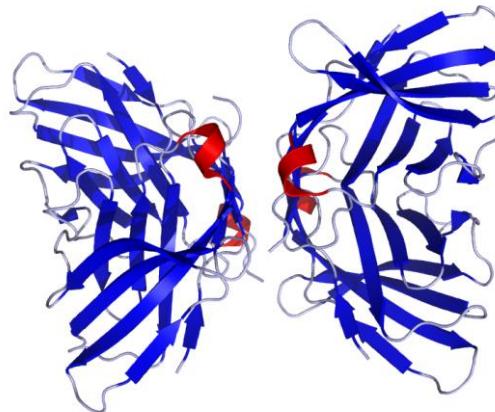


# Immuuntherapie in de oncologie, omgang met een dynamische behandeling



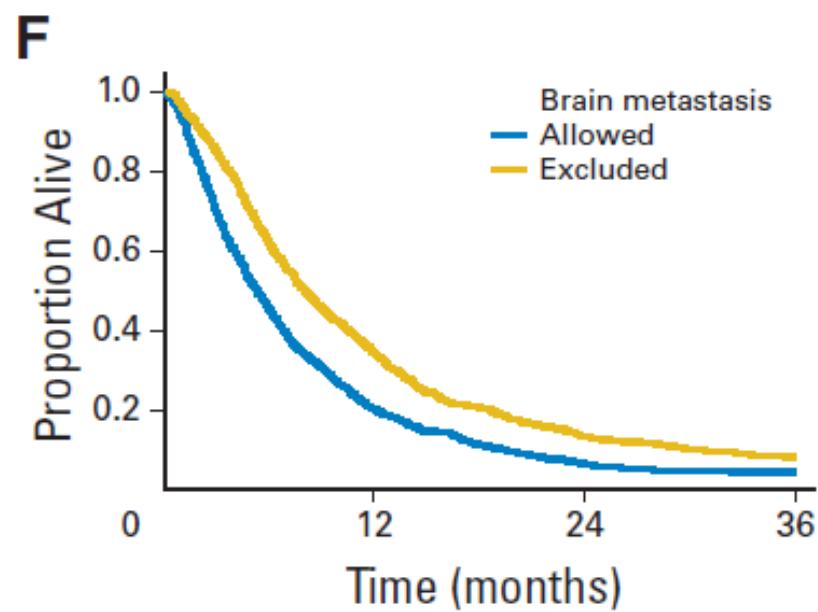
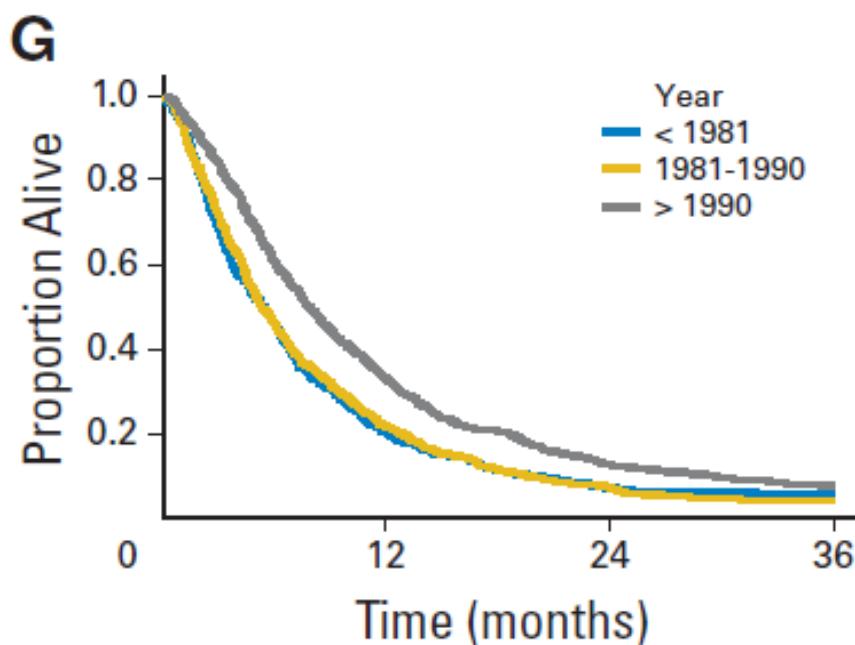
**Symposium immuuntherapie V&VN**  
**11 februari 2020**

Hans van Thienen  
Internist oncoloog

# Disclosures

(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
<ul style="list-style-type: none"><li>• Sponsoring of onderzoeksgeld</li><li>• Honorarium aan NKI-AvL voor nascholing</li><li>• Aandeelhouder</li><li>• Andere relatie, namelijk ...</li></ul>	<ul style="list-style-type: none"><li>•</li><li>• MSD, BMS, Novartis</li><li>•</li><li>•</li></ul>

## Overall survival stage IV melanoma meta analysis fase II studies



# 2013 Breakthrough of the Year



Science's editors pick the top discoveries of 2013, identify other notable developments, and offer forecasts for the year ahead

European Journal of Cancer (2013) 49, 2968–2971

Available at [www.sciencedirect.com](http://www.sciencedirect.com)



ScienceDirect

journal homepage: [www.ejancer.com](http://www.ejancer.com)



Drug of the year: Programmed Death-1 receptor/Programmed Death-1 Ligand-1 receptor monoclonal antibodies

Caroline Robert, Jean-Charles Soria, Alexander M.M. Eggermont \*

Gustave Roussy Comprehensive Cancer Center, 114 Rue Edouard Vaillant, 94800 Villejuif/Paris-Sud, France

Available online 29 July 2013

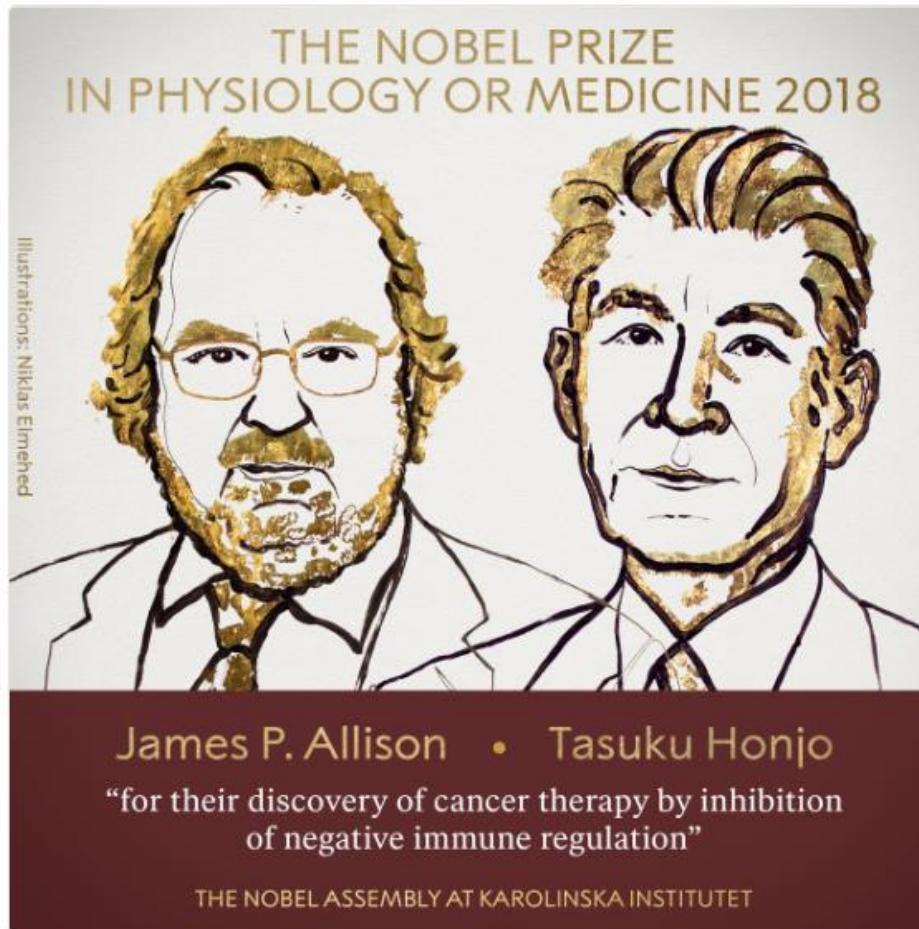
# Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

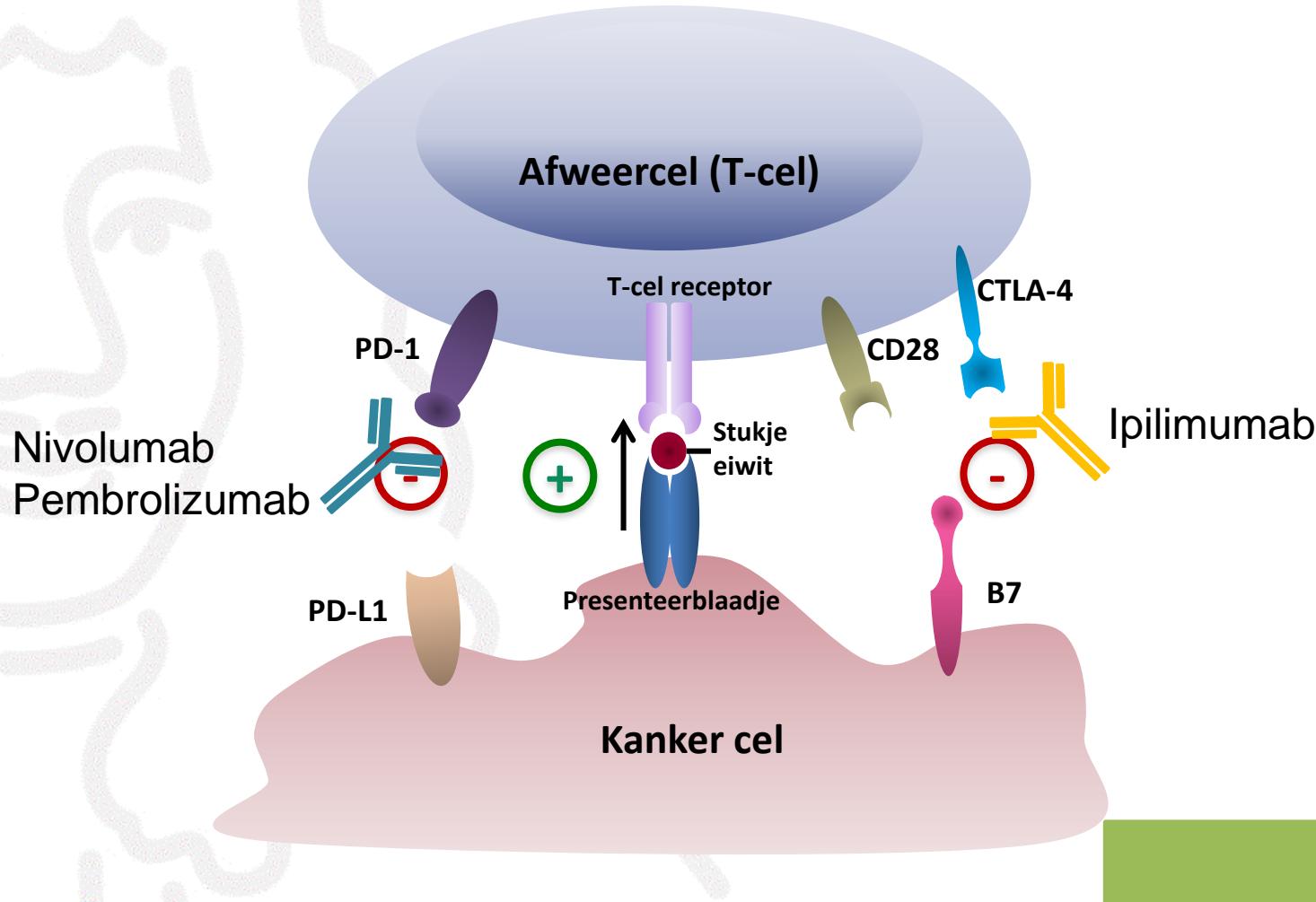


1 okt 2018

# NOBEL PRIZE MEDICINE FOR “MILESTONE IN THE FIGHT AGAINST CANCER”



# Werking checkpoint remmers



Let op deze s  
animati

Met checkpoint remmers wordt het blokkerende  
signaal vanuit de kankercel opgeheven

# Dynamics of immune-mediated tumor response

Screening



Week 12: swelling & progression



Week 14: improved



Week 16: continued improvement



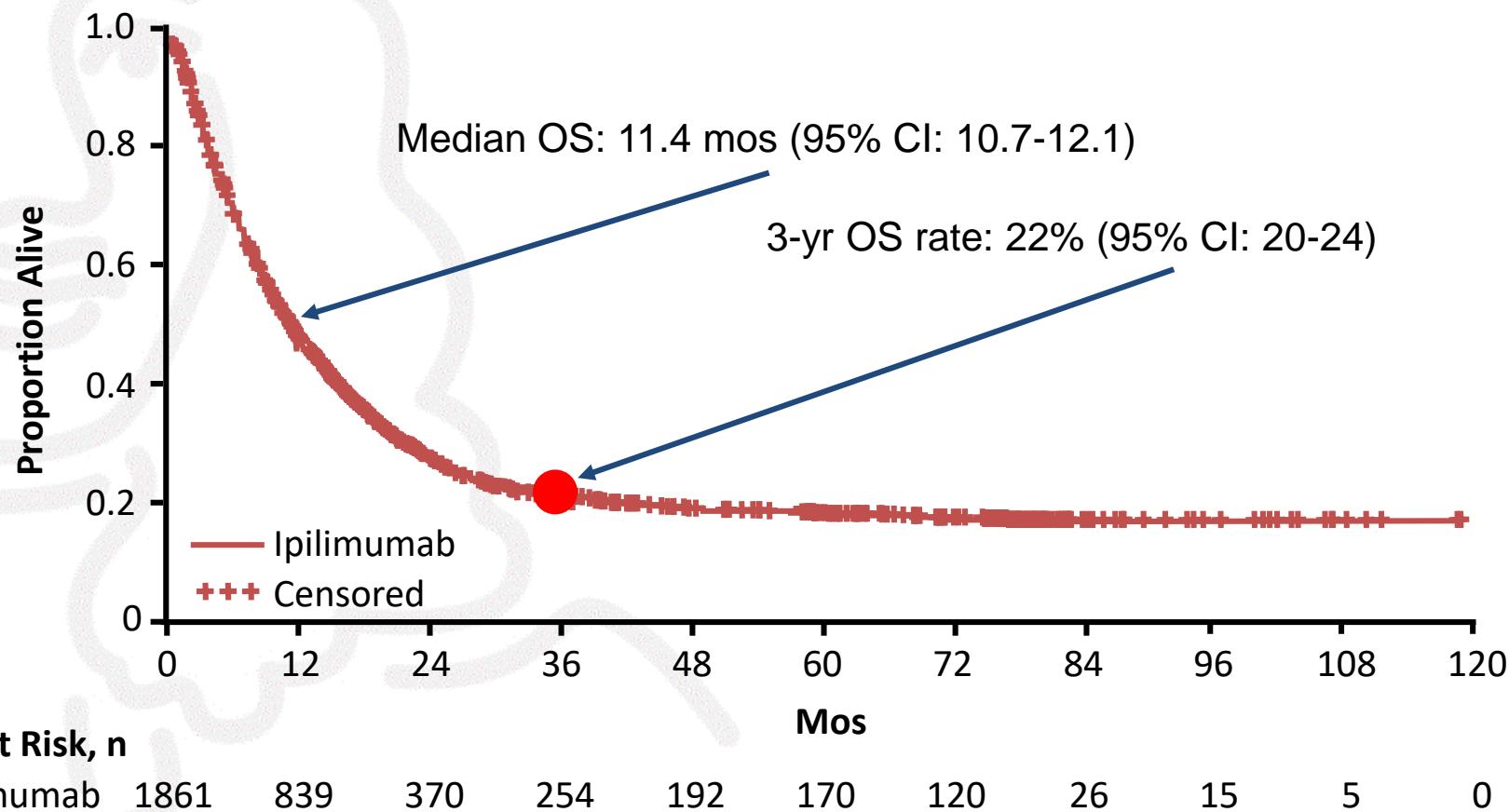
Week 72: complete remission



Week 108: complete remission

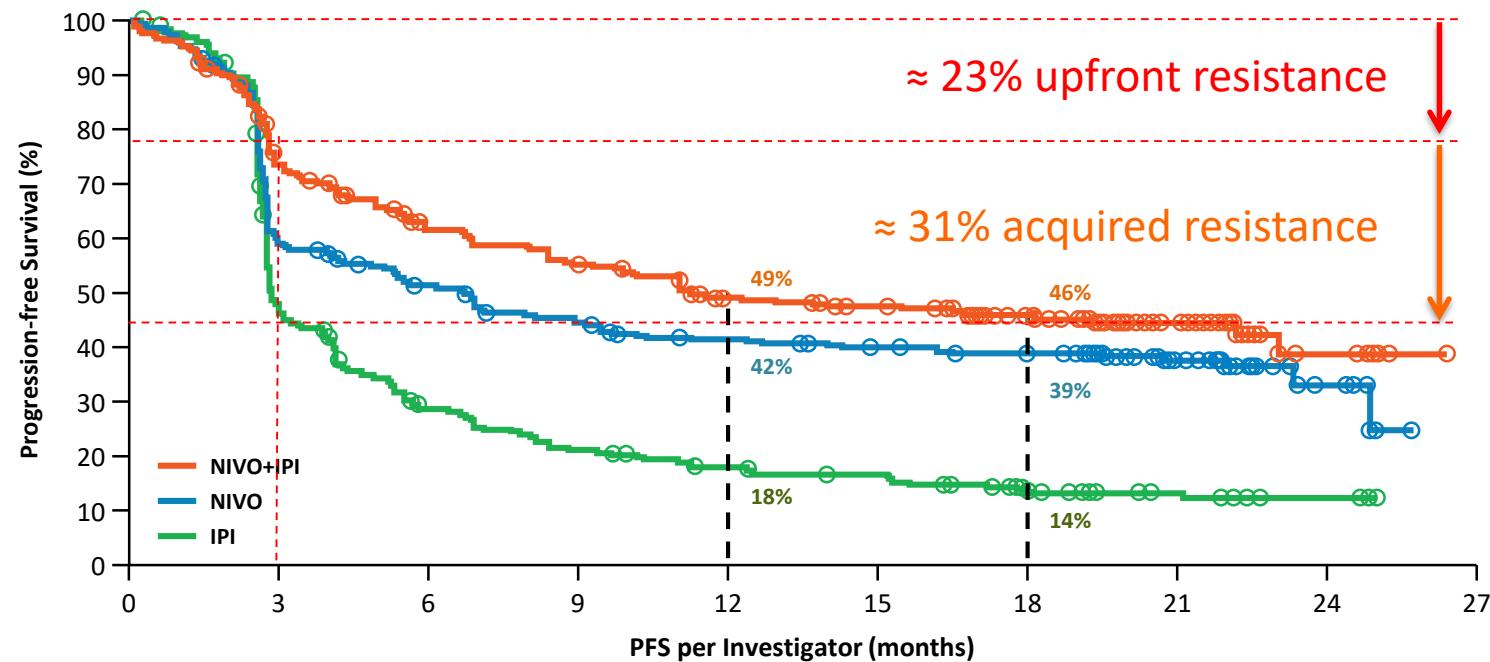


# Ipilimumab: Pooled survival analysis from phase II/III trials in advanced melanoma

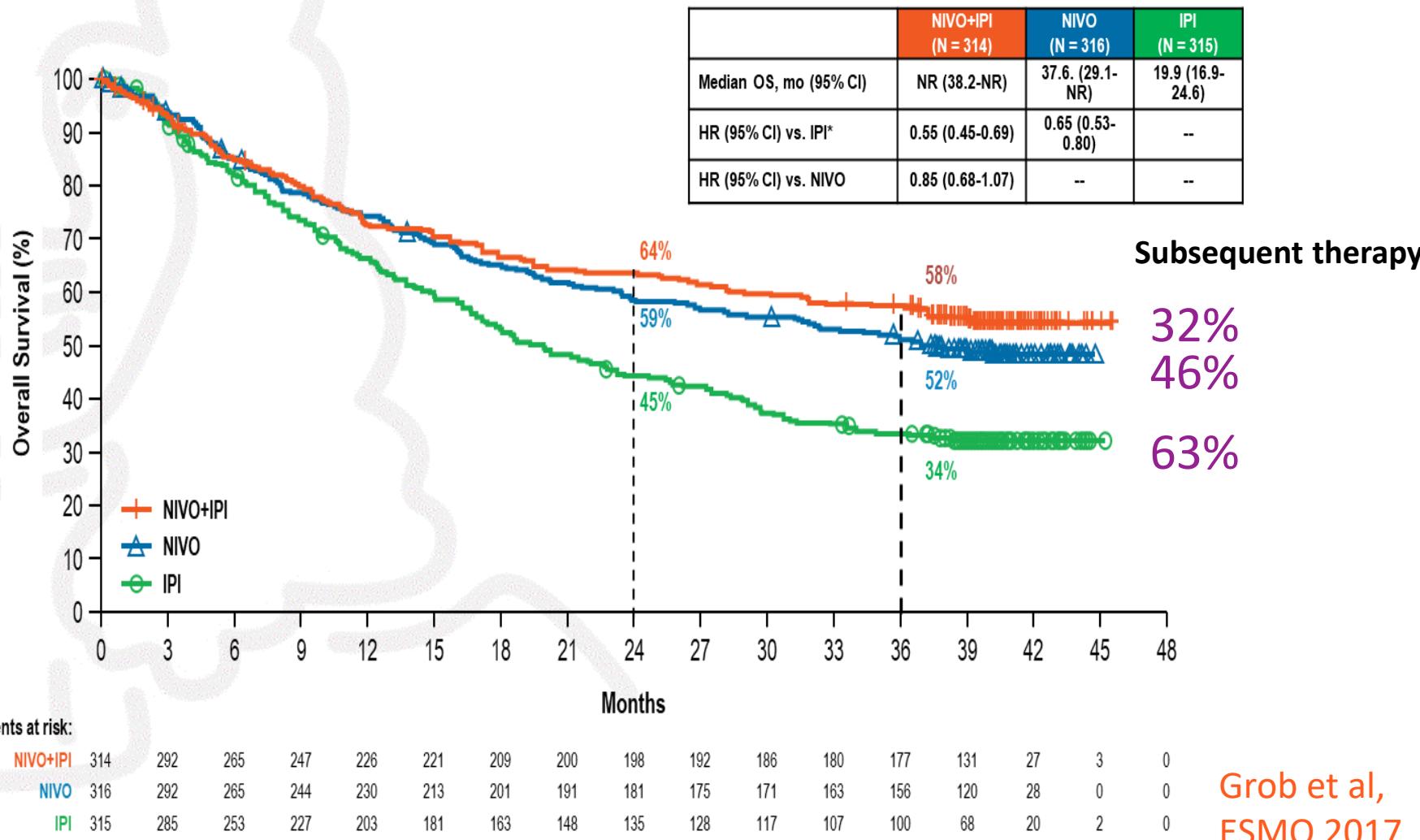


Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24.  
Schadendorf D, et al. J Clin Oncol. 2015;

# Around 50% of patients benefit long-term from current checkpoint therapies

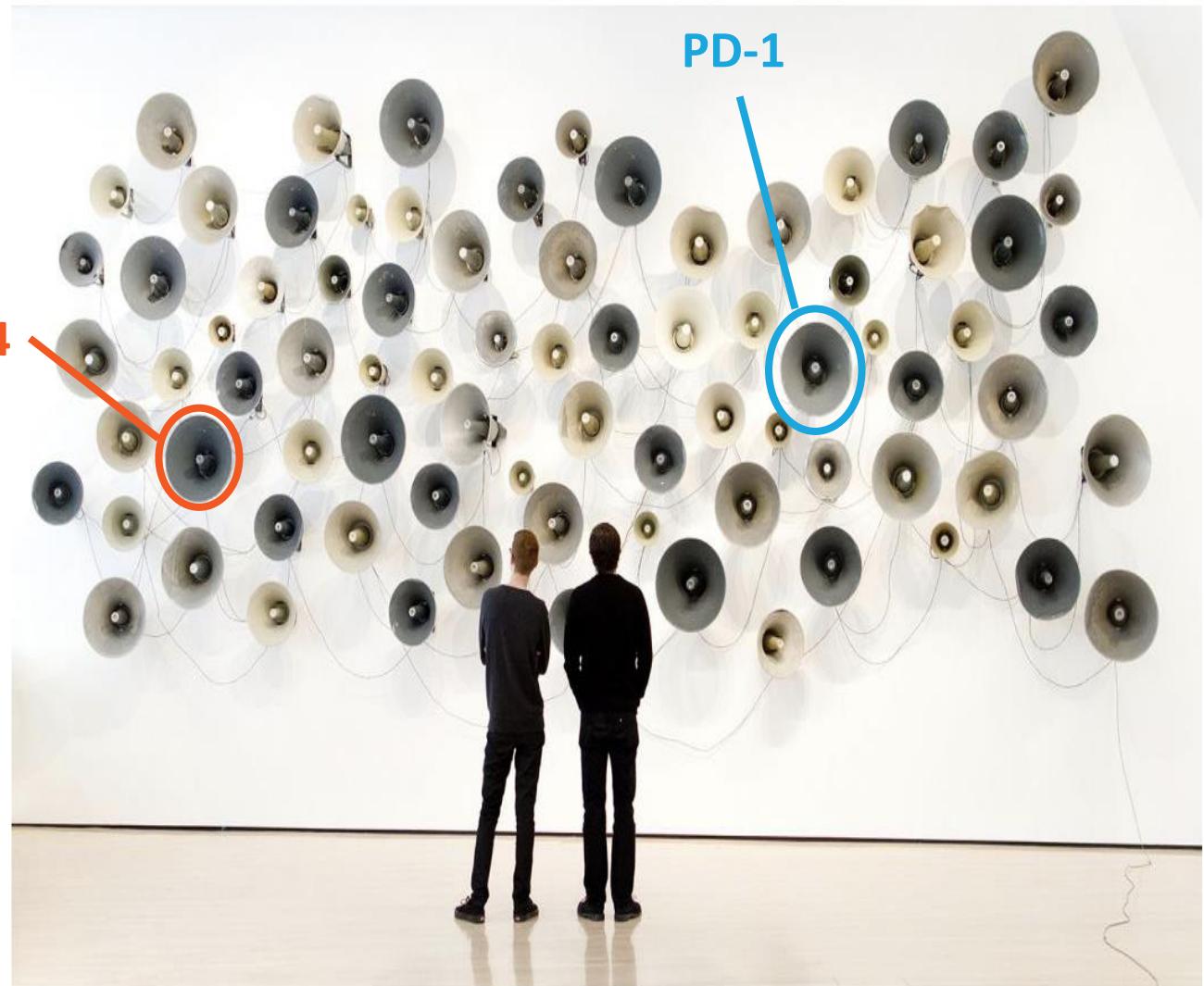


# Overall survival Checkmate 067



# The Checkpoint Signal Orchestra

Museum Of  
Contemporary Art  
Denver, October  
2012 – February  
2013  
<http://mcadenver.org/postscript.php>

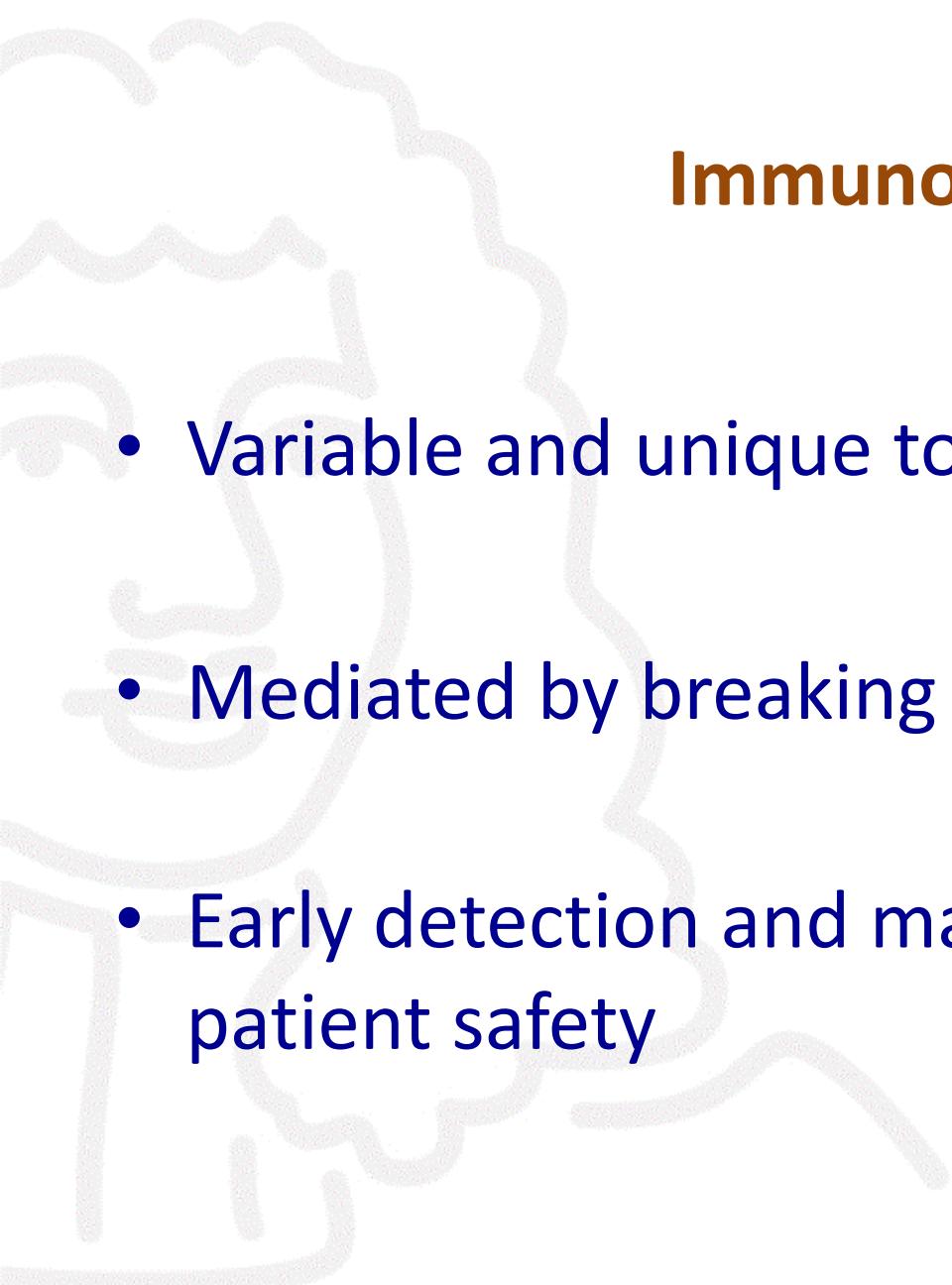


# Side-effects of anti-cancer therapies

- Chemotherapy
- Targeted therapy
- Immunotherapy

# Chemotherapy

- Classic side effects, off-target toxicity
  - Nausea, vomiting
  - Hairloss
  - Cytopenia
- Management
  - Dose-delay
  - Dose reduction
  - Supportive measures



# Immunotherapy

- Variable and unique toxicity
- Mediated by breaking of self-tolerance
- Early detection and management crucial for patient safety

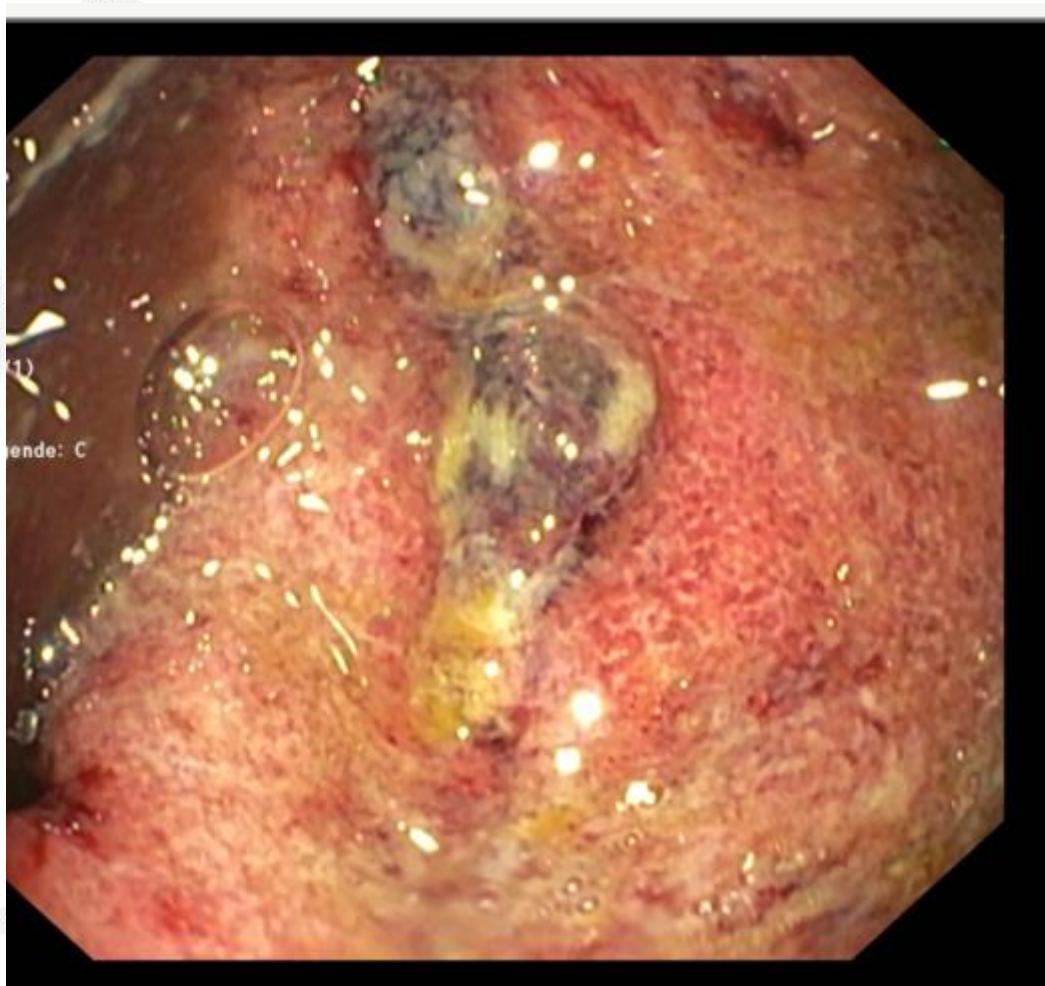
# Grade 3 skin toxicity



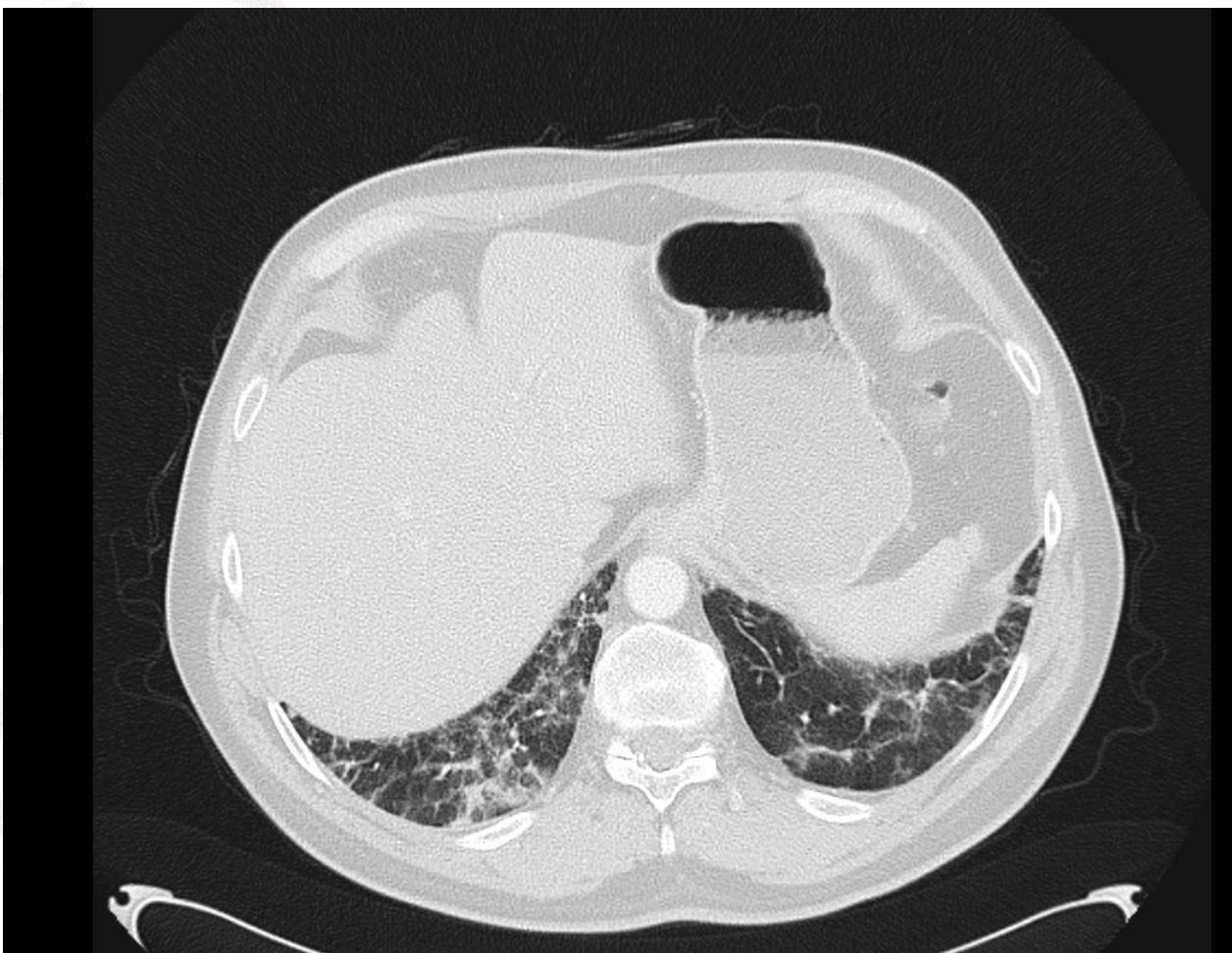
# Ipilimumab-induced vitiligo



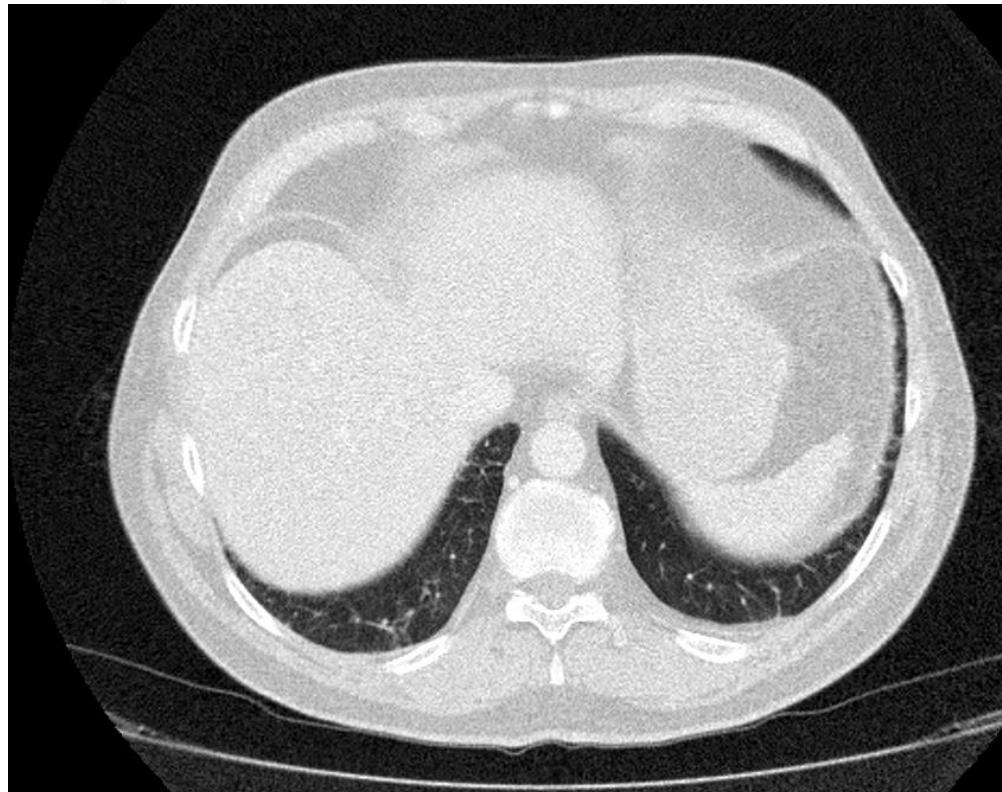
# Colitis



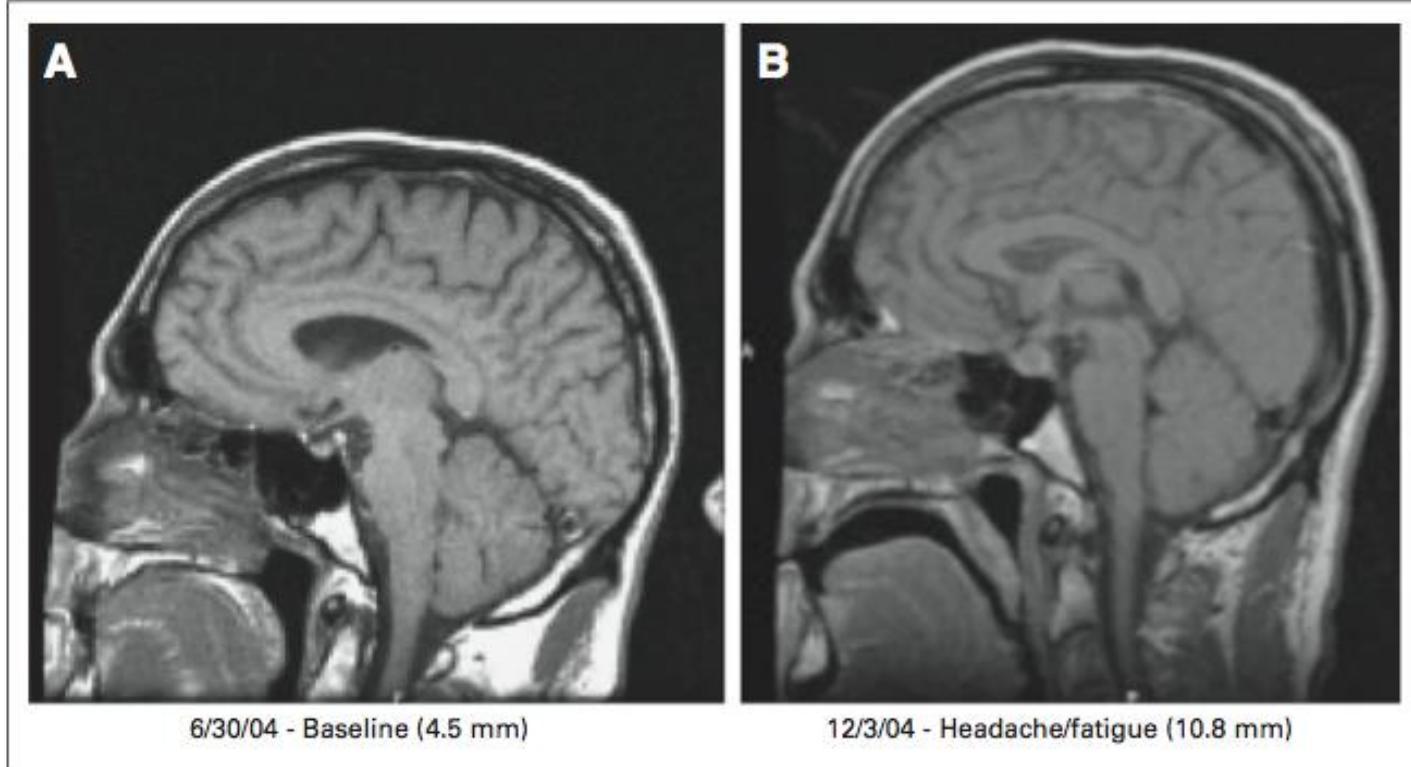
# Pneumonitis



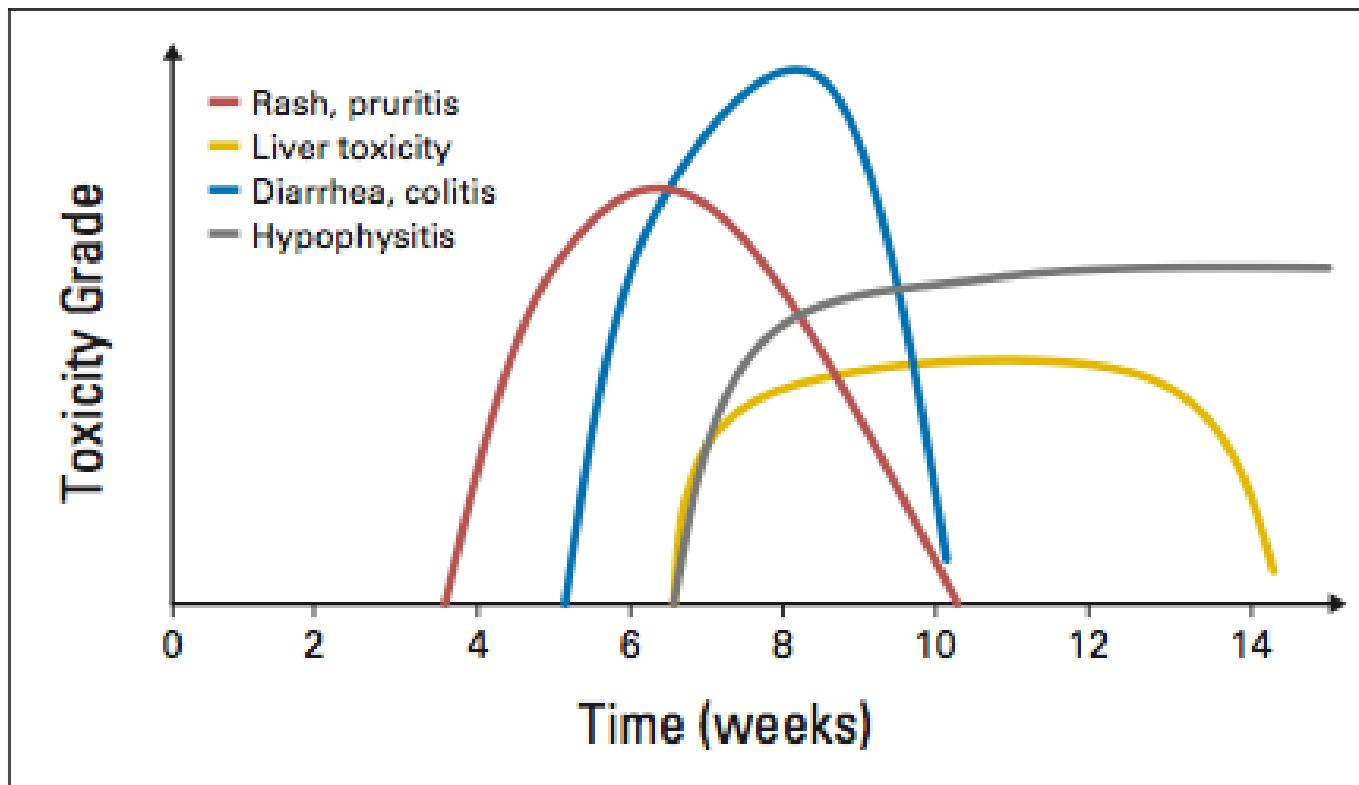
**After 6-week prednisone taper**



# Hypophysitis



# Dynamics of ipilimumab side effects



# Breaking the tolerance by CTLA-4 and PD-1/PD-L1 blockade – immune related adverse events (irAE)

## CTLA-4 blockade

(≈ 25% grade 3-4 irAE)

- Colitis
- Hypophysitis
- Hypothyroidism
- Adrenal insufficiency
- Dermatitis
- Uveitis
- Hepatitis
- Fatigue
- Pneumonitis
- Sarcoidosis
- “Guillain-Barre”
- “Leptomenigitis”
- Carditis
- Bone marrow failure,.....

## PD-1 blockade

(≈ 10 grade 3-4 irAE)

- Colitis
- Hypophysitis
- Hypothyroidism
- Adrenal insufficiency
- Dermatitis
- Uveitis
- Hepatitis
- Fatigue
- Arthralgia
- Pneumonitis
- Nephritis
- Type 1 diabetes

## PD-1+CTLA4 blockade

(≈ 55 grade 3-4 irAE)

- Colitis
- Hypophysitis
- Hypthyroidism
- Adrenal insufficiency
- Dermatitis
- Uveitis
- Hepatitis
- Fatigue
- Arthralgia
- Pneumonitis
- Nephritis
- Type 1 diabetes
- Pancreatitis

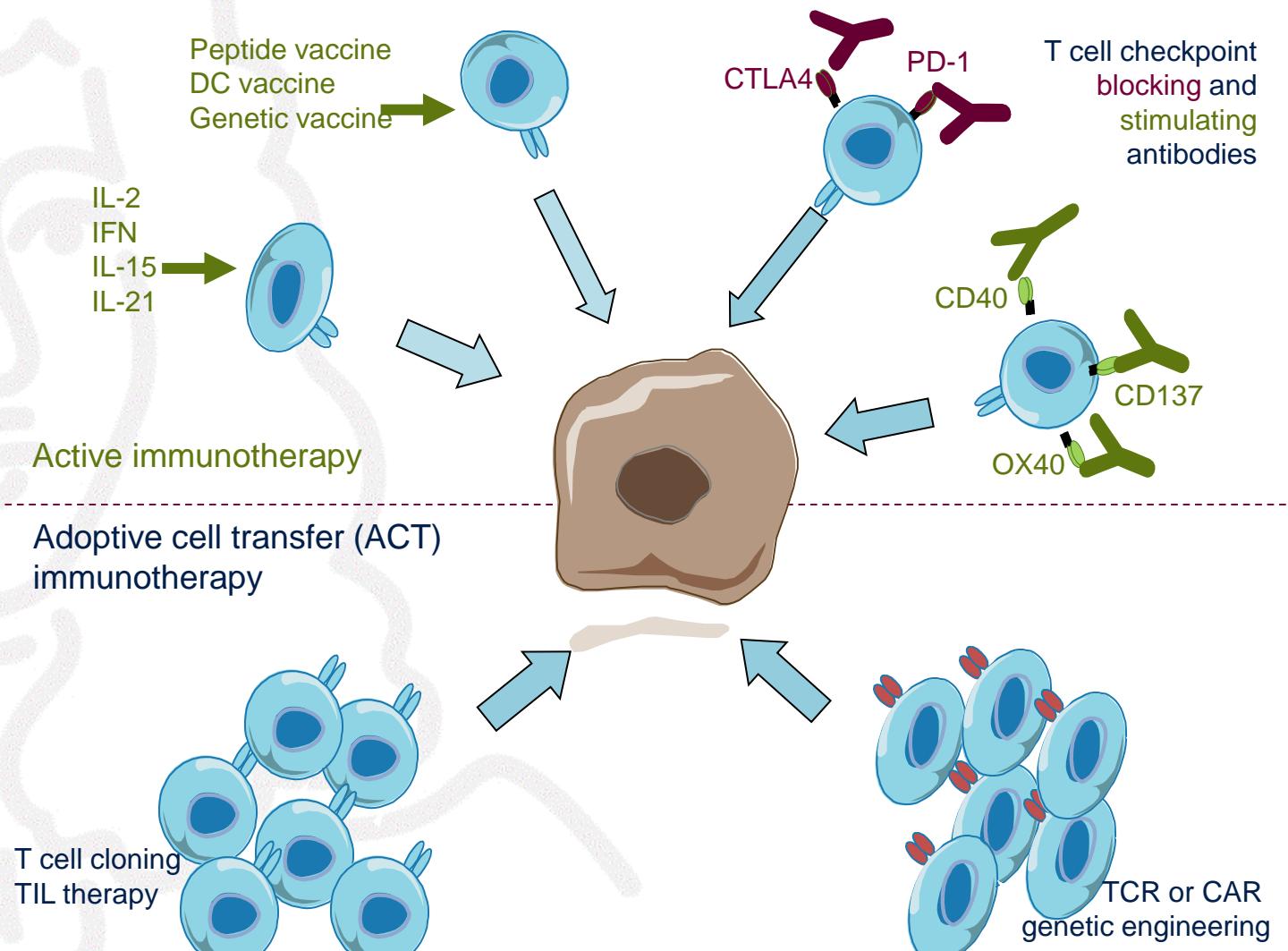
# How to manage irAEs

- Almost all irAEs are reversible
- The grade of the AE depends on the patient's and the physician's reaction, and to a lesser extent on the compounds
- Fast identification – **hit fast** -> 24/7 Immune-Oncology (I-O) and Internist-Oncologist expertise
- Start early immune suppression – **hit early**
- Do not hesitate to escalate – **hit strong**
- Consider to de-escalate – **hit short**

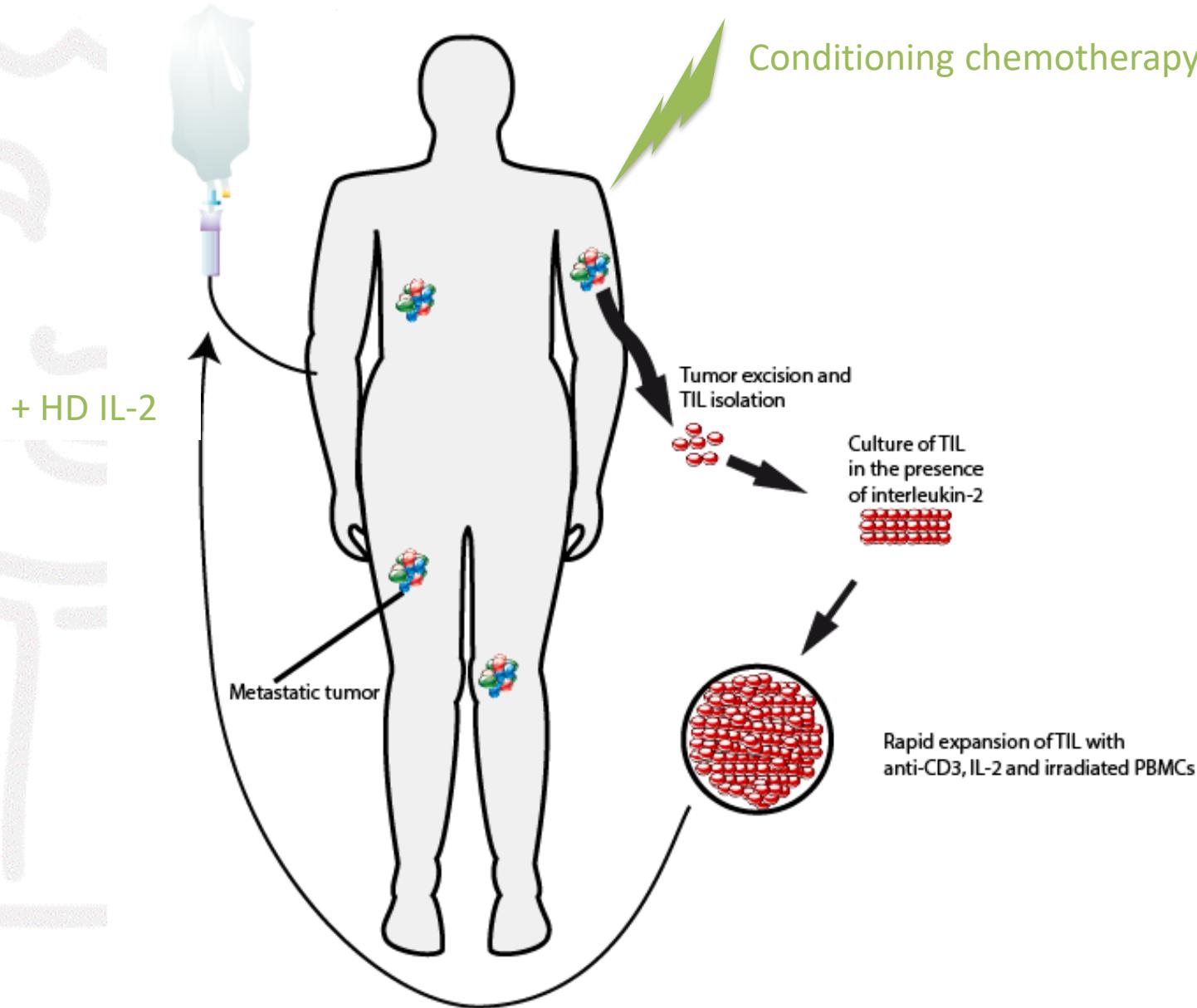
# How to manage irAEs – compounds to use

- symptomatic: metoclopramide, loperamide, levothyroxine, cooling crème (aloe vera), steroid crème
- prednisolon 1-2mg/kg
- infliximab 5mg/kg, repeat after one week
- mycophenolate mofetil 1g bid
- tacrolimus 0,10-0,15mg/kg/day, split in 2 doses/day
- substitution of hydrocortisone 10-5-5 mg + fludrocortisone 0,05-2mg/day, levothyroxine

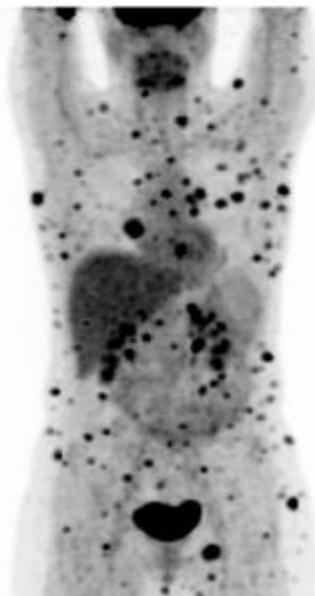
# Immunotherapy – several options



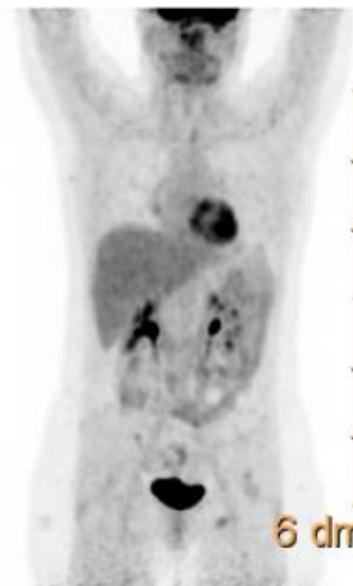
# TIL treatment



# CELTHERAPIE: Tumor-infiltrerende LYMFOCYTEN in studieverband



Vooraf aan TIL-behandeling

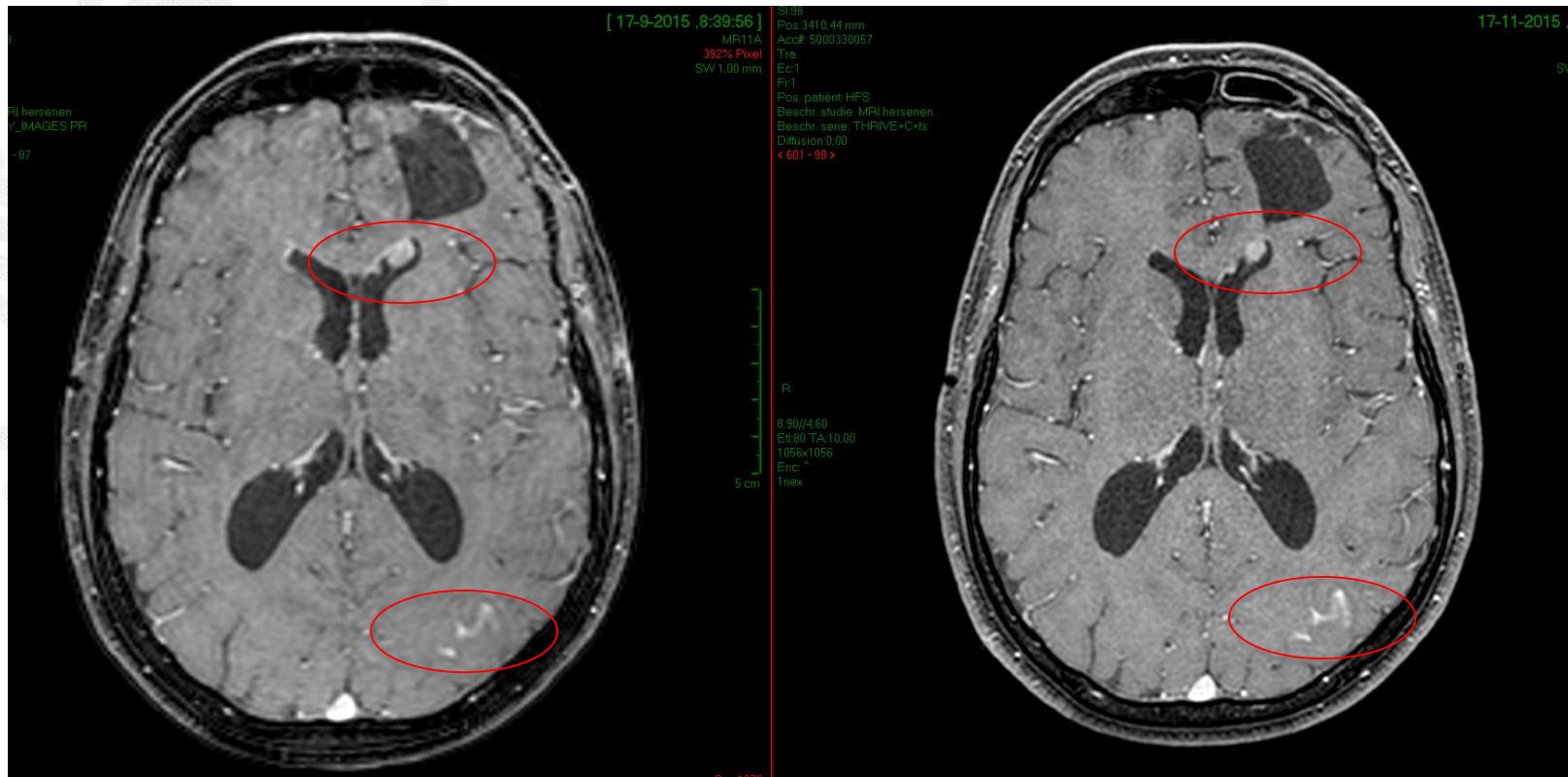


8 maanden na TIL-behandeling

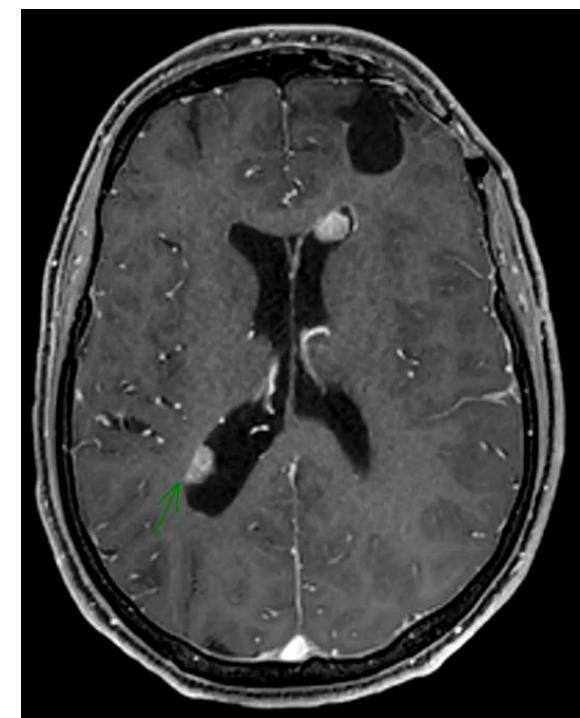
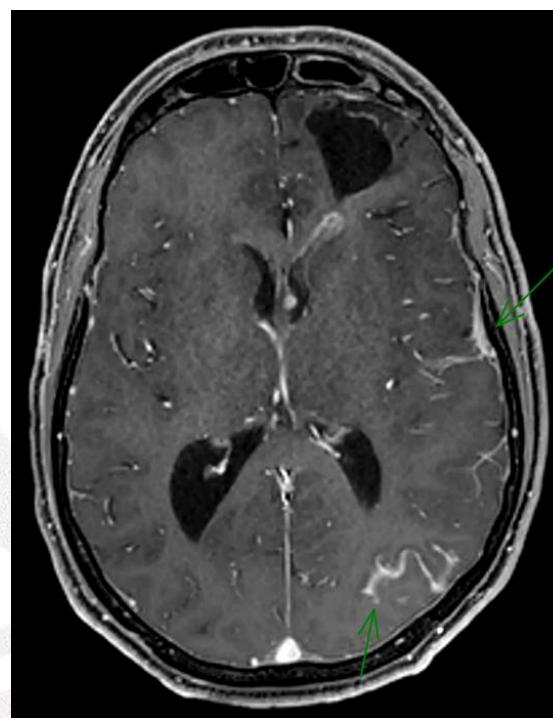
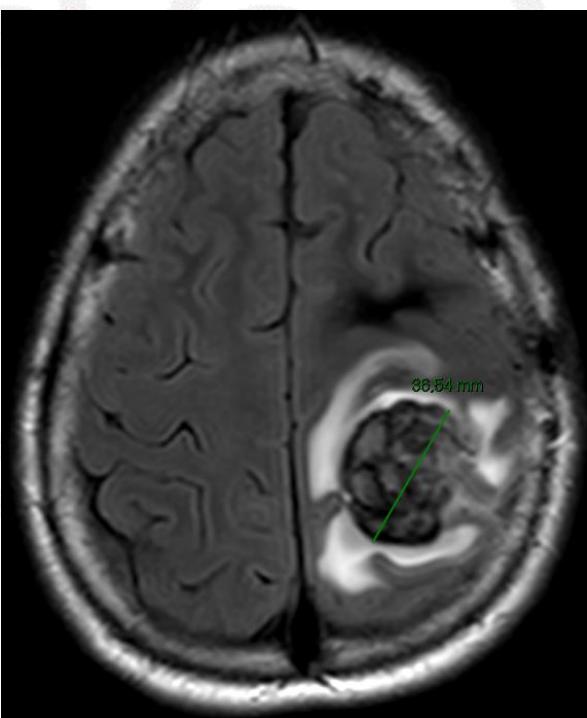
## 35-year male

- 2013 melanoma behind left ear, excised. Breslow 3mm
- 2014 re-excision, lymphadenectomy, radiotherapy
- 2015-4 Cerebral metastases (2), surgical removal
- 2015-7 leptomeningeal metastases, treatment with dabrafenib
- 2015-12 Stable disease, switch to pembrolizumab

# Stable disease upon BRAFi



# Progressive disease after switch to IT



# To brake, or not to brake?

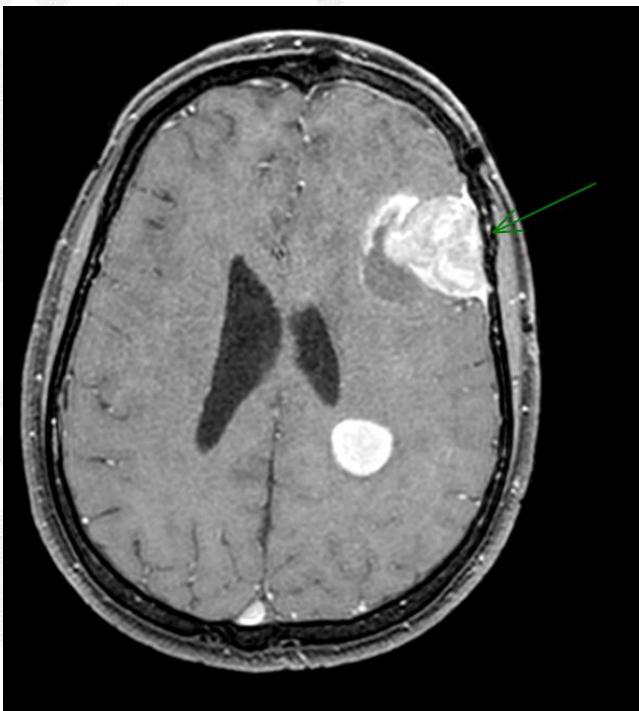
- No dexamethasone



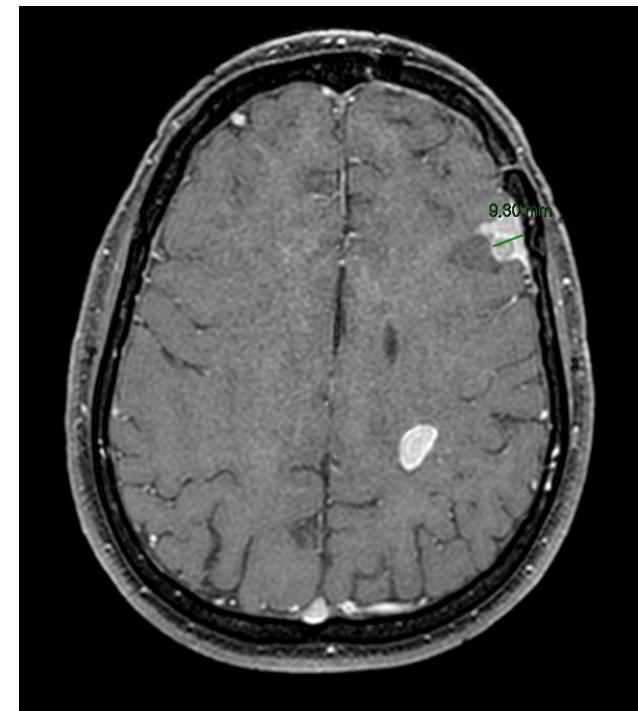
- Pembrolizumab continued

# Immune response!

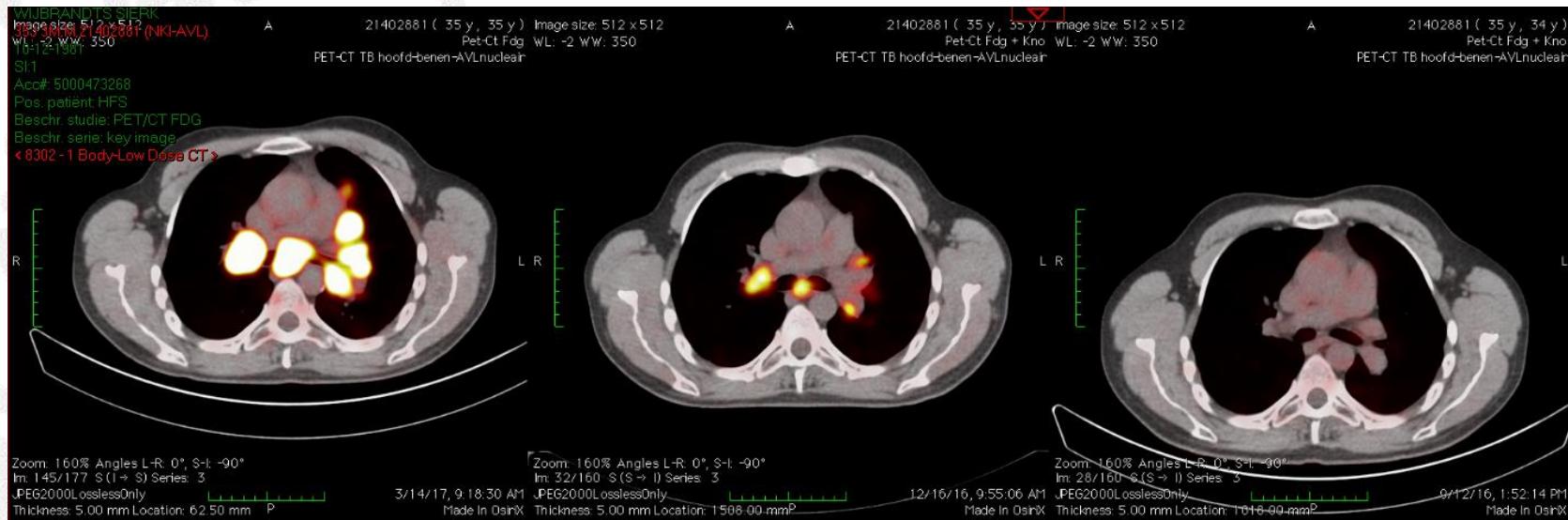
March 2016



June 2016



# Follow up after stopping treatment



## PET-CT

Conclusion:

Evident progression of melanoma metastases in several locations. Mainly pulmonary and mediastinal disease involvement.

# PA

## CONCLUSIE

A en B: endo-echo cytology of mediastinal lymphnodes two nodes with granulomatous inflammatory reaction.

No evidence of malignancy

## CONCLUSIE

Cytology parotid gland right side, echo-guided: fits granulomatous inflammatory reaction.

## Addendum to PET

Conclusie:

Evident progression of melanoma metastases in several locations. Mainly pulmonary and mediastinal disease involvement.

Addendum: Lymphnode and pulmonary lesions may reflect pseudo-progression.

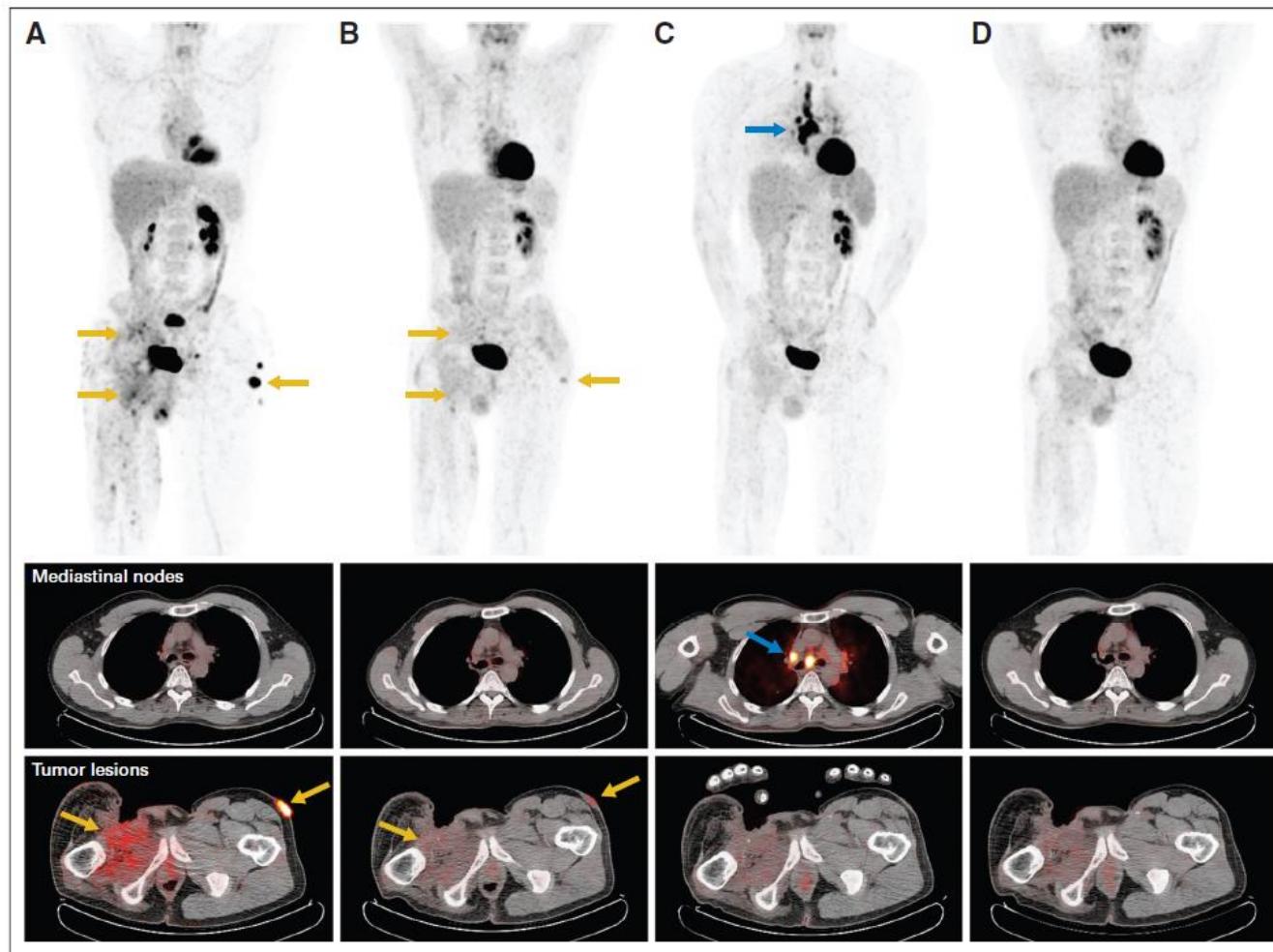
# Case reports ipilimumab

TABLE 1 ] Case Reports of Sarcoid-like Granulomatous Reaction Induced by Ipilimumab Used to Treat Melanoma

Authors	Melanoma Stage	Dose of Ipilimumab	Sarcoidosis Diagnosis After First Infusion	Organ Involved	Steroid Use	Ipilimumab Withdrawal	Sarcoidosis Evolution	Melanoma Evolution/Time (mo)
Sèvre, 2009 <sup>3</sup>	IV	NR/kg/wk 3 × 4	7 mo	Pulmonary stage II Cutaneous	No	No	Regression	Stable disease/NR
Eckert, 2009 <sup>4</sup>	IV	NR/kg/wk 3 × 4 + 10 mg/kg/wk 3 × 4	9 mo	Pulmonary stage II Cutaneous	No	No	Regression	NR
Tissot, 2013 <sup>5</sup>	IIIB	10 mg/kg/wk 3 × 4 + 10 mg/kg/wk 12 × 4	8 mo	Pulmonary stage II Cutaneous	No	Yes, after 6th infusion	Regression	NR
Vogel, 2012 <sup>6</sup>	IV	3 mg/kg/wk 3 × 4 (progression disease) + 3 mg/kg/wk 3 × 4	6 mo	Pulmonary stage I (PET-CT)	No	No	Regression after 4 months	Complete response/ 4 months
Berthod, 2012 <sup>7</sup>	IV	3 mg/kg/wk 3 × 4	16 mo	Pulmonary stage III	Yes Prednisone 1.5 mg/kg/d	No	Regression after 3 months	Progression disease (cerebral metastases)
Reule and North, 2013 <sup>9</sup>	IIIC	10 mg/kg/wk 3 × 4	6 wk	Pulmonary stage II Skin	Yes (NR)	Yes, after 2 infusions	Regression	Progression/NR
Wilgenhof, 2012 <sup>8</sup>	IV	3 mg/kg/wk 3 × 4	4 wk	Pulmonary stage II	Yes, methylprednisolone 48 mg/d	Yes, after 2 infusions	Regression	Progression/9 mo
Murphy, 2014 <sup>10</sup>	IV	3 mg/kg/wk 3 × 4	4 mo	Cerebral/pituitary gland Pulmonary, stage II Arthralgia	Yes Prednisone 40 mg/d	No	Regression	Stable disease/NR
Andersen, 2014 <sup>11</sup>	IV	3 mg/kg/wk 3 × 4	20 mo	Splenic lesions	No	No	Regression	Stable disease/NR

NR = not reported.

# Ipilimumab and sarcoidosis



# Nivolumab and sarcoidosis

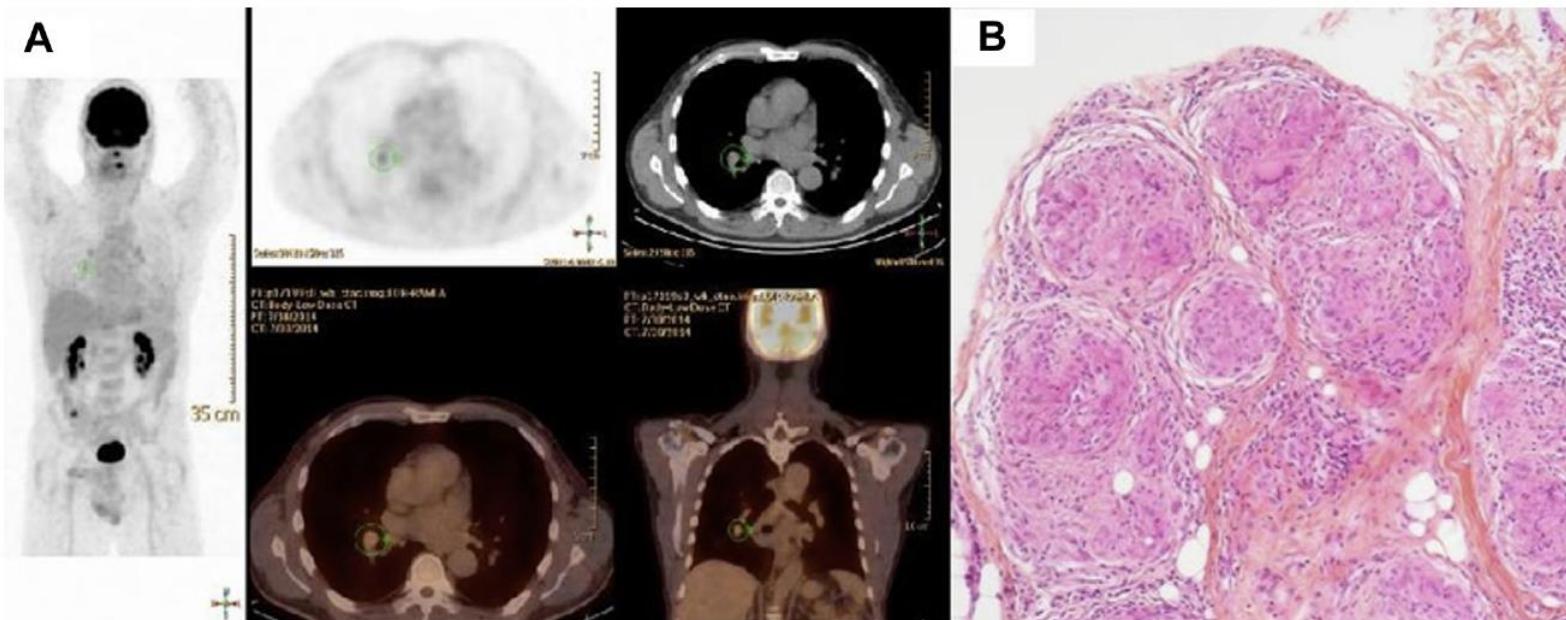
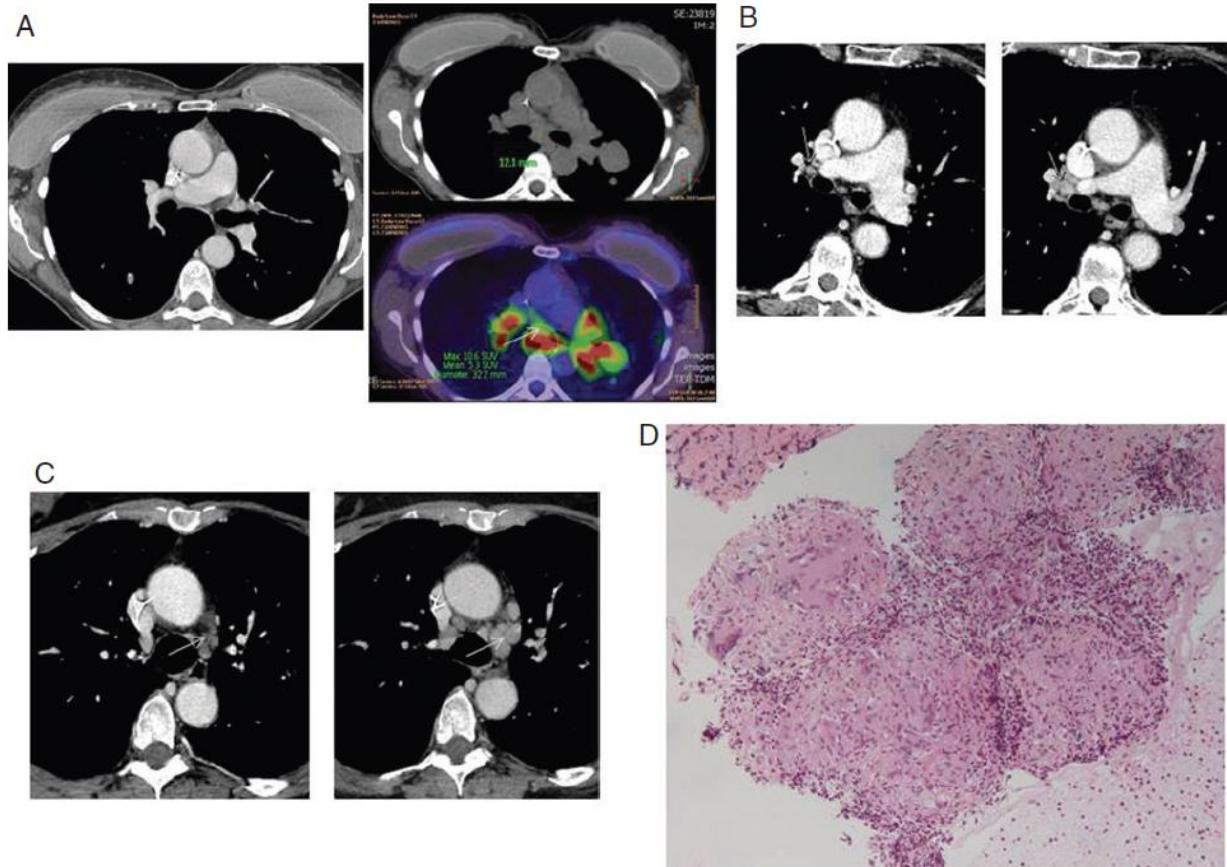


Figure 1 – (A) PET scan showing a moderate hypermetabolism (maximum standardized uptake value, 2.5) of bilateral hilar-mediastinal lymph nodes. (B) Epithelioid granulomatous infiltrate in the form of rounded granulomas, small to medium in size, surrounded by a thin lymphocytic halo, with some giant cells without necrosis.

# Pembrolizumab and sarcoidosis

Annals of Oncology

letters to the editor



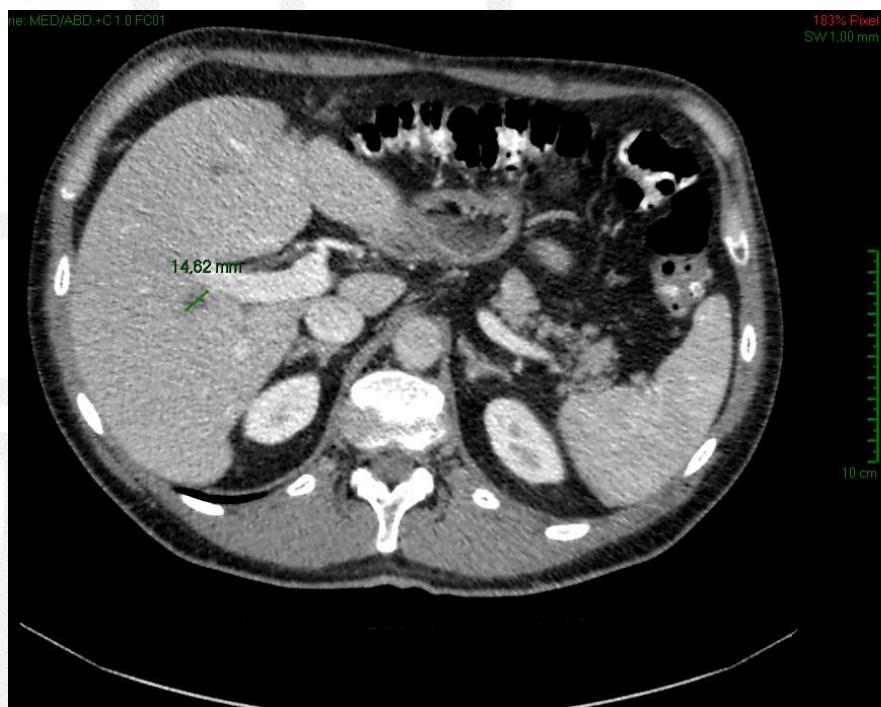
**Figure 1.** (A) CT scan and FDG-PET scan before and after 2 months of pembrolizumab treatment of the case report patient showing hypermetabolic mediastinal and hilar lymph nodes appearance. (B and C) CT scans of the second and third patients before and after 2 months of pembrolizumab treatment showing mediastinal lymph nodes appearance. (D) Lymph node biopsy showing well-formed giant cell granulomas.

# 64-year male

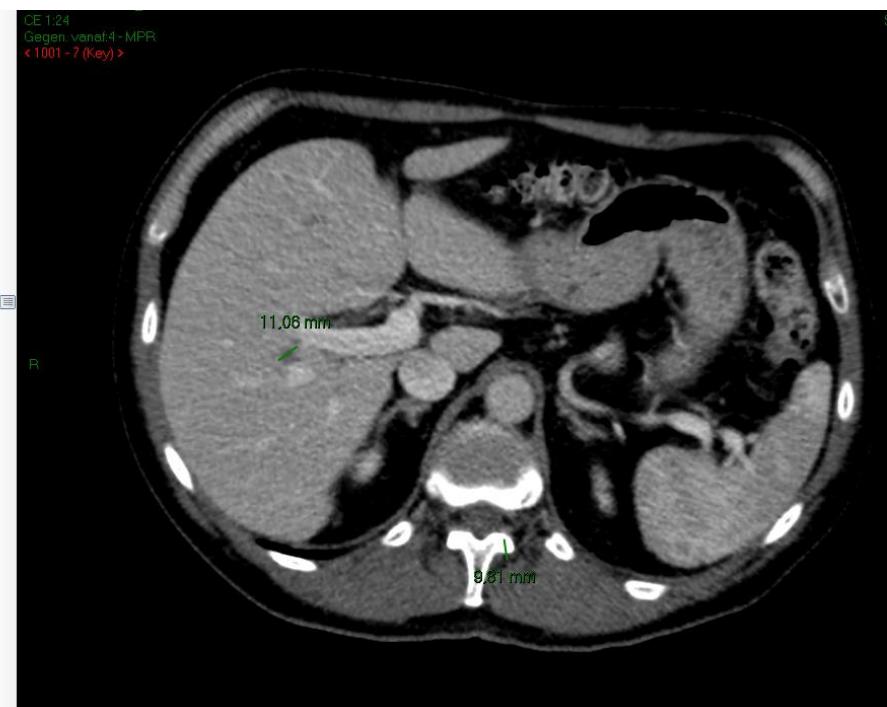
- 2013-03 melanoma on back, excised. Breslow 2.8mm
- 2013-04 re-excision, SN, wait-and-see
- 2013-10 Right axillary lymphnode dissection
- 2014-1 Excision of intransit
- 2015-6 Stage 4 melanoma, pulmonary, skeletal, liver
- 2015-6 2x ipilimumab, followed by pembrolizumab
- 2016-1 PR upon immunotherapy

# Response to pembrolizumab

October 2015

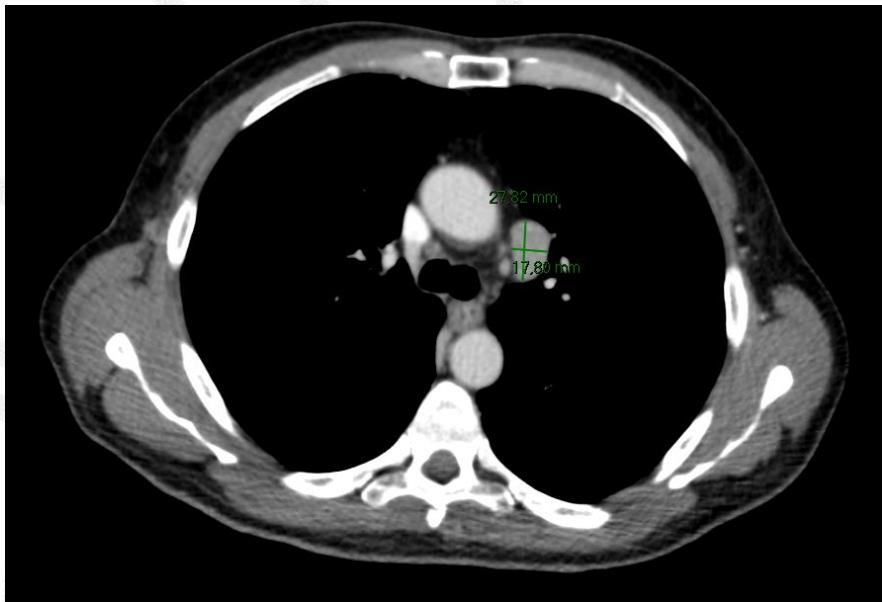


January 2016



# Progression of solitary mediastinal lymphnode

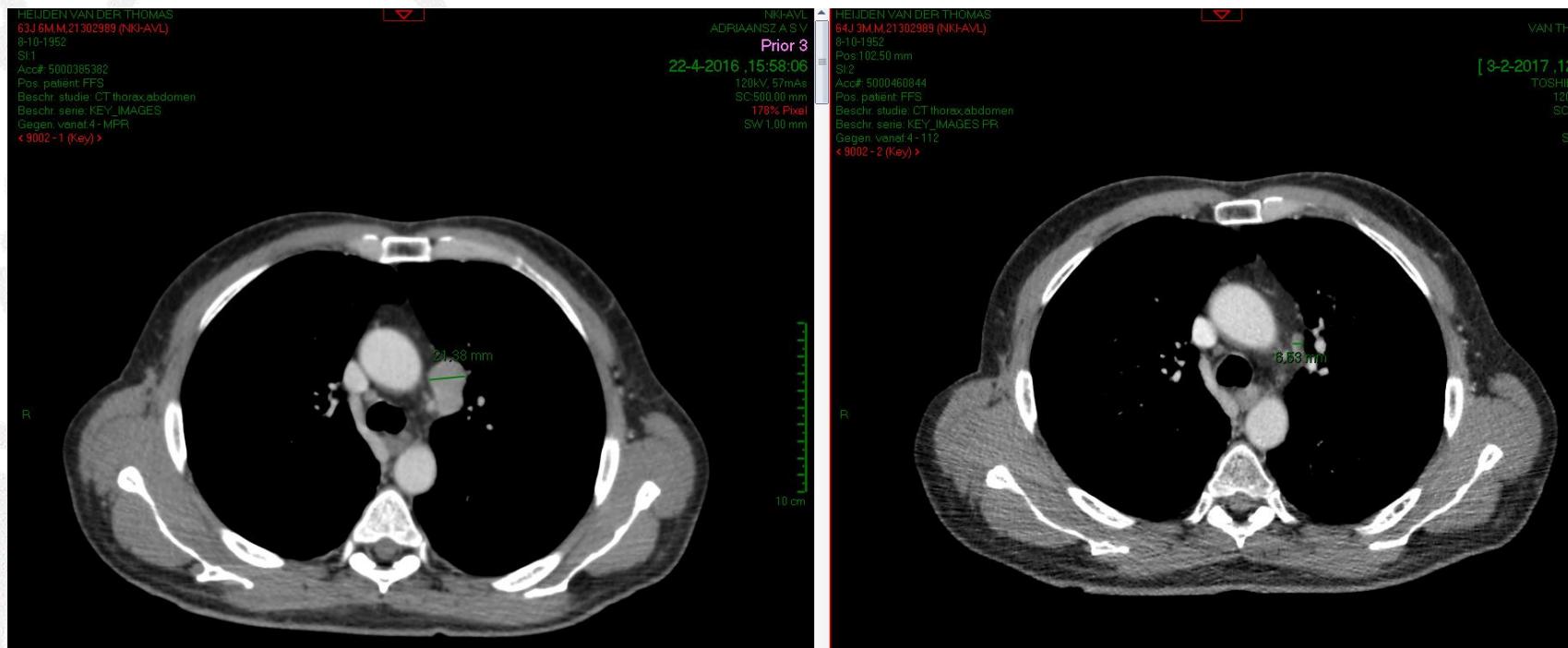
Jan 2016



Juli 2016



# After radiotherapy (51 Gy, 17 fractions)



# Conclusions

- Early recognition of immune related (IR) side effects is pivotal in safe treatment of patients
- Pattern recognition in IR side effects, but also in disease development, is key
- Know what to treat, when to treat and how to treat



**Dank voor uw aandacht!**