Introduction in Immuno-Oncology

What you need to know if you are not an oncologist

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No disclosures

Mrs X

- 2010
- Age: 29
- Melanoma + lung metastasis
- Teacher
- Loves travelling, yoga and cycling

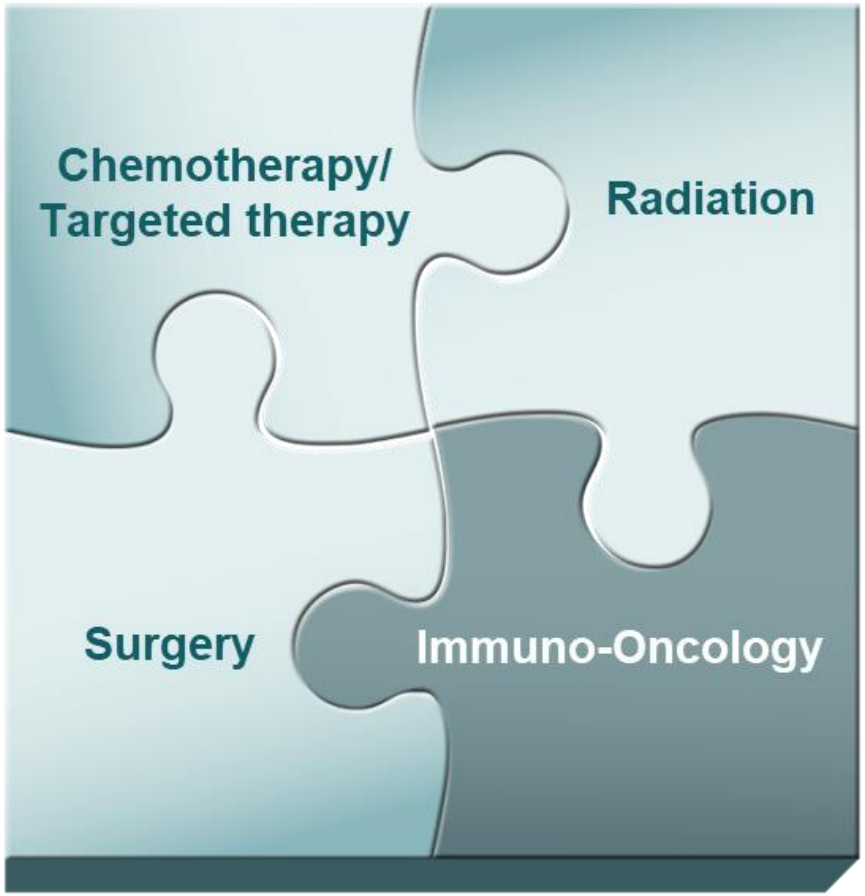
Mrs X

- No cure
- Short time to live (median 4 months)
- Option: treatment in study -> immunotherapy

Goals in cancer treatment

- Curative
- Palliative

Treatment modalities



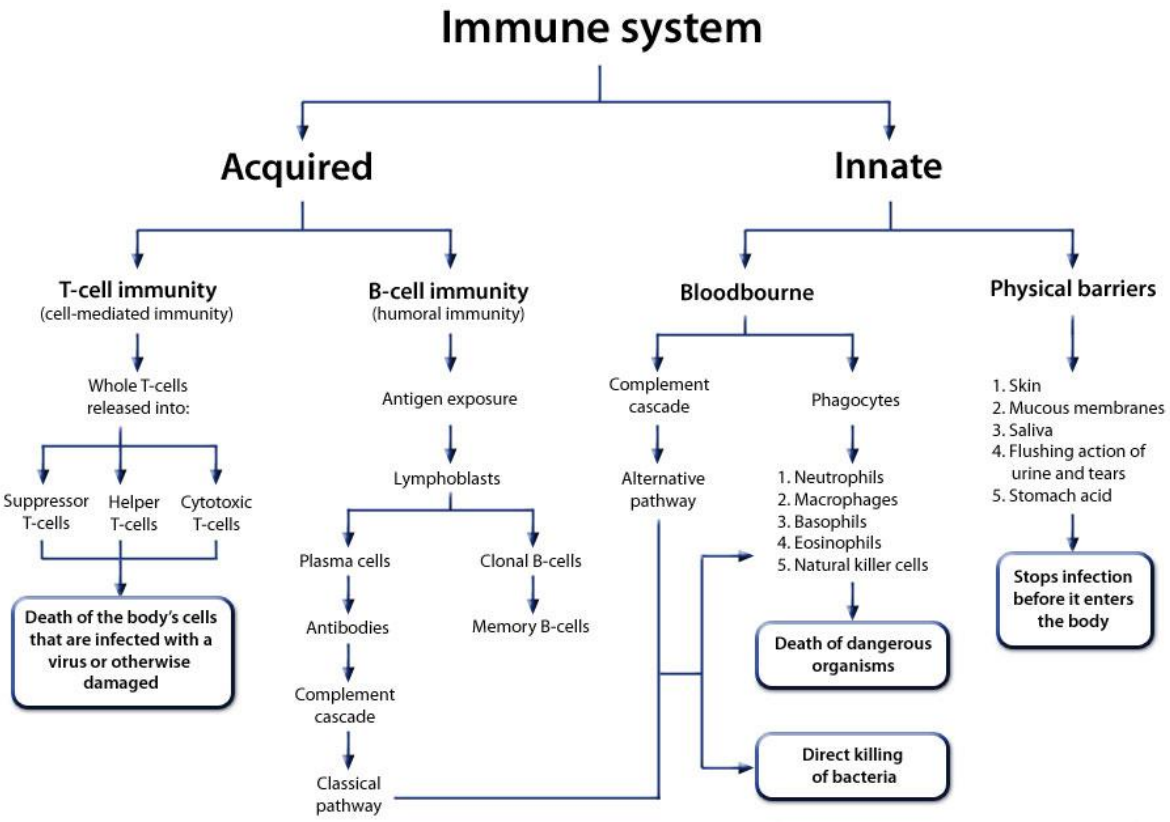
Immuno-Oncology as a Therapeutic Modality

- Immuno-oncology (I-O) therapies are **different** from other treatment modalities

- Rather than directly targeting the tumor, I-O therapies use the natural capability of the patient's own immune system to fight cancer
  - **Treat the patient**, rather than the tumor
  - **Adaptability** and **memory** of the immune system to offer potential for durable long-term survival

1. DeVita VT, Rosenberg SA. *N Engl J Med*. 2012;366:2207–2214. 2. Borghaei H, et al. *Eur J Pharmacol.* 2009;625:41–54. 3. Eggermont AM. *Ann Oncol*. 2012;23(suppl 8):viii53–viii57. 4. Finn OJ. *Ann Oncol*. 2012;23(suppl 8):viii6–viii9. 5. Hamid O et al. *N Engl J Med*. 2013;369:134–144. 6. Hodi FS et al. *N Engl J Med*. 2010;363:711–723. 7. Kantoff PW et al. *N Engl J Med*. 2010;363:411–422.

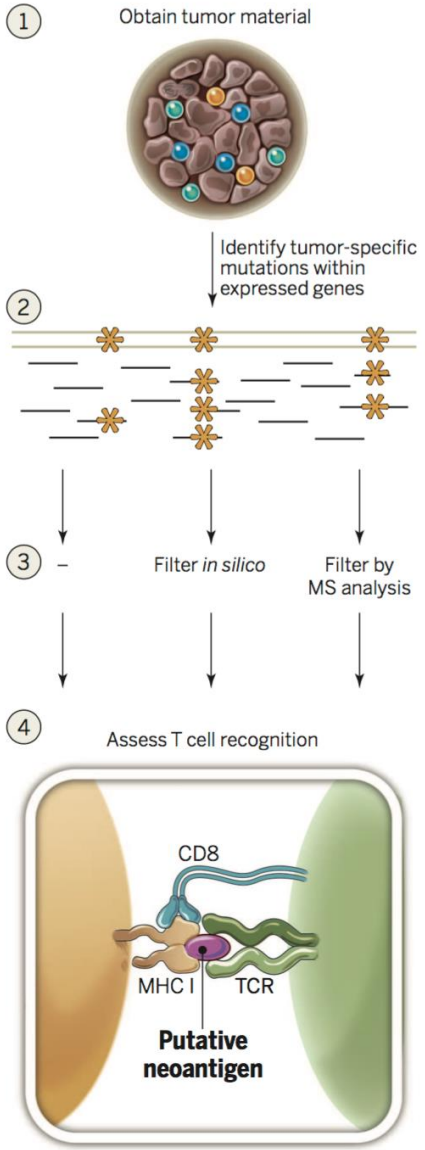
Immunesystem



Immunotherapy – tumorantigen recognition

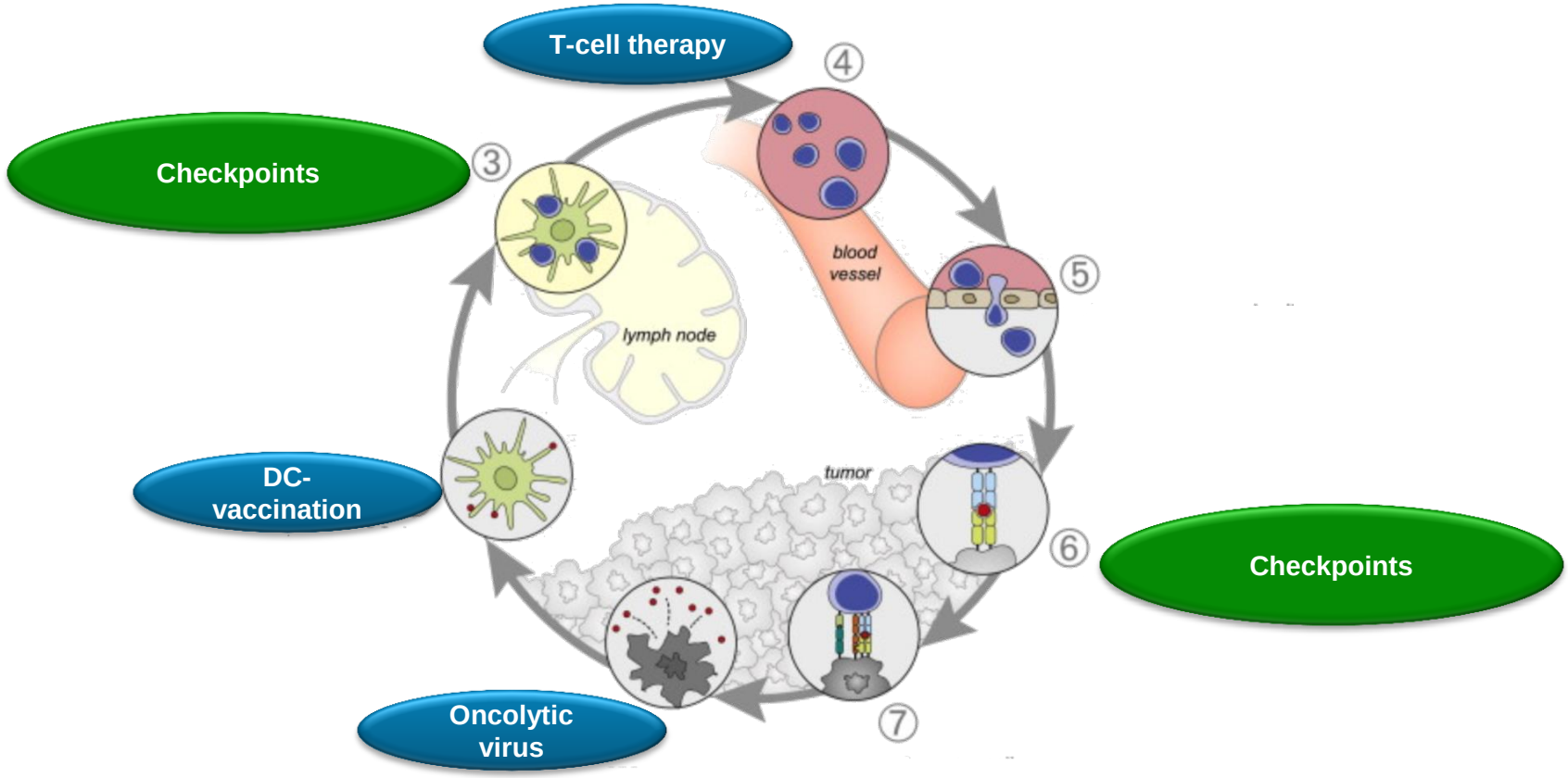
- Recent technological innovations have made it possible to dissect the immune response to ***tumor-specific neoantigens***
- tumor-specific mutations lead to tumor-specific neoantigens

- ***recognition*** of such ***neoantigens*** is a major factor in the ***activity of clinical immunotherapies***



Schumacher TN, Schreiber RD; Science 2015 348(6230):69-74.

The cancer-immunity cycle



DS. Chen and I. Mellman. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity 39, July 25, 2013*

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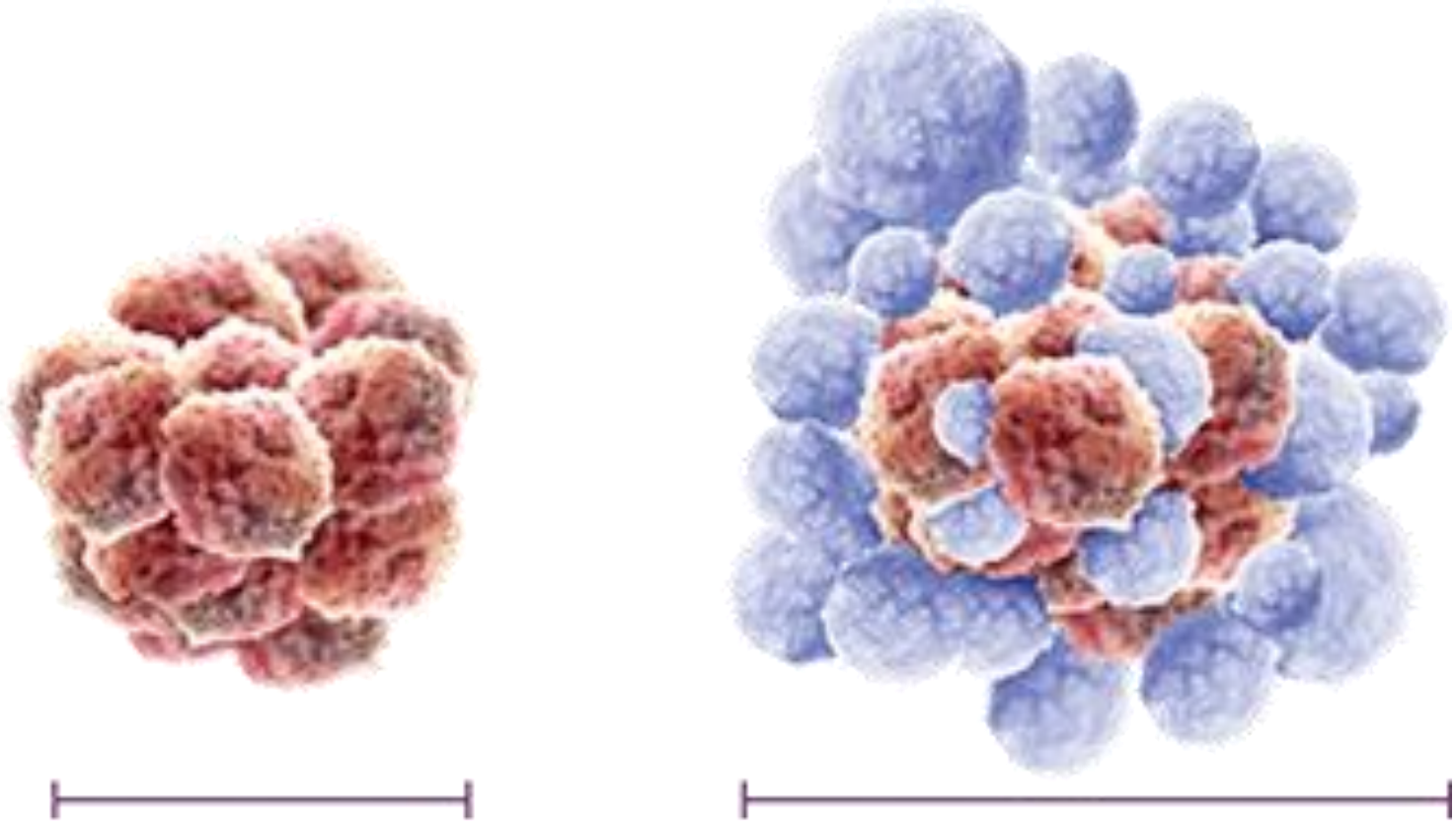
Tumor T-cell infiltration



Tumor

T-cell infiltration

The cancer-immunity cycle

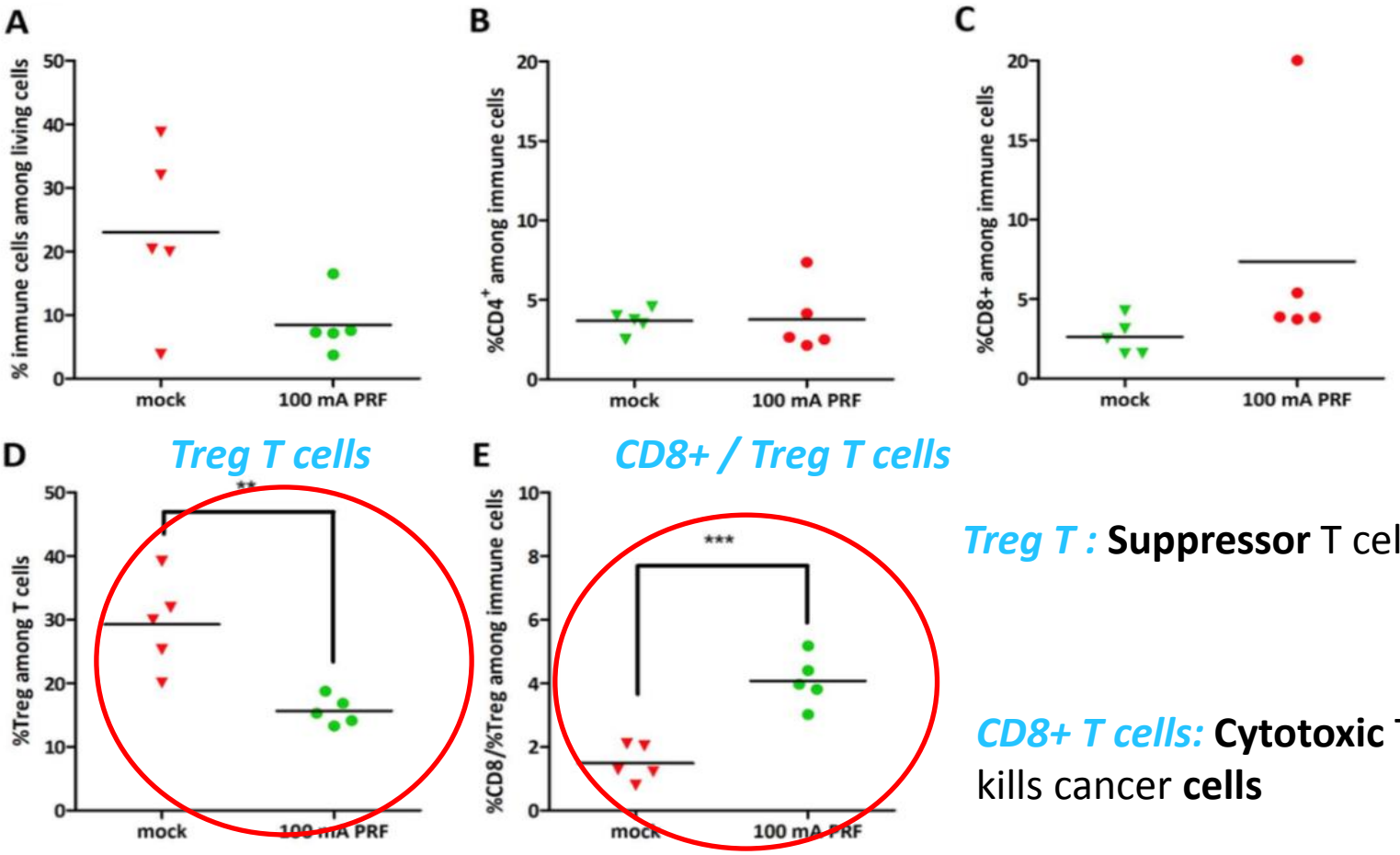
What goes wrong? Why isn't this system perfect?

- Tumor antigen not recognized
- Antigen recognized as "healthy/ own" instead of "strange/ disease"
- Inhibition of tumor infiltrating T-cells
- Inhibiting effect of the tumormicroenviroment

Pulsed Radio Frequency

- Effects on the immune system?

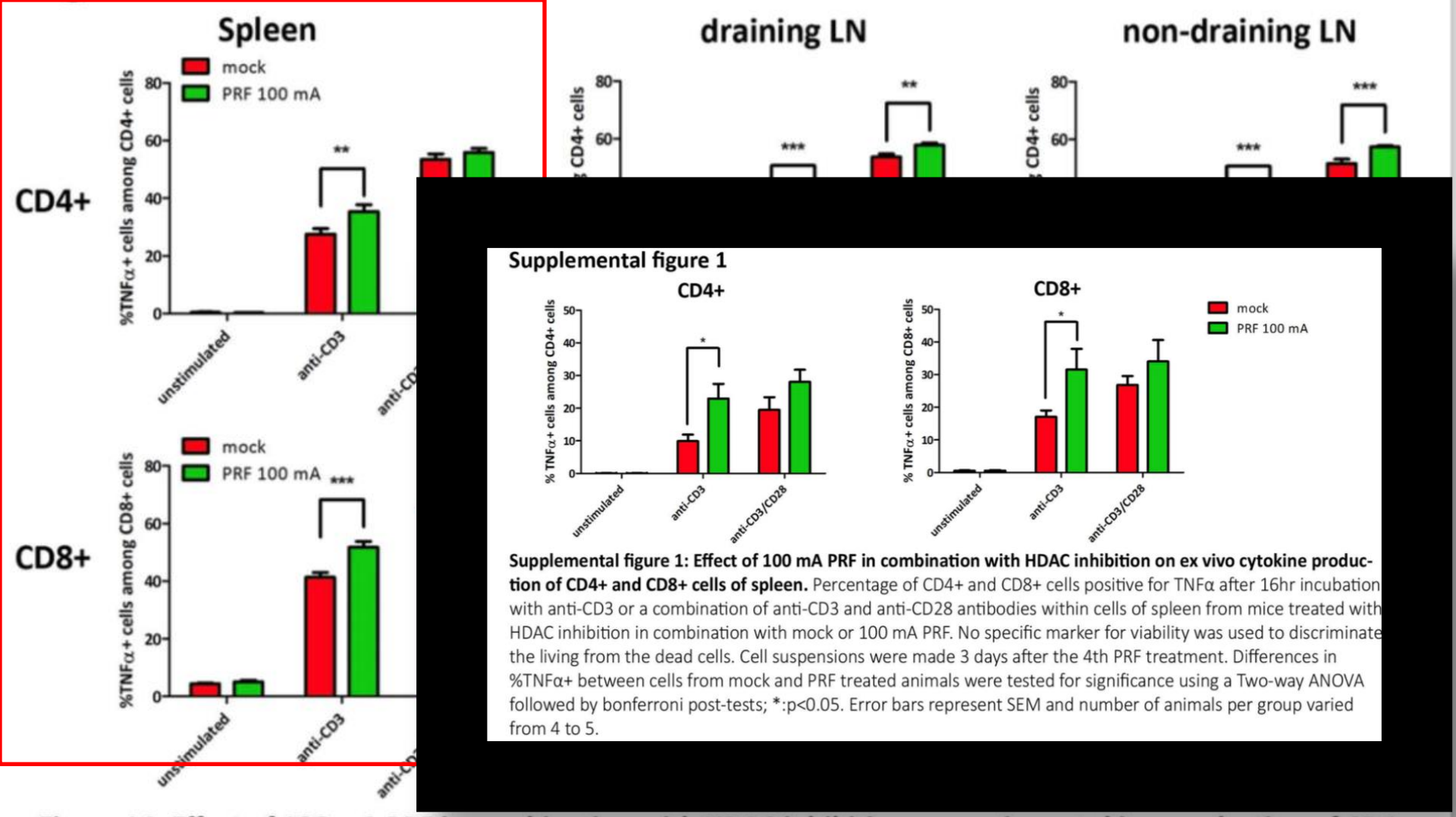
Figure 13



Treg T : **Suppressor** T cells

CD8+ T cells: **Cytotoxic** T cells, kills cancer **cells**

Figure 13: T cell populations in s.c. neuroblastoma tumors of mice treated with HDAC inhibition in combination with mock or 100 mA PRF. Three days after the 4th PRF treatment single cell suspensions were made of the tumors from mice treated with vorinostat in combination with mock or 100 mA PRF. Using flow cytometry the percentage of immune cells, and T cells was determined. Lines represent means of 5 mice per group. Differences in populations between mice treated with mock or PRF treatment were tested for significance using t-tests; *:p<0.05, **:p<0.01, ***:p<0.001. Viability dye eFluor780 was used to gate on living cells and CD45.2 to gate on immune cells (A). CD4 (B) and CD8 (C) were used to gate on T cells. Within CD4+ cells, CD25 and Foxp3 were used to gate on regulatory T cells (Treg) (D). To determine the balance between activating and inhibiting T cells the ratio between CD8+ and Treg cells was calculated (E).



Supplemental figure 1: Effect of 100 mA PRF in combination with HDAC inhibition on ex vivo cytokine production of CD4+ and CD8+ cells of spleen. Percentage of CD4+ and CD8+ cells positive for TNFα after 16hr incubation with anti-CD3 or a combination of anti-CD3 and anti-CD28 antibodies within cells of spleen from mice treated with HDAC inhibition in combination with mock or 100 mA PRF. No specific marker for viability was used to discriminate the living from the dead cells. Cell suspensions were made 3 days after the 4th PRF treatment. Differences in %TNFα+ between cells from mock and PRF treated animals were tested for significance using a Two-way ANOVA followed by bonferroni post-tests; *:p<0.05. Error bars represent SEM and number of animals per group varied from 4 to 5.

Figure 14: Effect of 100 mA PRF in combination with HDAC inhibition on ex vivo cytokine production of CD4+ and CD8+ cells of spleen and lymph nodes. Percentage of CD8+ and CD4+ cells positive for TNFα after 16hr incubation with anti-CD3 or a combination of anti-CD3 and anti-CD28 antibodies within cells of spleen or lymph nodes (draining and non-draining inguinal) from mice treated with HDAC inhibition in combination with mock or 100 mA PRF. Cell suspensions of organs were made 3 days after the 4th PRF treatment. Differences in %TNFα+ between cells from mock and PRF treated animals were tested for significance using a Two-way ANOVA followed by bonferroni post-tests; *:p<0.05, **:p<0.01, ***:p<0.001. Error bars represent SEM and number of animals per


Science
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack

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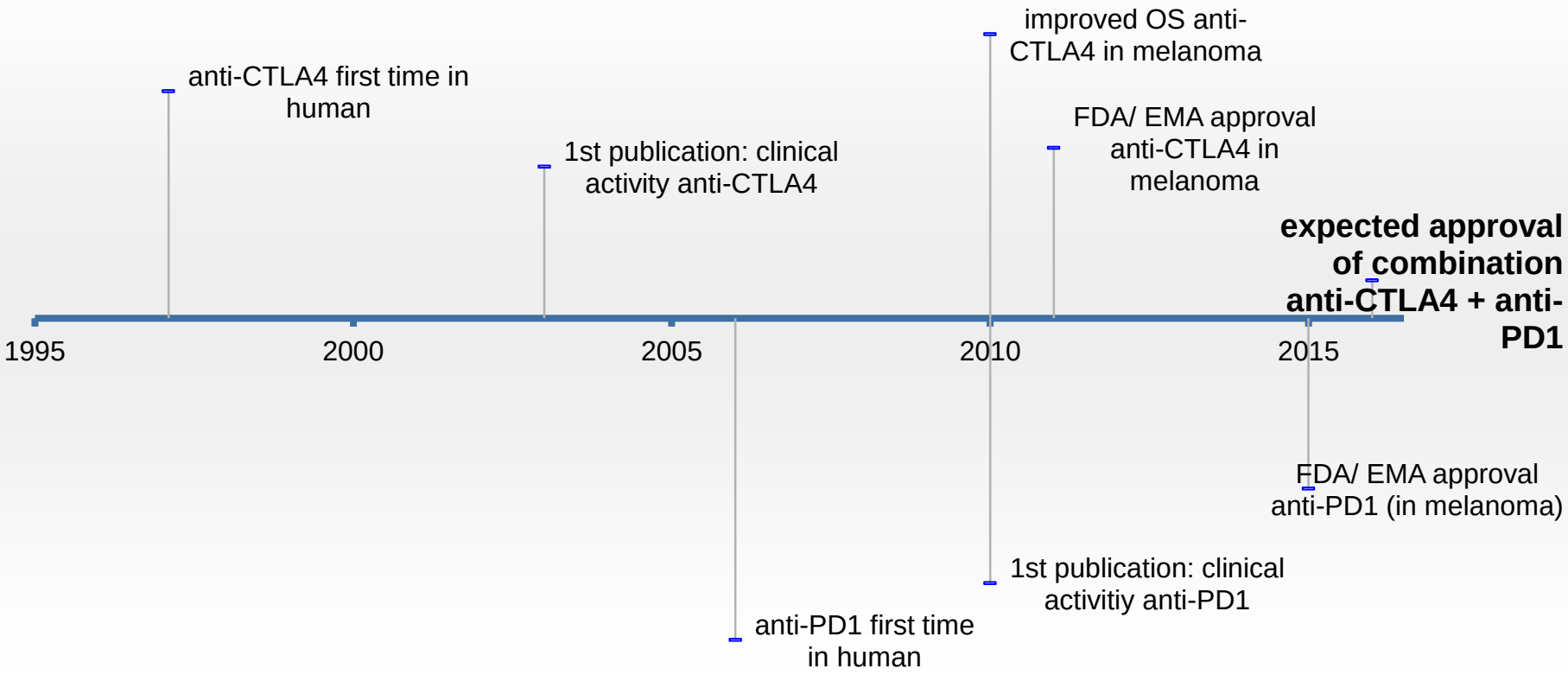
- 2011
- Ipilimumab or placebo
- Side effects: rash, some diarrhoea, fatigue

Immuno-oncology in last 2 decades

Immuno-oncology in a nutshell

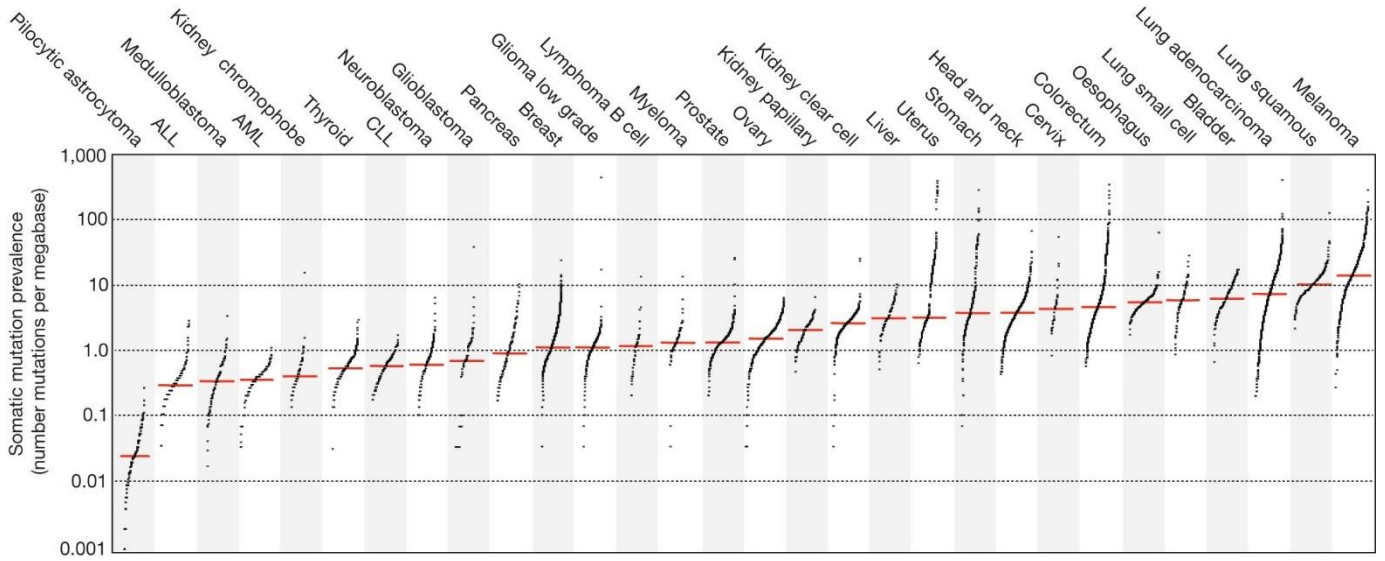


Hodi et al., Proc Natl Acad Sci U S A. 2003 Apr 15;100(8); Hodi et al., N Engl J Med. 2010 Aug 19;363(8):711-23; Brahmer JR, et al. J Clin Oncol. 2010;28:3167-3175; BMS Press release 19 June 2015; Merck Press release 22 July 2015; Robert C, et al. N Engl J Med. 2011;364:2515-2526

Every cancer?

- Cancer with high mutational load

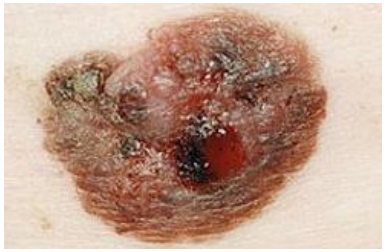
The prevalence of somatic mutations across human cancer types.



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

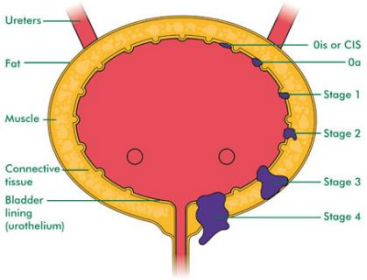
Highest mutational load

- Melanoma



- Lung cancer

- Bladder cancer



Treatment

- Checkpoint inhibitors
  - CTLA 4 – ipilimumab
  - PD 1 – nivolumab / pembrolizumab
  - PD L1 – atezolizumab / avelumab / durvalumab

Immuno-Oncology

Clinical efficacy

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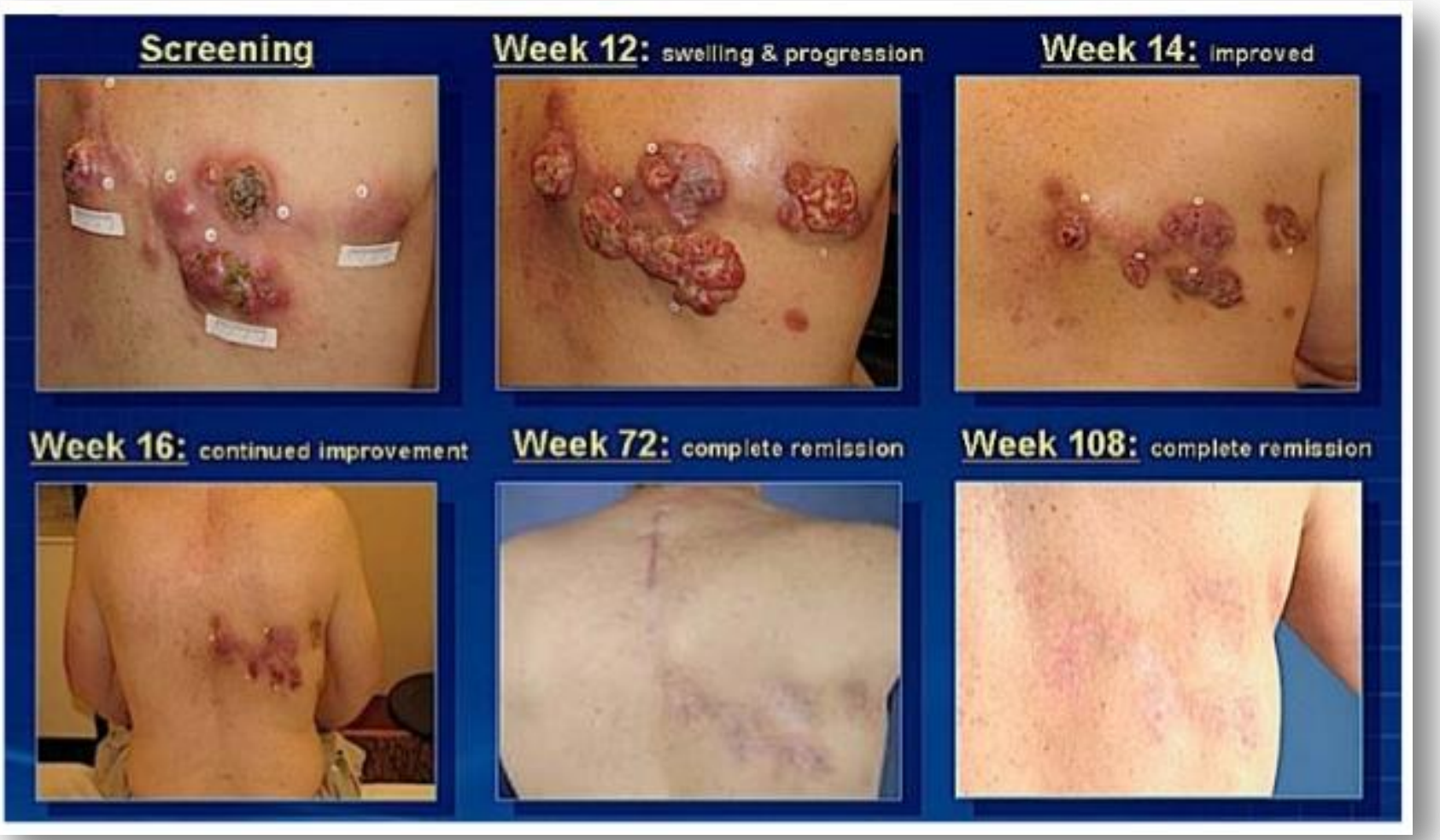
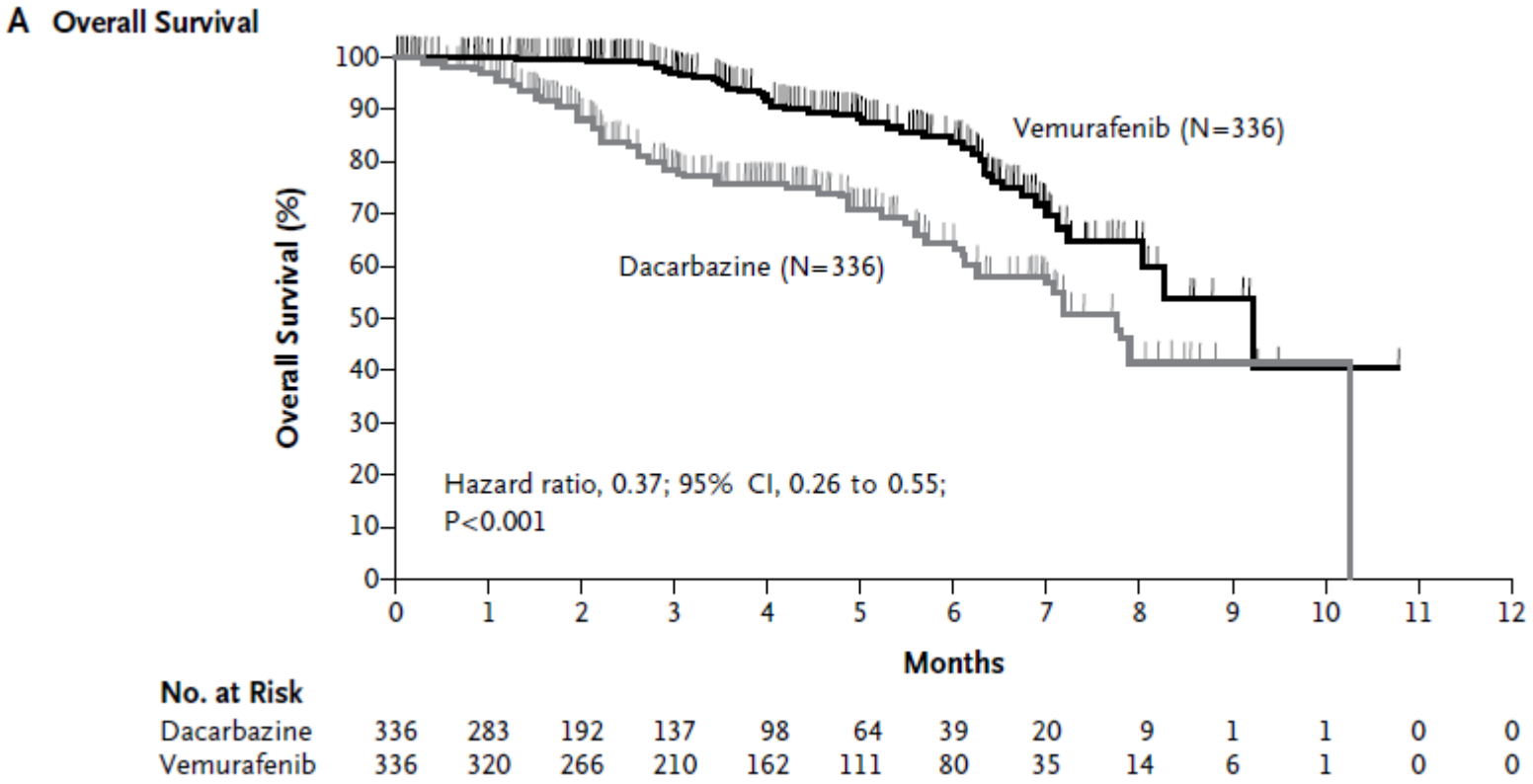
Ipilimumab: example of response



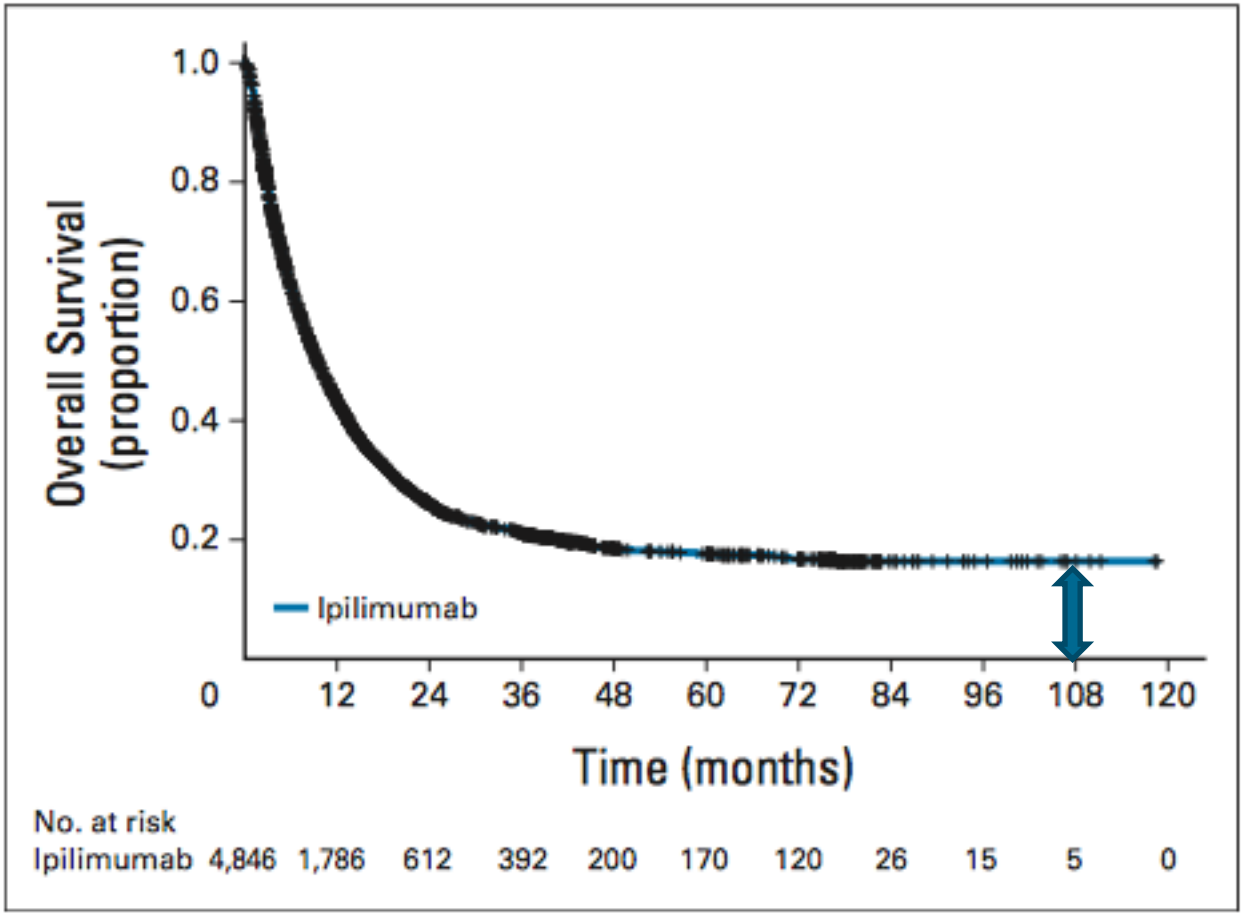
Images courtesy of Jedd Wolchock

Vemurafenib – melanoma (BRAF v600 mutation)



Chapman, NEJM 2011

Melanoma - ipilimumab (>10 yr followup)



Schadendorf D, et al., Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma, JCO 2015, 33(17):1889-94.

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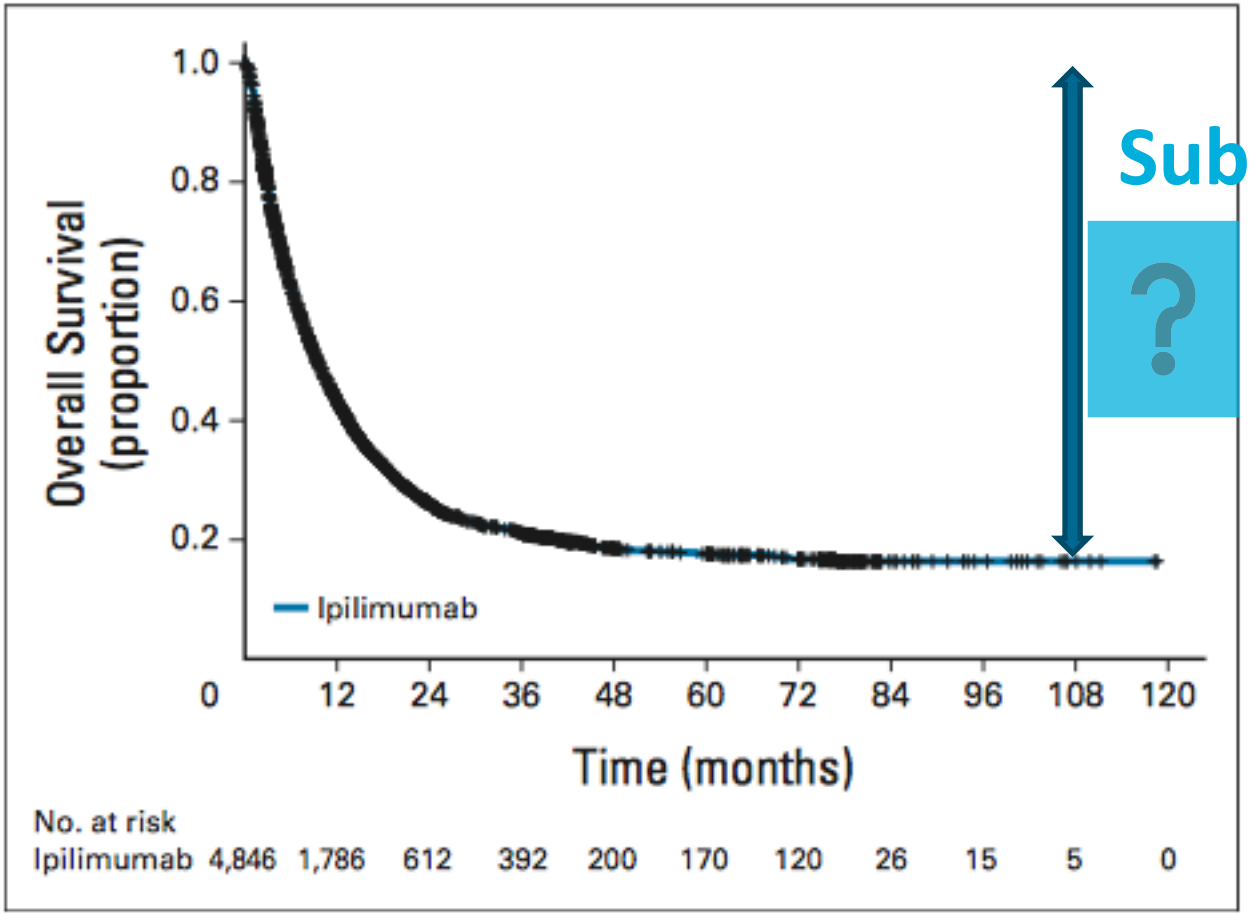
Melanoma - ipilimumab (>10 jr followup)



Sub-groups?

?

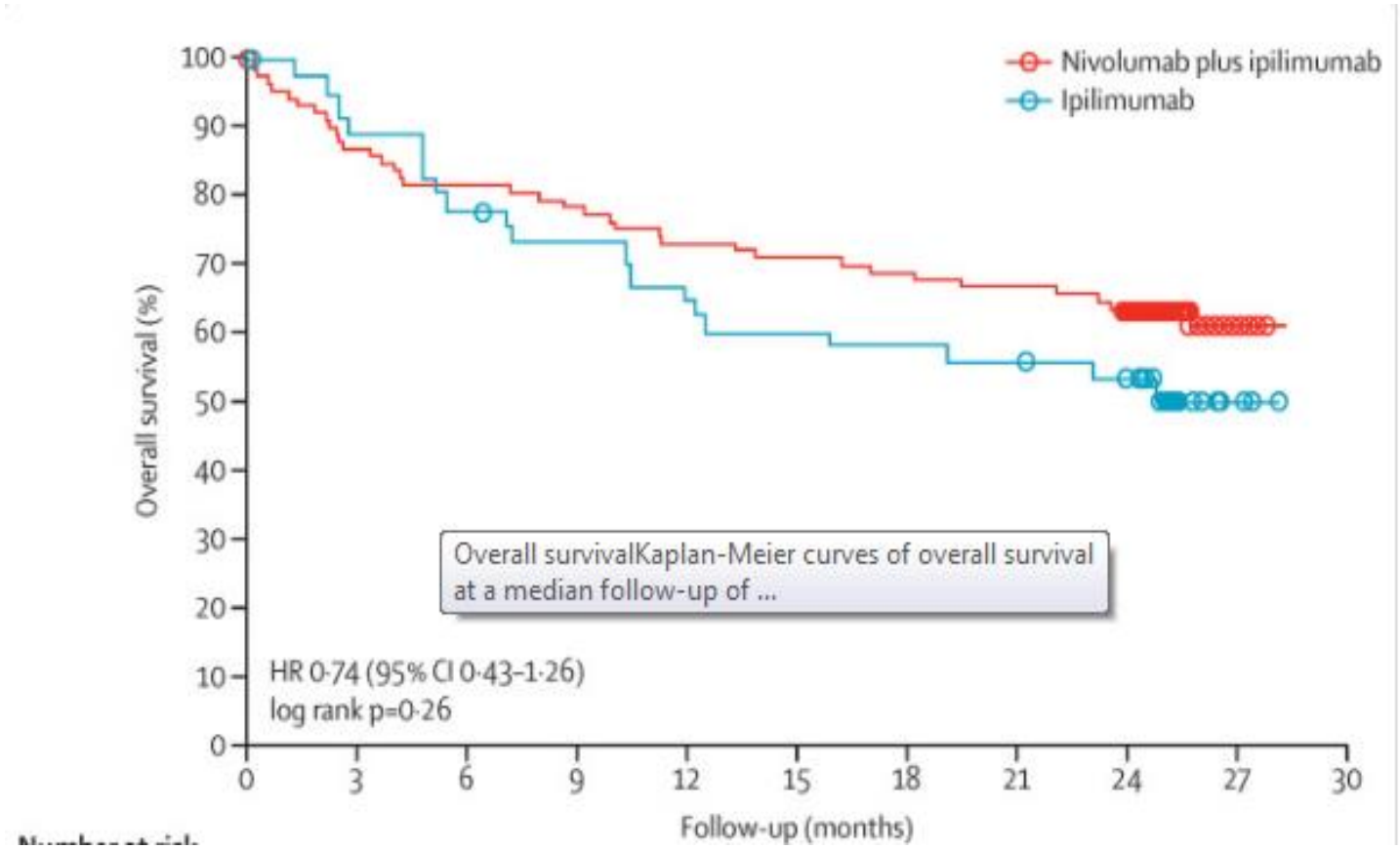
Schadendorf D, et al., Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma, JCO 2015, 33(17):1889-94.

Mrs X

- 2017
- 36 years
- ~~Melanoma + lung metastasis~~
- Teacher
- Married
- Loves travelling, yoga and cycling

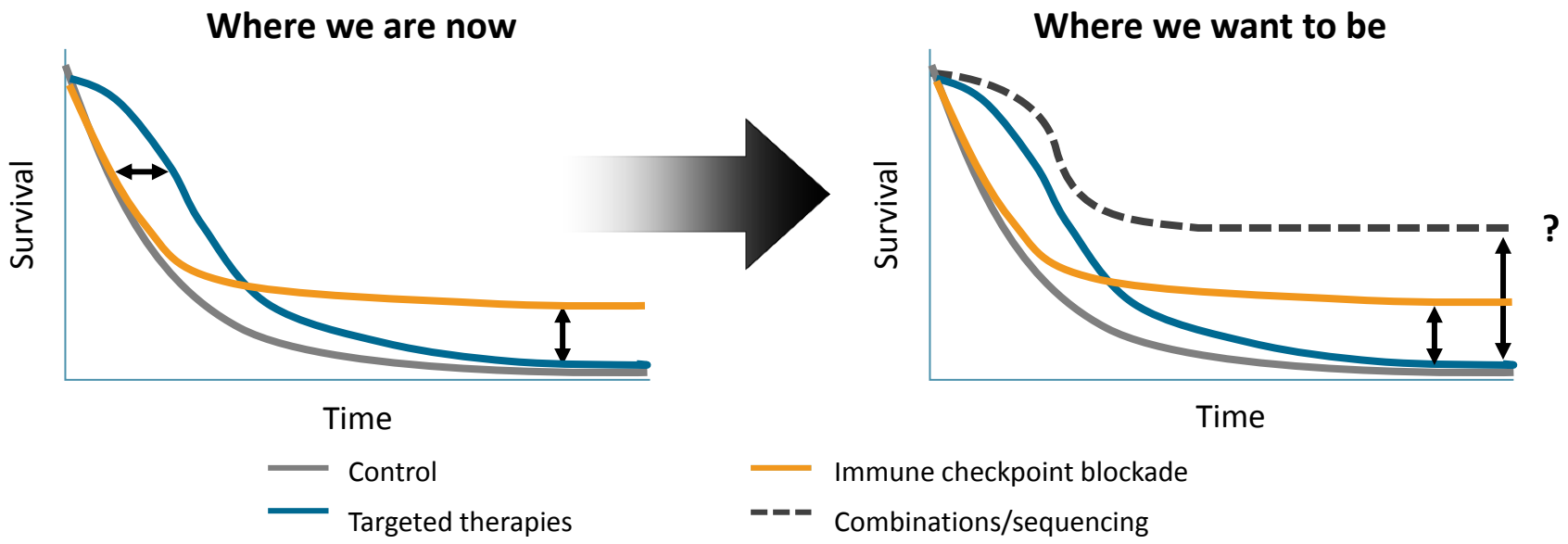
- Future?

Ipilimumab and nivolumab – metastasized melanoma



Hodi, Lancet Oncology, 2016

Immunotherapy combinations: goals and potential response patterns



Hypothetical slide illustrating a scientific concept that is beyond data available so far.
These charts are not intended to predict what may actually be observed in clinical studies

Adapted from Ribas A. Presented at WCM 2013. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46. Hellmann MD et al. Presented at ECC 2015. Abstract P349.

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Bladder cancer:

- Bladder cancer
  - Nivolumab; ORR 19.6%[1]
  - Pembrolizumab; ORR 21% vs 14 %; median survival 10.3 vs 7.4 months[2]
  - Atezolizumab[3]; 15 % respons in total patient population
    - 26% respons in pt with high PDL1 expression

  - Overall; durable respons for 20% of the responders

[1] Sharma et al; Oncology 2017

[2] Bellmunt et al; NEJM 2017

[3] Balar et al; Lancet 2017

Immuno-oncology

toxicity

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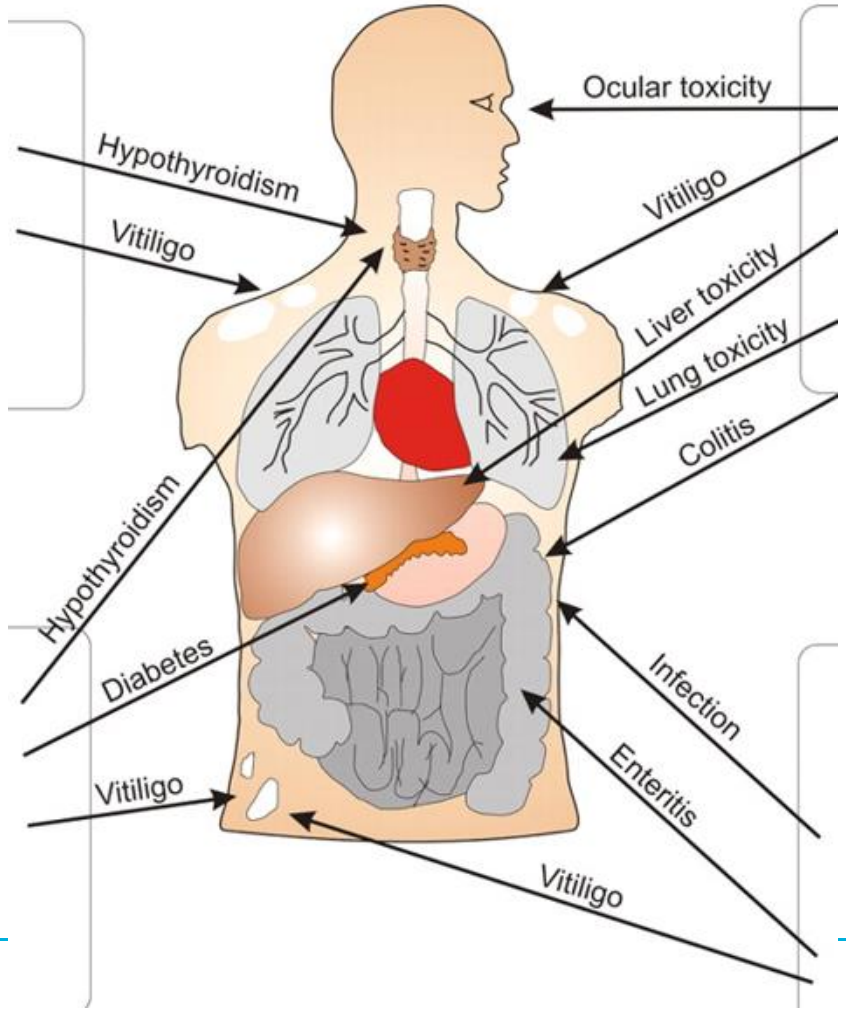
Does checkpoint-toxicity happen?

- Most patients (**84.8%**) suffer from any form of drug-related adverse events (AEs); most are only mild to moderate
- **25.3%** grade 3/4 drug-related AE
- Mainly immuun mediated
- Beware: ±**1%** fatal

Camacho LH, Cancer Med. 2015 May; 4(5): 661–672.

Immune-related toxicity



Immune-related toxicity (irAE's)

Gastrointestinal 40% (gr 3-4:16%)	Colitis, intestinal perforation, stomatitis
Skin (50%)	Dermatitis, vitiligo
Endocrine (5%)	Adrenal insufficiency, hypophysitis, thyroiditis
Eye	Conjunctivitis, episcleritis, ocular inflammation
Hepatobiliary (3%)	Autoimmune hepatitis (increased ALT and AST)
Immune System	Sarcoidosis
Musculoskeletal	Arthritis/arthralgia
Renal	Granulomatous tubulointerstitial nephritis, nephritis (autoimmune)
Respiratory	Lung infiltration, pneumonitis

Adapted from own institute internal teaching material/ reference

Endocrinopathies

- **Symptoms:**

  Headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment [1-3]

- Hypophysitis, hypothyroidism, hyperthyroidism, and adrenal insufficiency

[1]Blansfield JA et al. *J Immunother* 2005;28:593-598;
[2]Attia P et al. *J Clin Oncol* 2005;23:6043-6053;
[3]Phan GQ et al. *Proc Natl Acad Sci USA* 2003;100:8372-8377.

Treatment of IR-toxicities

Treatment of IR-toxicities

Future

- Cancer as chronic disease
  - Longer life expectancy
  - Extremely variable life expectancy
  - (serious) toxicities during treatment

- Immunotherapy as first line treatment

- Need for better predictors of positive effects of immunotherapy

Next?