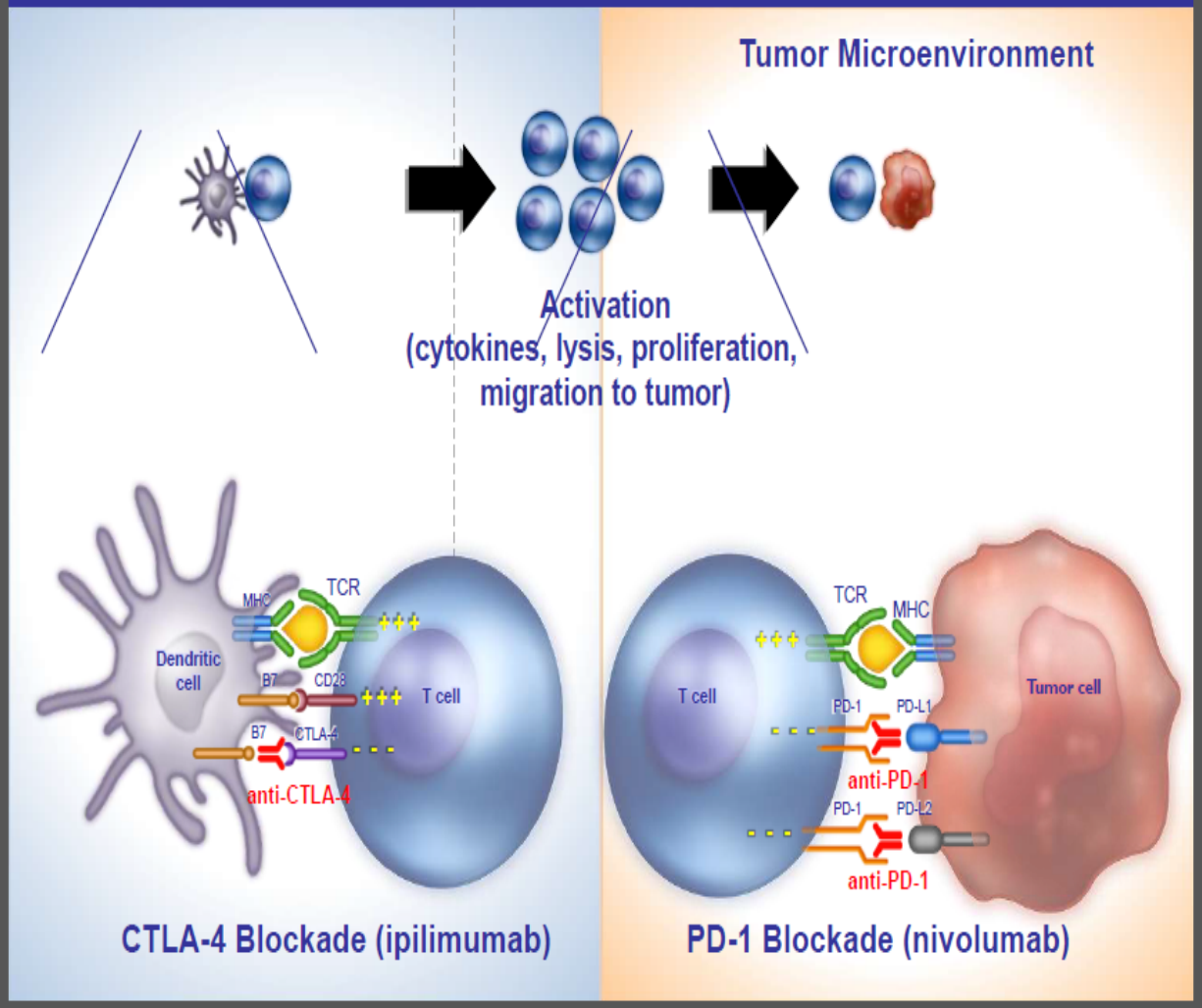

Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-1736.

# Mécanisme d'action *PD-1*

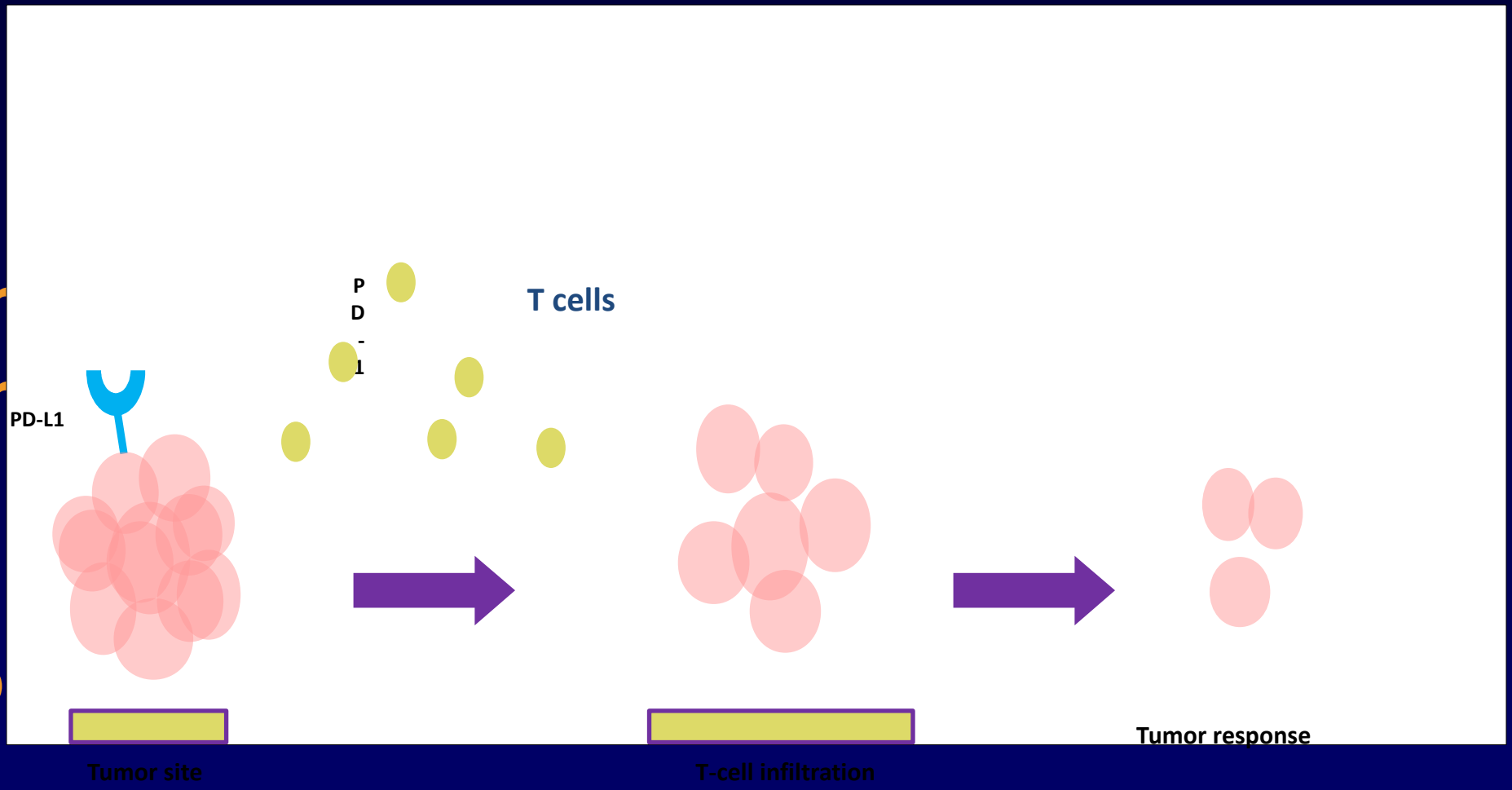
PD-1 ≪ Programmed cell death-1 ≫ récépteur de mort programmée -1 :
protéine naturellement exprimée a la surface des lymphocytes T,
récepteur inhibiteur pour les lymphocytes T activés.
La liaison du récepteur PD-1 a l'un de ses ligands PD-L1 ou PD-L2 inhibe l'activité des lymphocytes T => mort du LT activé.
PD-L1 et PD-L2 sont des protéines de surface cellulaire de la famille de B7. PD-L1 se retrouve sur les cellules immunitaires et tumorales. PD-L2 est exprimé par les macrophages, les cellules dendritiques et le parenchyme rénal et pulmonaire.
PD-1 limite l'activité des LT dans les tissus périphériques lors des réactions infectieuses.
Les cellules tumorales développent un échappement au contrôle immunitaire par l'activation des voies inhibitrices par des co-stimulateurs semblables à PD-L1 et PD-L2.

Le Nivolumab réactive les reponses des lymphocytes T, incluant les reponses antitumorales, par un blocage de la liaison de PD-1 aux ligands PD-L1 et PD-L2.

# Blocking CTLA-4 and PD-1



# and Immunoth




PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1.

Data from West H. *JAMA Oncol*. 2015;1(1):115; Tirkes T, et al. *RadioGraphics*. 2013;33(5):1323-1342.

# Toxicities Associated with Immune Checkpoint Inhibitors

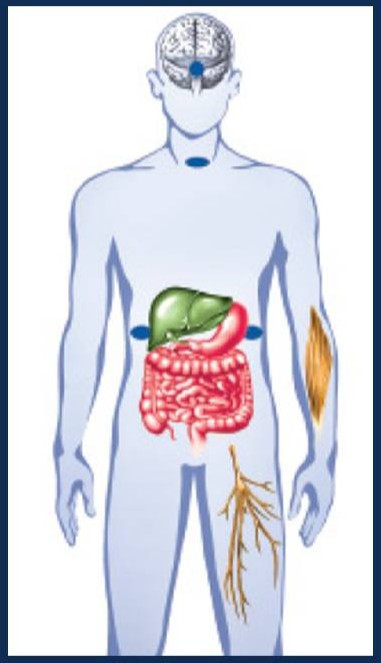
Hypophysitis

Thyroiditis

Adrenal insufficiency

Colitis

Dermatitis



Pneumonitis

Hepatitis

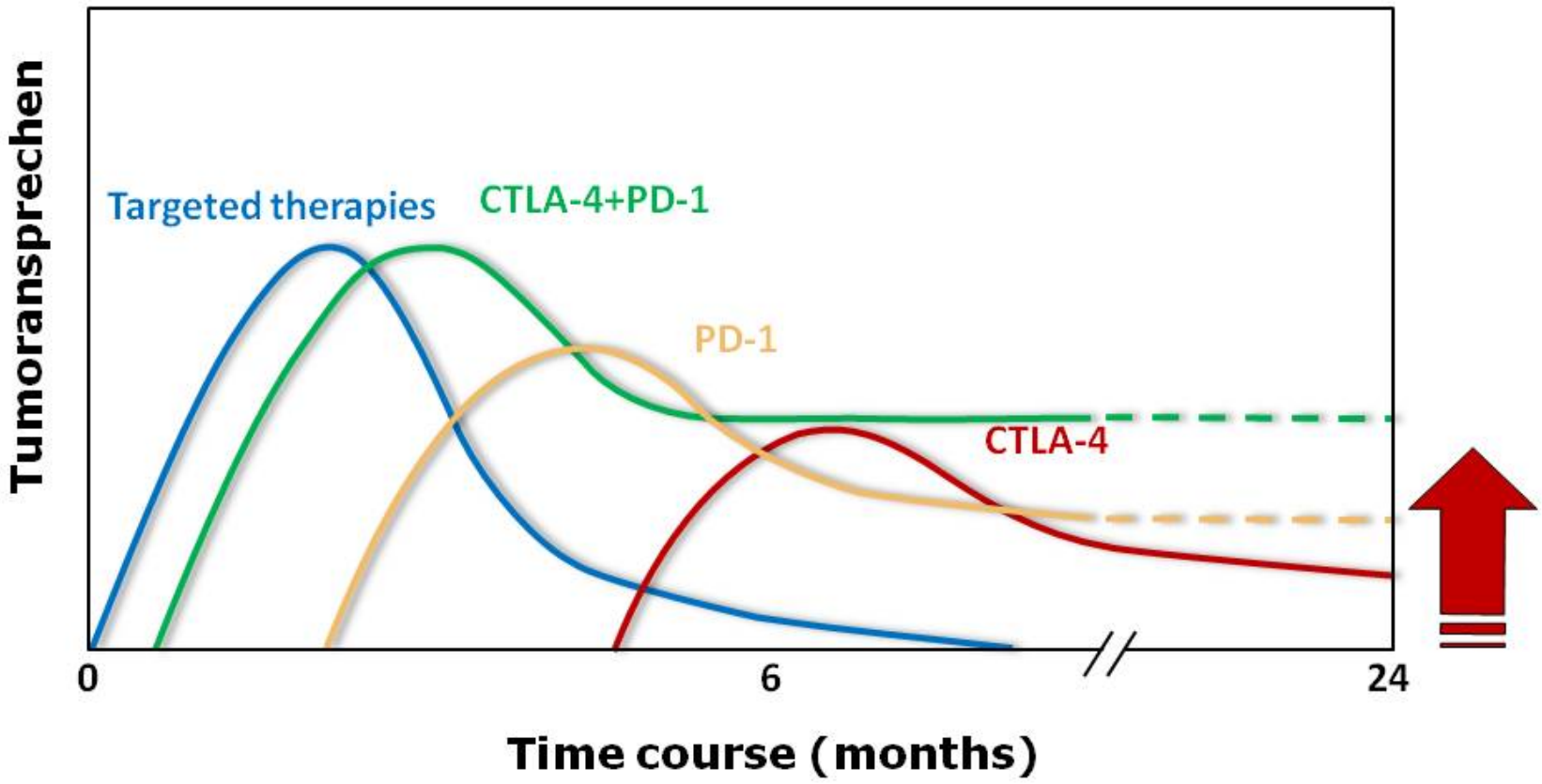
Pancreatitis

Motor & sensory neuropathies

Arthritis

- Less common: hematologic; cardiovascular; ocular, renal

# Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)



# General properties of targeted therapies vs checkpoint immunotherapy

| | Targeted Therapy | Immunotherapy |
|---|---|---|
| PK | Short (hours) | Long (weeks) |
| PD | Short (hours) | Long (years) |
| What kills the cancer | The small molecule stopping an oncogenic signal | A body system designed to kill its targets anywhere in the body |
| Body distribution | Passive (blood distribution) | Active (T cells searching for antigen) |
| Memory | No | Yes |

# Conclusions

- **Le traitement par blocage PD-1 est une immunothérapie ciblée:**
  - en réactivant les LyT dirigés spécifiquement  contre l'Ag tumoral,
  - d'activité anti-tumorale de longue durée,
  - capable de trouver les cellules tumorales dans tout l'organisme.

- **Les inhibiteurs BRAF**
  - bonne activité anti-tumorale précoce
  - Induisent des changements tumoraux immuno-suppresseurs après une exposition persistante


Toni Ribas
Keith Flaherty

BRAF/MEKi

Anti-PD-1