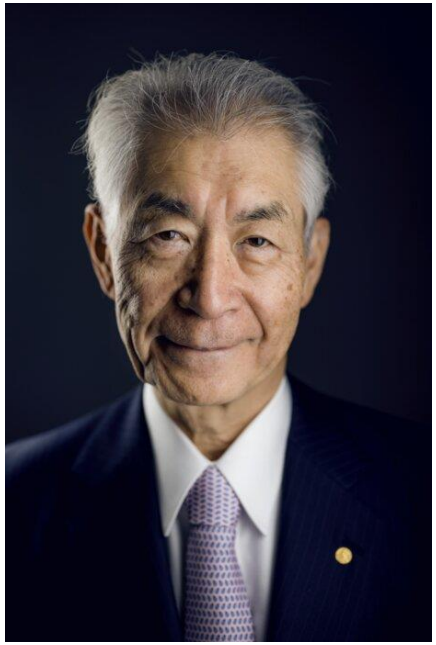
Immunterapi i kreftbehandling

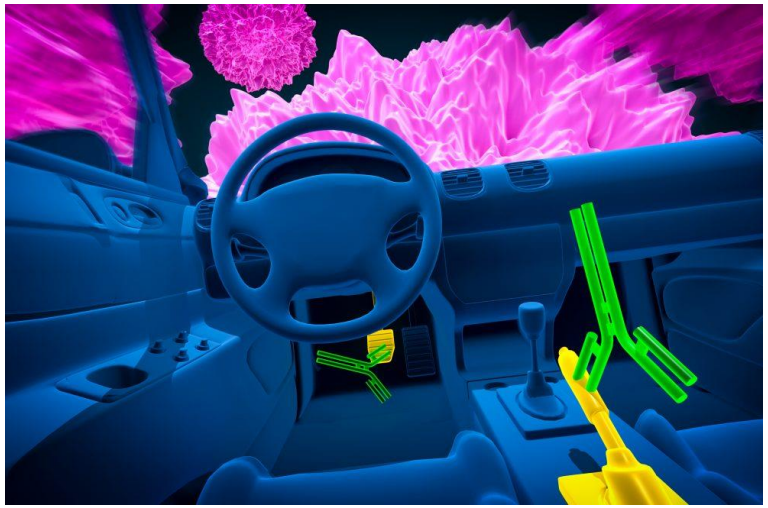
Cancer therapy: Releasing the brakes of immunity

The Nobel Prize in Physiology or Medicine 2018 was awarded to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation." The Laureates have shown how different strategies for inhibiting the brakes on the immune system can be used in the treatment of cancer. Their discoveries are a landmark in our fight against cancer.

Anti CTLA-4



PD-1



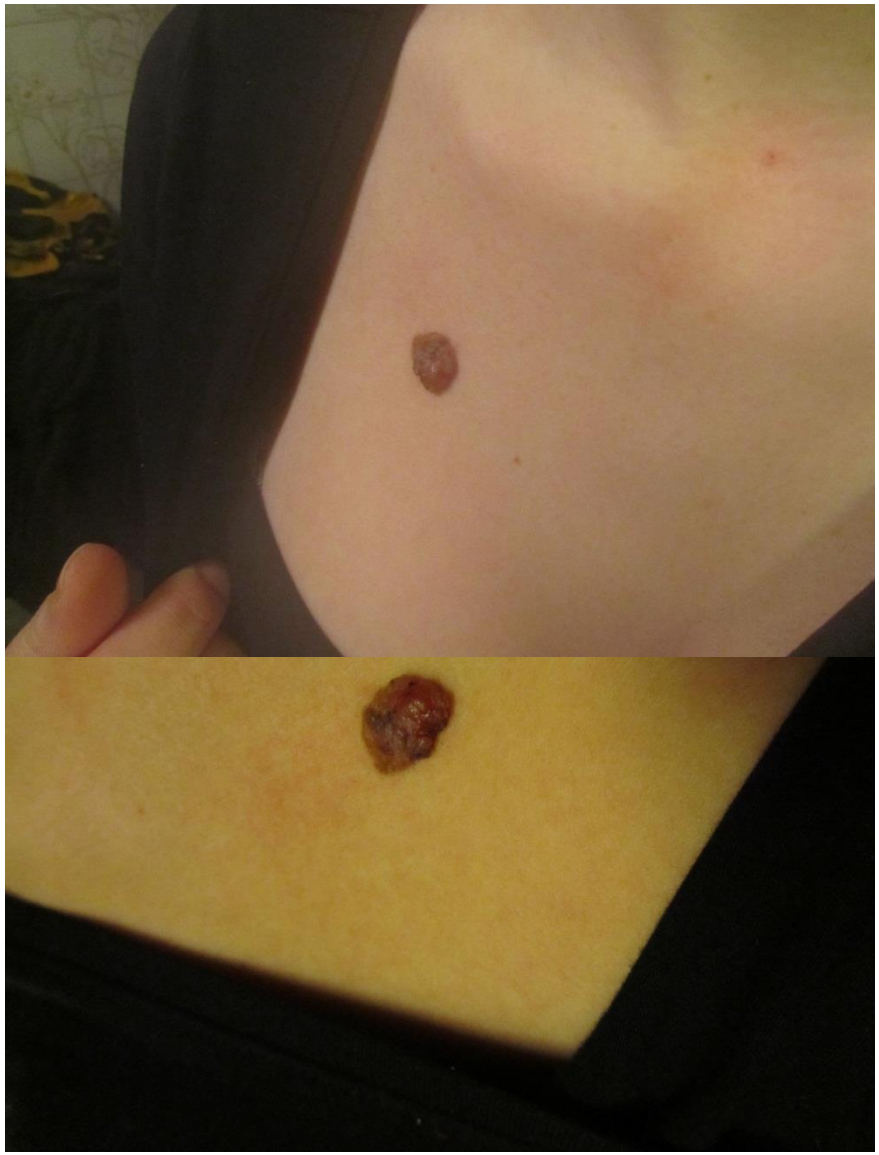
Woman born 1987

Pigmented lesion from age 8 right breast 2009 growth, irritation

2009: Doctor: «Nothing to worry about, in fact if we romove it you will get an ugly scar»

2011: Continued to grow, doctor finally referred her to a surgeon.

March 2011: Nodular melanoma, breslow 3.8 mm, Clark 4, Ulcerated, 2.5 mitoses/mm3.



Woman born 1987

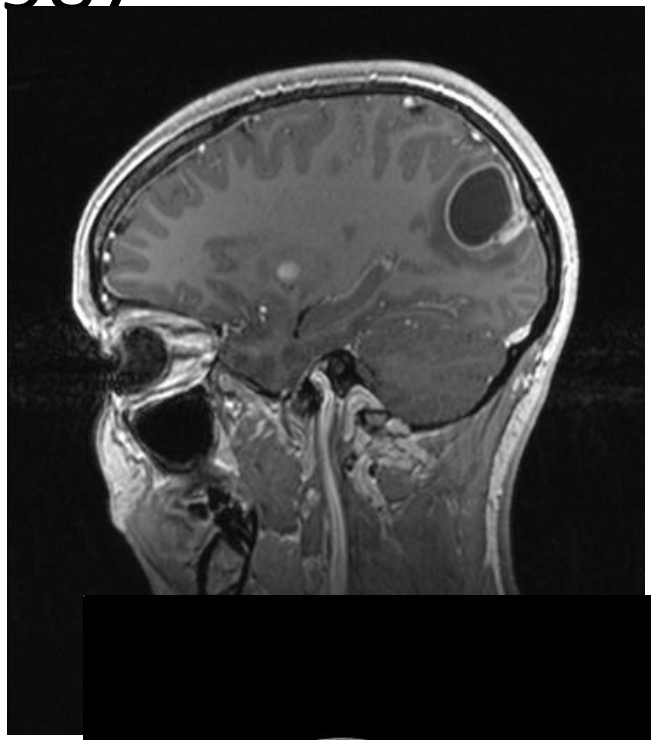
June 2014: Two brain metastases. The largest was surgically removed, the smallest treated with gammaknife

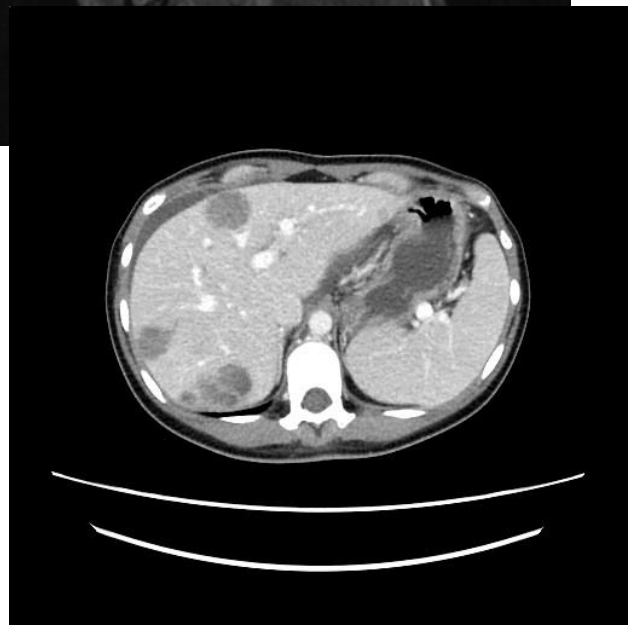
June 2014: Progression of lung mets.

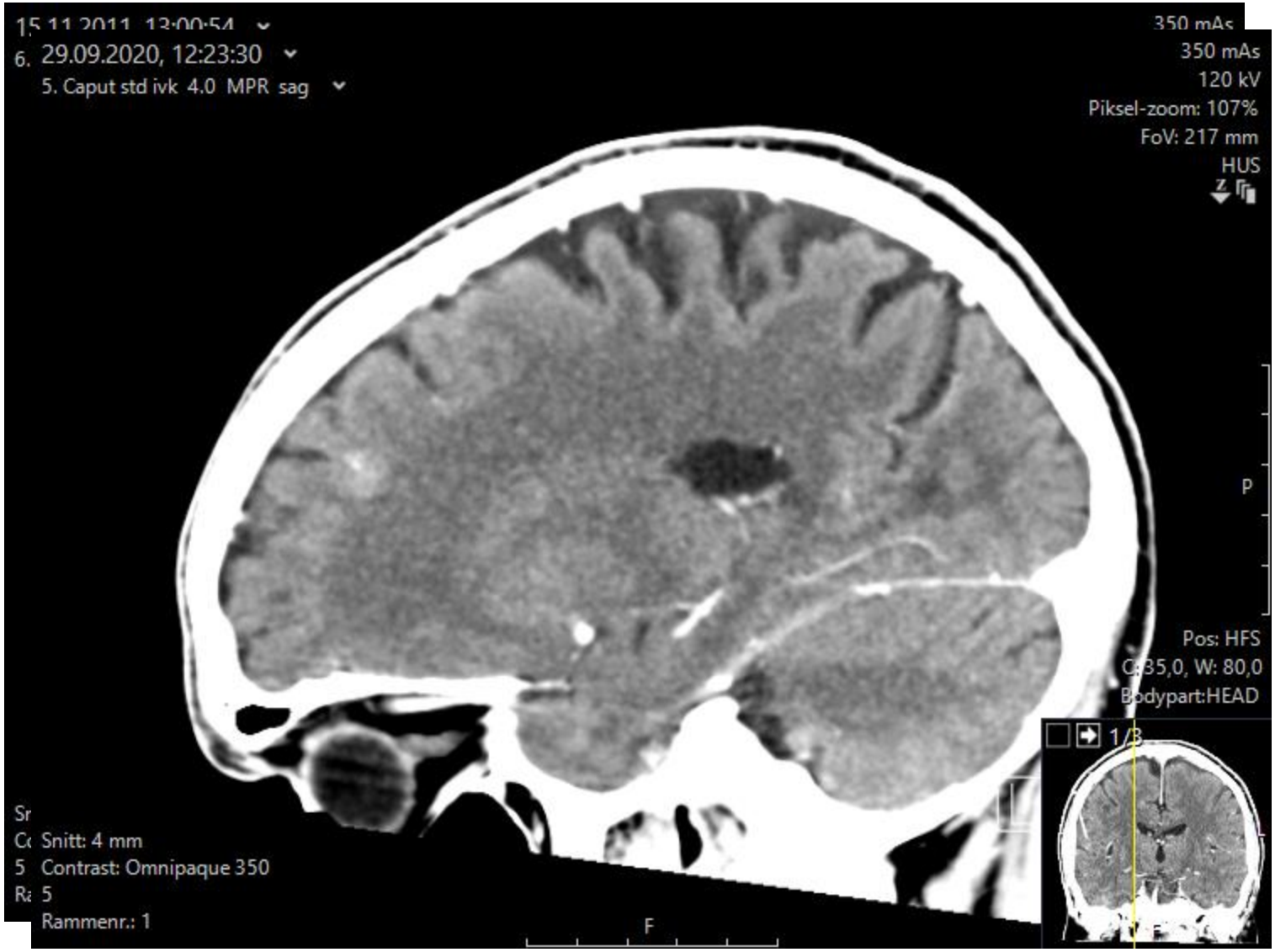
July 2014: Massive progression.

August 2014: 1 IPI

Sept 2014: Mors






15.11.2011, 13:00:54
6. 29.09.2020, 12:23:30
5. Caput std ivk 4.0 MPR sag
350 mAs
350 mAs
120 kV
Piksel-zoom: 107%
FoV: 217 mm
HUS
P
Pos: HFS
C: 35,0, W: 80,0
Bodypart:HEAD
1/3
Snitt: 4 mm
Contrast: Omnipaque 350
Rammenr.: 1
F

IJC
International Journal of Cancer

Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008—A Swedish population-based study

Britta Krynitz[1,2], Gustaf Edgren[3], Bernt Lindelöf[2], Eva Baecklund[4], Christina Brattström[5], Henryk Wilczek[5] and Karin E. Smedby[6]

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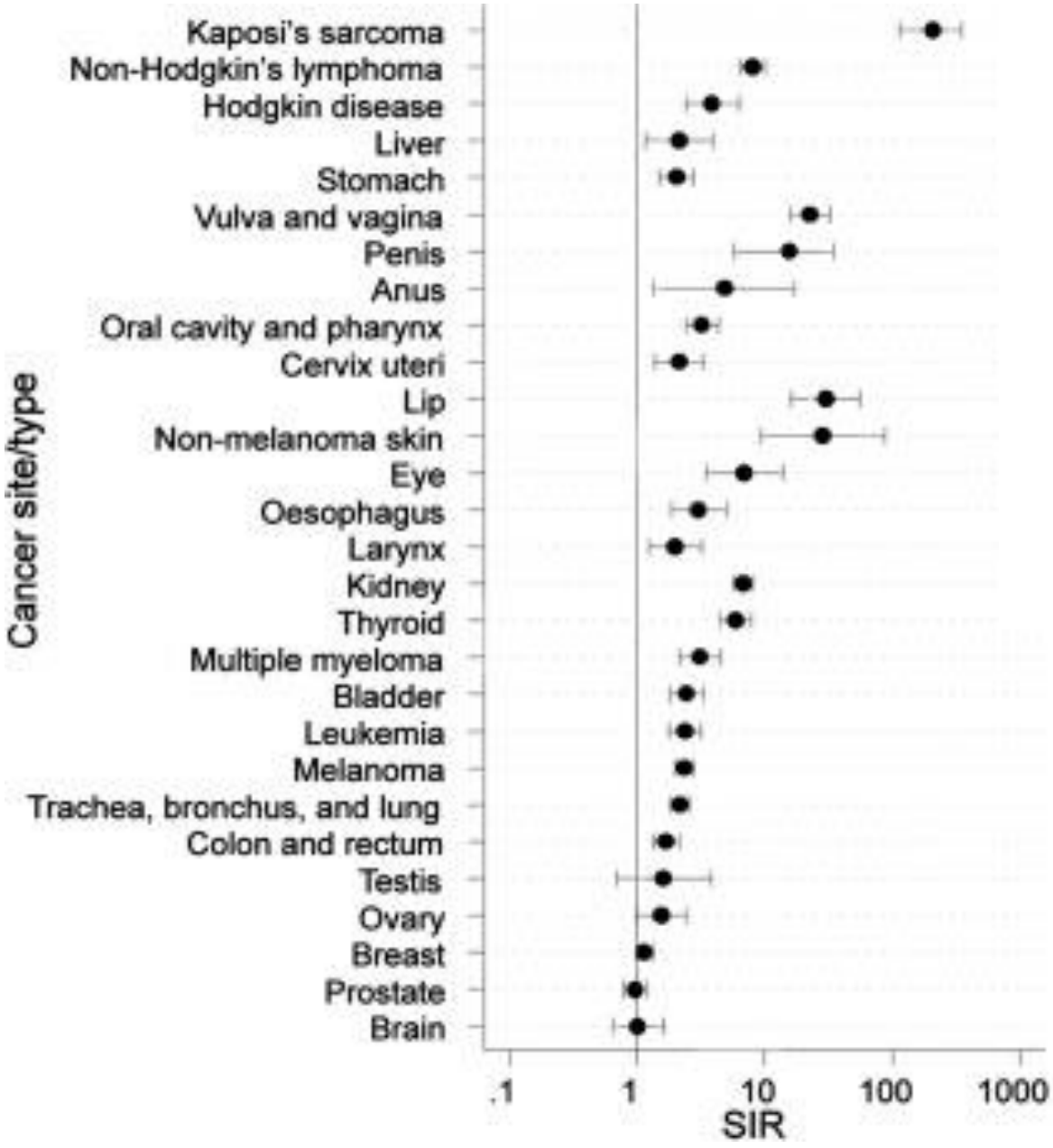
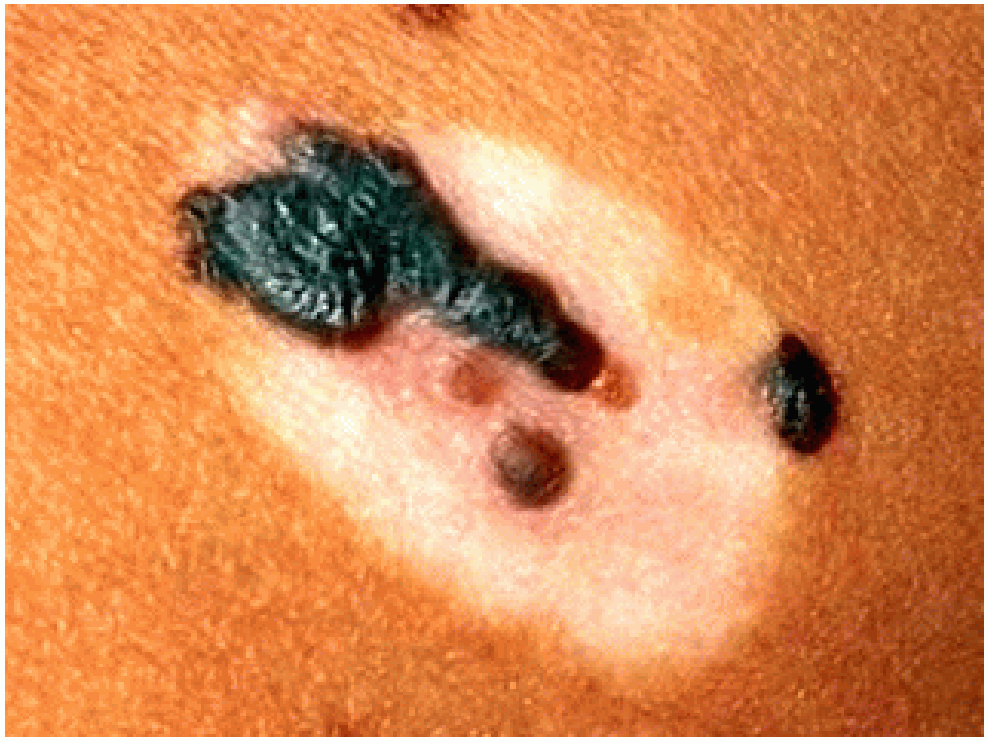
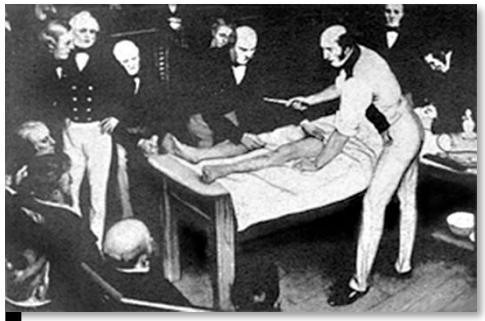
[2] Unit of Dermatology and Venereology, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden
[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet and Department of Epidemiology, Harvard School of Public Health, Boston, MA
[4] Unit of Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[5] Division of Transplantation Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
[6] Unit of Clinical Epidemiology, Department of Medicine, Karolinska University Hospital, Stockholm, Sweden

Organ transplant recipients are at increased risk of a wide range of malignancies, especially cutaneous squamous cell carcinomas (SCC). Few previous population-based studies have quantified and compared cancer risks according to graft type and with long-term follow-up. Using nationwide Swedish registers, we identified 10,476 recipients transplanted from 1970 to 2008 and followed them for cancer occurrence. Relative risks of cancer in comparison with the general population were expressed as standardized incidence ratios (SIR) and within the transplanted cohort as incidence rate ratios (IRR). During a total follow-up of 93,432 person-years, patients were diagnosed with 1,175 cancers excluding SCC, and with 2,231 SCC, $SIR_{cancer\ excl\ SCC}$ 2.4 (95% CI, 2.2–2.5); SIR_{SCC} 121 (95% CI, 116–127). Cancer risks were most increased among heart and/or lung recipients $SIR_{cancer\ excl\ SCC}$ 3.3 (95% CI, 2.8–4.0); SIR_{SCC} 198 (95% CI, 174–224), followed by kidney $SIR_{cancer\ excl\ SCC}$ 2.3 (95% CI, 2.1–2.4); SIR_{SCC} 121 (95% CI, 116–127) and liver recipients $SIR_{cancer\ excl\ SCC}$ 2.3 (95% CI, 1.9–2.8); SIR_{SCC} 32 (95%


Kaposi's sarcoma
Non-Hodgkin's lymphoma
Hodgkin disease
Liver
Stomach
Vulva and vagina
Penis
Anus
Oral cavity and pharynx
Cervix uteri
Lip
Non-melanoma skin
Eye
Oesophagus
Larynx
Kidney
Thyroid
Multiple myeloma
Bladder
Leukemia
Melanoma
Trachea, bronchus, and lung
Colon and rectum
Testis
Ovary
Breast
Prostate
Brain
Cancer site/type
.1
1
10
100
1000
SIR



Evolution of Cancer Therapy: Core Treatment Modalities[1–3]

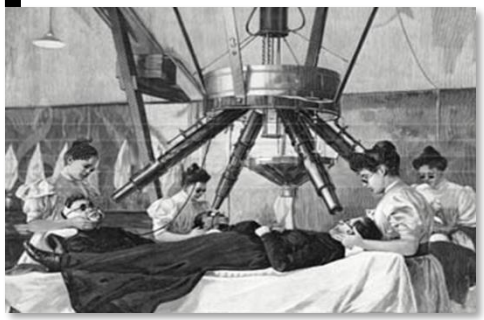


Surgery
1846

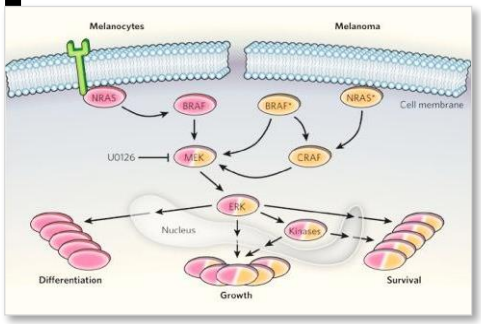
Chemotherapy
1946

Immunotherapy
2010

Radiation Therapy
1901



Targeted Therapy
1997



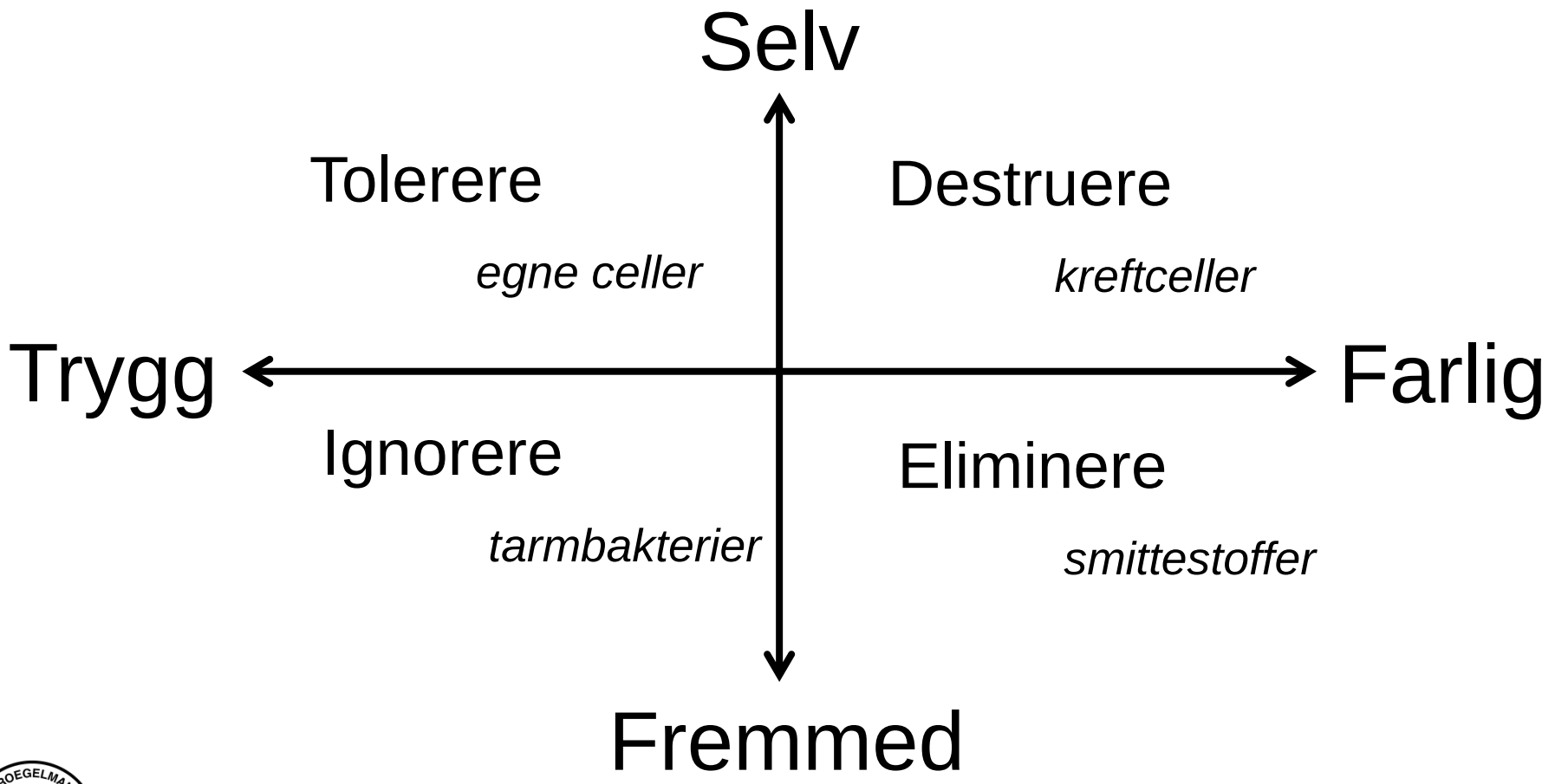
1. DeVita VT Jr, et al. *Cancer Res*. 2008;68:8643–8653; 2. American Cancer Society. http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/; 3. Ross JS, et al. *Am J Clin Pathol*. 2004;122:598–609.

Mercury No: ONCHQ14NP02639-01 (modified after)

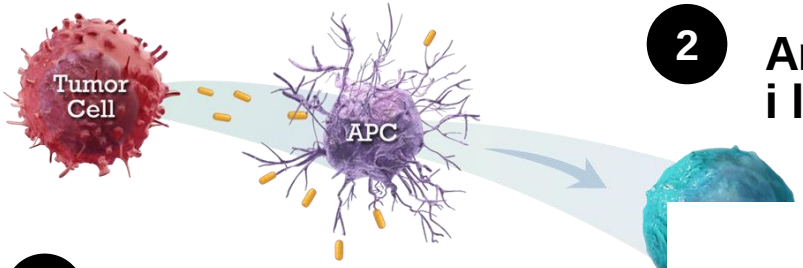
Malignt melanom:

Immunterapi

Immunsystemets utfordring



Anti tumor immun respons

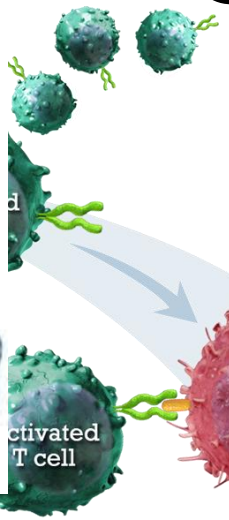


1 **Kreftcellen skiller ut unormale proteiner** (antigener)

2 **Antigener presenteres i lymfeknuten**

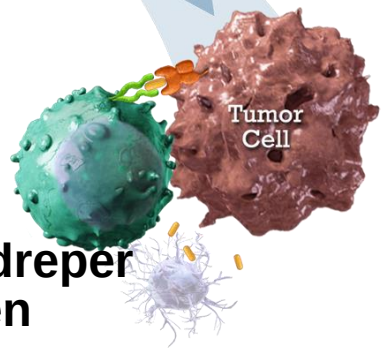
Til T-cellene

3

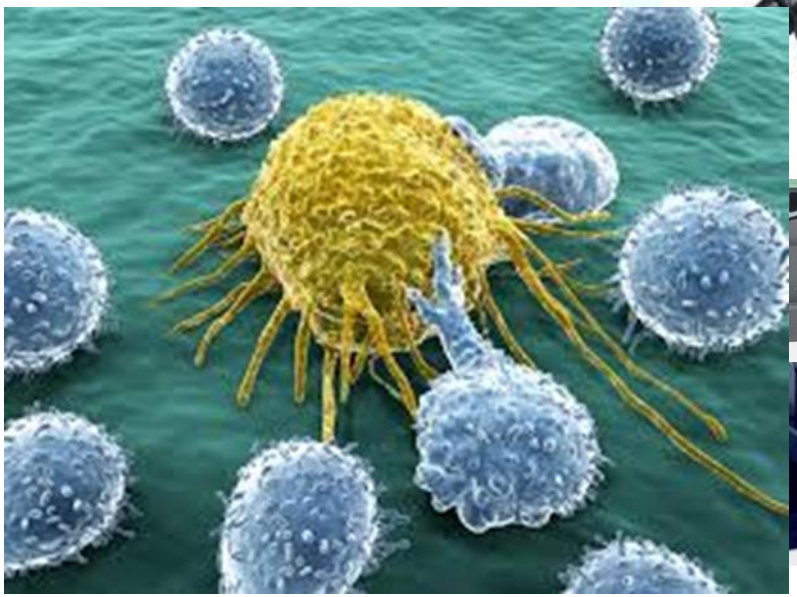


er antigenet

np



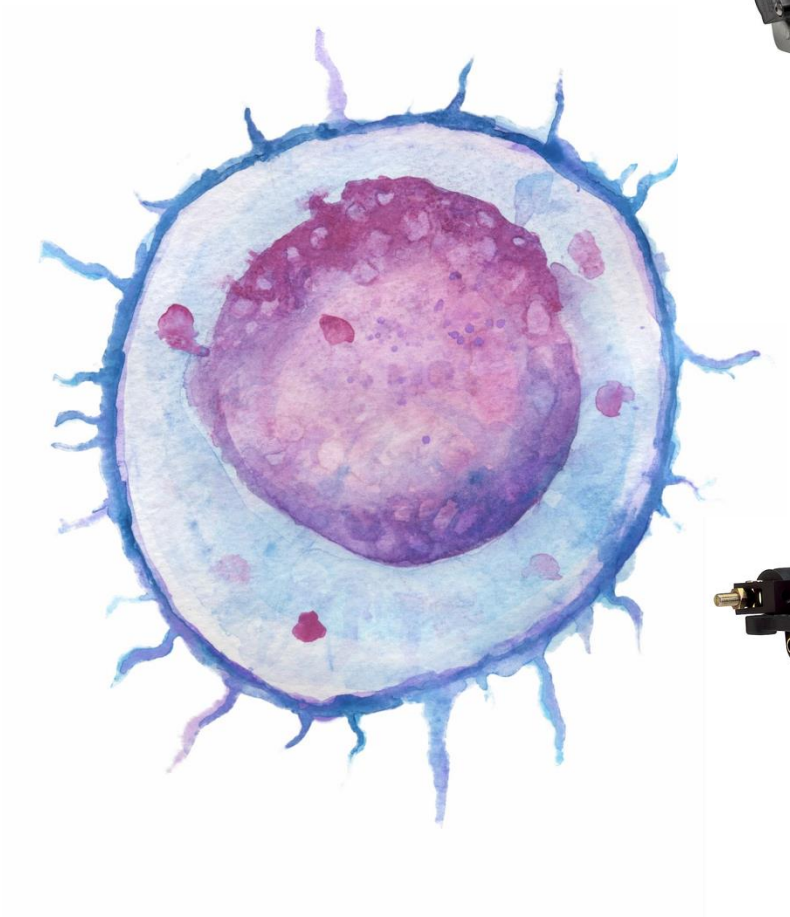
5 **T-cellen dreper kreftcellen**



2005-10: Paradigmeskifte

- Strategi 1: Stimulere immunsystemet

- Strategi 2: Ta bort hemmerne
  - Immune checkpoint inhibitors
    - Anti CTLA-4
    - Anti PD-1
    - Anti PDL-1



Stimulere immunsystemet
Kost tilskudd
Vaksiner
Mirakelkurer
Diverse medisiner
30 år med resultatløs forskning

Hemmer immunsystemet
CTLA-4
PD-1

(immune checkpoints)

Bryanmjones.com

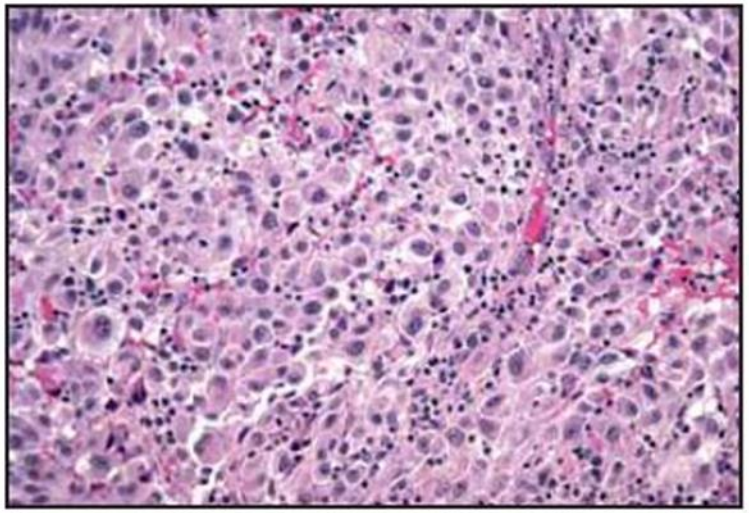
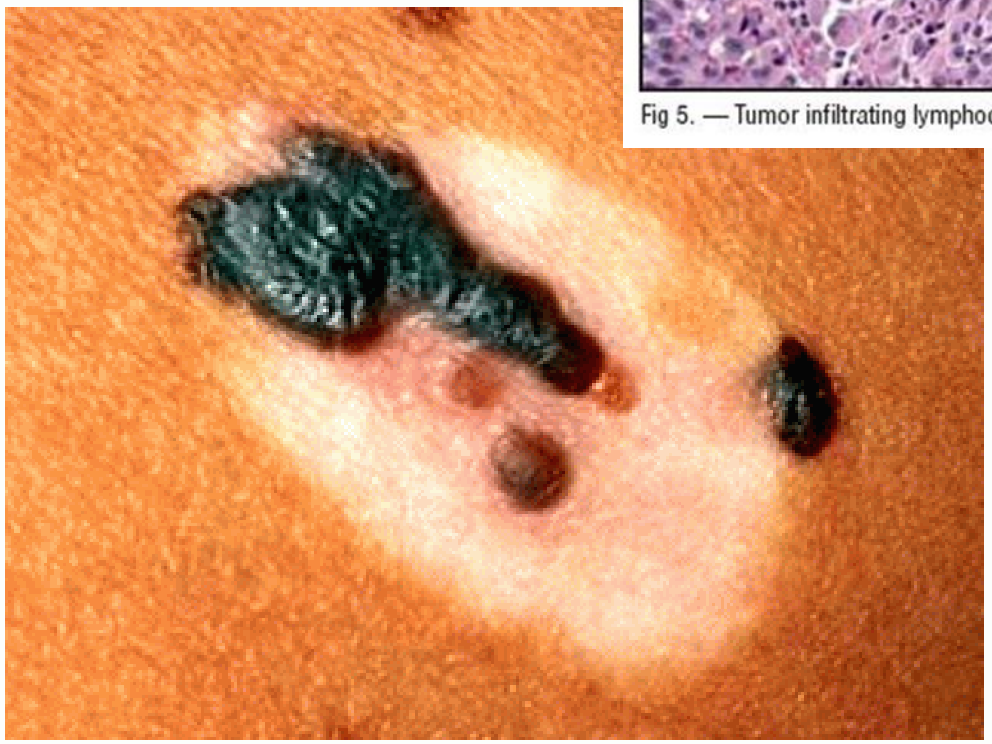
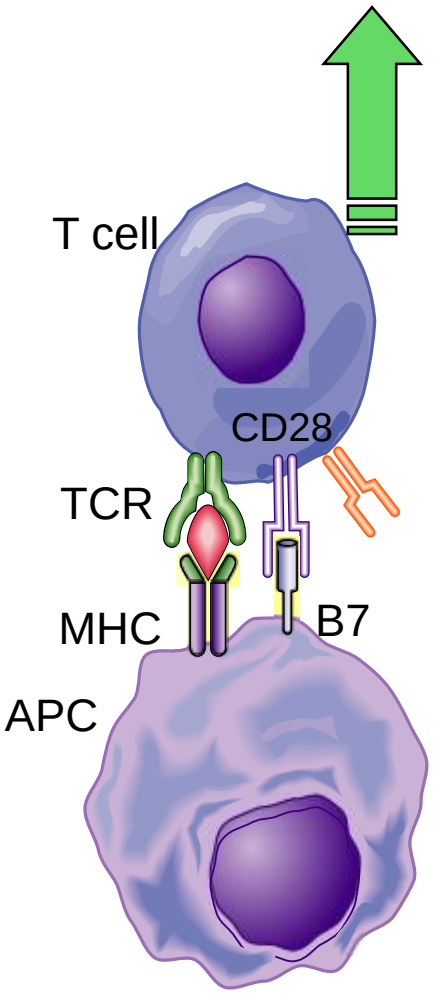


Fig 5. — Tumor infiltrating lymphocytes (original magnification × 200).

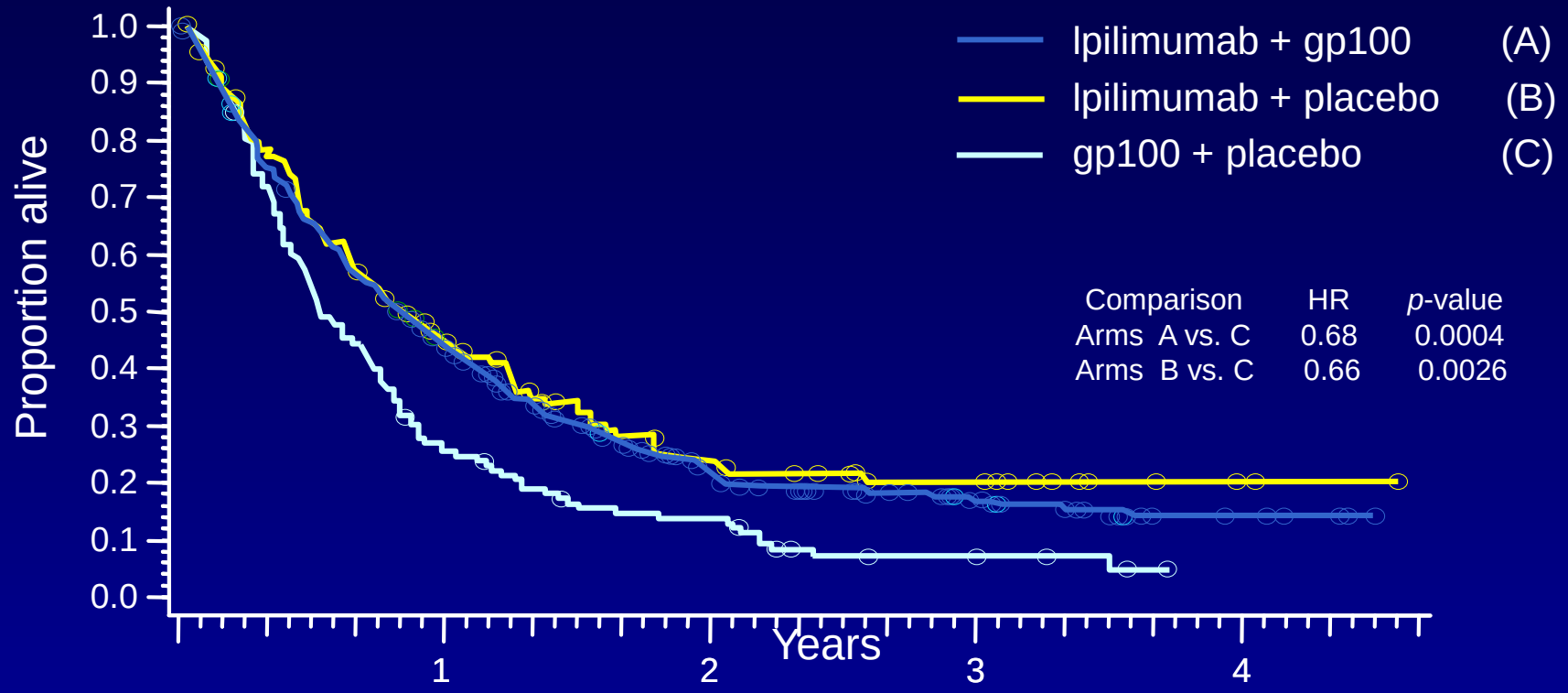


T-cell activation



Adapted from: Coico RF et al. *Immunology: A Short Course.* 5th ed. Wiley-Liss, NJ, 2003 and Abbas AK et al. *Cellular and Molecular Immunology* 5th ed. Elsevier Saunders, 2005

Kaplan-Meier analysis of survival



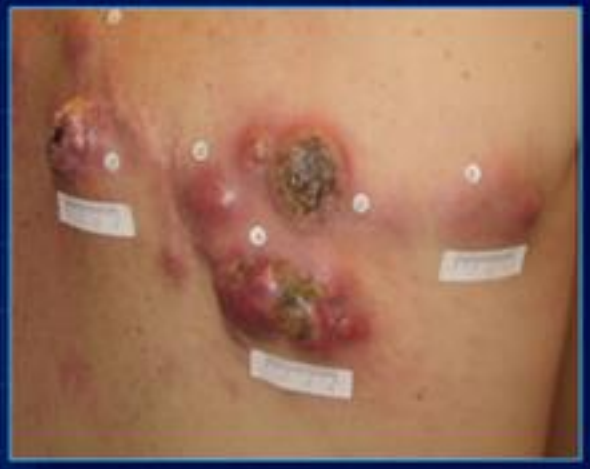
Survival Rate	Ipilimumab + gp100 (n=403)	Ipilimumab + placebo (n=137)	gp100 + placebo (n=136)
1 year	44%	46%	25%
2 year	22%	24%	14%
median OS (mts) (95% CI)	10.0 8.5-11.5	10.1 8.0-13.8	6.4 5.5-8.7

Hodi S et al. NEJM 2010;363(8):711-23

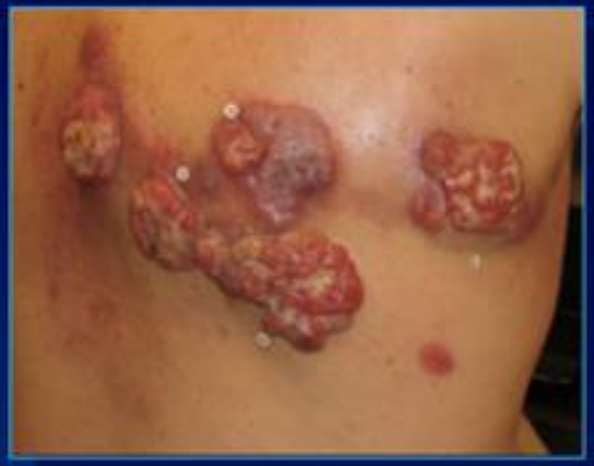
The approved dose for ipilimumab is 3mg/kg, q3w for 4 times (SmPC)

Ipilimumab: Helping Patients Prevail Over Serious Disease

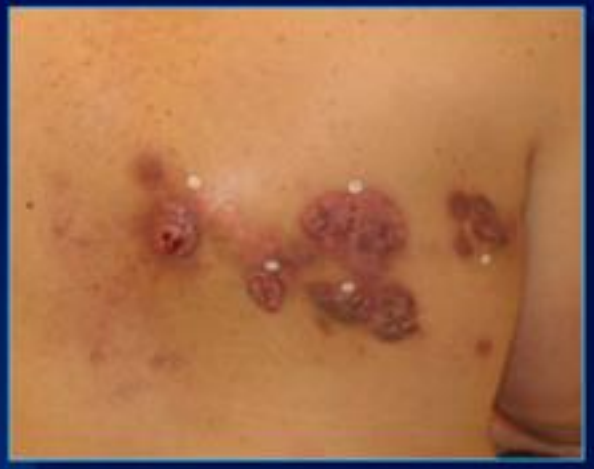
Screening



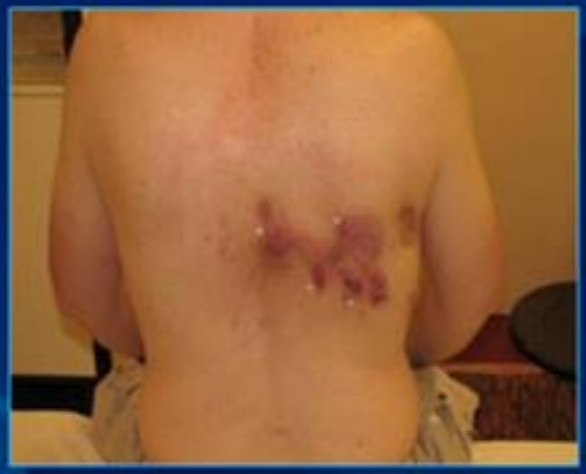
Week 12: swelling & progression



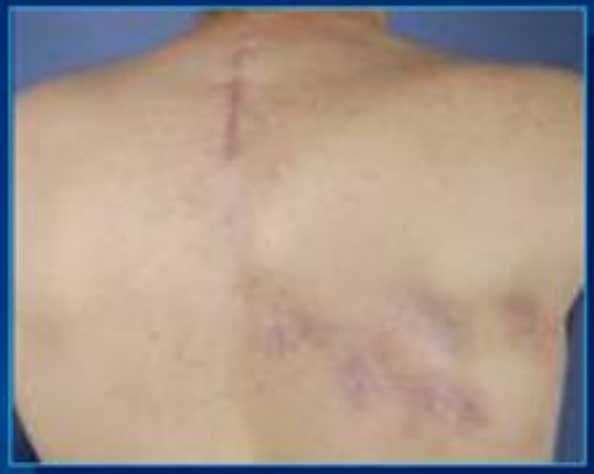
Week 14: improved



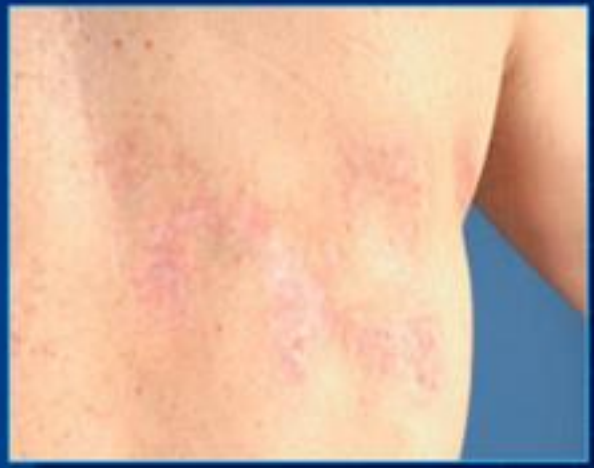
Week 16: continued improvement



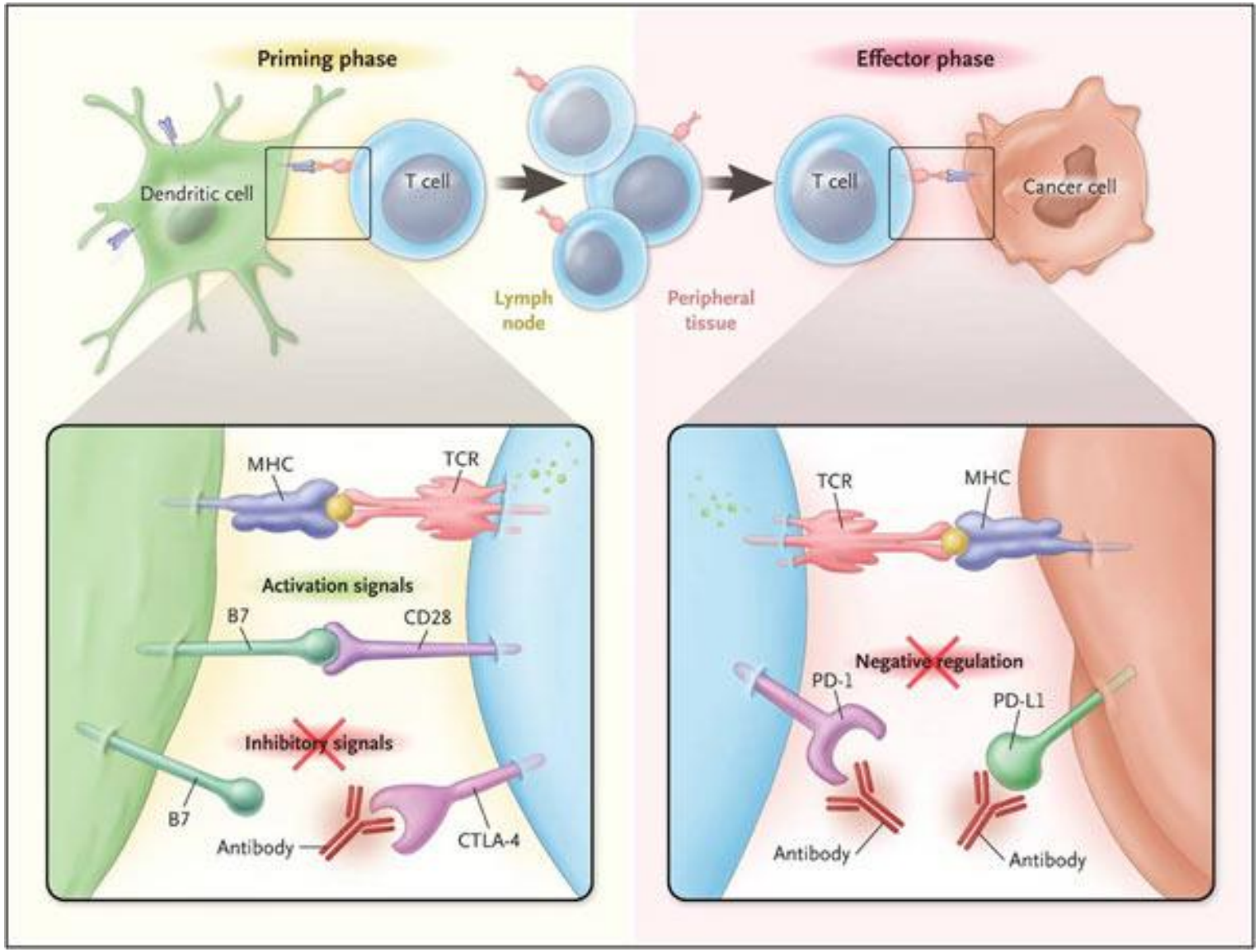
Week 72: complete remission



Week 108: complete remission



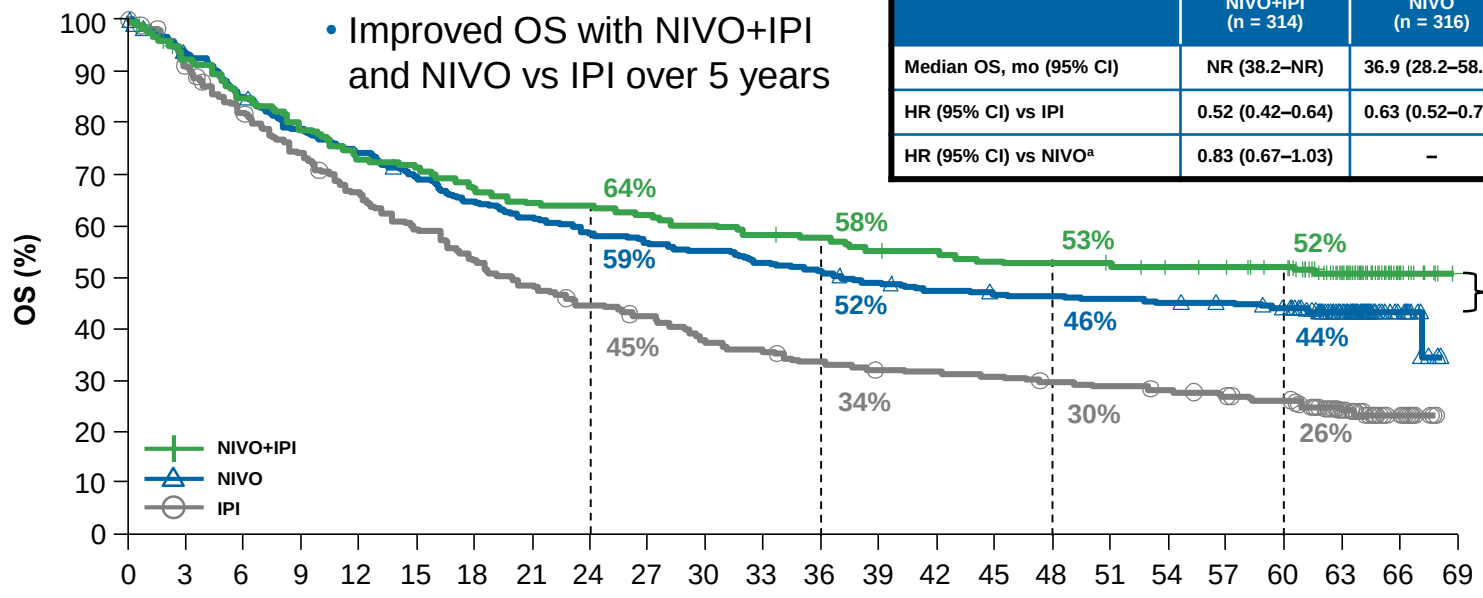
Anti CTLA-4 vs. Anti PD-1



Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

Safety Summary

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis[a]

Patients reporting event	NIVO+IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Treatment-related AE, %	96	59	87	23	86	28
Treatment-related AE leading to discontinuation, %	42	31	13	8	15	14
Treatment-related death, n (%)	2 (1)		1 (< 1)		1 (< 1)	

- Survival outcomes were not impacted by discontinuing NIVO+IPI early due to a TRAE[b]
  - Patients who discontinued NIVO+IPI during induction due to a TRAE had 5-year PFS (35%) and OS rates (51%) similar to patients in the overall population (36% and 52%, respectively)

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1); [b]Post-hoc analysis. TRAE, treatment-related adverse event.

Immune-related Adverse Reactions

GASTROINTESTINAL[1]
GO TO PAGE 6

Signs and symptoms such as

- Diarrhoea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

LIVER[1]
GO TO PAGE 8

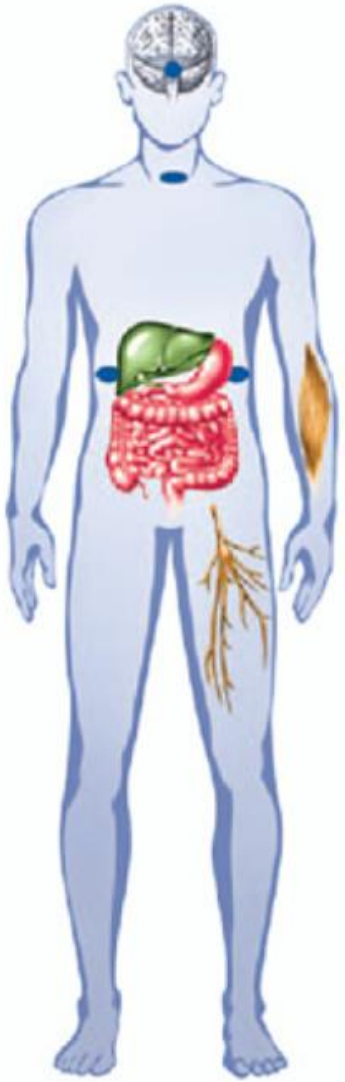
Signs such as

- Abnormal liver function tests (e.g. AST, ALT or total bilirubin)

SKIN[1]
GO TO PAGE 10

Symptoms such as

- Pruritus
- Rash



NEUROLOGIC[1]
GO TO PAGE 12

Symptoms such as

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

ENDOCRINE[1]
GO TO PAGE 14

Signs and symptoms such as

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

OTHER ADVERSE REACTIONS[1] including ocular manifestations
GO TO PAGE 16

Please see each organ system section for related guidance.

Immune-Related Adverse Events

Any grade – grade 3-4 (%)

(0.2% = 1 patient)

L. Eggermont AACR 2018

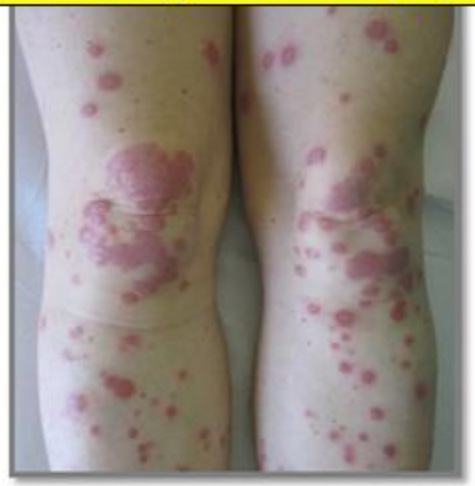
(0.2% = 1 patient)

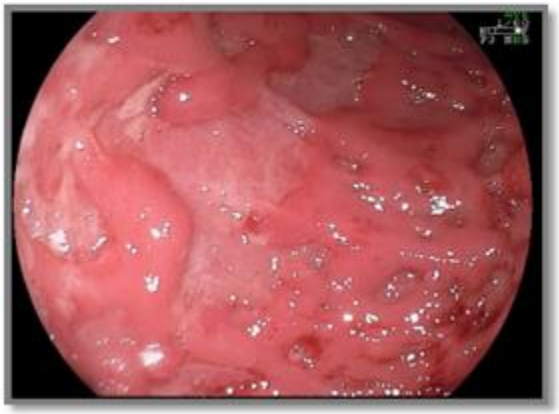
Skin
5.3 – 0.6

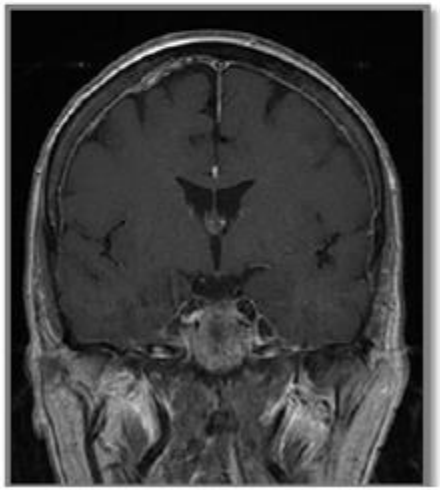
Myositis*
(grade 5)
0.2 – 0.2

Pancreatitis
0.4 – 0.2

Colitis
3.7 – 2.0







Pneumonitis
3.3 – 0.8

Myocarditis
0.2 – 0.2

Hepatitis
1.8 – 1.4

Nephritis
0.4 – 0.4

Thyroid
20.8 – 0.2

Hypophysitis
2.2 – 0.6

Diabetes
1.0 – 1.0

Adrenal
1.0 – 0.2

EORTC

The future of cancer therapy

Received: 13 March 2020 | First decision: 29 March 2020 | Accepted: 6 July 2020

DOI: 10.1111/apt.15998

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review with meta-analysis: effectiveness of anti-inflammatory therapy in immune checkpoint inhibitor-induced enterocolitis

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[1]Division of Digestive Diseases, Faculty of Medicine, Imperial College London, London, UK

[2]The Royal Marsden Hospital, London, UK

[3]Kings College Hospital, London, UK

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Summary

Background: Immune checkpoint inhibitors have revolutionised cancer treatment, but at the cost of off-target immune-mediated organ damage. This includes checkpoint inhibitor-induced enterocolitis which frequently requires hospitalisation and may be life-threatening. Empirical treatment typically includes corticosteroids and infliximab, although, no large-scale studies have confirmed their effectiveness.

Conclusion: Corticosteroids, infliximab and vedolizumab, are effective in the treatment of checkpoint inhibitor-induced enterocolitis. Checkpoint inhibitor regimen and cancer type were significant moderators in response to corticosteroid therapy.

CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients

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Anti–PD-1–based immunotherapy has had a major impact on cancer treatment but has only benefited a subset of patients. Among the variables that could contribute to interpatient heterogeneity is differential composition of the patients' microbiome, which has been shown to affect antitumor immunity and immunotherapy efficacy in preclinical mouse models. We analyzed baseline stool samples from metastatic melanoma patients before immunotherapy treatment, through an integration of 16*S* ribosomal RNA gene sequencing, metagenomic shotgun sequencing, and quantitative polymerase chain reaction for selected bacteria. A significant association was observed between commensal microbial composition and clinical response. Bacterial species more abundant in responders included *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*. Reconstitution of germ-free mice with fecal material from responding patients could lead to improved tumor control, augmented T cell responses, and greater efficacy of anti–PD-L1 therapy. Our results suggest that the commensal microbiome may have a mechanistic impact on antitumor immunity in human cancer patients.

CANCER IMMUNOTHERAPY

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

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REPORT

CLINICAL TRIALS

Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients

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The gut microbiome has been shown to influence the response of tumors to anti–PD-1 (programmed cell death–1) immunotherapy in preclinical mouse models and observational patient cohorts. However, modulation of gut microbiota in cancer patients has not been investigated in clinical trials. In this study, we performed a phase 1 clinical trial to assess the safety and feasibility of fecal microbiota transplantation (FMT) and reinduction of anti–PD-1 immunotherapy in 10 patients with

CLINICAL TRIALS

Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients

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Anti–programmed cell death protein 1 (PD-1) therapy provides long-term clinical benefits to patients with advanced melanoma. The composition of the gut microbiota correlates with anti–PD-1 efficacy in preclinical models and cancer patients. To investigate whether resistance to anti–PD-1 can be overcome by changing the gut microbiota, this clinical trial evaluated the safety and efficacy of responder-derived fecal microbiota transplantation (FMT) together with anti–PD-1 in patients with PD-1–refractory melanoma. This combination was well tolerated, provided clinical benefit in 6 of 15 patients, and induced rapid and durable microbiota perturbation. Responders exhibited increased abundance of taxa that were previously shown to be associated with response to anti–PD-1, increased $CD8^+$ T cell activation, and decreased frequency of interleukin-8–expressing myeloid cells. Responders had distinct proteomic and metabolomic signatures, and transkingdom network analyses confirmed that the gut microbiome regulated these changes. Collectively, our findings show