Western Australia
Oncology
Menopause
Endometriosis
New Mothers

Through the looking glass:
Anti-cancer treatments for the non-oncologist

Tarek Meniawy *MBBS FRACP PhD*
Medical Oncologist - Women Centre, SJOG Subiaco,
and Sir Charles Gairdner Hospital
Clinical Senior Lecturer, University of Western Australia

May 4th 2016

Outline

- Basic stats
- Anti-cancer therapies – a historical perspective
- Ehrlich's "magische Kugel" – a dream realised
- Immunotherapy comes of age
- The search for biomarkers
- Future directions

Cancer Incidence and mortality in WA (2013)

Incidence

Mortality

FEMALES				
Site	Cases	%	ASR	Risk
Breast	1569	30.8	86.1	11
Melanoma	498	9.8	26.5	35
Uterus	200	3.9	10.7	78
Ovary	113	2.2	6.1	152
Cervix	77	1.5	5.0	223
Lung	333	19.1	14.4	60
Breast	256	14.7	12.2	75
Ovary	78	4.5	3.2	285
Uterus	49	2.8	2.0	438
Cervix	22	1.3	1.3	804

Threlfall TJ, Thompson JR (2015). Cancer incidence and mortality in Western Australia, 2013 Department of Health, Western Australia, Perth. Statistical Series Number 101

Observed incidence (2009) and mortality (2010) of ovarian cancer, and estimated for 2012

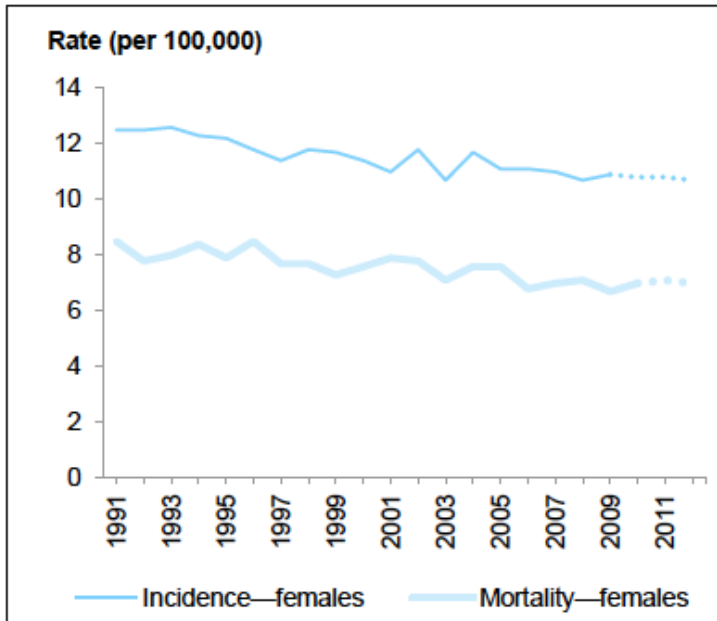

Figure B29.1: Ovarian cancer incidence and mortality rates[d], 1991–2012

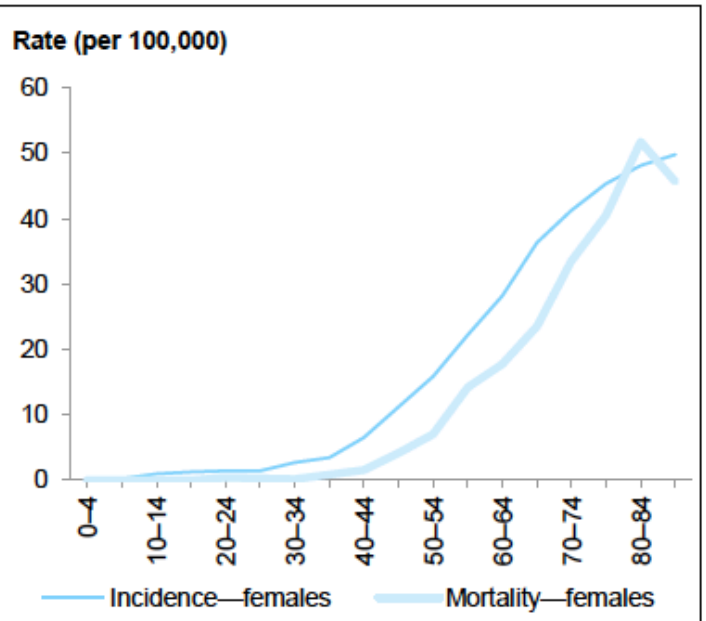

Figure B29.2: Ovarian cancer incidence (2009) and mortality (2010) rates[f] by age group

AIHW Australian Cancer Database 2009, AIHW National Mortality Database

Observed incidence (2009) and mortality (2010) of melanoma of the skin, and estimated for 2012

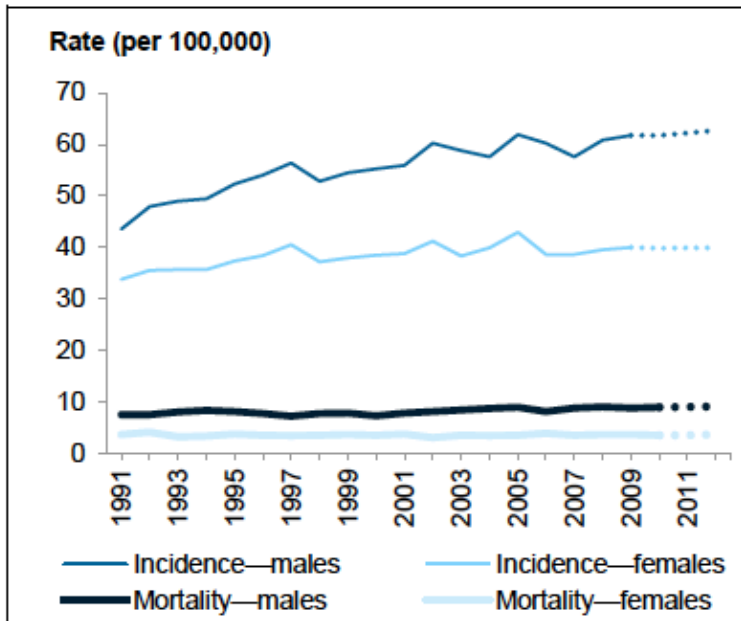

Figure B17.1: Melanoma of the skin incidence and mortality rates[d], 1991–2012

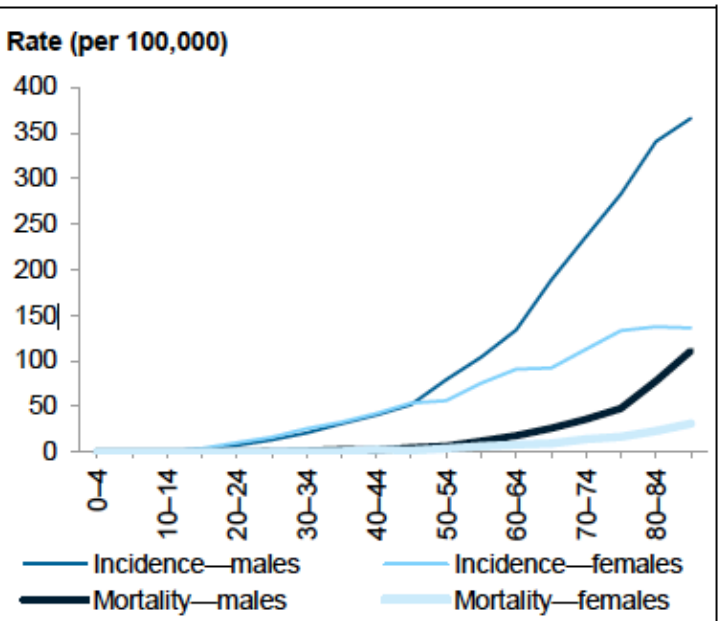

Figure B17.2: Melanoma of the skin incidence (2009) and mortality (2010) rates[f] by age group

AIHW Australian Cancer Database 2009, AIHW National Mortality Database

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Cancer and the immune system

- 1863 – Virchow observed that tumours were infiltrated by leukocytes
- A link was proposed between cancer and inflammation

Rudolph Carl Virchow (1821-1902)

“The f unotherapy”

- 1891 – Co ccal bacterial to
- ‘Coley’s t ssue sarcoma fo success

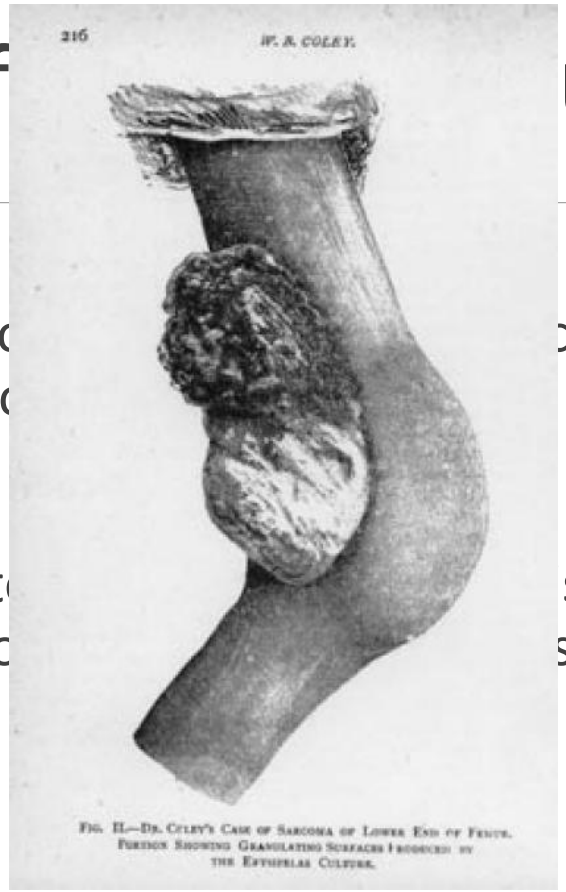
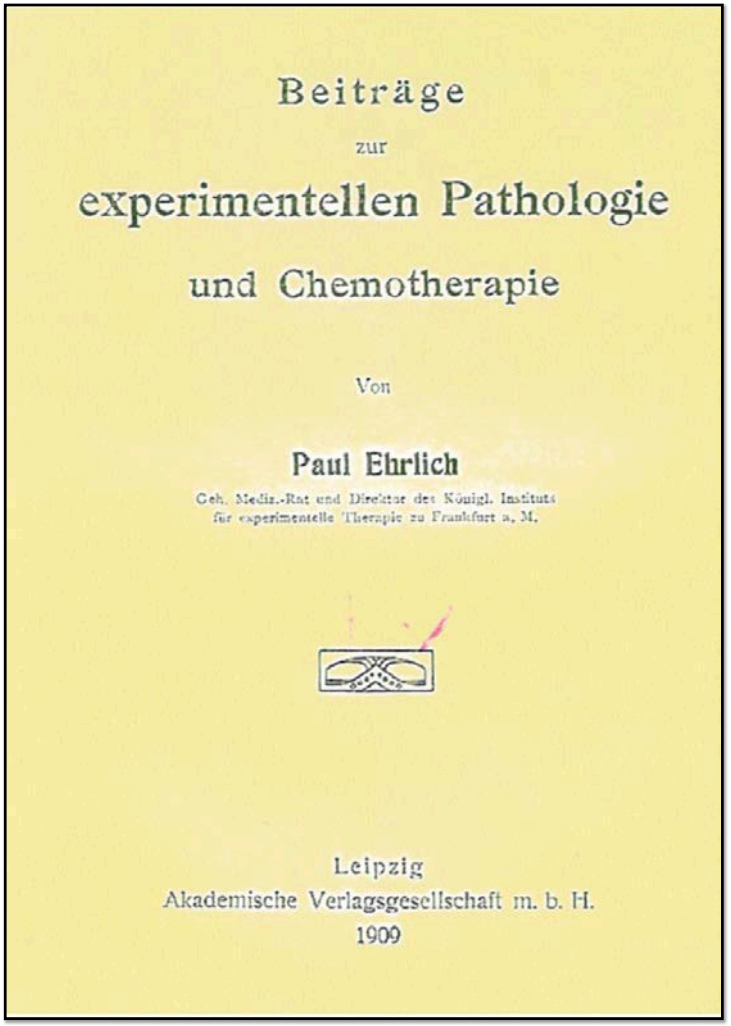


Fig. II.—Dr. Coley's Case of Sarcoma of Lower End of Femur. Patient Showing Granulating Surfaces Produced by the Erysipelas Culture.

William Coley (1862-1936)

Paul Ehrlich

(1854 –1915)



Paul Ehrlich: Birth of Targeted Therapy

(1) Antibodies: Nobel Prize for serum therapy in 1908
(2) Targeted chemotherapy: 1910-1911

Receptors on cells

Postulated "side-chains," or "receptors" specific for external substances (dyes), antigens, and nutrients

A bacterial toxin *and* a targeted chemotherapy

Model: bifunctional agent, containing a chemical structure that binds to the "receptor" linked to a toxic molecule

Mendelsohn, J. (2013). Personalizing oncology: perspectives and prospects. *JCO*, *31*(15), 1904–11.

The first targeted therapies

- Huggins demonstrated the hormone-dependency of prostate cancer
- In 1940, oestrogen therapy for prostate cancer became the first targeted systemic therapy, against receptors or pathways upon which a cancer was dependent

Charles Huggins (1901-1997)

Chemotherapy – emerging from the horrors of chemical warfare

2 Dec 1943 - The 'Bari incident'

SS *John Harvey*

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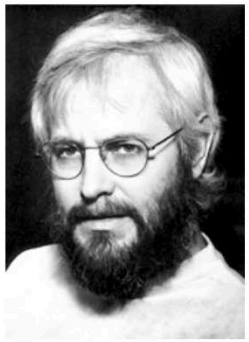
The Nobel Prize in Physiology or Medicine 1984

Niels K. Jerne
Prize share: 1/3



Georges J.F. Köhler
Prize share: 1/3

César Milstein
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein *"for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"*.

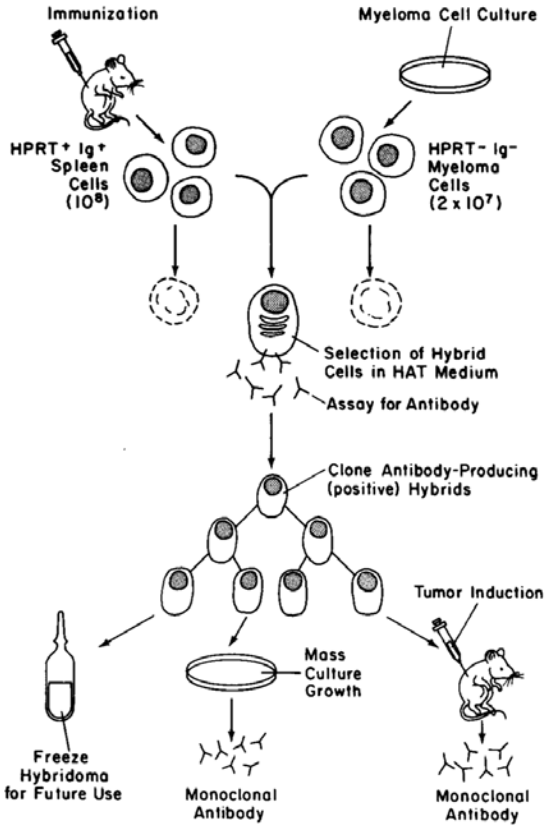


Figure 1. Fusion of Mouse Myeloma Cells and Immune Spleen Cells.

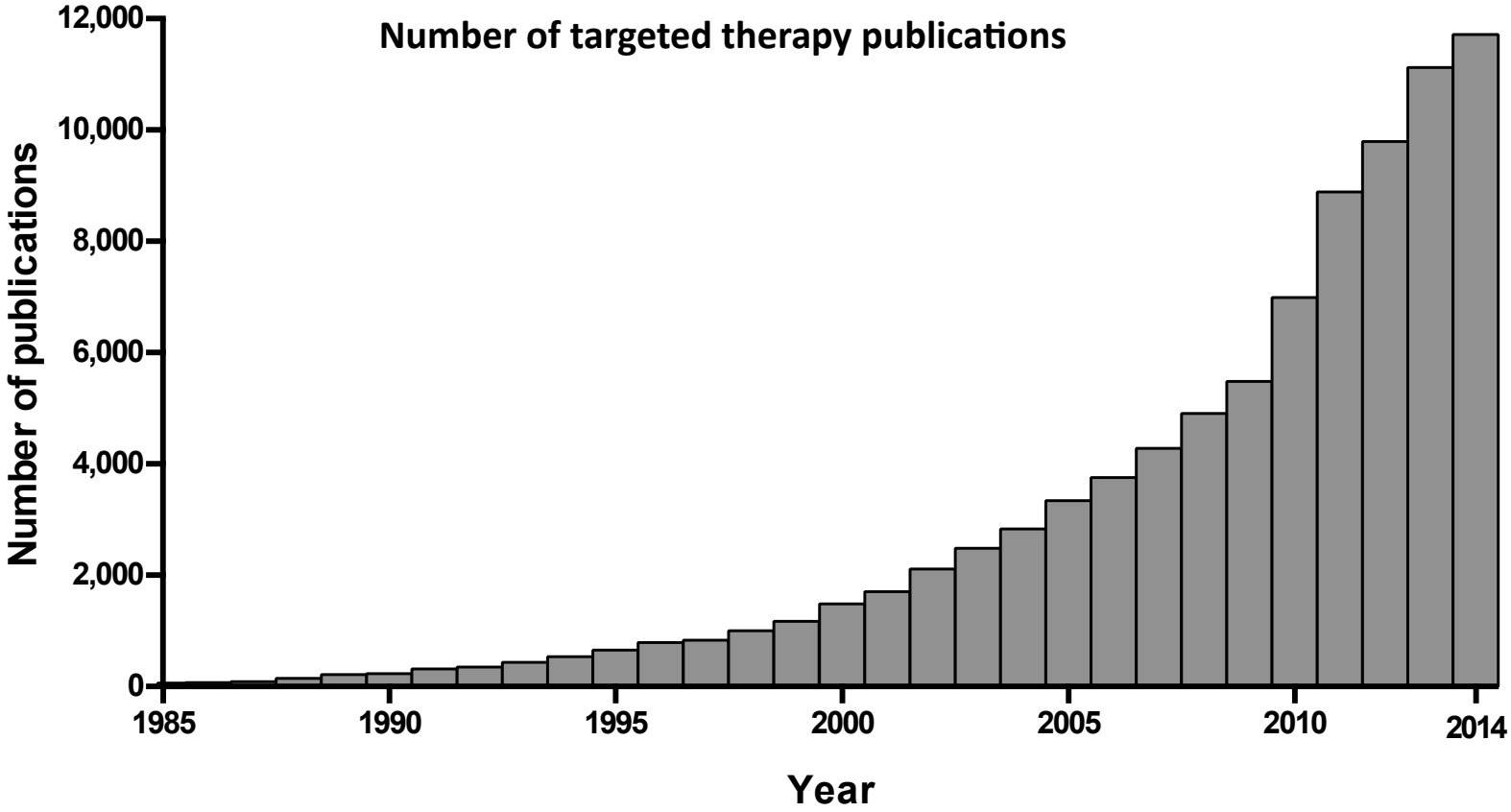
Diamond, B. A., Yelton, D. E., & Scharff, M. D. (1981). Monoclonal Antibodies. *NEJM*, *304*(22), 1344–1349

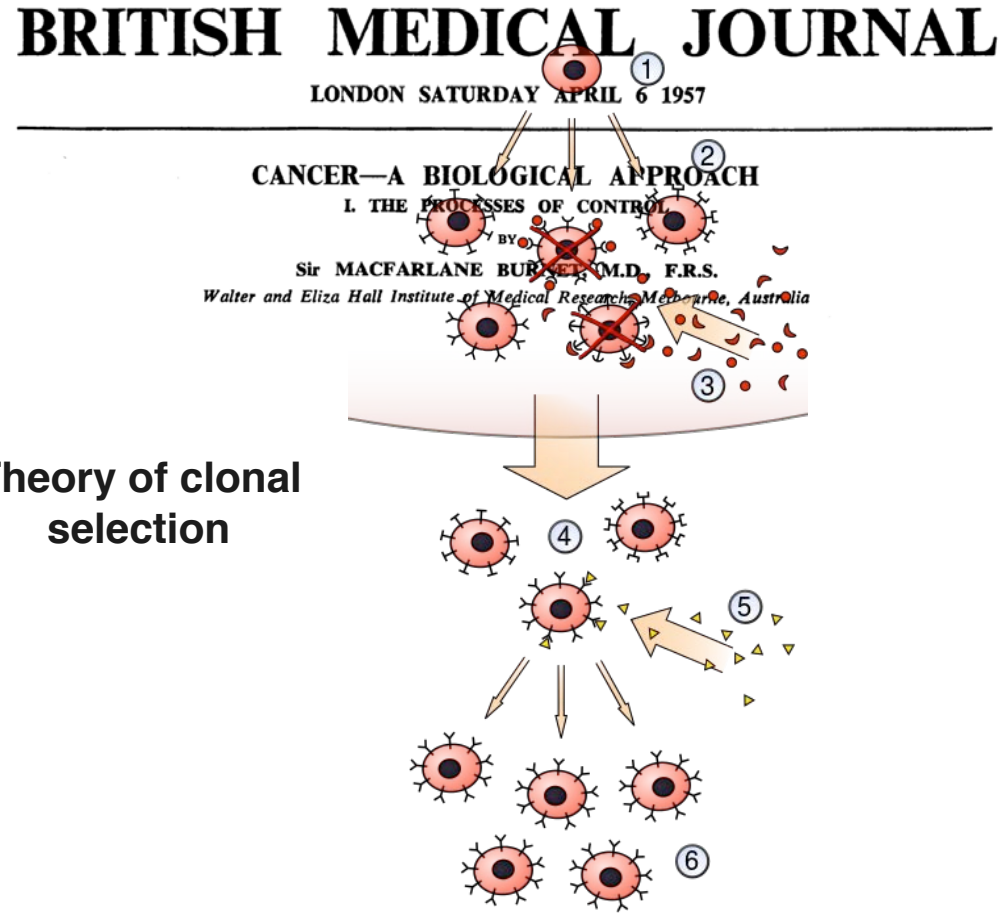
The magic bullet “r

1997 – Rituximab (NHL)

1998 – Herceptin (breast ca)

2001 – Imatinib (CML)


Number of targeted therapy publications
Number of publications
12,000
10,000
8,000
6,000
4,000
2,000
0
1985
1990
1995
2000
2005
2010
2014
Year



BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 6 1957

CANCER—A BIOLOGICAL APPROACH

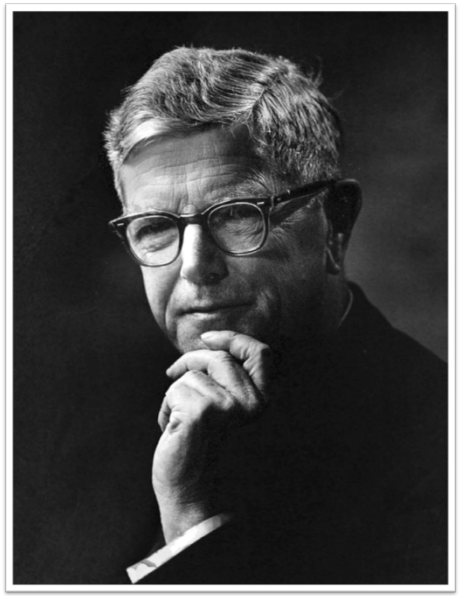
I. THE PROCESSES OF CONTROL

BY

Sir MACFARLANE BURNET, M.D., F.R.S.

Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

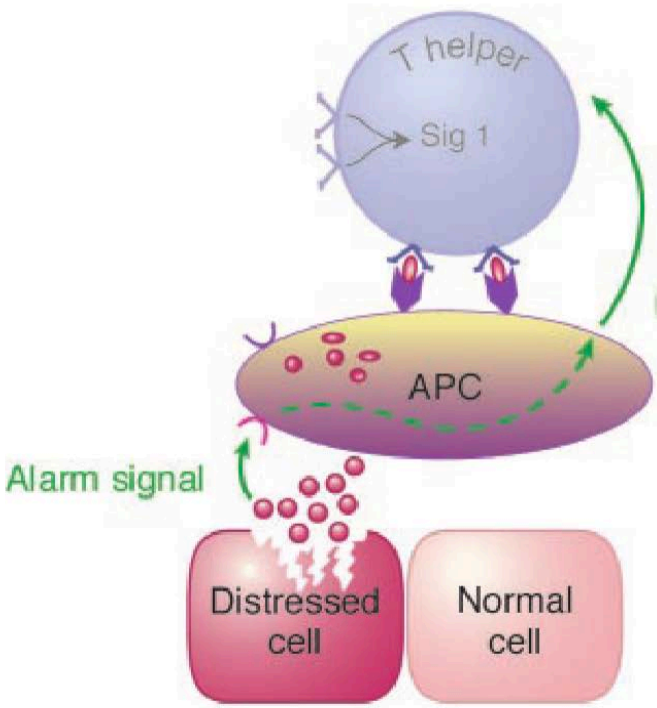
Theory of clonal selection



Sir Frank Macfarlane Burnet (1899-1985)

VIEWPOINT

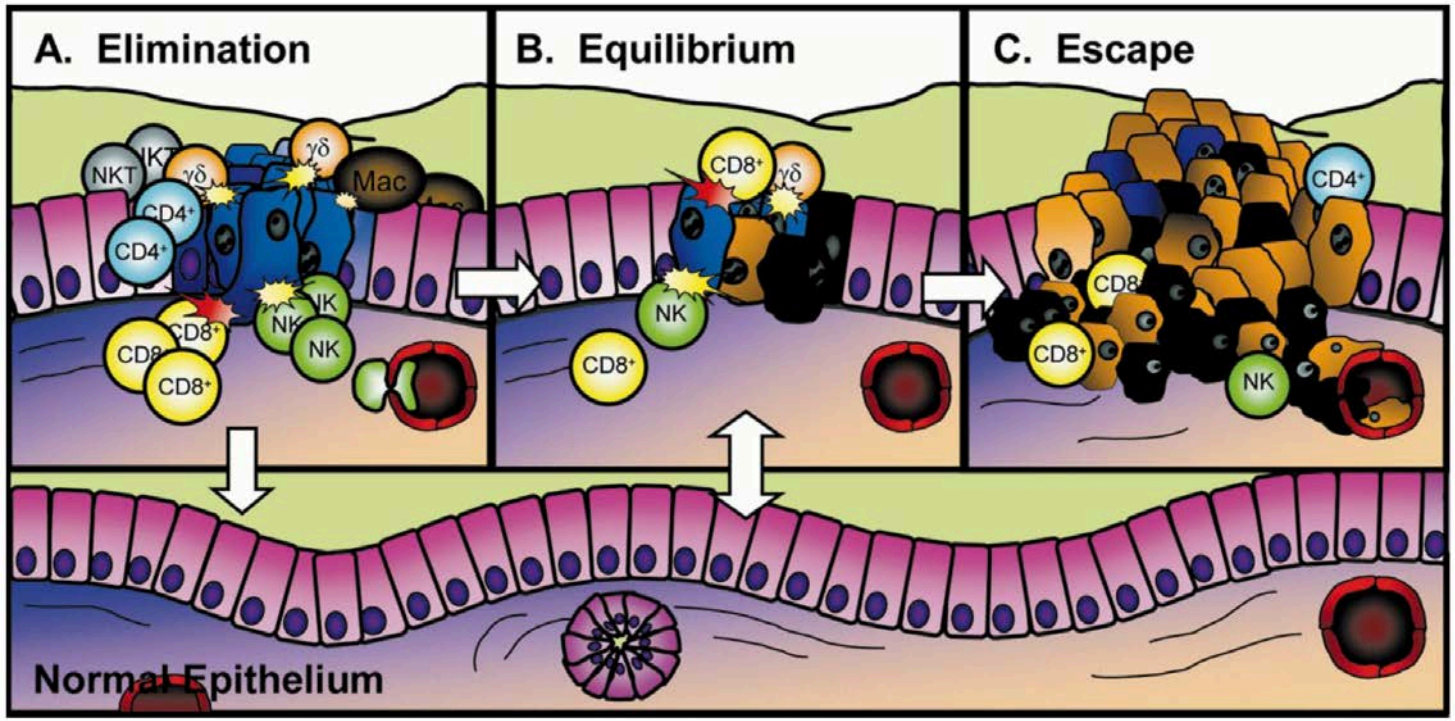
The Danger Model: A Renewed Sense of Self



e) 1994, 4th modification (Danger model : major change) APCs are activated by endogenous cellular alarm signals from distressed or injured cells.

Sig 2 (Co-stimulation)

Matzinger, P. (2002). *Science*, *296*(5566), 301–5.



Dunn, G. P., Old, L. J., & Schreiber, R. D. (2004). The Three Es of Cancer Immunoediting. *Annual Review of Immunology*, *22*(1), 329–360

Fatal Melanoma Transferred in a Donated Kidney 16 Years after Melanoma Surgery

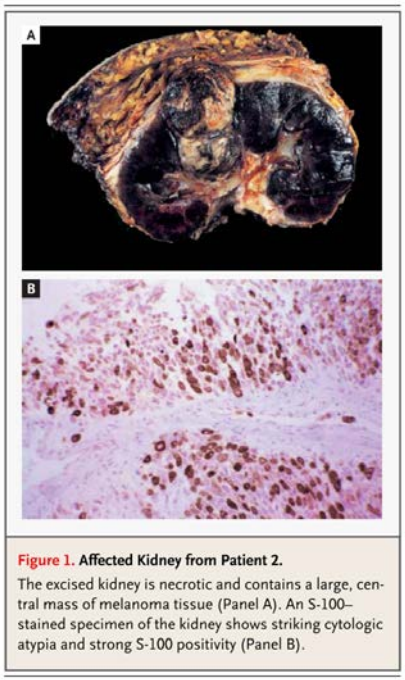
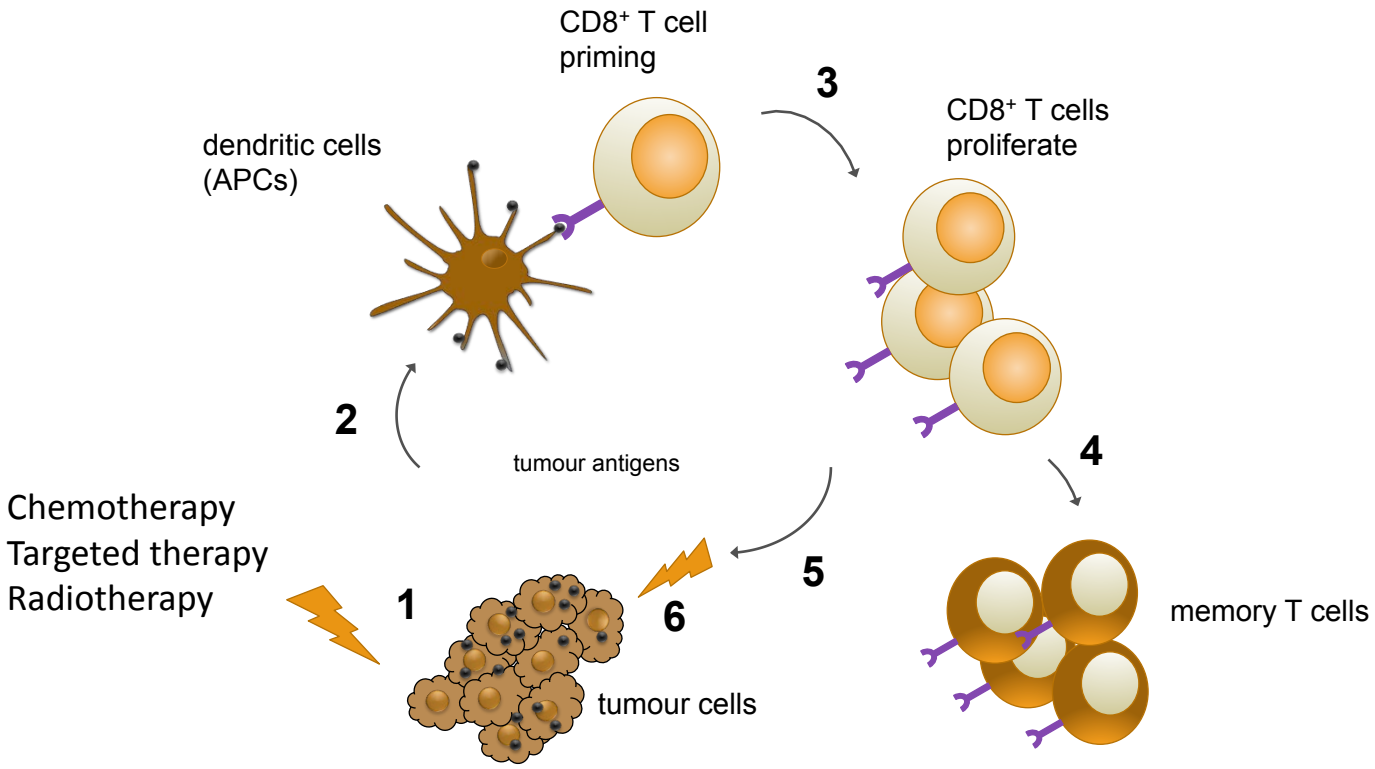


Figure 1. Affected Kidney from Patient 2.
The excised kidney is necrotic and contains a large, central mass of melanoma tissue (Panel A). An S-100–stained specimen of the kidney shows striking cytologic atypia and strong S-100 positivity (Panel B).

N ENGL J MED 348;6 WWW.NEJM.ORG FEBRUARY 6, 2003

6 steps of the anti-tumour immune response



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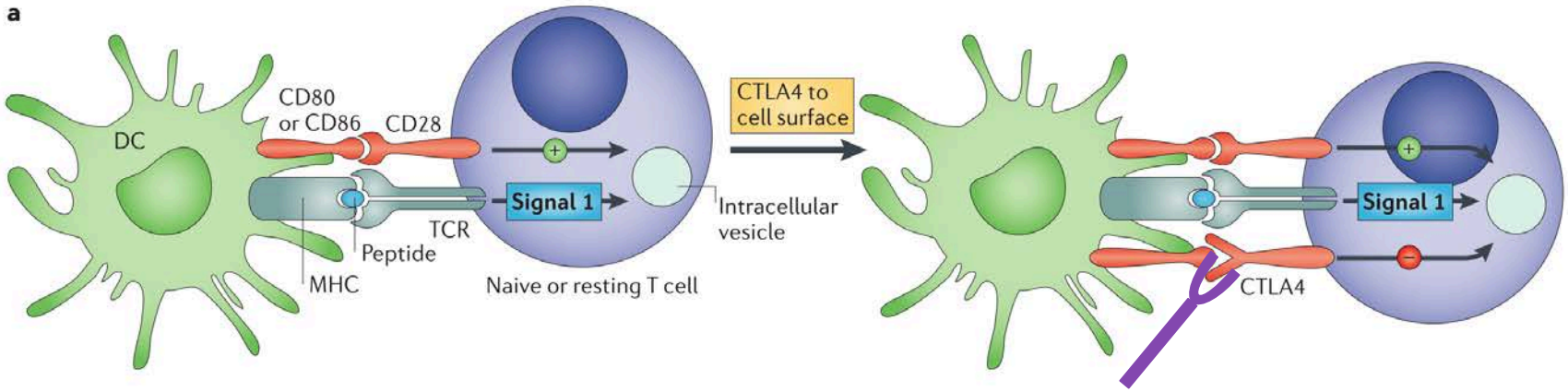
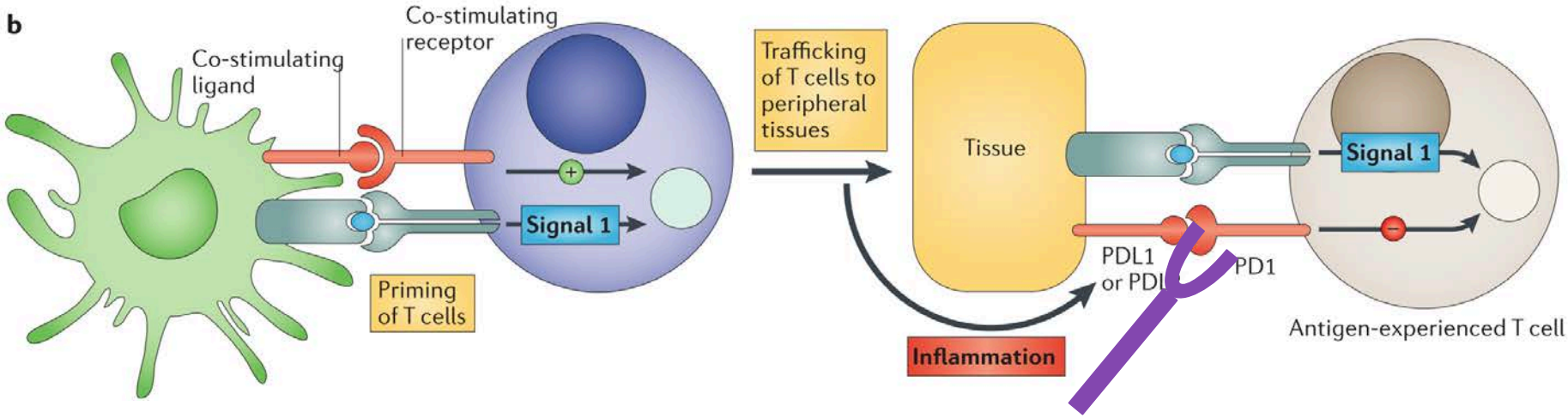
Immune checkpoints



Ipilimumab (anti-CTLA-4)

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews. Cancer*, *12*(4), 252–64.



PD-1/PD-L1 inhibition

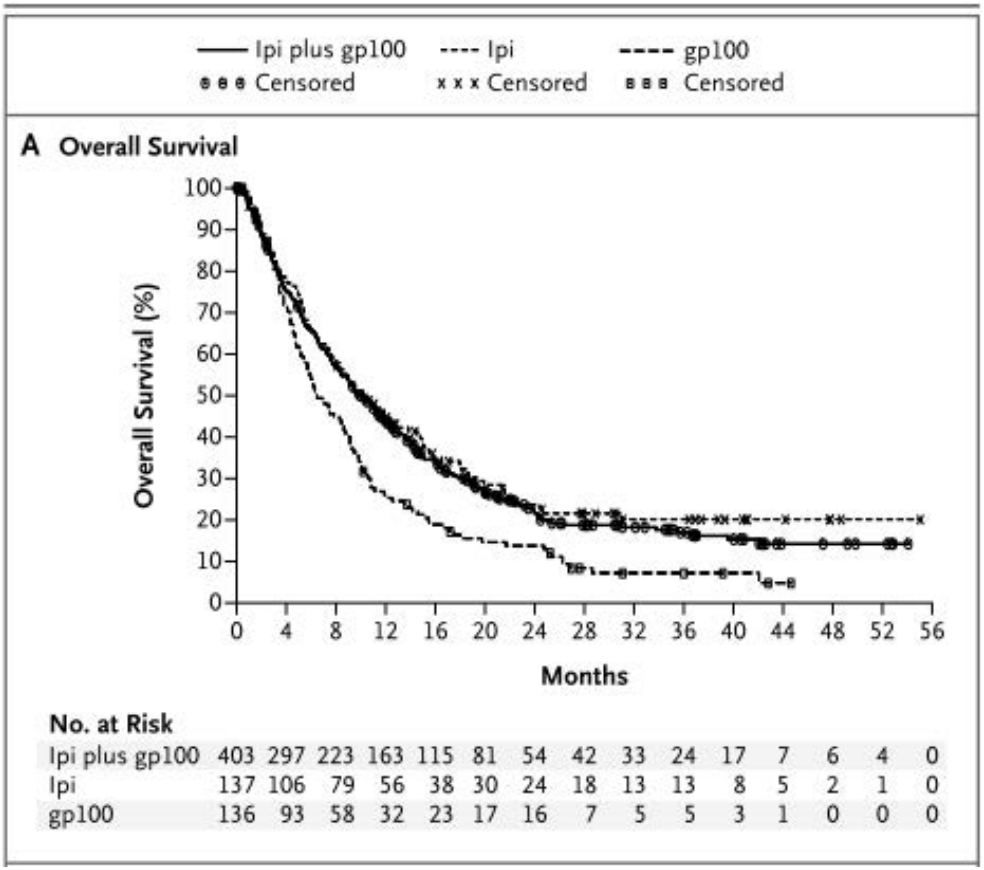
Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews. Cancer*, *12*(4), 252–64.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

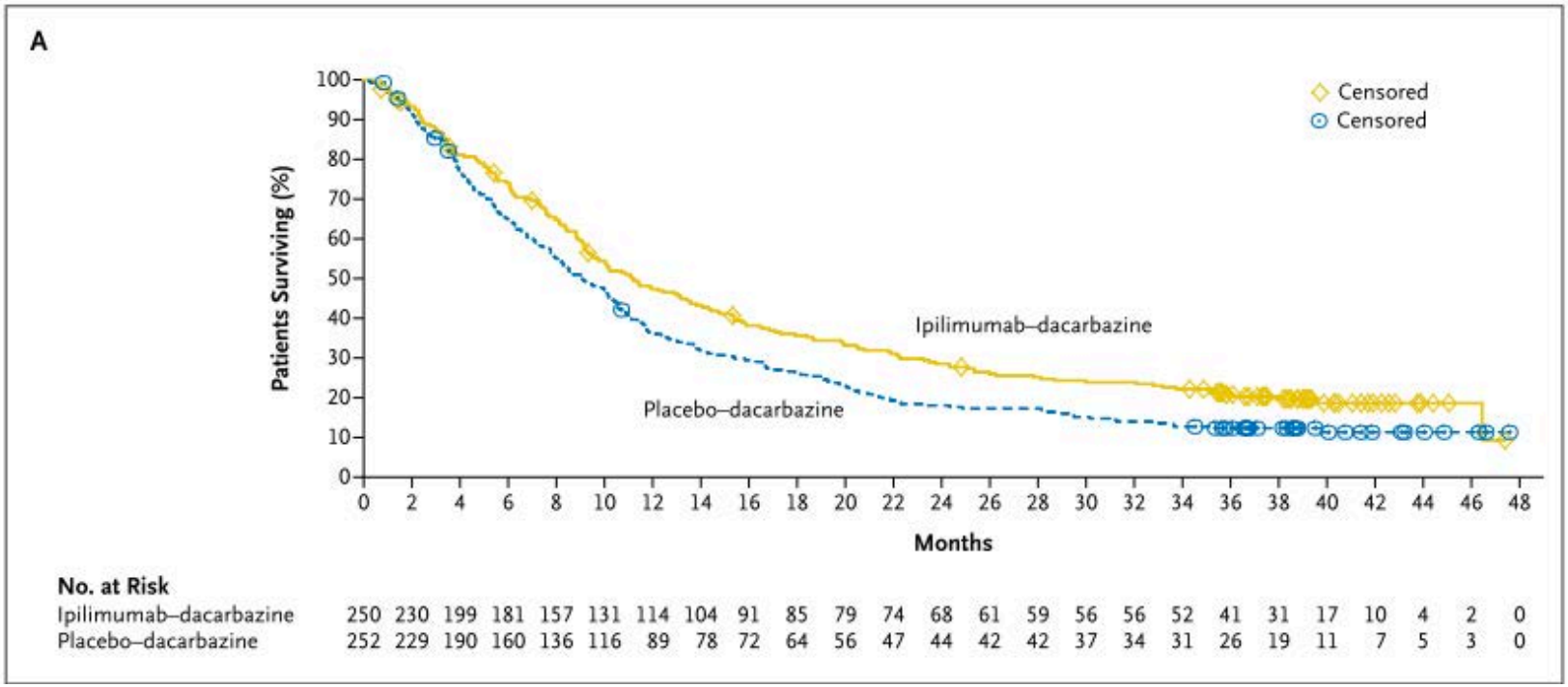
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



Hodi, F. S., O'Day, S. J., McDermott, D. F., Weber, R. W., Sosman, J. A., Haanen, J. B., … Urba, W. J. (2010). *Improved survival with ipilimumab in patients with metastatic melanoma. The New England journal of medicine* (Vol. 363). doi:10.1056/NEJMoa1003466

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma



Robert, C. (2011). *NEJM*(Vol. 364)

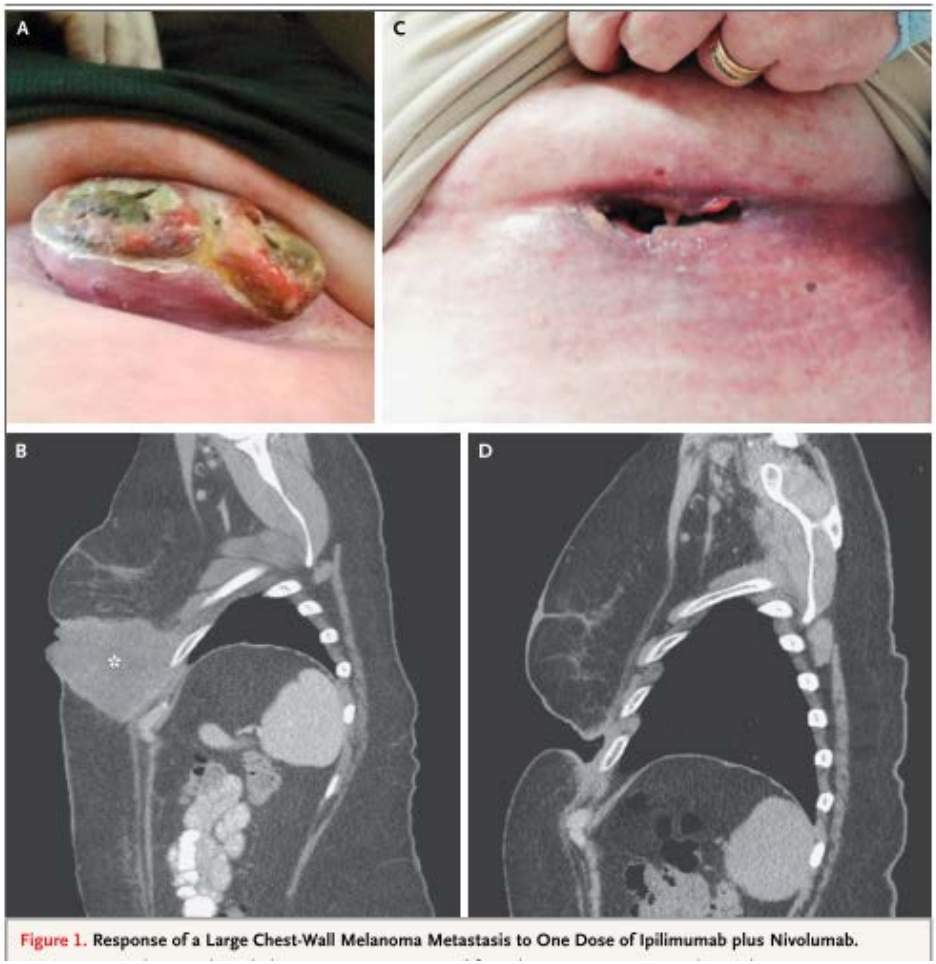


Figure 1. Response of a Large Chest-Wall Melanoma Metastasis to One Dose of Ipilimumab plus Nivolumab.

CORRESPONDENCE

Rapid Eradication of a Bulky Melanoma Mass with One Dose of Immunotherapy

Chapman (2015). *NEJM*, (Panel D)
doi:10.1056/NEJMc1501894


Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

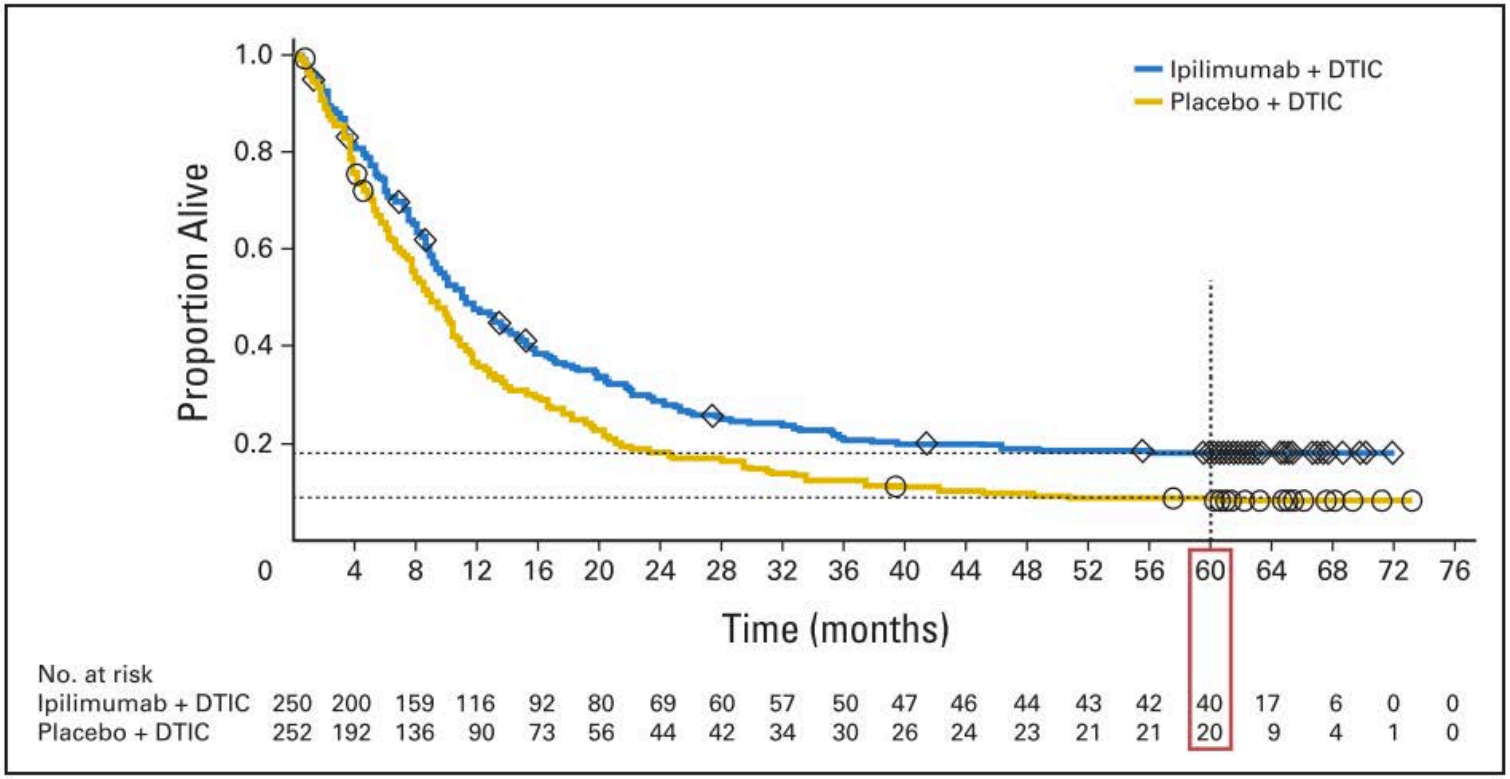
VOLUME 33 · NUMBER 10 · APRIL 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Five-Year Survival Rates for Treatment-Naive Patients With Advanced Melanoma Who Received Ipilimumab Plus Dacarbazine in a Phase III Trial

Michele Maio, Jean-Jacques Grob, Steinar Aamdal, Igor Bondarenko, Caroline Robert, Luc Thomas, Claus Garbe, Vanna Chiarion-Sileni, Alessandro Testori, Tai-Tsang Chen, Marina Tschaika, and Jedd D. Wolchok



Maio, M (2015). *JCO*, *33*(10).

VOLUME 33 · NUMBER 17 · JUNE 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ONCOLOGY GRAND ROUNDS

Swinging for the Fences: Long-Term Survival With Ipilimumab in Metastatic Melanoma

VOLUME 33 · NUMBER 17 · JUNE 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid, Debra Patt, Tai-Tsang Chen, David M. Berman, and Jedd D. Wolchok

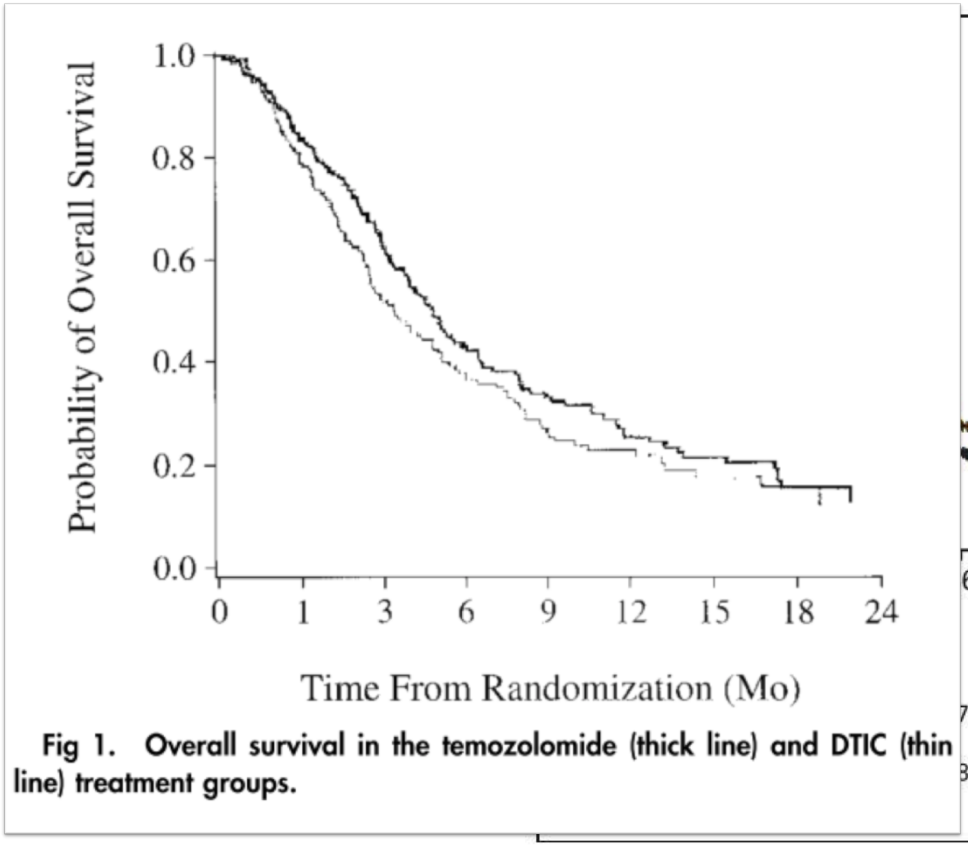
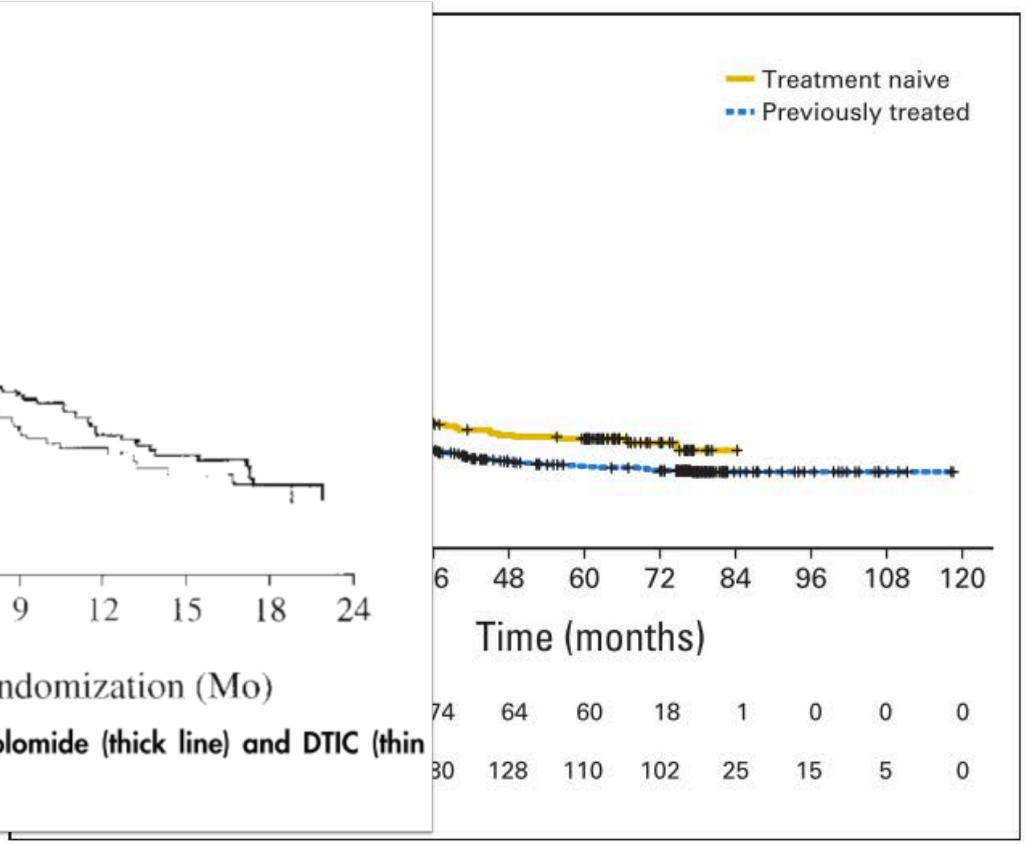
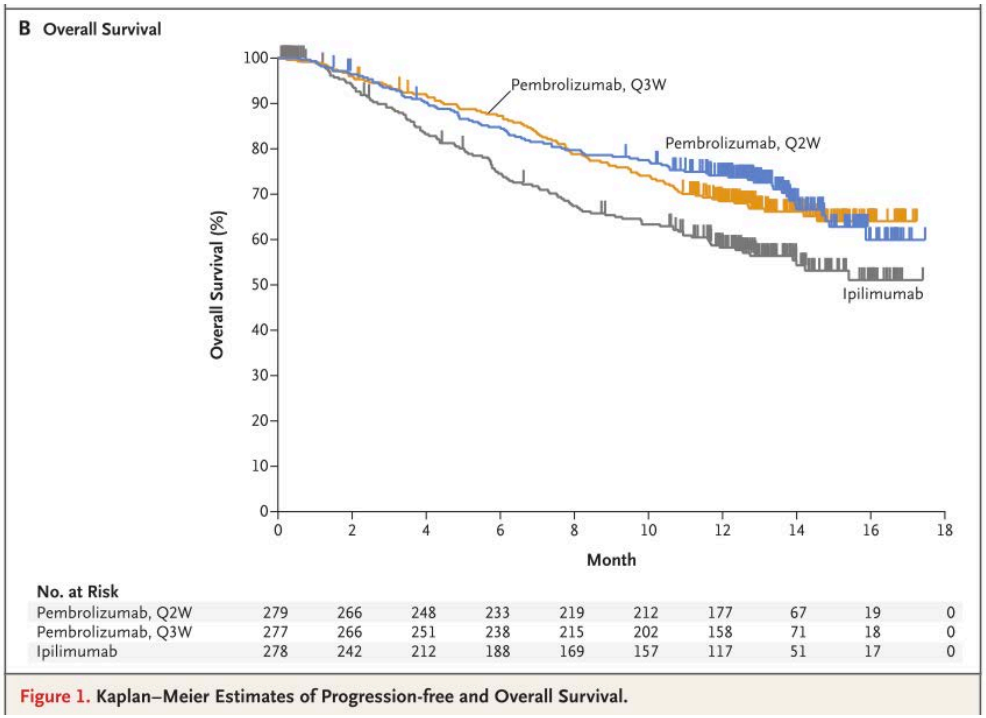


Fig 1. Overall survival in the temozolomide (thick line) and DTIC (thin line) treatment groups.



Schadendorf, D. (2015). *JCO*, *33*(17). doi:10.1200/JCO.2014.56.2736

Pembrolizumab versus Ipilimumab in Advanced Melanoma

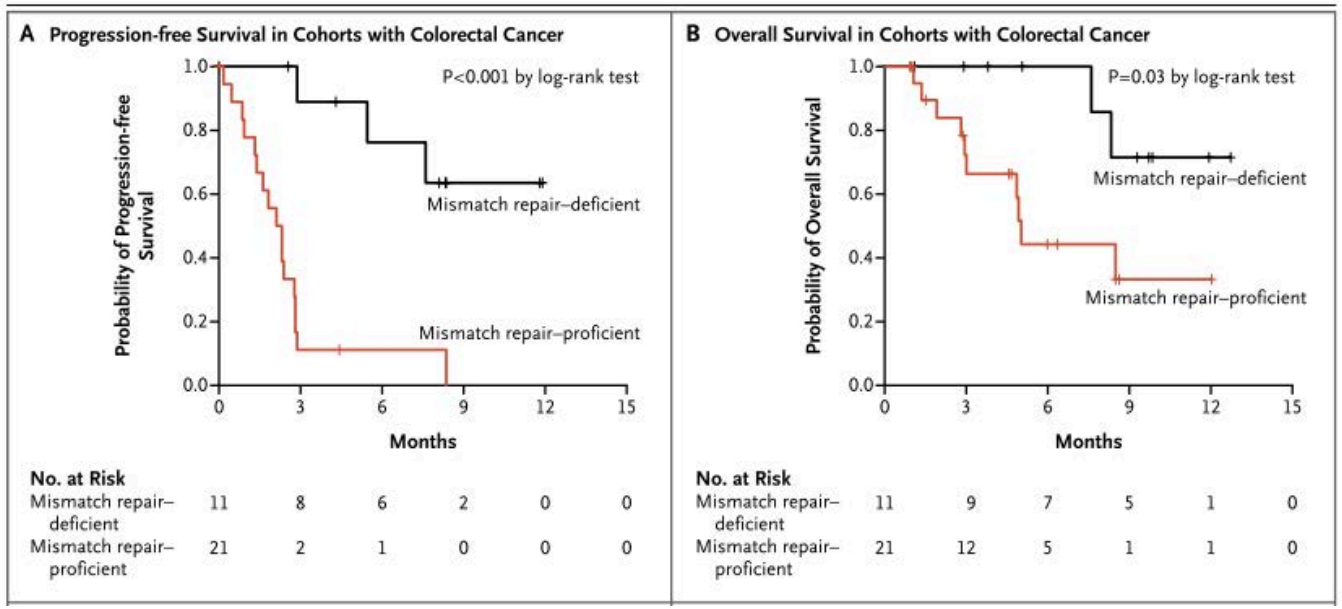


No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.

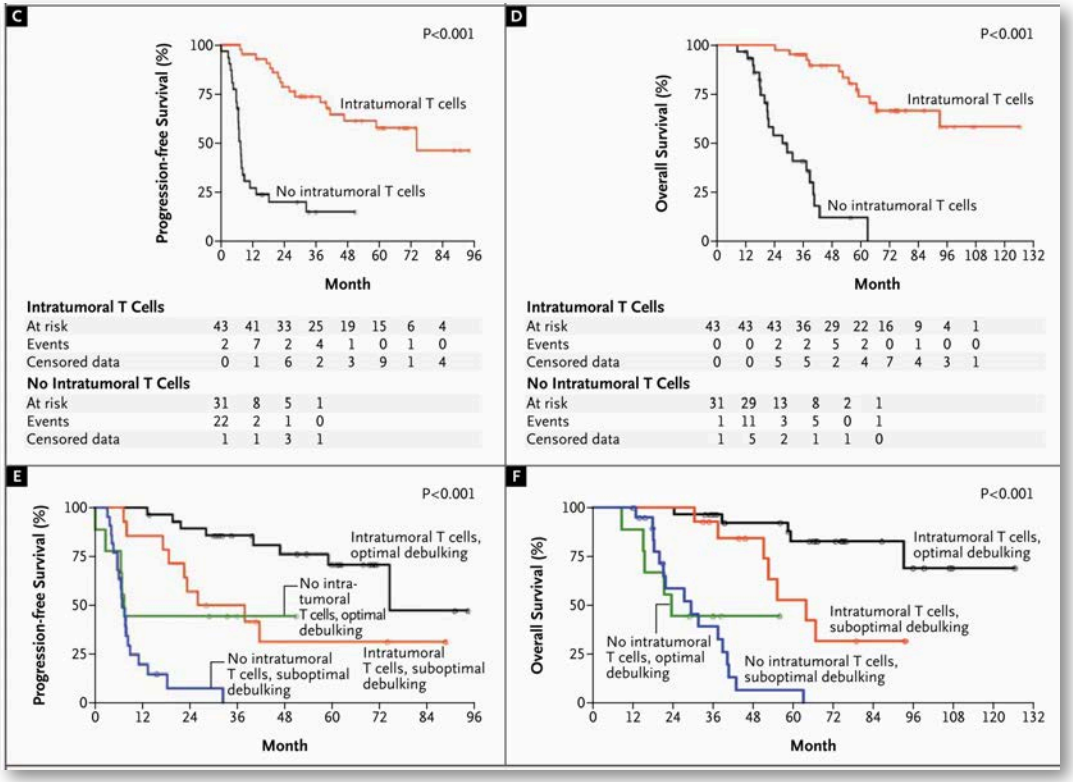
Robert, C (2015). *NEJM*, 150419053123009. doi:10.1056/NEJMoa1503093

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency



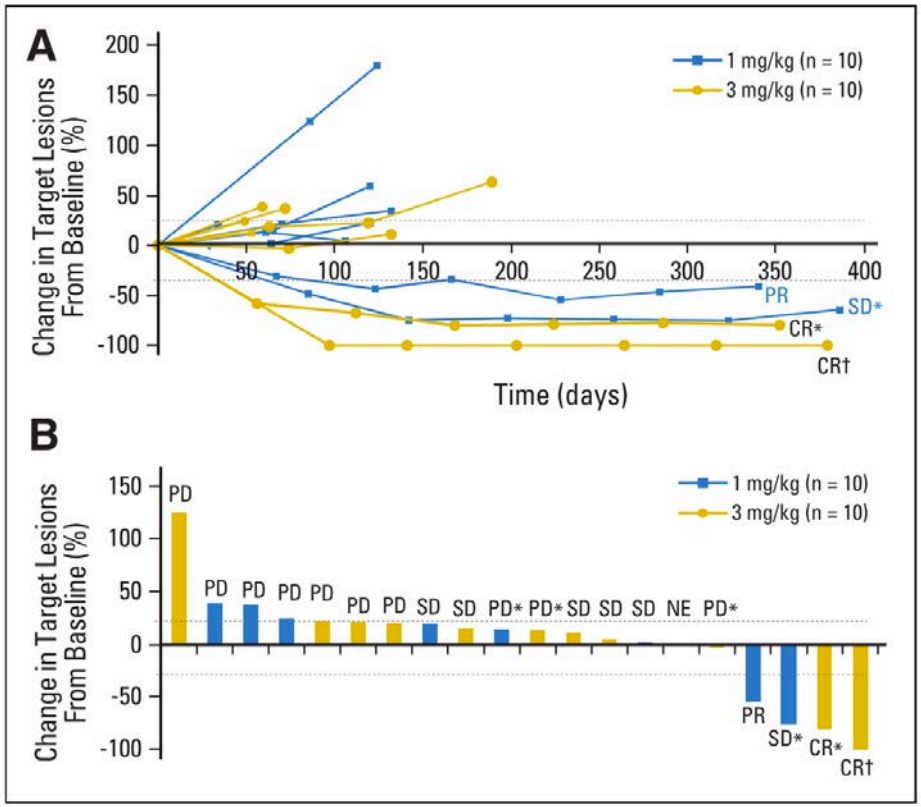
Le, D.T., (2015). *NEJM*, 150530061707006. doi:10.1056/NEJMoa1500596

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer



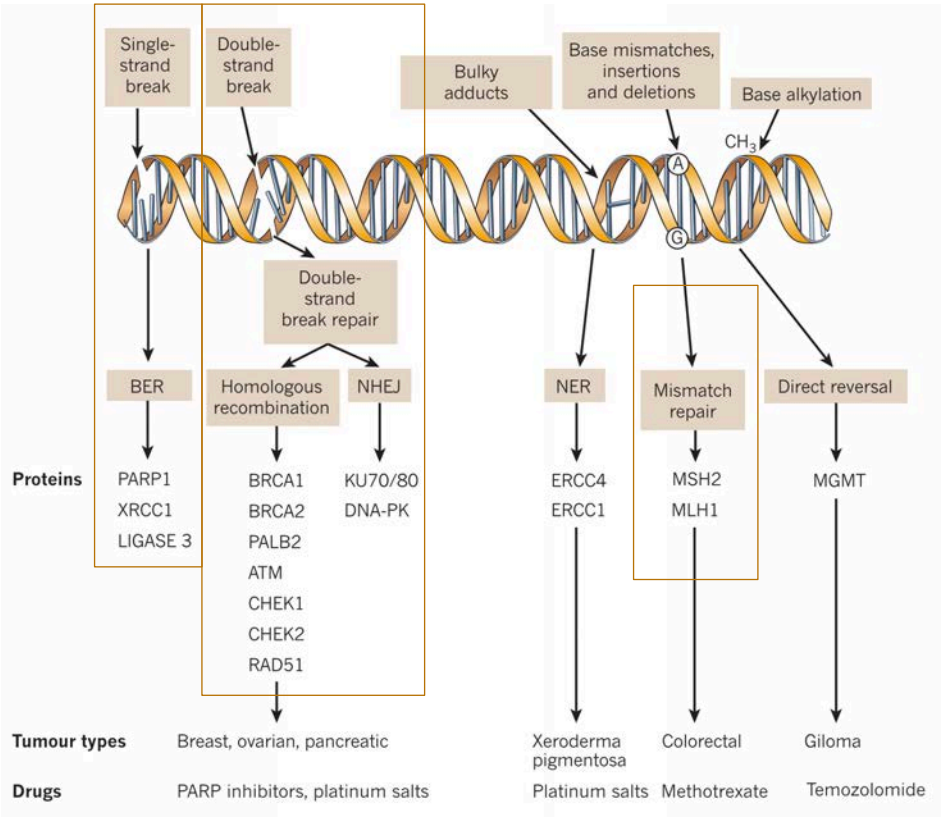
Zhang, L (2003). *The New England Journal of Medicine*, *348*(3), 203–13

Nivolumab (anti-PD-1) in Patients with Platinum-Resistant Ovarian Cancer

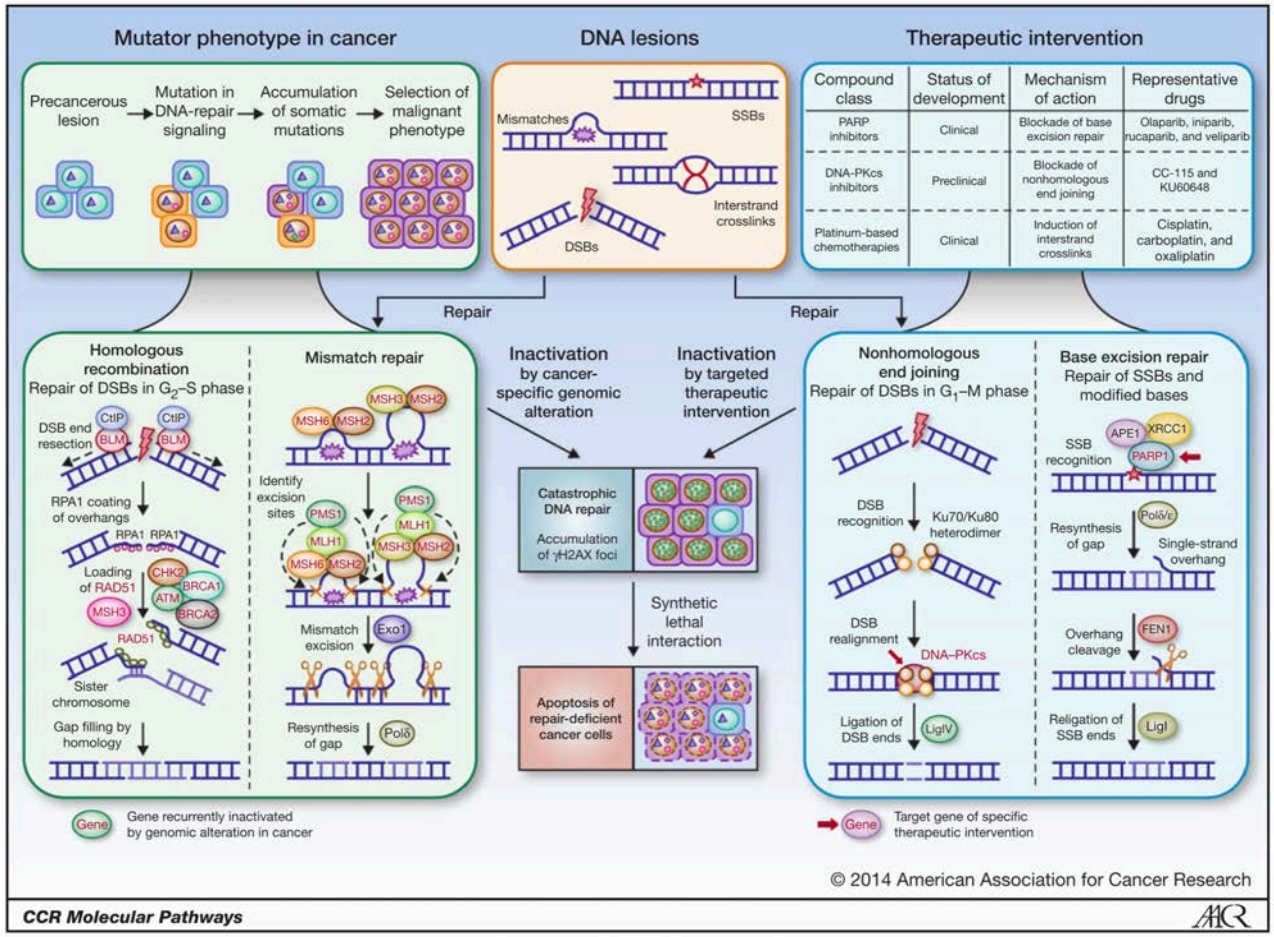


Hamanishi, J (2015. *Journal of Clinical Oncology*, *33*(34), 4015–4022.

The DNA damage response



Lord, C. J., & Ashworth, A. (2012). *Nature*, *481* (7381), 287–294



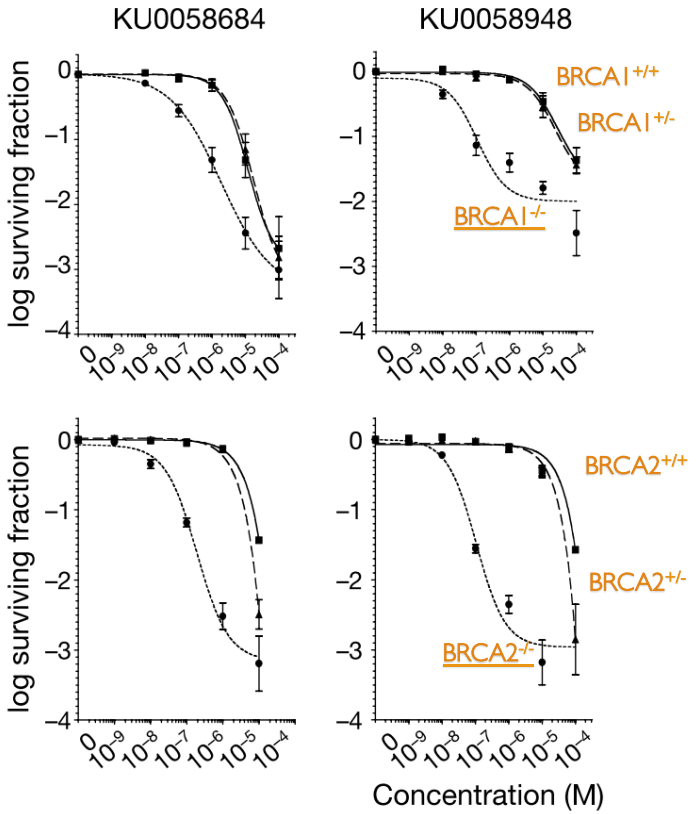
Dietlein, F., & Reinhardt, H. C. (2014). *Clinical Cancer Research*, *20*(23), 5882–5887

Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

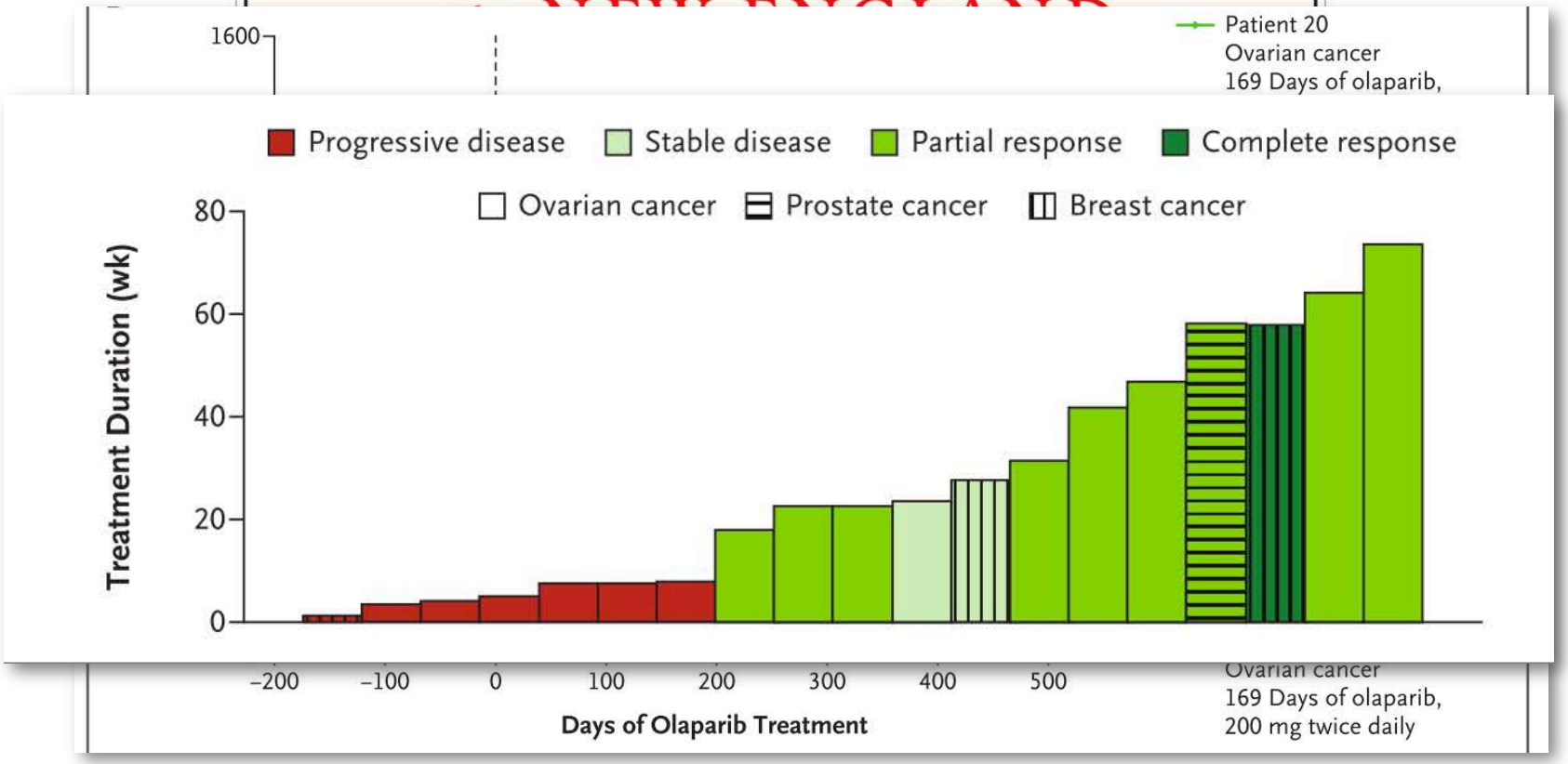
Hannah Farmer[1,2*], Nuala McCabe[1,2*], Christopher J. Lord[2*], Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2†], Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[1], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]

Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

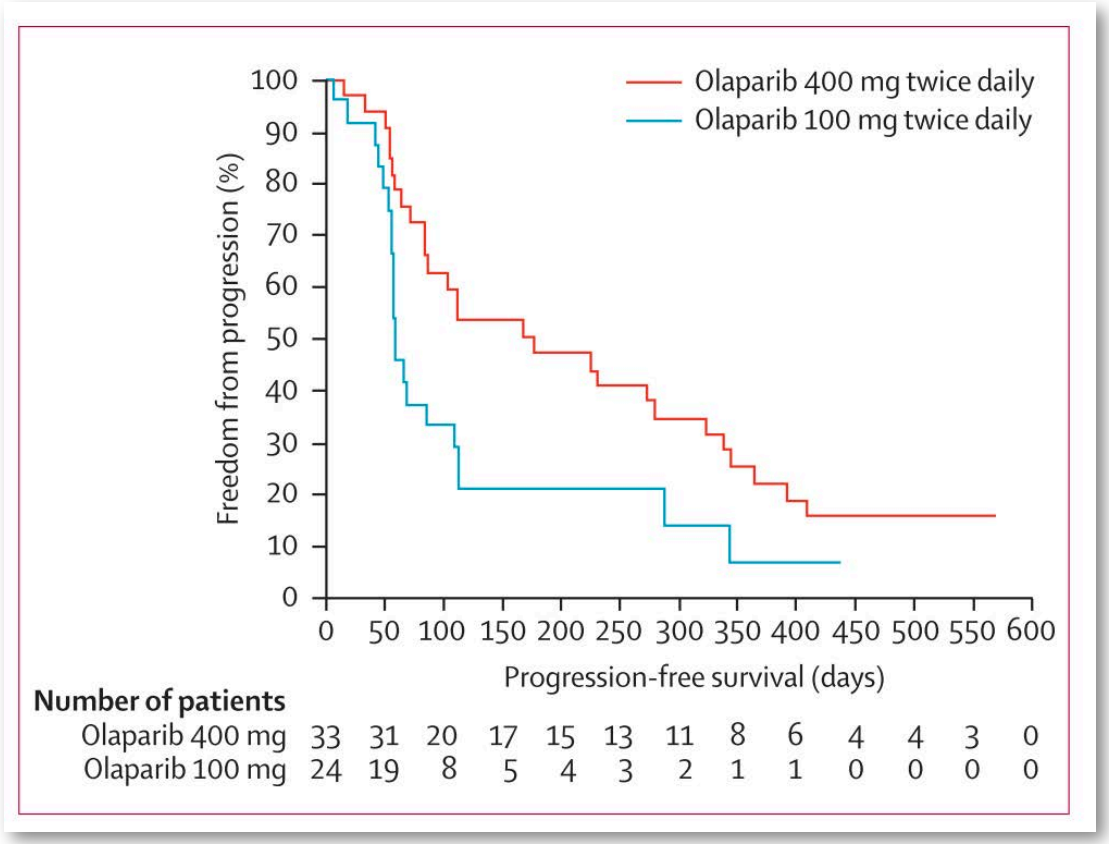
Helen E. Bryant[1], Niklas Schultz[2], Huw D. Thomas[3], Kayan M. Parker[1], Dan Flower[1], Elena Lopez[1], Suzanne Kyle[3], Mark Meuth[1], Nicola J. Curtin[3] & Thomas Helleday[1,2]



NATURE | VOL 434 | 14 APRIL 2005



Fong, P. C (2009). *New England Journal of Medicine*, *361* (2), 123–134.



Audeh, M.W (2010). *The Lancet*, *376*(9737), 245–251.

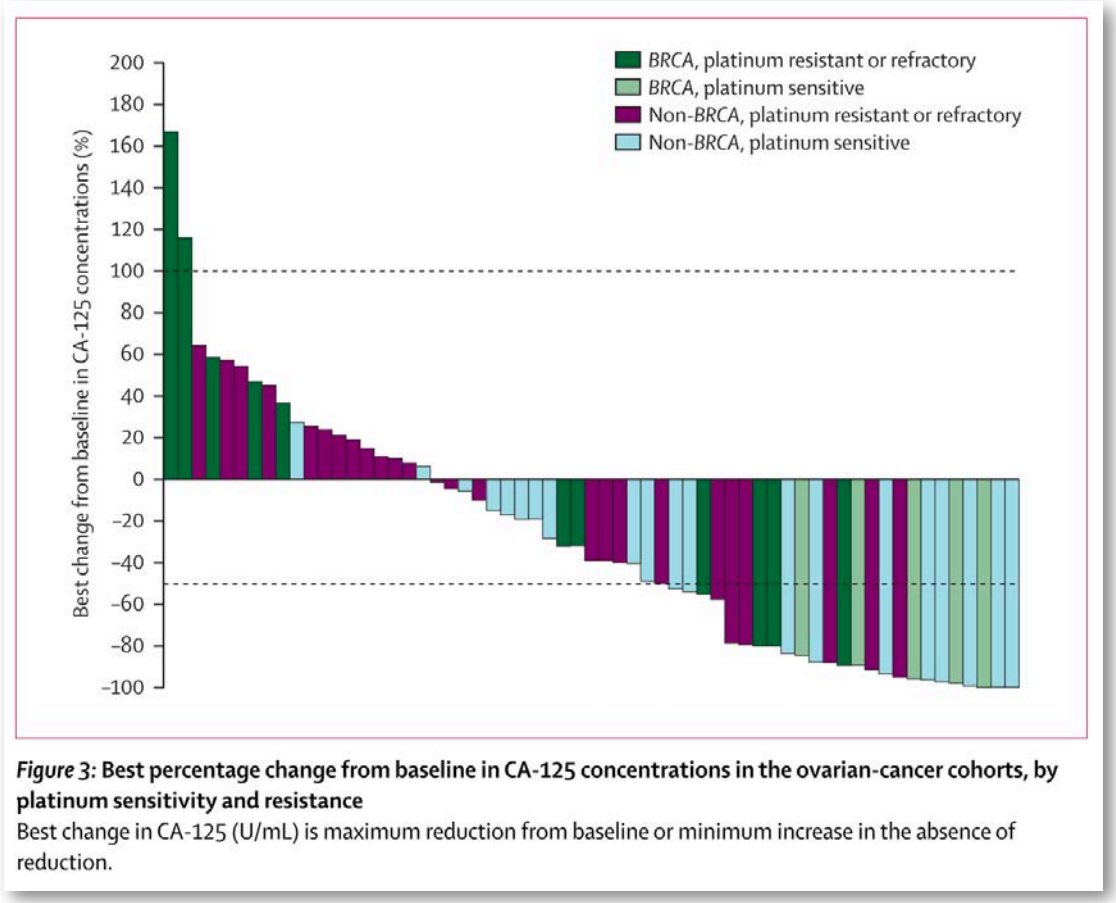
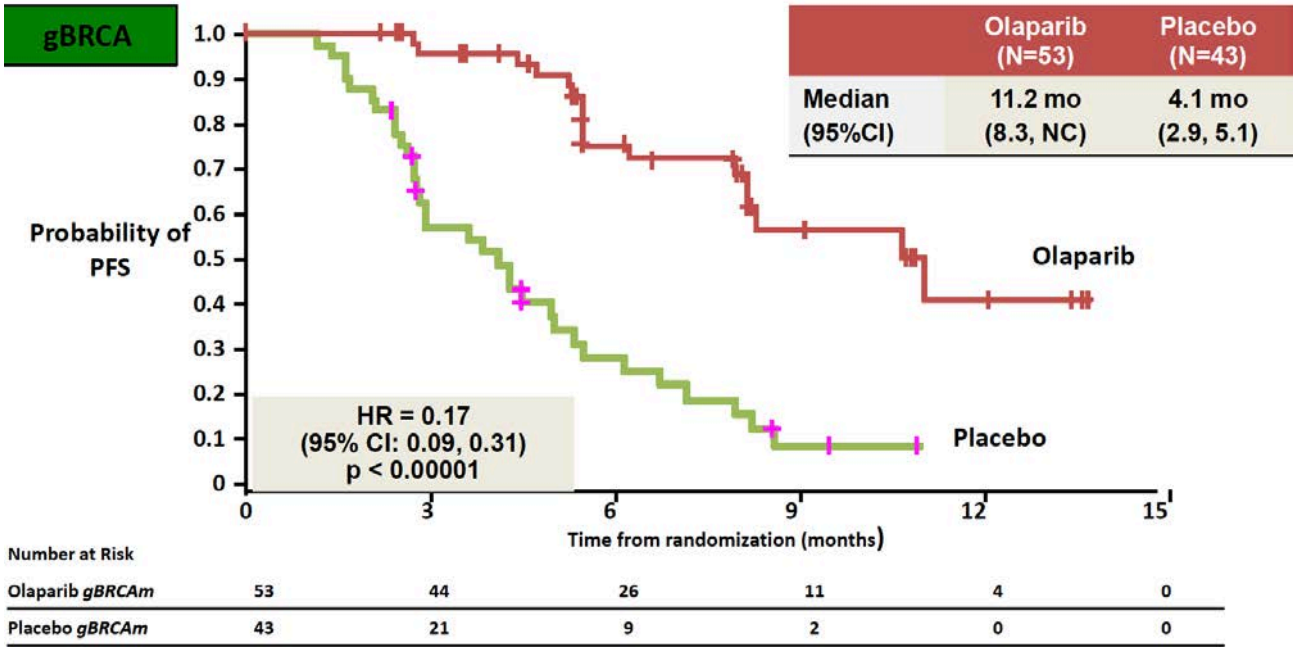


***Figure 3*: Best percentage change from baseline in CA-125 concentrations in the ovarian-cancer cohorts, by platinum sensitivity and resistance**

Best change in CA-125 (U/mL) is maximum reduction from baseline or minimum increase in the absence of reduction.

Gelmon (2011). *The Lancet Oncology*, *12*(9), 852–861

As maintenance treatment, gBRCAm patients derive most PFS benefit: 7.1 months median PFS improvement



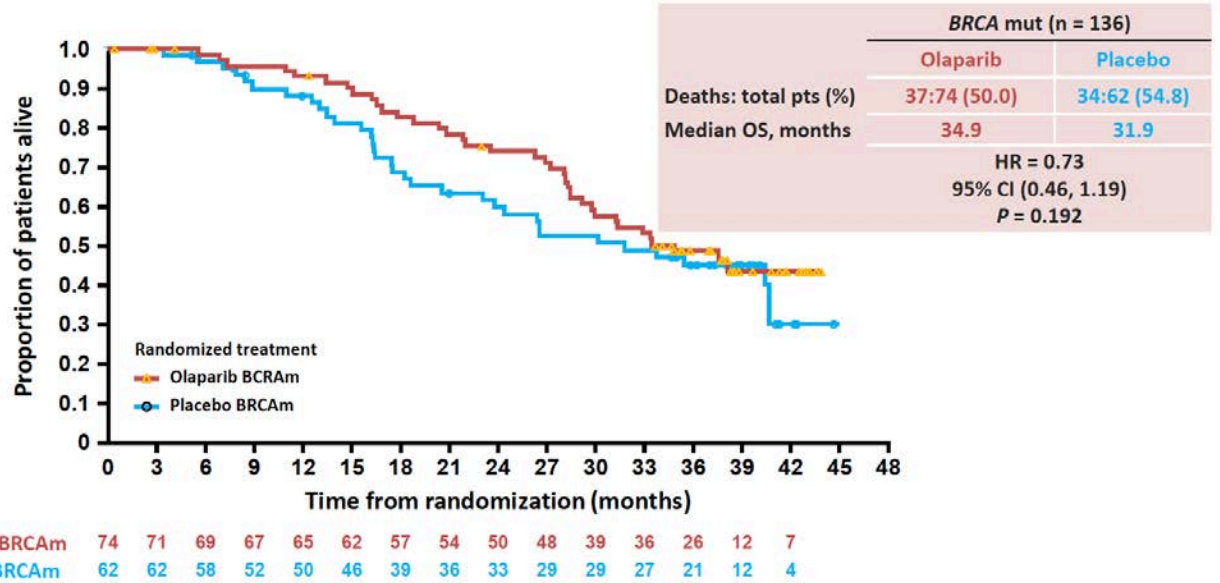
	Olaparib (N=53)	Placebo (N=43)
Median (95%CI)	11.2 mo (8.3, NC)	4.1 mo (2.9, 5.1)

Number at Risk

Olaparib *gBRCAm*	53	44	26	11	4	0
Placebo *gBRCAm*	43	21	9	2	0	0

J Ledermann et al. Lancet Oncology 2014 **15** 852- 861

Overall Survival in Patients With *BRCA* Mutation



	BRCA mut (n = 136)	
	Olaparib	Placebo
Deaths: total pts (%)	37:74 (50.0)	34:62 (54.8)
Median OS, months	34.9	31.9
	HR = 0.73 95% CI (0.46, 1.19) *P* = 0.192	

Olaparib BRCAm	74	71	69	67	65	62	57	54	50	48	39	36	26	12	7
Placebo BRCAm	62	62	58	52	50	46	39	36	33	29	29	27	21	12	4

- 14/62 (22.6%) placebo patients switched to a PARP inhibitor
- OS in *BRCA WT* patients: HR = 0.98; 95% CI, 0.62–1.55; *P* = .946
  - Median OS: olaparib, 24.5 months; placebo, 26.2 months

J Ledermann et al. Lancet Oncology 2014 **15** 852- 861

Table 2. Adverse Events.*

Event	Olaparib (N=136)				Placebo (N=128)			
	Any Grade	Grade 1	Grade 2	Grade 3 or 4	Any Grade	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Any	130 (95.6)	NA	NA	48 (35.3)	116 (90.6)	NA	NA	26 (20.3)
Nausea	93 (68.4)	71 (52.2)	19 (14.0)	3 (2.2)	45 (35.2)	35 (27.3)	10 (7.8)	0
Fatigue	66 (48.5)	32 (23.5)	25 (18.4)	9 (6.6)	48 (37.5)	36 (28.1)	8 (6.3)	4 (3.1)†
Vomiting	43 (31.6)	27 (19.9)	13 (9.6)	3 (2.2)	18 (14.1)	12 (9.4)	5 (3.9)	1 (0.8)
Diarrhea	31 (22.8)	23 (16.9)	5 (3.7)	3 (2.2)	29 (22.7)	21 (16.4)	5 (3.9)	3 (2.3)
Headache	25 (18.4)	16 (11.8)	9 (6.6)	0	15 (11.7)	13 (10.2)	1 (0.8)	1 (0.8)
Decreased appetite	25 (18.4)	17 (12.5)	8 (5.9)	0	17 (13.3)	13 (10.2)	4 (3.1)	0
Abdominal pain	24 (17.6)	11 (8.1)	11 (8.1)	2 (1.5)	33 (25.8)	26 (20.3)	3 (2.3)	4 (3.1)
Anemia	23 (16.9)	3 (2.2)	13 (9.6)	7 (5.1)	6 (4.7)	3 (2.3)	2 (1.6)	1 (0.8)
Dyspepsia	22 (16.2)	19 (14.0)	3 (2.2)	0	11 (8.6)	9 (7.0)	2 (1.6)	0
Dysgeusia	19 (14.0)	17 (12.5)	2 (1.5)	0	8 (6.3)	8 (6.3)	0	0
Cough	18 (13.2)	14 (10.3)	4 (2.9)	0	12 (9.4)	11 (8.6)	1 (0.8)	0
Upper abdominal pain	18 (13.2)	12 (8.8)	6 (4.4)	0	10 (7.8)	6 (4.7)	3 (2.3)	1 (0.8)
Arthralgia	16 (11.8)	10 (7.4)	6 (4.4)	0	17 (13.3)	14 (10.9)	3 (2.3)	0
Nasopharyngitis	17 (12.5)	12 (8.8)	5 (3.7)	0	14 (10.9)	11 (8.6)	3 (2.3)	0
Constipation	17 (12.5)	12 (8.8)	5 (3.7)	0	13 (10.2)	11 (8.6)	2 (1.6)	0
Dizziness	17 (12.5)	14 (10.3)	3 (2.2)	0	9 (7.0)	9 (7.0)	0	0
Asthenia	16 (11.8)	10 (7.4)	5 (3.7)	1 (0.7)	12 (9.4)	11 (8.6)	1 (0.8)	0
Back pain	16 (11.8)	9 (6.6)	4 (2.9)	3 (2.2)	10 (7.8)	8 (6.3)	2 (1.6)	0
Hot flush	5 (3.7)	4 (2.9)	1 (0.7)	0	15 (11.7)	13 (10.2)	2 (1.6)	0
Abdominal distention	14 (10.3)	13 (9.6)	1 (0.7)	0	11 (8.6)	10 (7.8)	1 (0.8)	0

Ledermann (2012) *New England Journal of Medicine*, *366*(15), 1382–1392

Current status of olaparib (Lynparza)

- **Australia** – TGA approved

  "Olaparib is indicated as monotherapy for the **maintenance treatment** of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens."

- **Europe** – approved as **maintenance treatment** for platinum sensitive relapsed BRCA m ovarian cancer –patients in remission following platinum-based therapy

- **USA** - approved as monotherapy
  - For patients who have received ≥ ?3 lines of chemotherapy
  - **Not** approved as maintenance therapy
  - Approval also for companion diagnostic (Myriad Genetics BRCA analysis CDx)

Table 2 Ongoing phase III studies of PARP inhibitors for ovarian cancer treatment

Trial and NCI trial number	Study arms	Trial population	Primary endpoint	Total accrual	Trial status
Newly diagnosed ovarian cancer					
SOLO1 (NCT01844986)	Olaparib versus placebo post-platinum-based chemotherapy	BRCAm only, HGSOC, or endometrioid stage III and IV only	PFS	344	Accrual completed; results pending
GOG-3005 (NCT02470585)	Carboplatin and paclitaxel versus carboplatin, paclitaxel, and veliparib versus carboplatin, paclitaxel, and veliparib followed by veliparib maintenance therapy	Advanced HGSOC, both BRCAm and BRCAwt	PFS	1100	Accrual ongoing
PAOLA1 (NCT02477644)	Platinum/taxane/bev, bev maintenance versus platinum/taxane/bev, bev/olaparib maintenance	Newly diagnosed high-grade ovarian cancer	PFS	612	Accrual ongoing
Recurrent ovarian cancer					
NOVA (NCT01847274)	Niraparib versus placebo post platinum-based chemotherapy	Platinum-sensitive, HGSOC, BRCA-stratified	PFS	360	Accrual completed; results pending
SOLO2 (NCT01874353)	Olaparib versus placebo post platinum-based chemotherapy	Platinum-sensitive BRCAm only, HGSOC, or endometrioid	PFS	264	Accrual completed; results pending
ARIEL3 (NCT01968213)	Rucaparib versus placebo post-platinum-based chemotherapy	Platinum-sensitive recurrence, HGSOC or endometrioid BRCA-stratified	PFS	540	Accrual ongoing
SOLO3 (NCT02282020)	Olaparib versus MD choice non-platinum chemotherapy	Platinum-sensitive BRCAm HGSOC	PFS	411	Accrual ongoing
NRG-GY004 (NCT02446600)	Olaparib versus olaparib/cediranib versus platinum doublet	Platinum-sensitive recurrent high-grade ovarian cancer BRCA-stratified	PFS	450	Accrual ongoing
NRG-GY005 (NCT02502266)	Olaparib/cediranib versus single-agent chemotherapy	Platinum resistant recurrent high-grade ovarian cancer	PFS (ph 2) OS (ph 3)	680	Accrual ongoing

HGSOC high-grade serous ovarian cancer, *BRCAm* BRCA mutation carrier, *PFS* progression-free survival, *Bev* bevacizumab

Liu, J. F., & Matulonis, U. A. (2016). *Current Oncology Reports*, *18*(5), 29

What about toxicity?

Chemotherapy	Targeted therapies	Immunotherapy
• Neutropenia / immune suppression • Hair loss • Nausea and vomiting • Lethargy	• Skin rash • GI effects (diarrhoea, nausea) • Drug induced liver injury • 'off-target toxicity' e.g. skin SCC	• NOT immune suppressive • Immune-related side effects • Skin (rash, pruritis) • Diarrhoea / colitis (<5%) • Pneumonitis (<3%) • Endocrine • Any auto-immune '-itis'

Immune checkpoint blockade (ICB) toxicities

Frequent (>10%) ICB toxicities

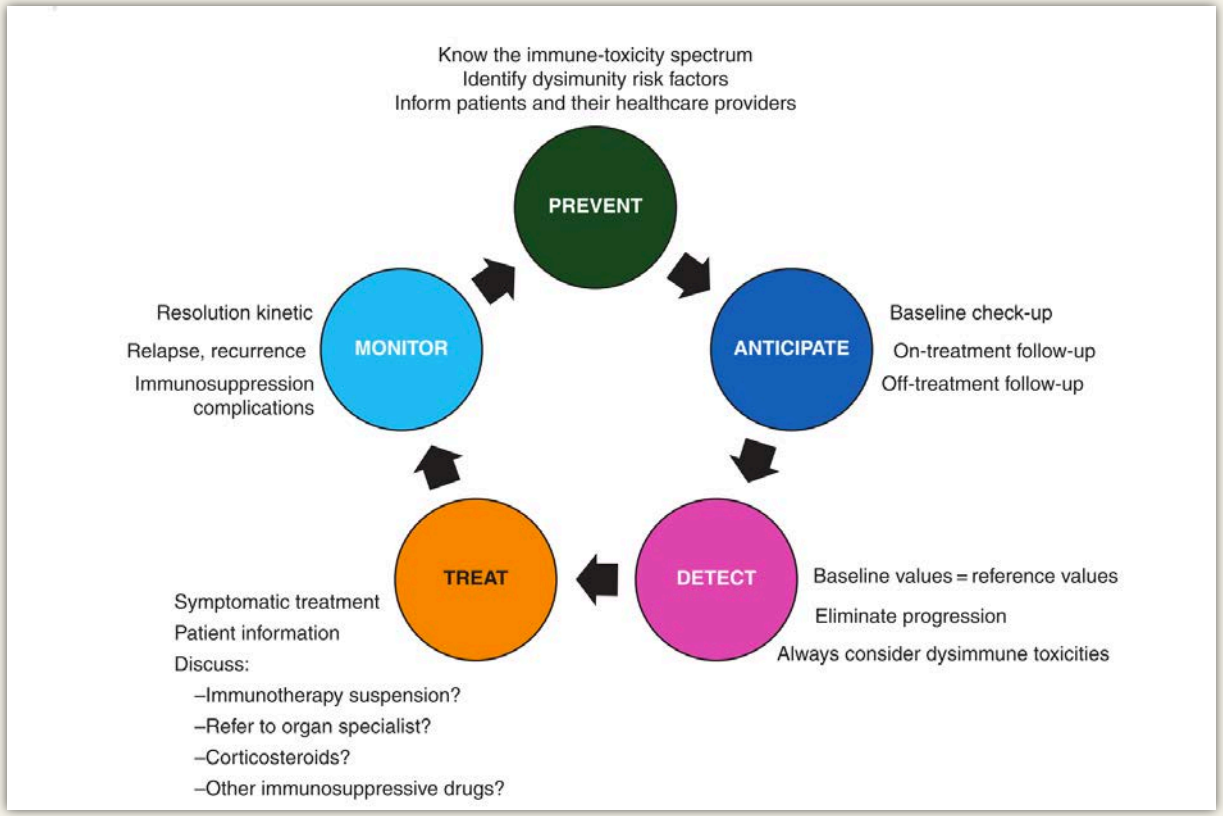
- Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain
- Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea
- Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue

Rare (<10%) life-threatening ICB toxicities

- Colitis and risk of gastrointestinal perforation
- Pneumonitis including acute interstitial pneumonia / ARDS
- Infusion reaction and anaphylactic shock
- Type 1 diabetes and risk of diabetic ketoacidosis
- Severe skin reactions, DRESS, Stevens Johnson syndrome
- Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk
- Neutropenia and sepsis risk
- Encephalopathy and neurological sequelae
- Guillain–Barré syndrome and respiratory risk
- Myelitis and motor sequelae
- Myocarditis and cardiac insufficiency
- Acute adrenal insufficiency and hypovolemic shock
- Pleural and pericardial effusion
- Nephritis

Champiat, S. et al. (2016). Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Annals of Oncology*, *27*(4), 559–574.

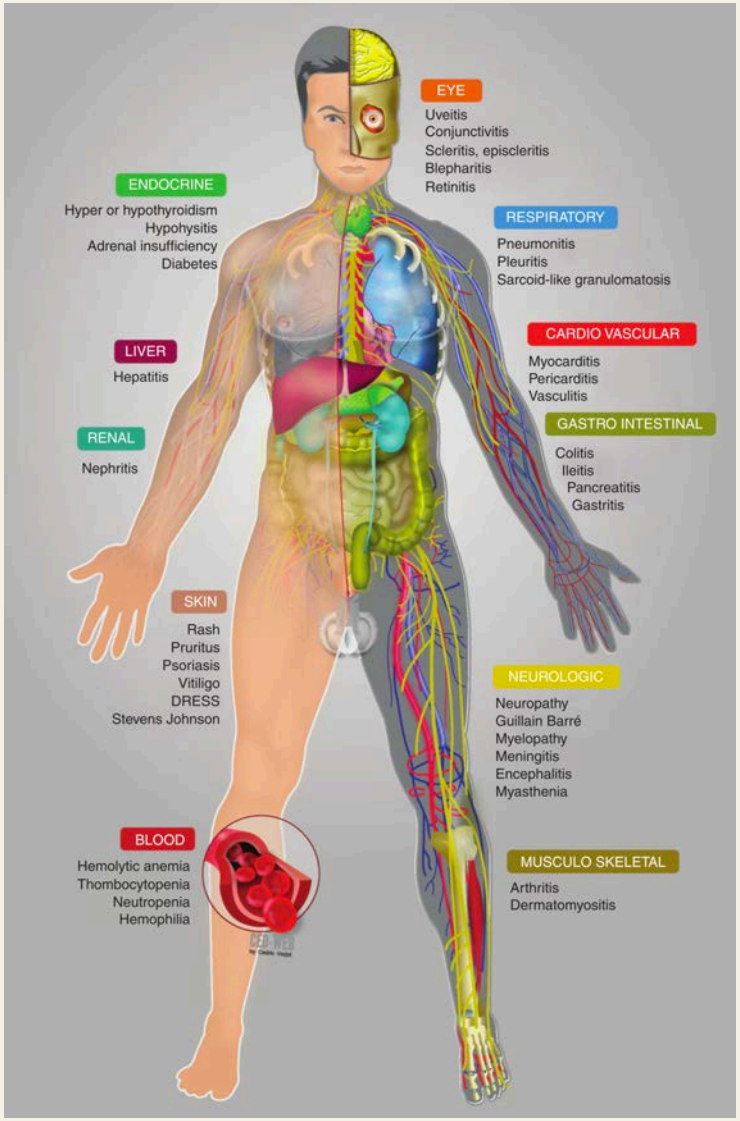
The five pillars of immunotherapy toxicity management



Champiat, S., Lambotte, O., Barreau, E., Belkhir, R., Berdelou, A., Carbonnel, F., … Marabelle, A. (2016). Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Annals of Oncology*, *27*(4), 559–574.

Spectrum of toxicity of immune checkpoint blockade agents

Champiat, S. et al. (2016). Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper
Annals of Oncology, 27(4), 559–574.



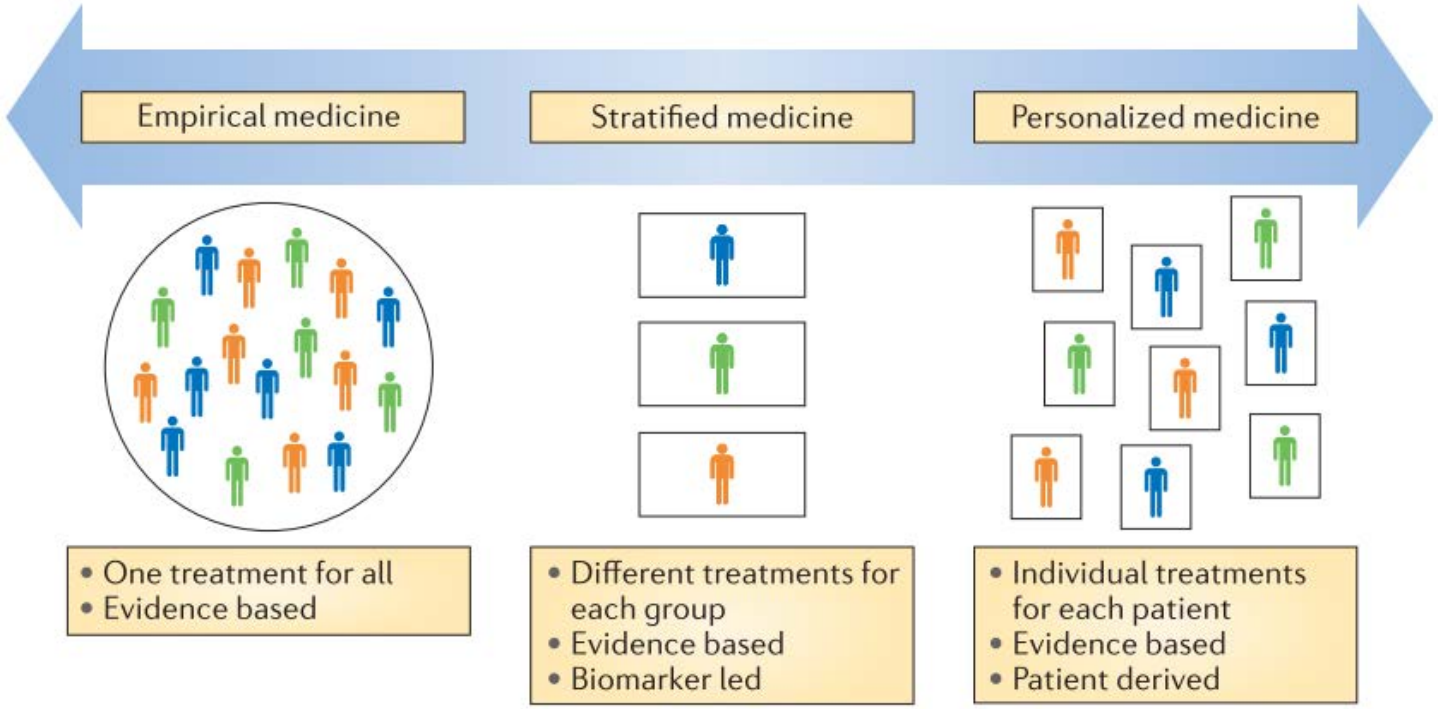
Outline

- Basic stats
- Anti-cancer therapies – a historical perspective
- Ehrlich's "magische Kugel" – a dream realised
- Immunotherapy comes of age
- The search for biomarkers
- Future directions

SCIENCE AND SOCIETY

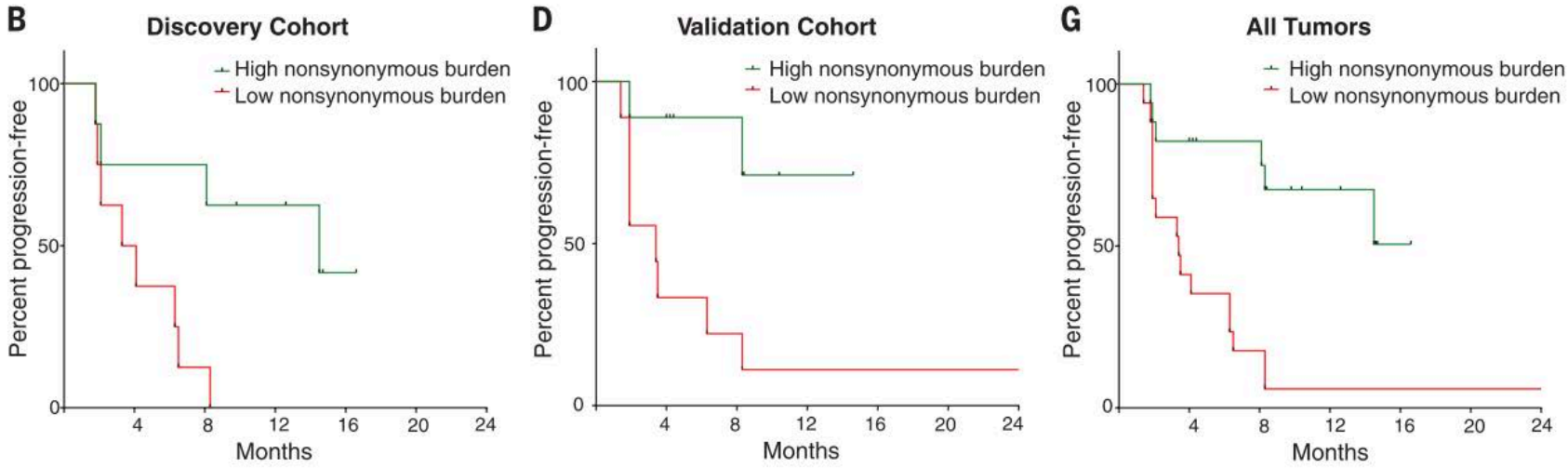
Immune biomarkers: the promises and pitfalls of personalized medicine

Joanna C. D. Willis and Graham M. Lord

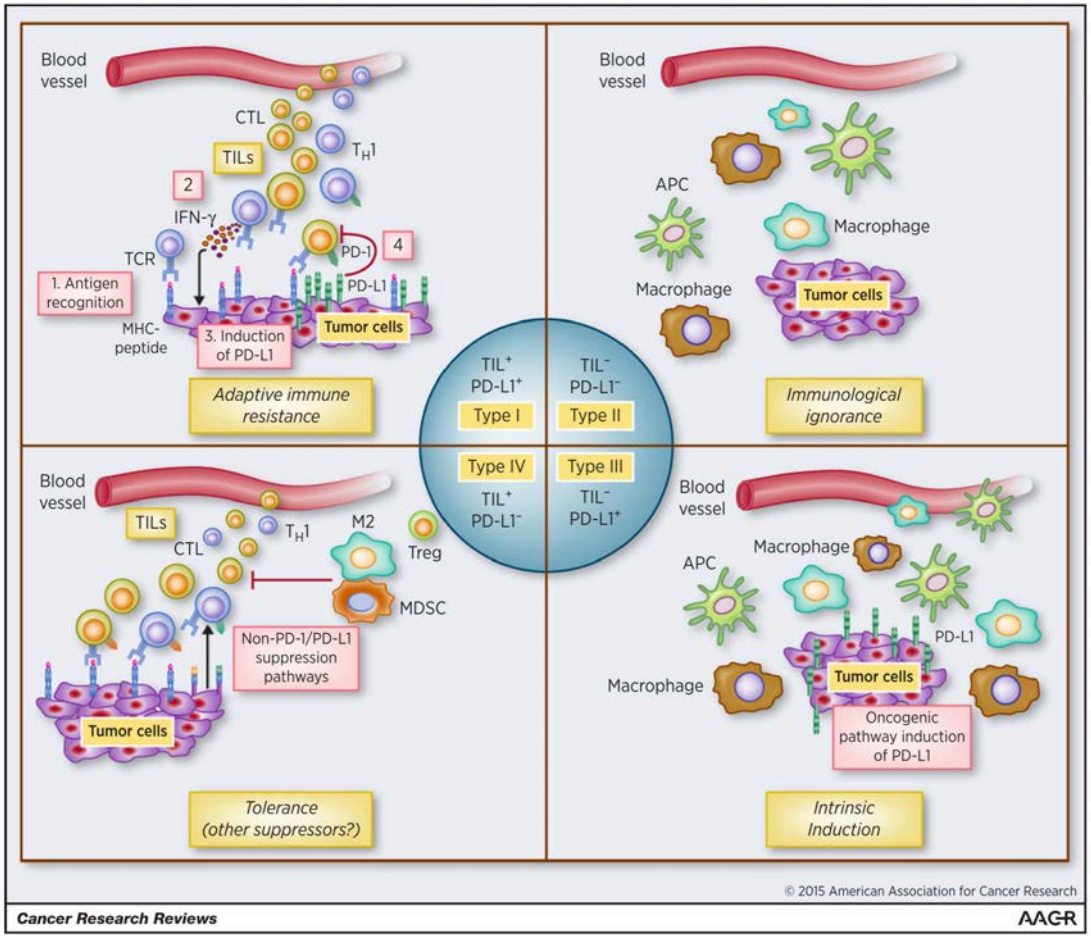


Willis, J. C. D (2015). *Nature Reviews Immunology*, *15*(March), 1–7. doi:10.1038/nri3820

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer



Rizvi, N. A (2015). *Science*, *348*(6230), 124–129. doi:10.1126/science.aaa1348



Teng, M. W. L., Ngiow, S. F., Ribas, a., & Smyth, M. J. (2015). Classifying Cancers Based on T-cell Infiltration and PD-L1. *Cancer Research*, *75*(11), 2139–2145

Neoantigens in cancer immunotherapy

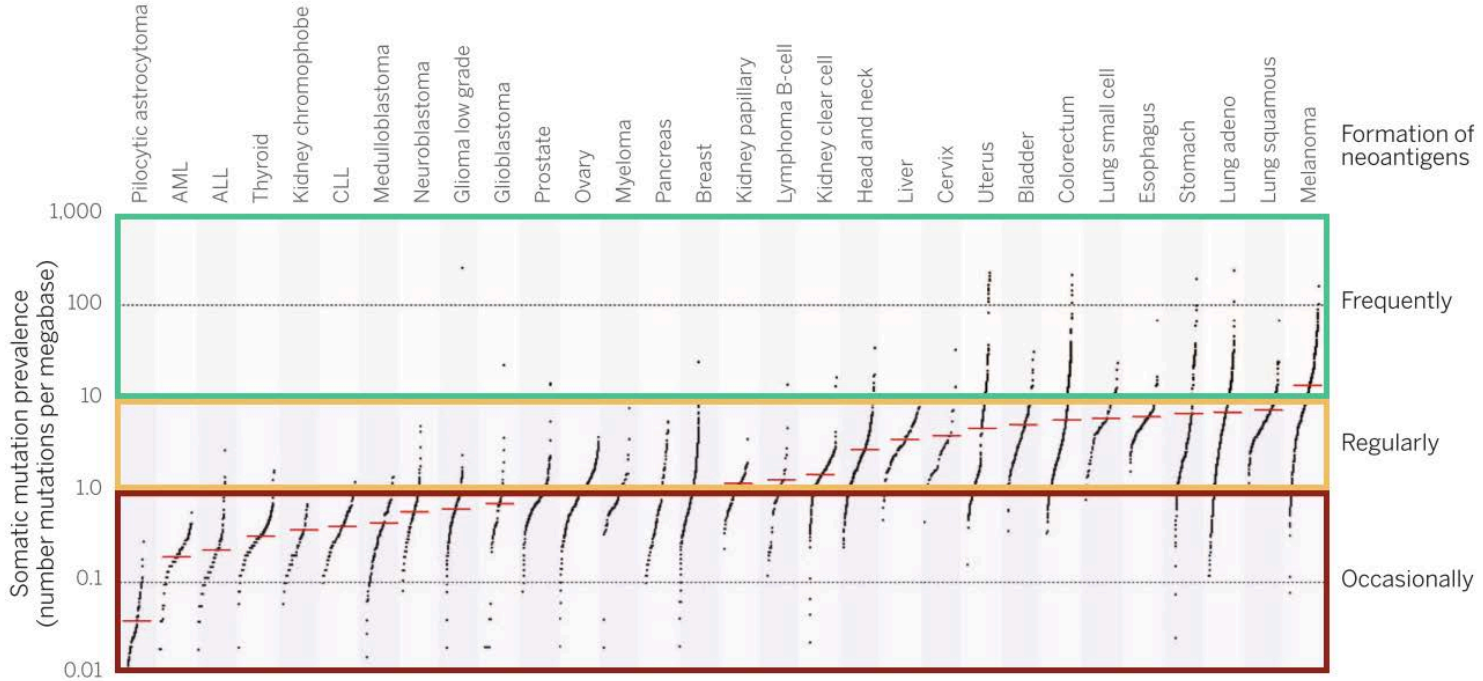


Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Schumacher, T. N. & Schreiber, R. D. (2015). *Science*, *348*(6230), 69–74. doi:10.1126/science.aaa4971

Neoantigens in cancer immunotherapy

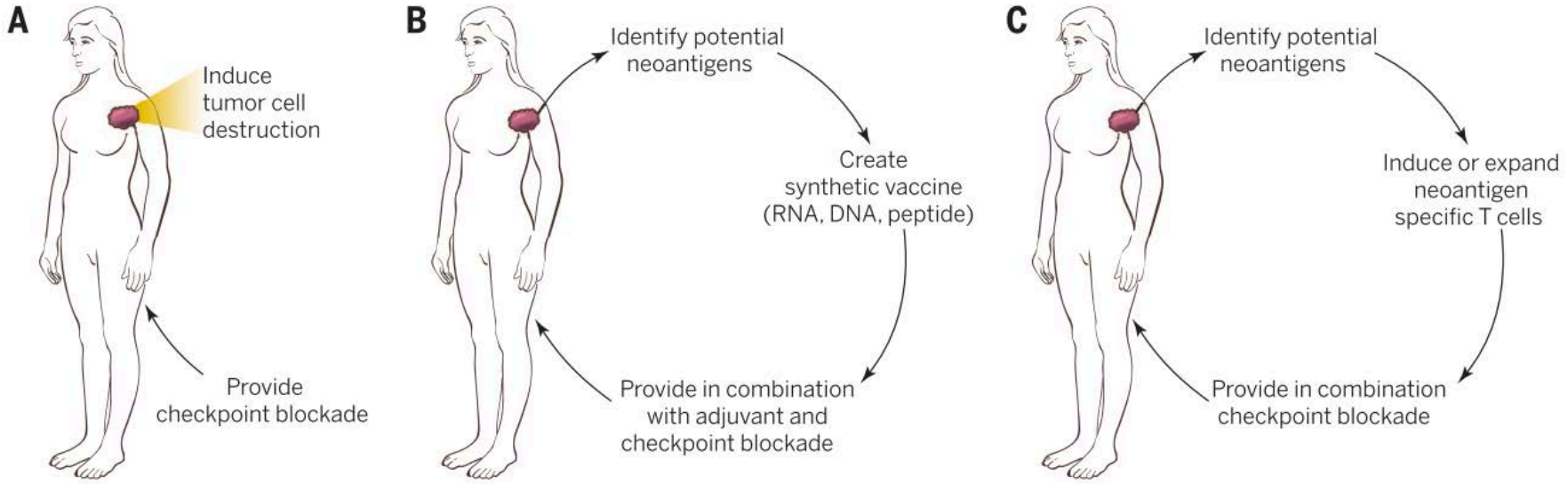
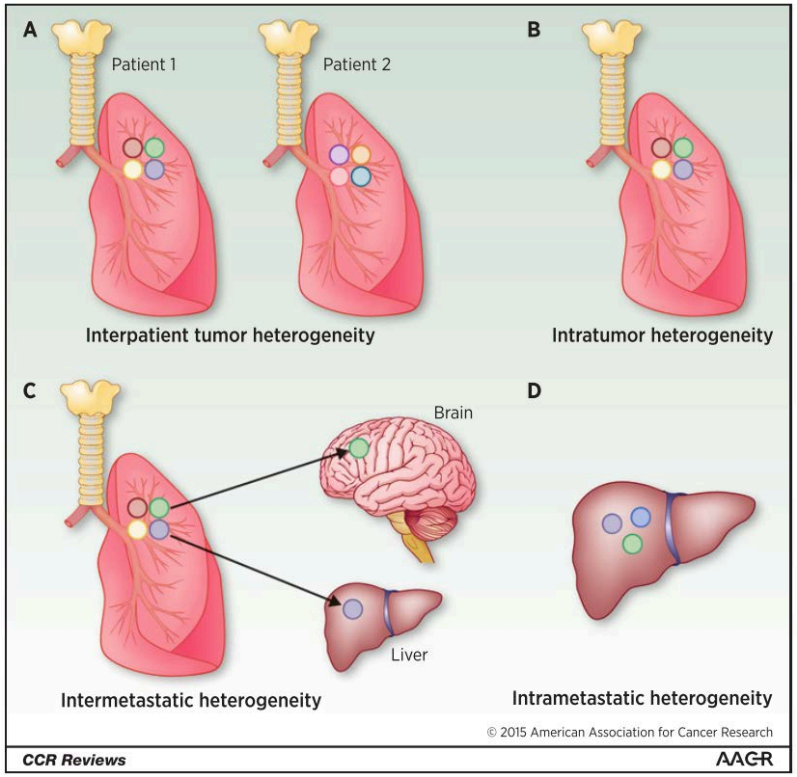
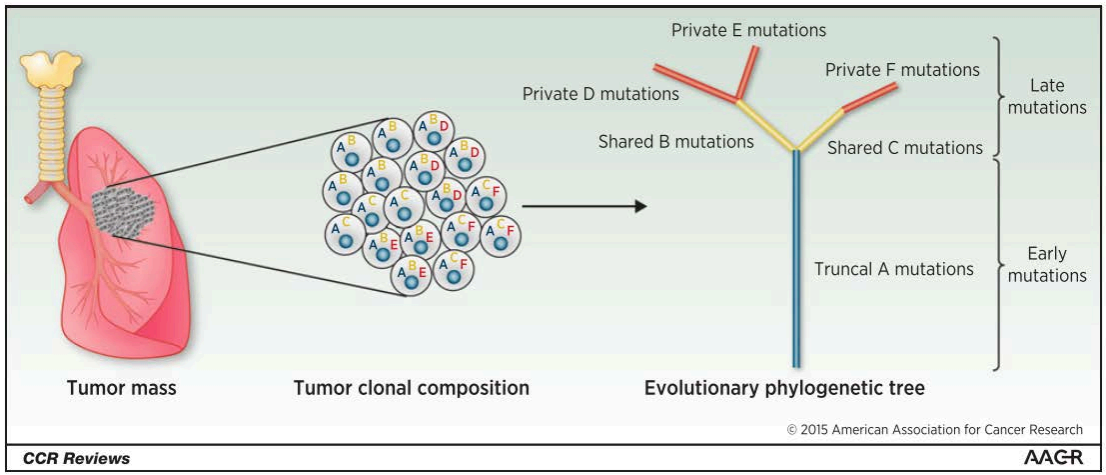


Fig. 4. Strategies to target the patient-specific neoantigen repertoire. (**A**) Immunotherapy is given in combination with interventions such as radiotherapy that enhance exposure to autologous neoantigens. (**B**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, a patient-specific vaccine is produced, and this vaccine is given together with adjuvant and T cell checkpoint-blocking antibodies. (**C**) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, T cells that are specific for these neoantigens are induced or expanded in vitro, and the resulting T cell product is given together with T cell checkpoint-blocking antibodies.

Schumacher, T. N. & Schreiber, R. D. (2015). *Science*, *348*(6230), 69–74. doi:10.1126/science.aaa4971

Translational Implications of Tumor Heterogeneity



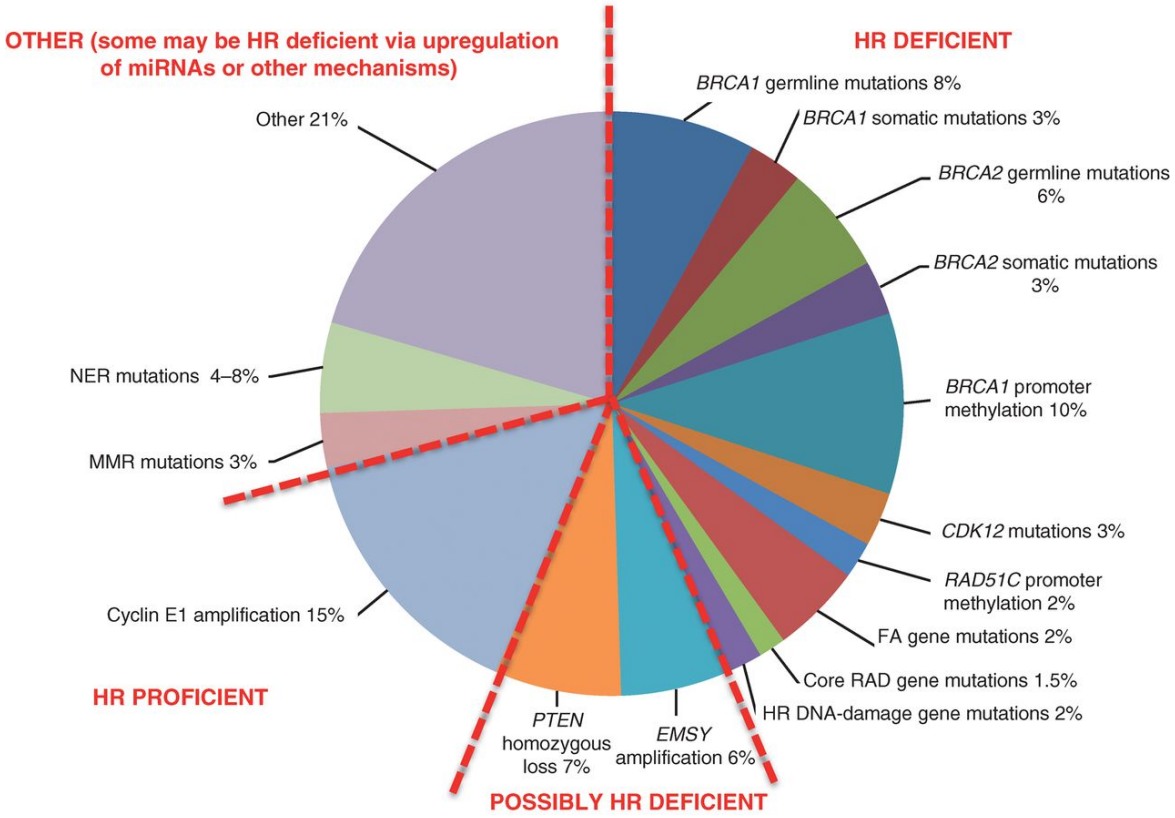


Jamal-Hanjani, M (2015). *Clinical Cancer Research*, *21*(6), 1258–1266. doi:10.1158/1078-0432.CCR-14-1429

Biomarkers of PARPi response

- BRCA1/2 germline mutations (~14% of high-grade serous EOC)
- BRCA ½ somatic mutations (~6%)
- Other genetic and epigenetic alterations in HR genes ?>30%

Approximately 50% of high-grade serous EOCs have alterations in HR repair genes.

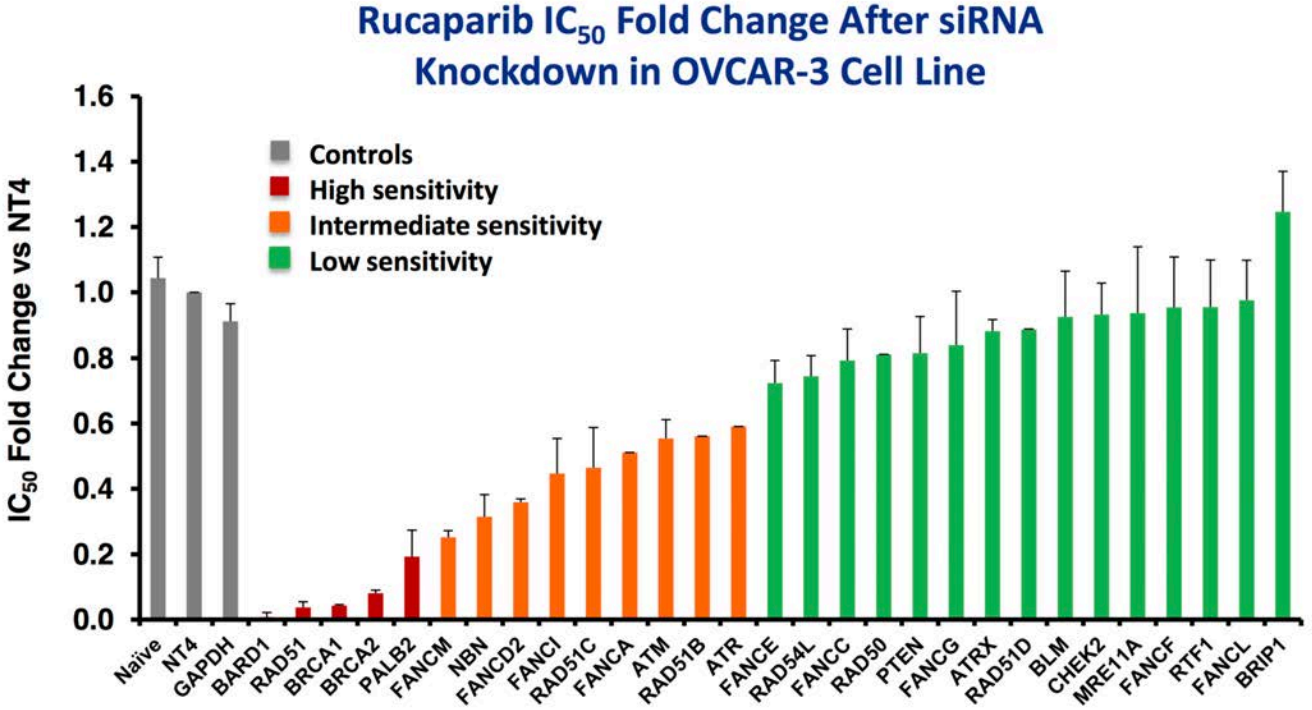


Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154

Homologous recombination deficiency (HRD) assays

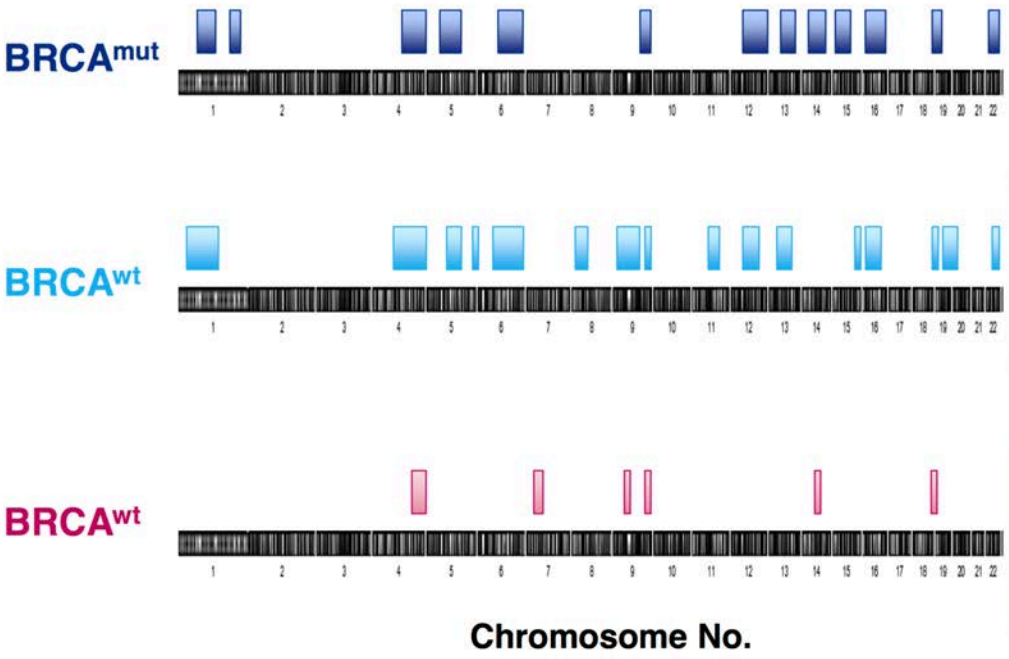
Validation, validation, validation!!

Defining a BRCA-like signature through single gene analysis is complex – not all genes are functionally relevant



IC_{50}=half maximal inhibitory concentration.

HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS



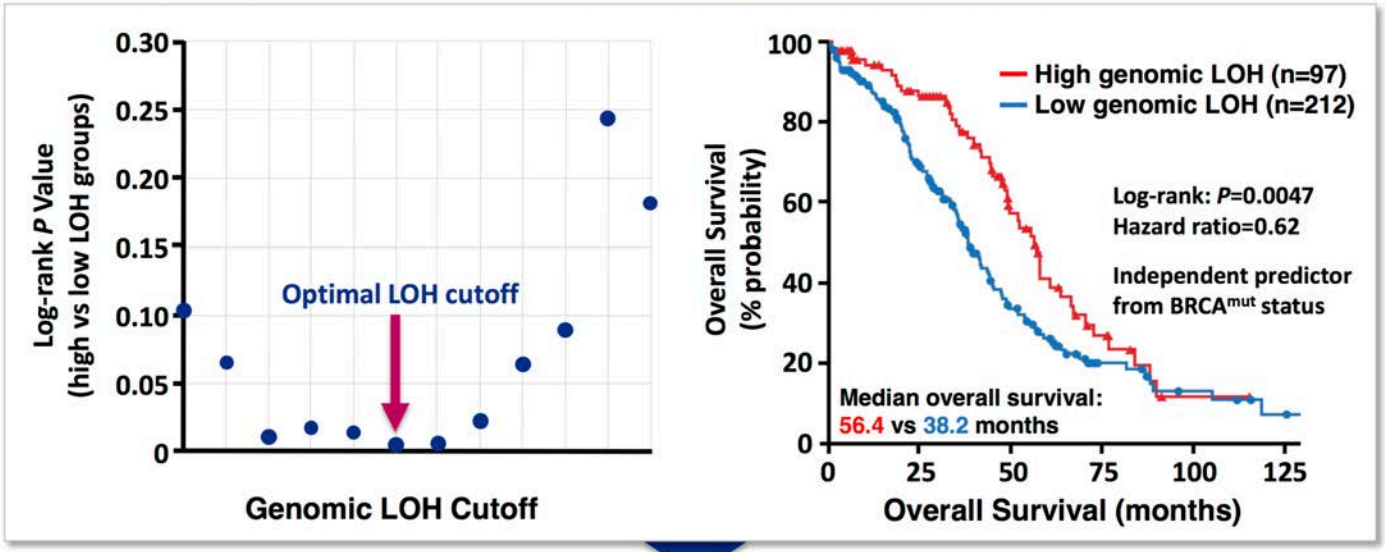
Hypothesis 1:
Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

Hypothesis 2:
Ovarian cancer patients who are "biomarker negative" (ie, with low genomic LOH) will not respond to PARPi.

mut=mutation; NGS=next-generation sequencing; wt=wild type.

Diagnostic development: Cutoff defined for BRCA-like signature, being tested and refined

TCGA and AOCS Overall Survival Data Used to Develop LOH Cutoff to Identify High-Grade Ovarian Cancer Patient Tumors with BRCA-Like Signature

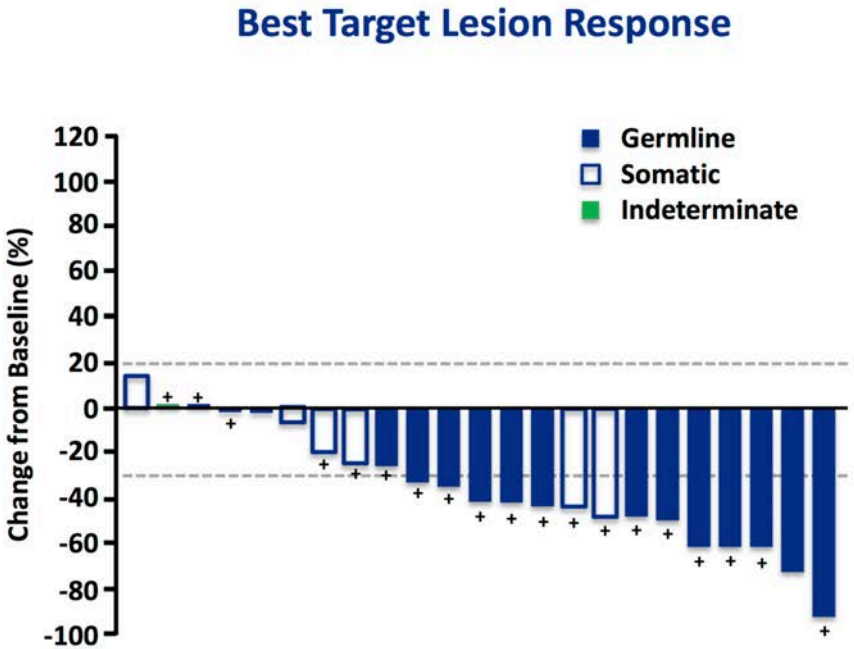


Prospective testing of prespecified cutoff in ARIEL2 and ARIEL3

The Cancer Genome Atlas (TCGA) Research Network. *Nature*. 2011;474:609-615; Wang ZC et al; Australian Ovarian Cancer Study (AOCS). *Clin Cancer Res*. 2012;18:5806-5815.

Greatest rucaparib activity observed in BRCA^{mut} patients…

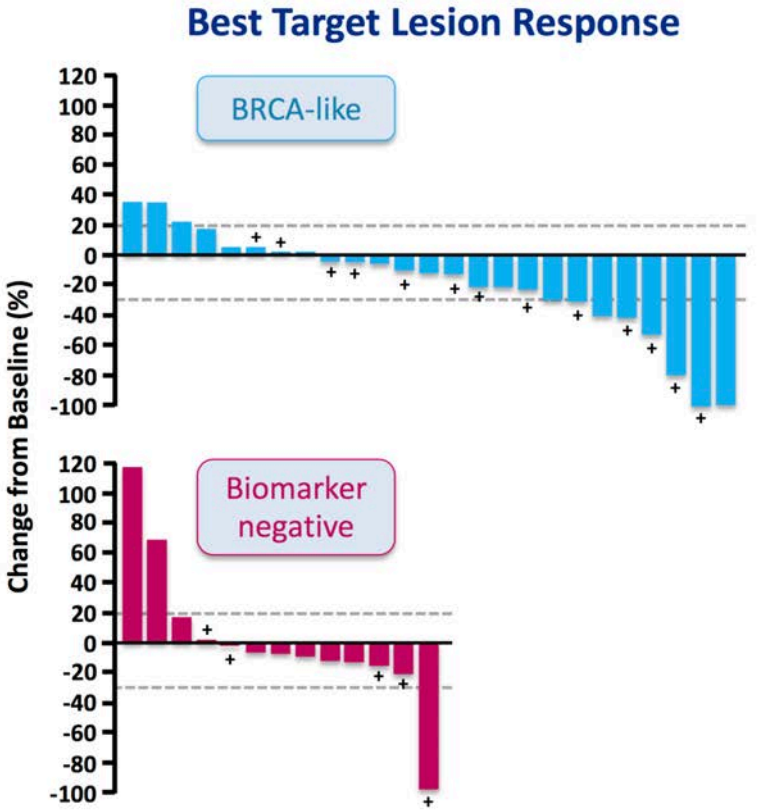
- Robust clinical activity observed in BRCA^{mut} patients (n=23)
  - 61% ORR (RECIST)
  - 70% ORR (RECIST & CA-125)
  - 83% of patients continuing on treatment (+)
- Responses observed in germline and somatic BRCA^{mut} tumors



+=ongoing.

…and differential rucaparib activity seen in patients with/without BRCA-like signature

- Clinical activity observed in BRCA^{wt} patients **with** BRCA-like signature (n=25)
  - 32% ORR (RECIST)
  - 40% ORR (RECIST & CA-125)
  - 52% of patients continuing on treatment (+)
- Few responses observed in BRCA^{wt} patients **without** BRCA-like signature (n=13)
  - 8% ORR (RECIST)
  - 8% ORR (RECIST & CA-125)
  - 38% of patients continuing on treatment (+)



+=ongoing.

Outline

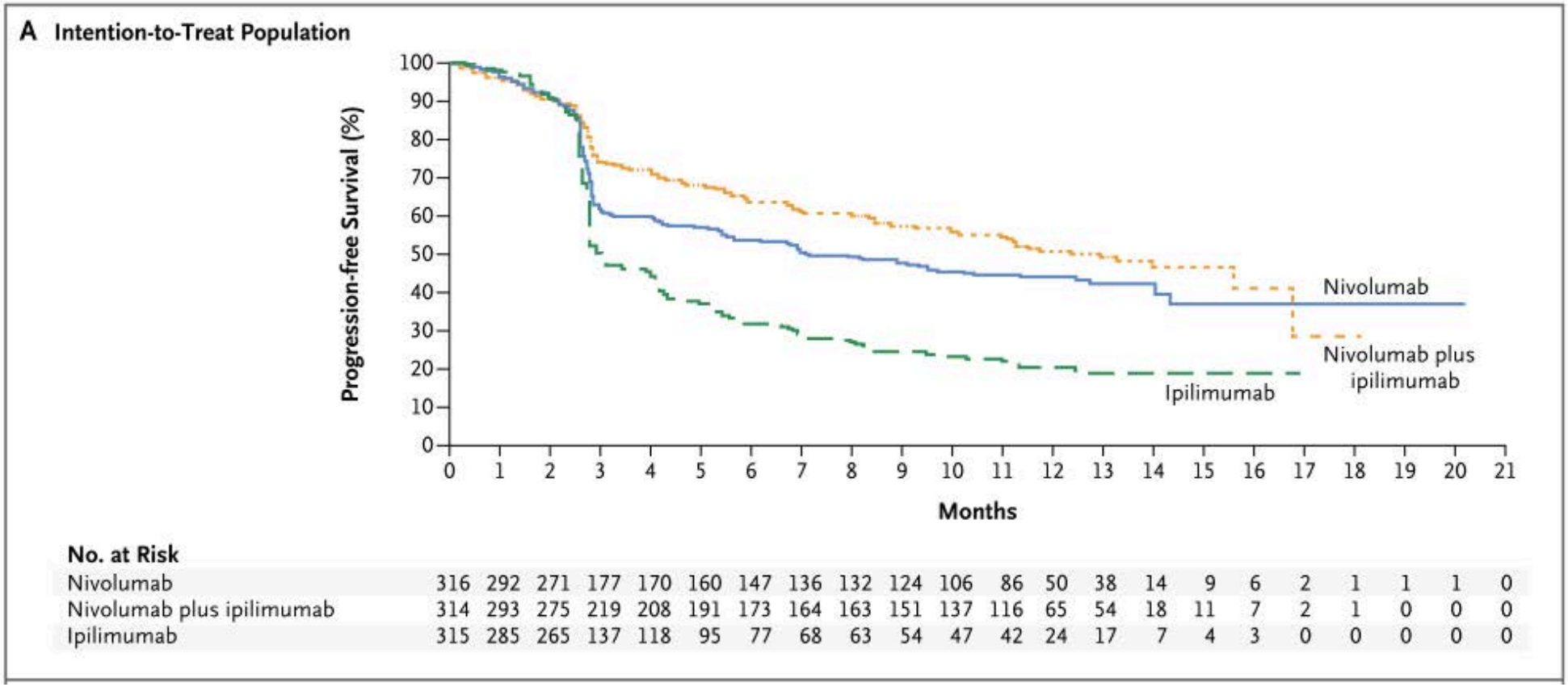
- Basic stats
- Anti-cancer therapies – a historical perspective
- Ehrlich's "magische Kugel" – a dream realised
- Immunotherapy comes of age
- The search for biomarkers
- Future directions

ORIGINAL ARTICLE

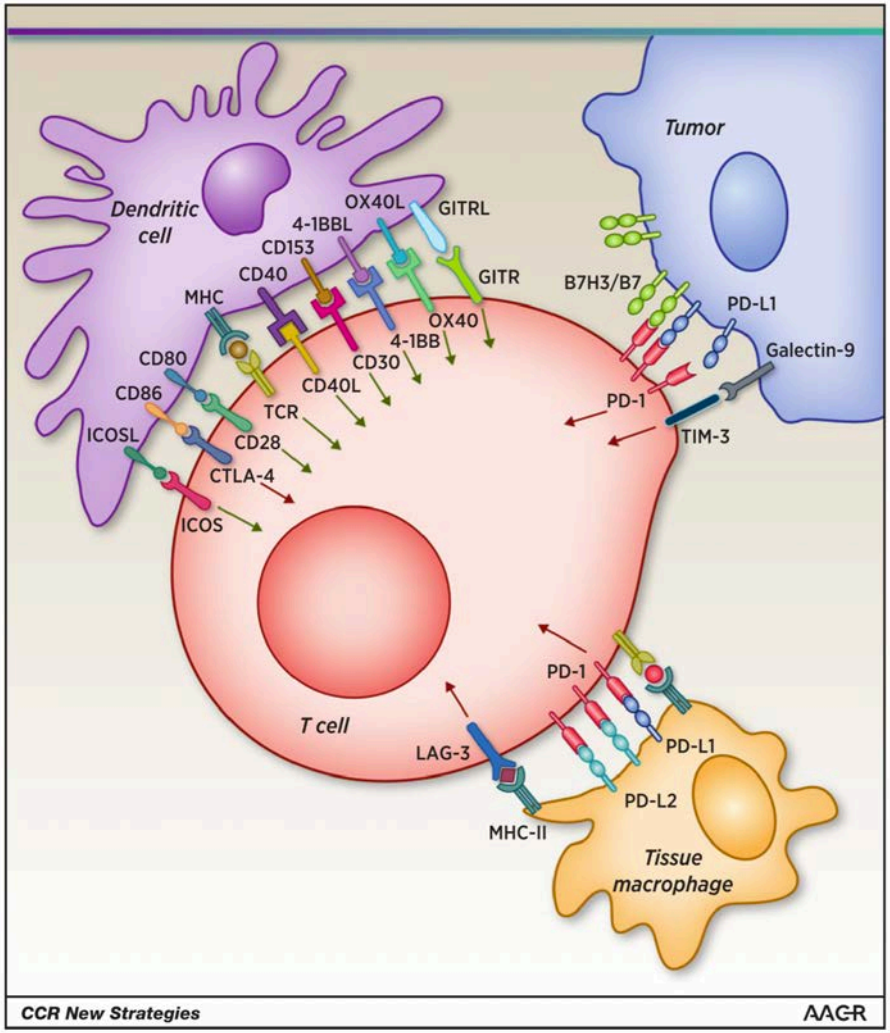
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

Larkin, J (2015). *NEJM*, 150531115012002. doi:10.1056/NEJMoa1504030

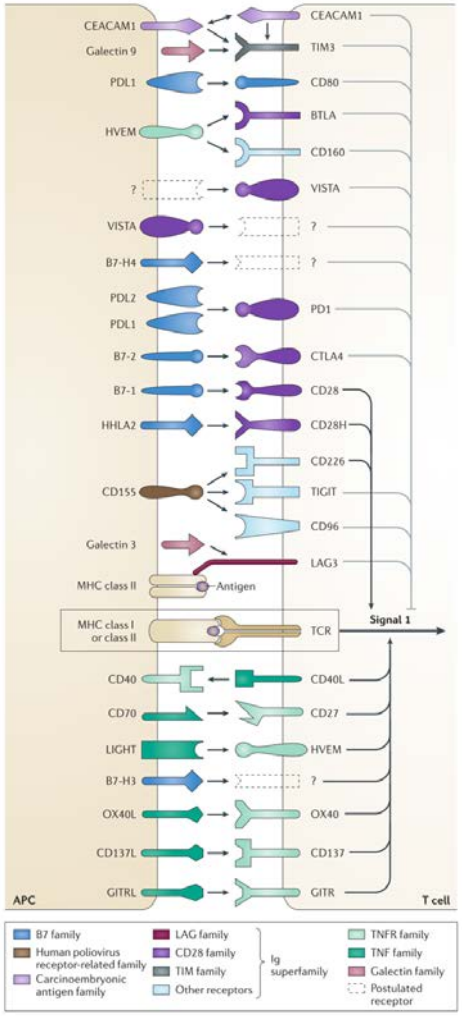


Larkin, J (2015). *NEJM*, 150531115012002. doi:10.1056/NEJMoa1504030



Novel combinations

Sullivan, R. J., & Flaherty, K. T. (2015). New Strategies in Melanoma: Entering the Era of Combinatorial Therapy. *Clinical Cancer Research*, *21*(11), 2424–2435.



Box 1 | **Immunotherapies that are approved or in development**

Vaccines

- Dendritic cell-based vaccines
- Autologous granulocyte–macrophage colony-stimulating factor (GM-CSF)-transfected vaccines
- Viral vector vaccines
- mRNA-based vaccines
- Multipeptide-based vaccines
- Locally released virotherapy

Targets of modulatory monoclonal antibodies

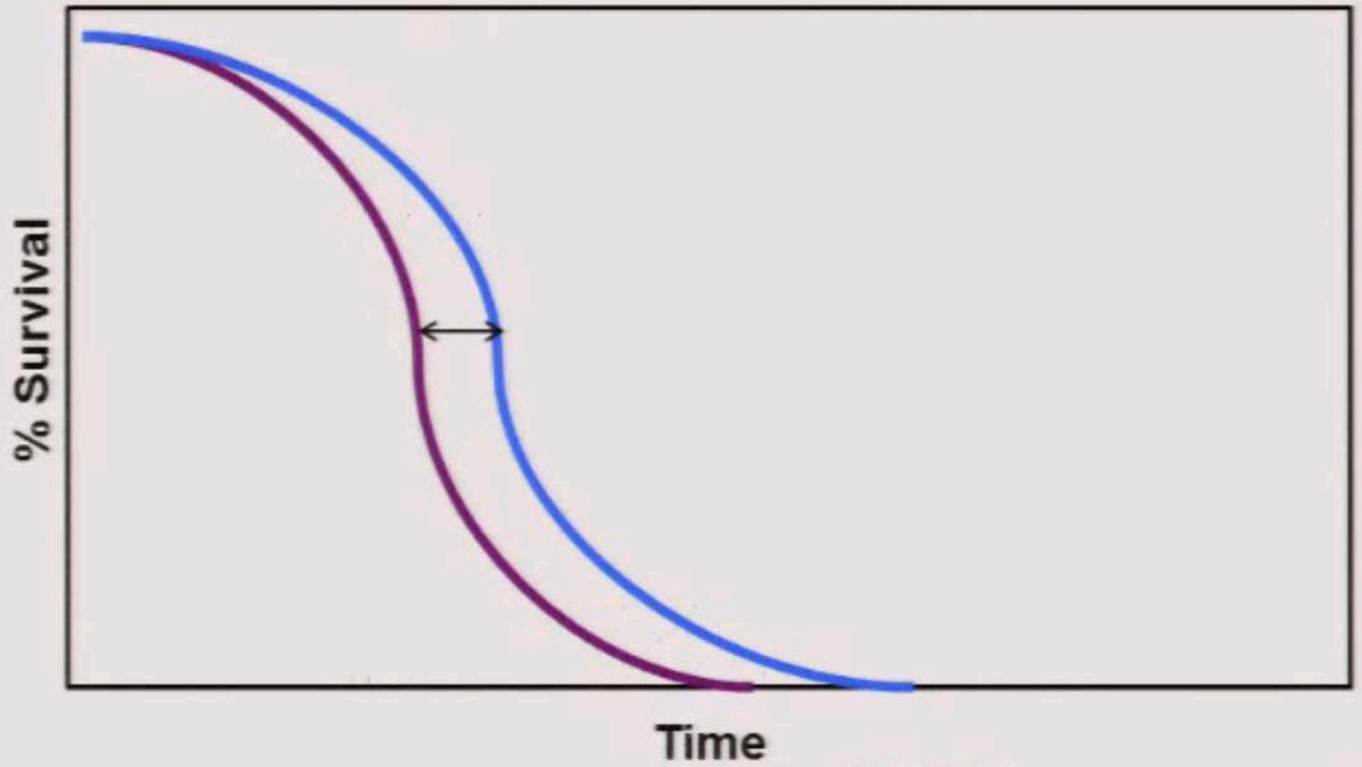
- Cytotoxic T lymphocyte-associated antigen 4 (CTLA4)
- Programmed cell death protein 1 (PD1)
- PD1 ligand 1 (PDL1)
- CD137
- OX40
- Lymphocyte activation gene 3 protein (LAG3)
- T cell immunoglobulin and mucin-domain containing 3 (TIM3)
- Glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR)
- CD27

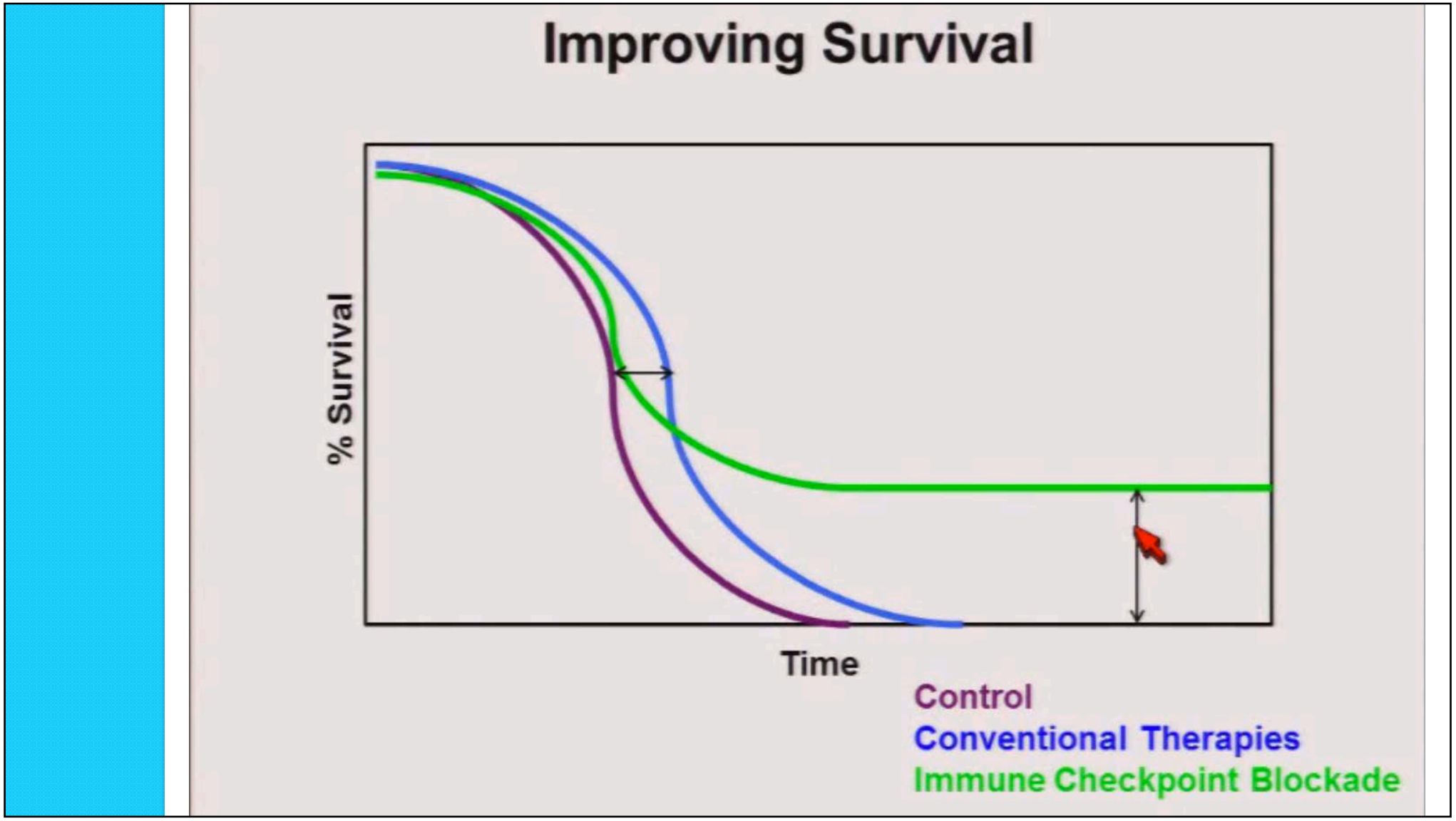
Adoptive T cell therapy

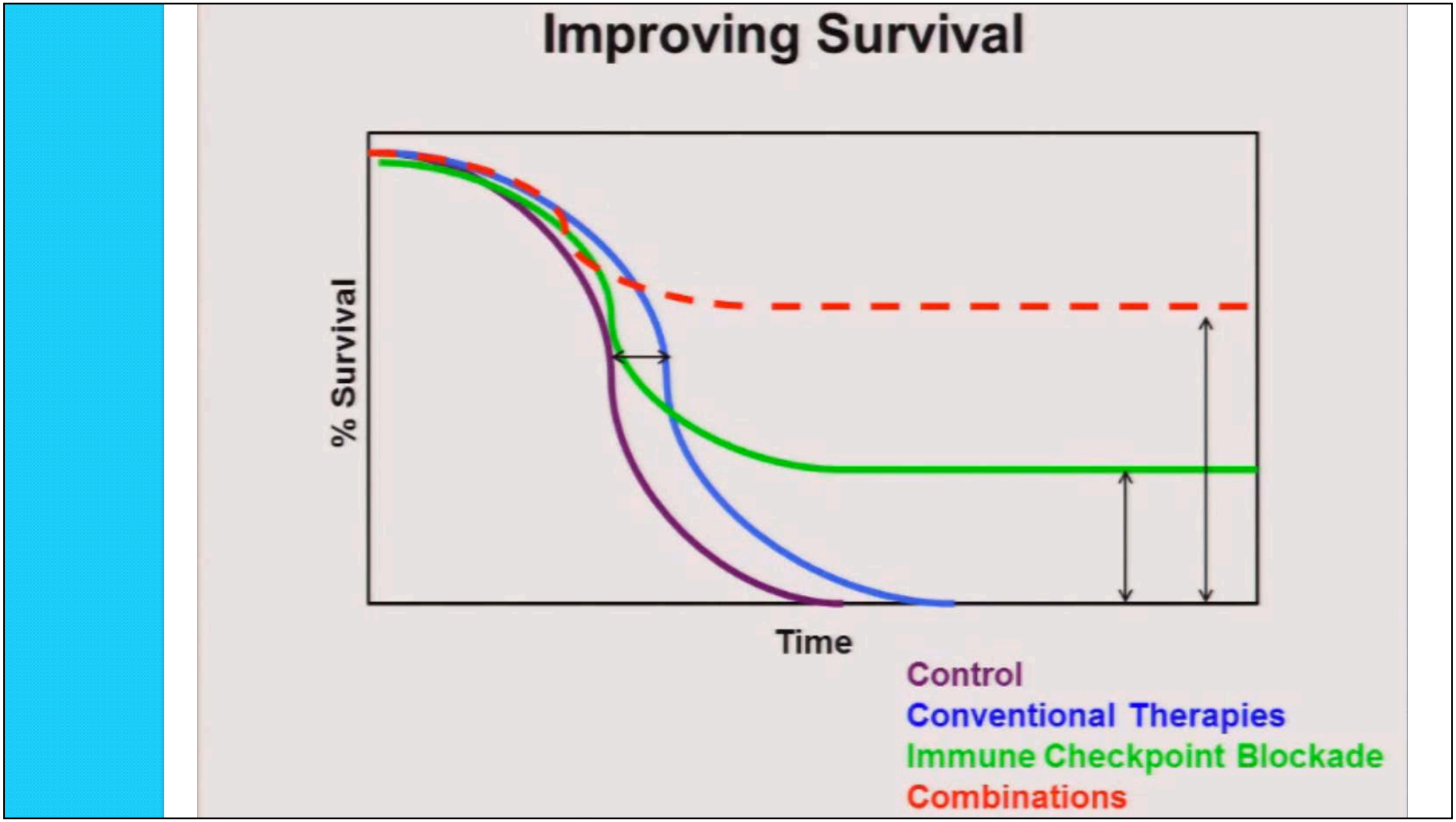
- Tumour-infiltrating lymphocytes
- Chimeric antigen receptors (CARs)
- CAR-transduced T lymphocytes

Melero, I., Berman, D. M., Aznar, M. A., Korman, A. J., Gracia, J. L. P., & Haanen, J. (2015). *Nature Reviews Cancer*, *15*(8), 457–472

Improving Survival




Improving Survival
% Survival
Time
Control
Conventional Therapies
Immune Checkpoint Blockade


Improving Survival
% Survival
Time
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Immune Checkpoint Blockade
Combinations

Thank you!!