Dr Chris Jackson

Consultant Medical Oncologist

Southern Blood and Cancer Service (Southern DHB), Senior Lecturer in Medicine with the University of Otago

Friday, August 12, 2016

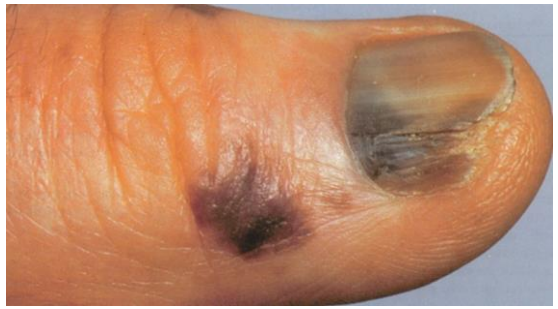
(Plenary)

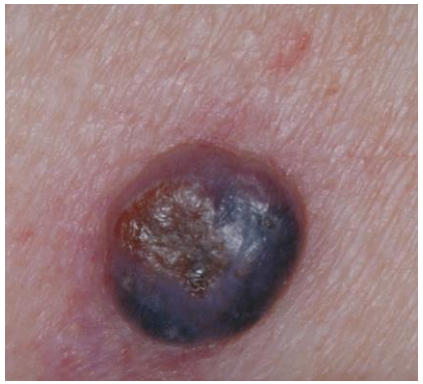
8:35 - 9:00 A Paradigm Shift in The Treatment of Advanced Melanoma

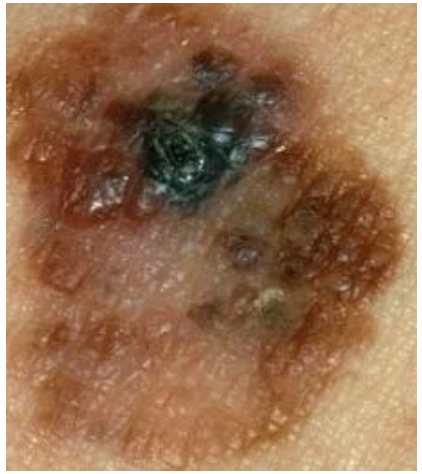
A paradigm shift in the treatment of advanced melanoma

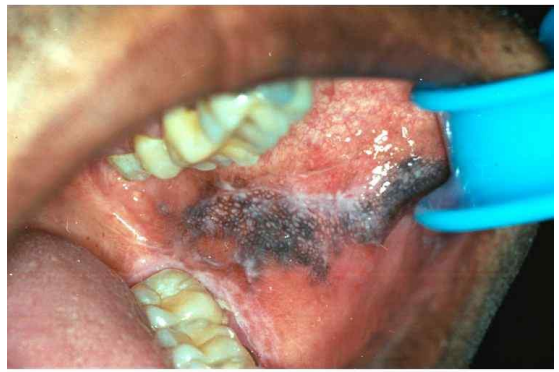
Dr. Christopher Jackson
Medical Oncologist, SDHB
Senior Lecturer in Medicine, University of Otago

Multiple phenotypes; multiple diseases

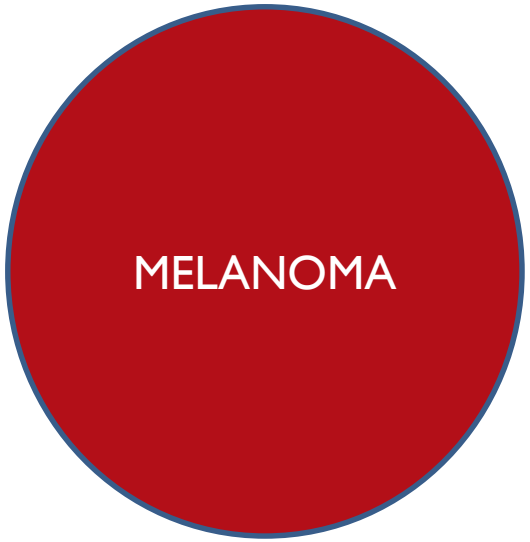








Multiple phenotypes; multiple diseases



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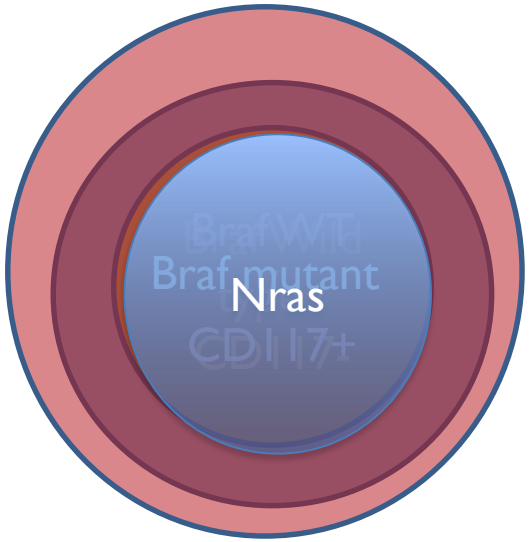
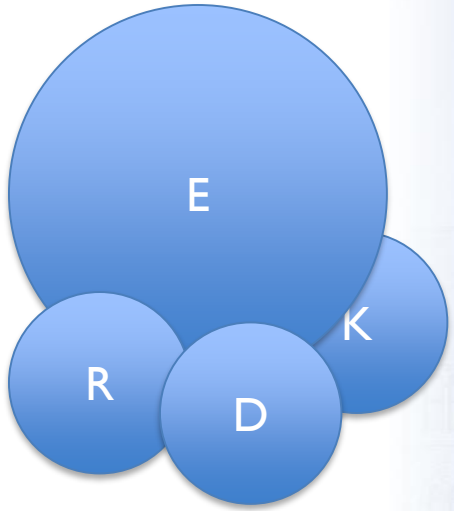
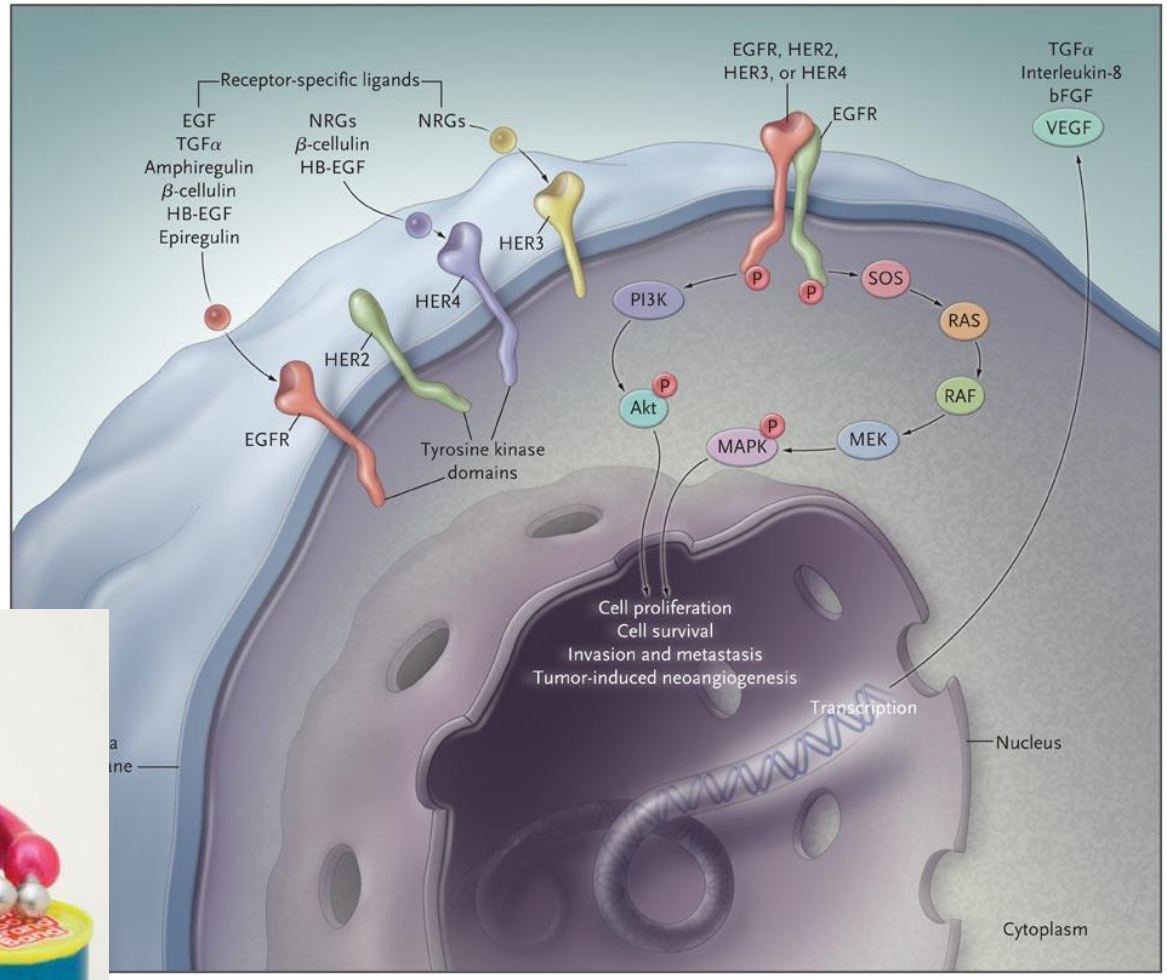


Multiple phenotypes; multiple diseases

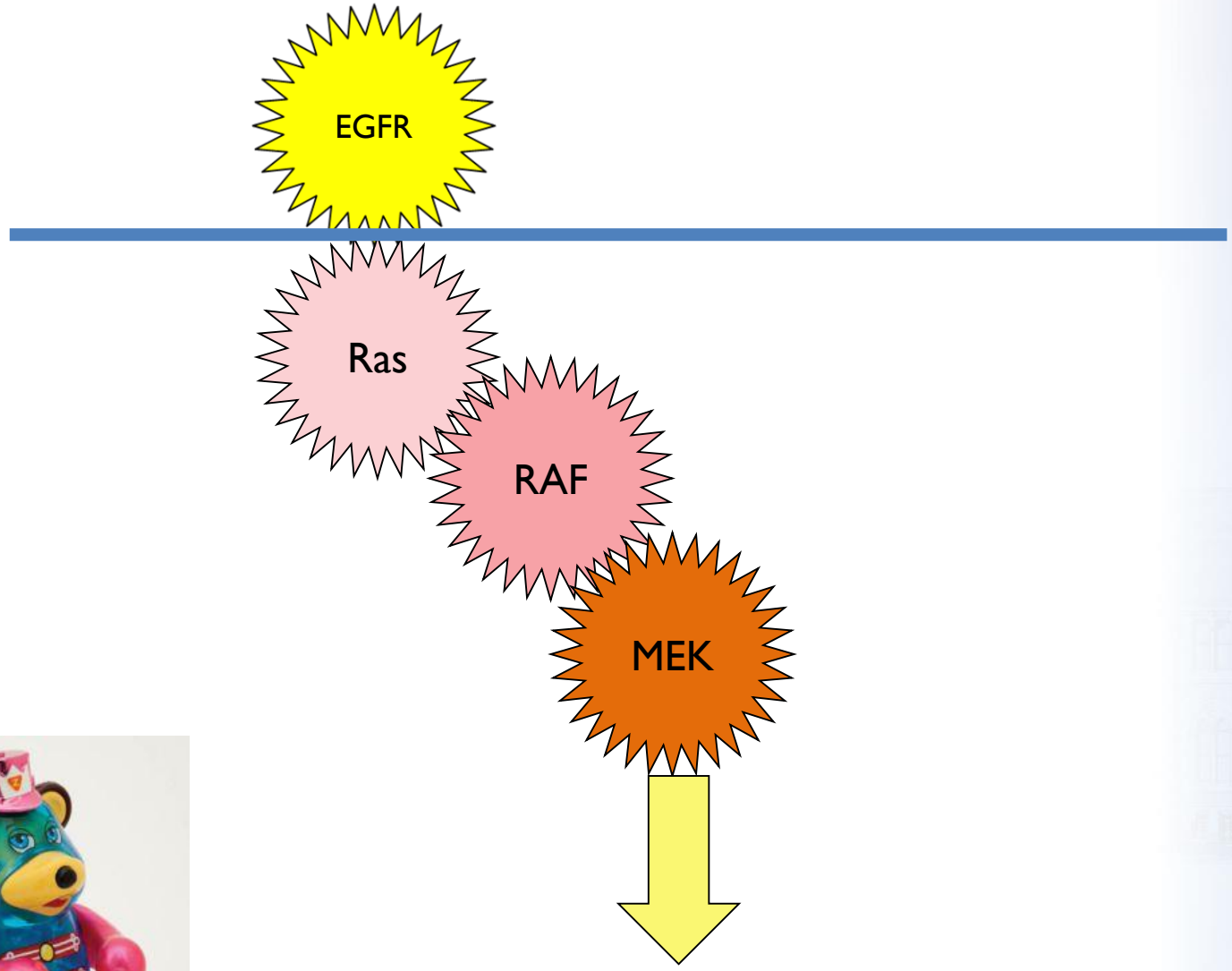
Cutaneous Melanoma	
	Oncogenes
	BRAF (50-70%)
	NRAS (15-30%)
	AKT3 (over-expressed)
	Tumour suppressors
	CDKN2A (30-70% deleted, mutated, or silenced)
	PTEN (5-20% deleted or mutated)
	APAF1 (40% silenced)
	TP53 (10% lost or mutated)
	Others
	CCND1 (6-44% amplified)
	MITF (10-16% amplified)
Uveal Melanoma	
	Oncogenes
	GNAQ (46% mutated)
	GNA11 (35% mutated)



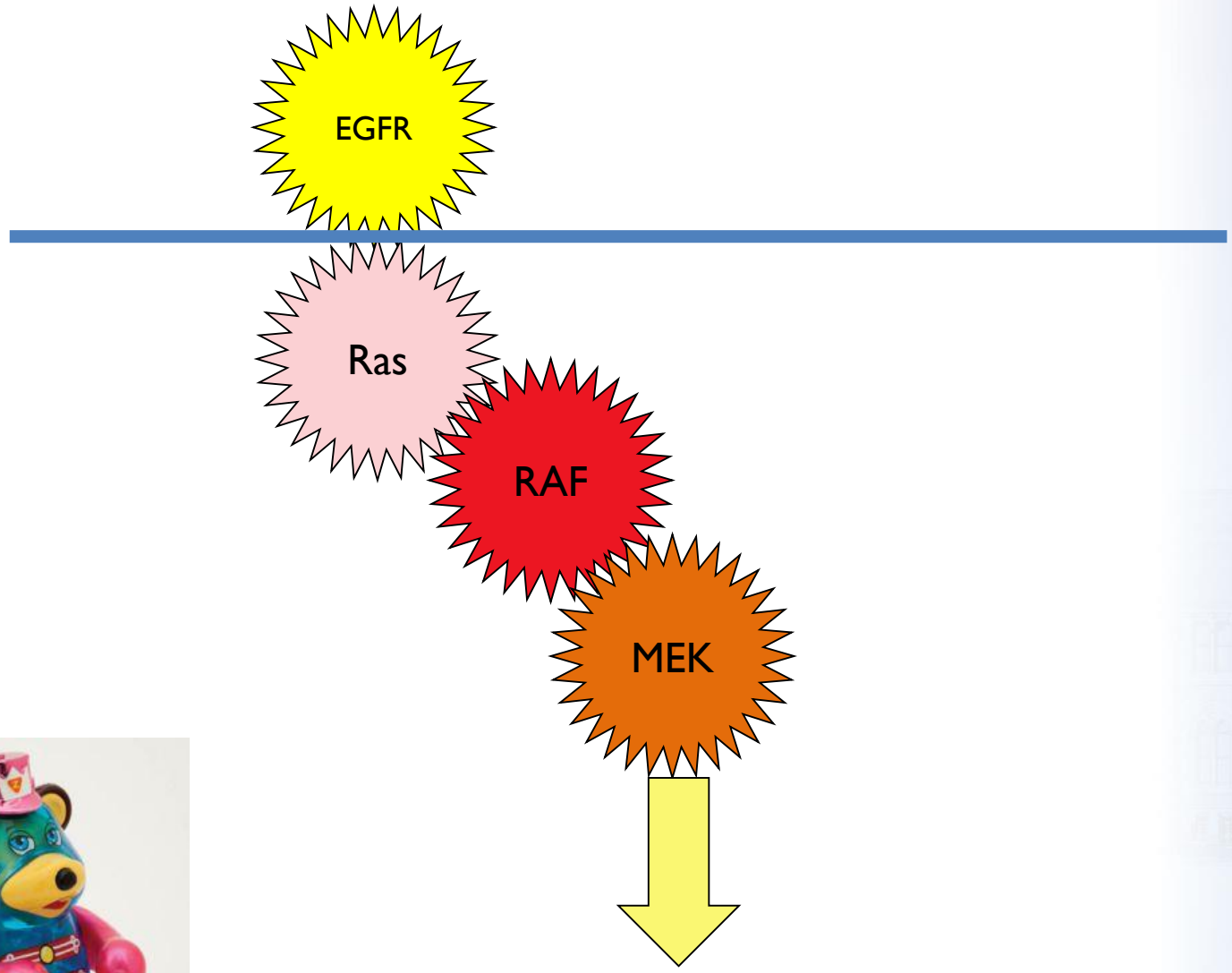
EGFR family – activated in many cancers



Ciardiello F and Tortora G. N Engl J Med 2008



Cell growth, proliferation,
invasion and metastases



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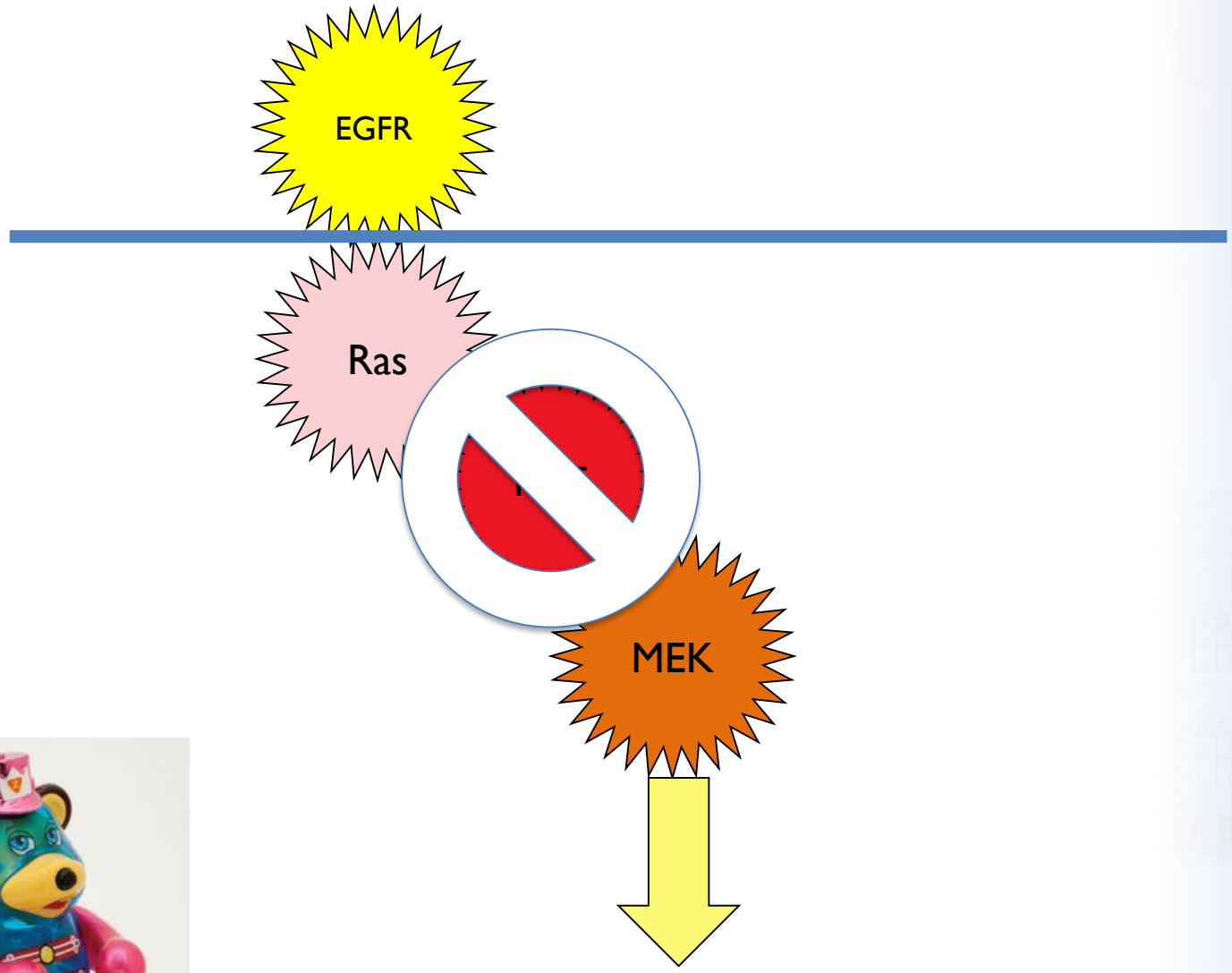
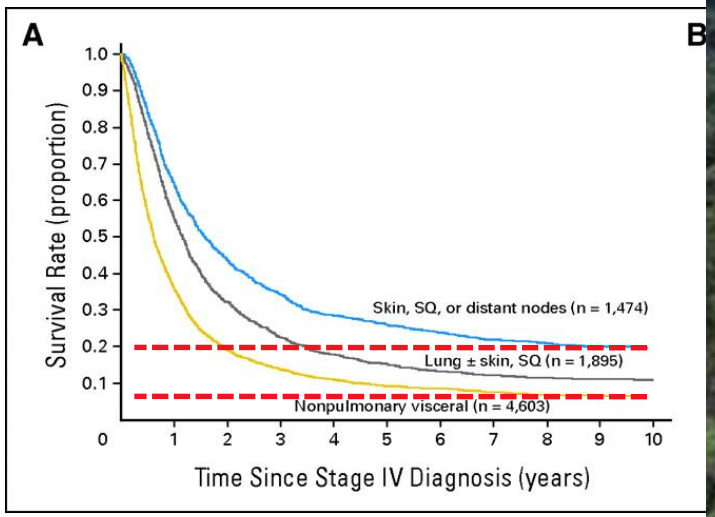


Cell growth, proliferation,
invasion and metastases

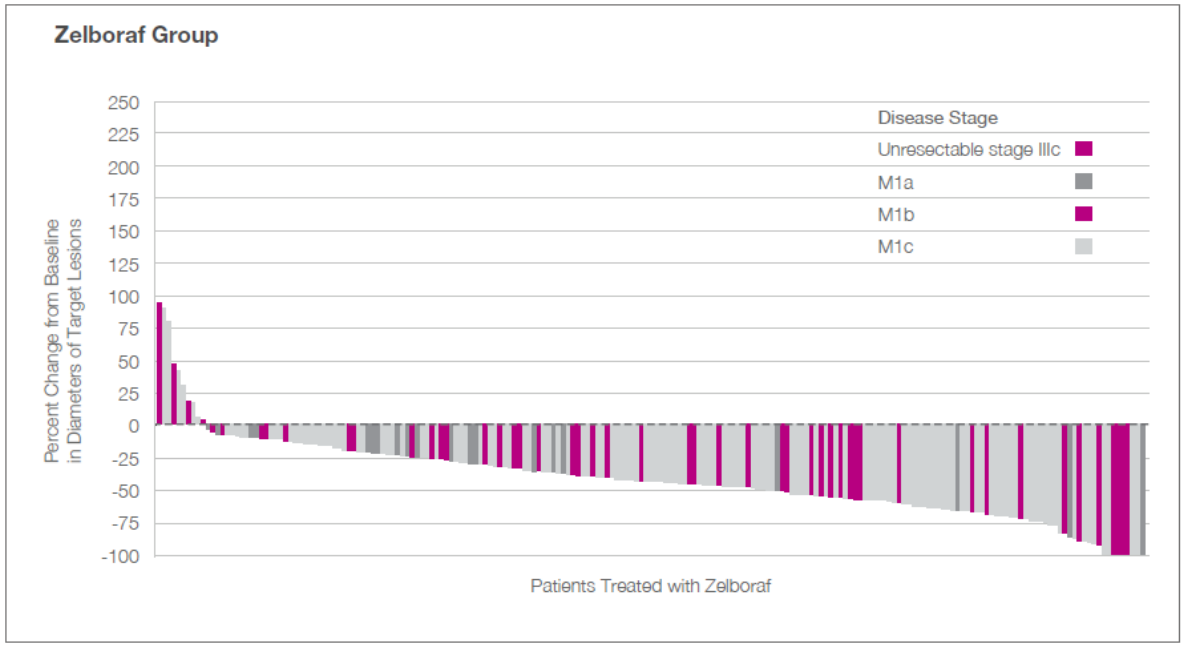
Long term outcomes



- Dacarbazine:
  - 5% “objective response rate”
  - PFS: 1.6 months
  - 1 year OS: approx 35%
- IL-2:
  - 16% response; high toxicity
  - Not used in NZ

Charles M. Balch et al. JCO 2009;27:6199-6206

Vemurafenib in V600E mutated melanoma



Adapted from Chapman PB, et al. 2011[1]

- “Objective response”: 57%
- Rapid: days
- Well tolerated
- Photosensitivity, diarrhoea, HFS, KA and SCC

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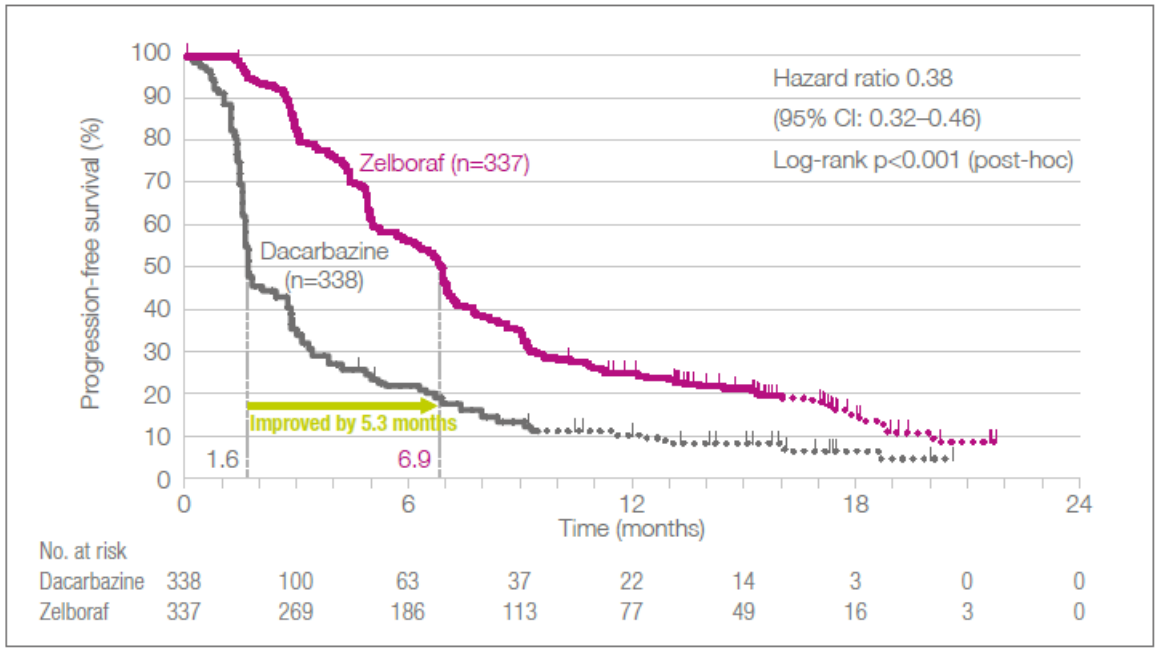
Duration of tumour control



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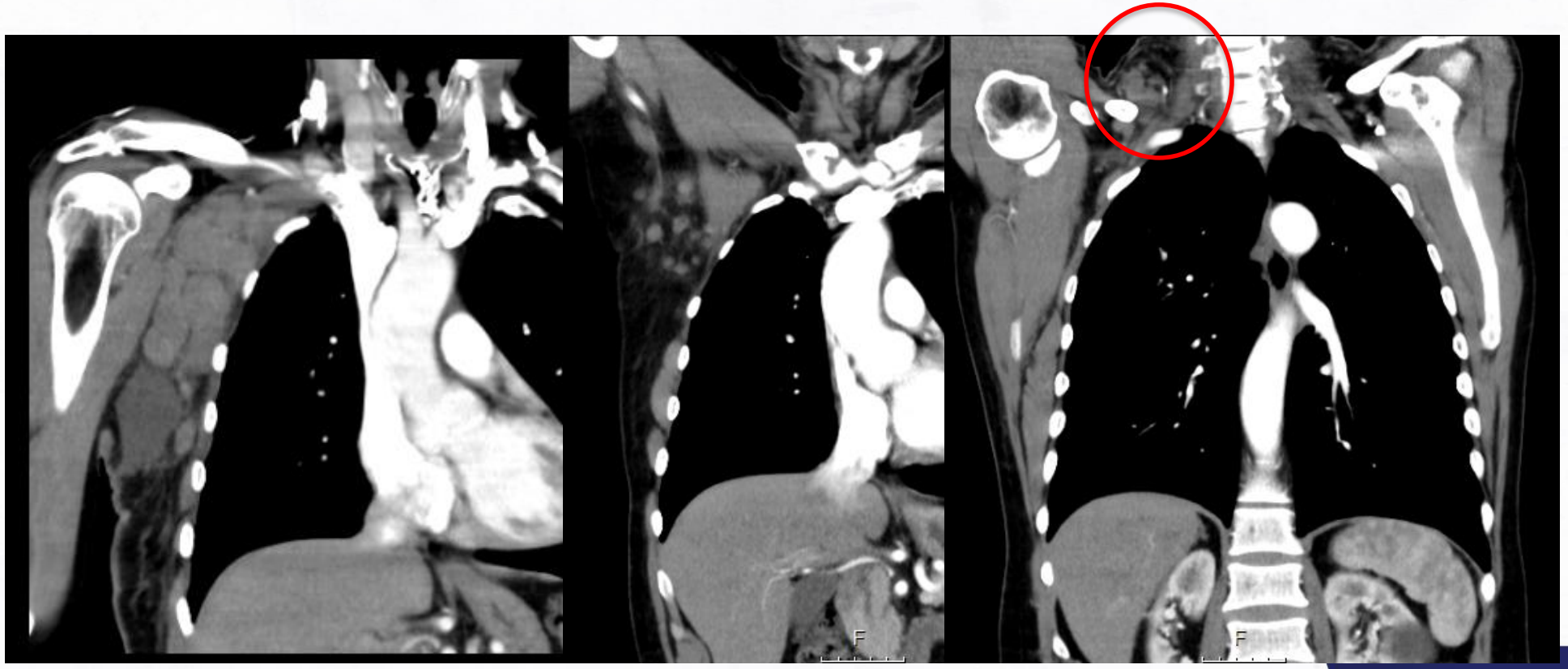
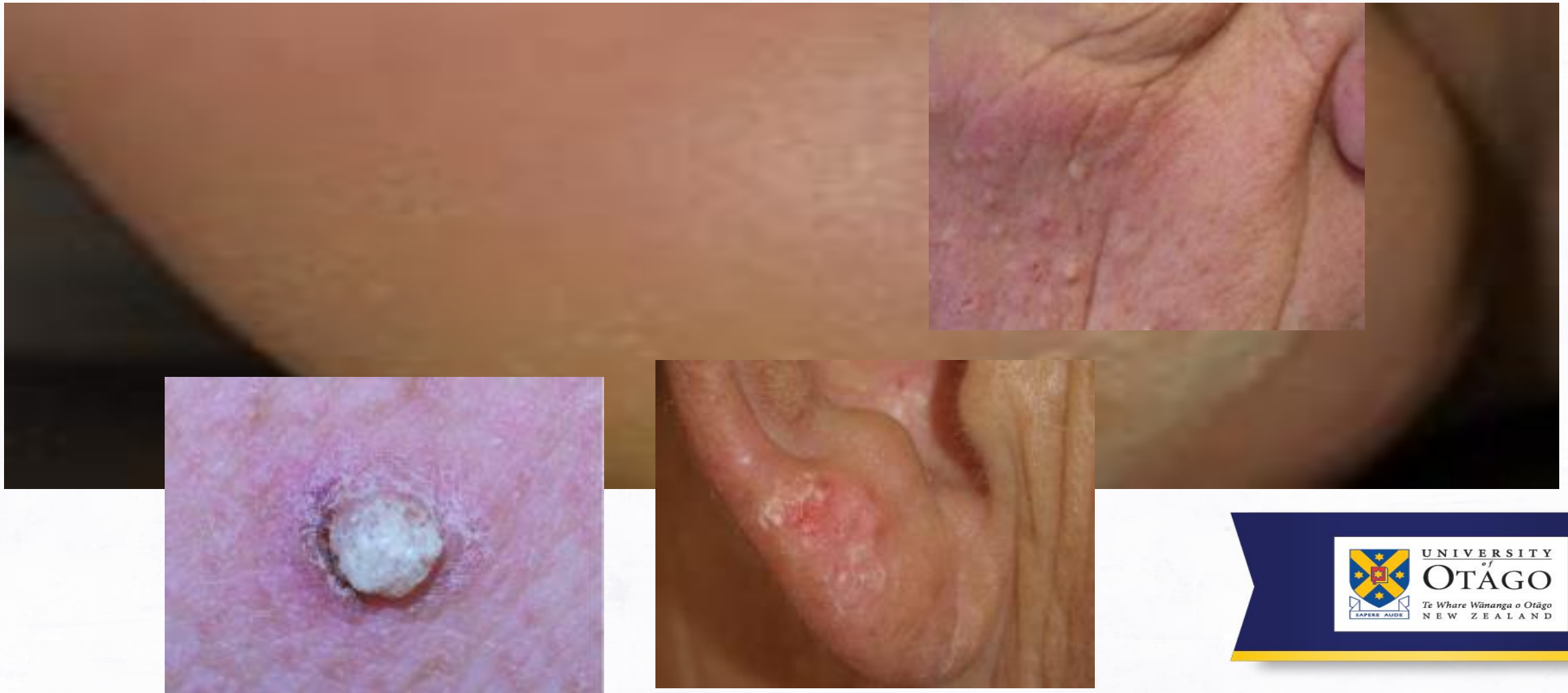
Differential responses observed



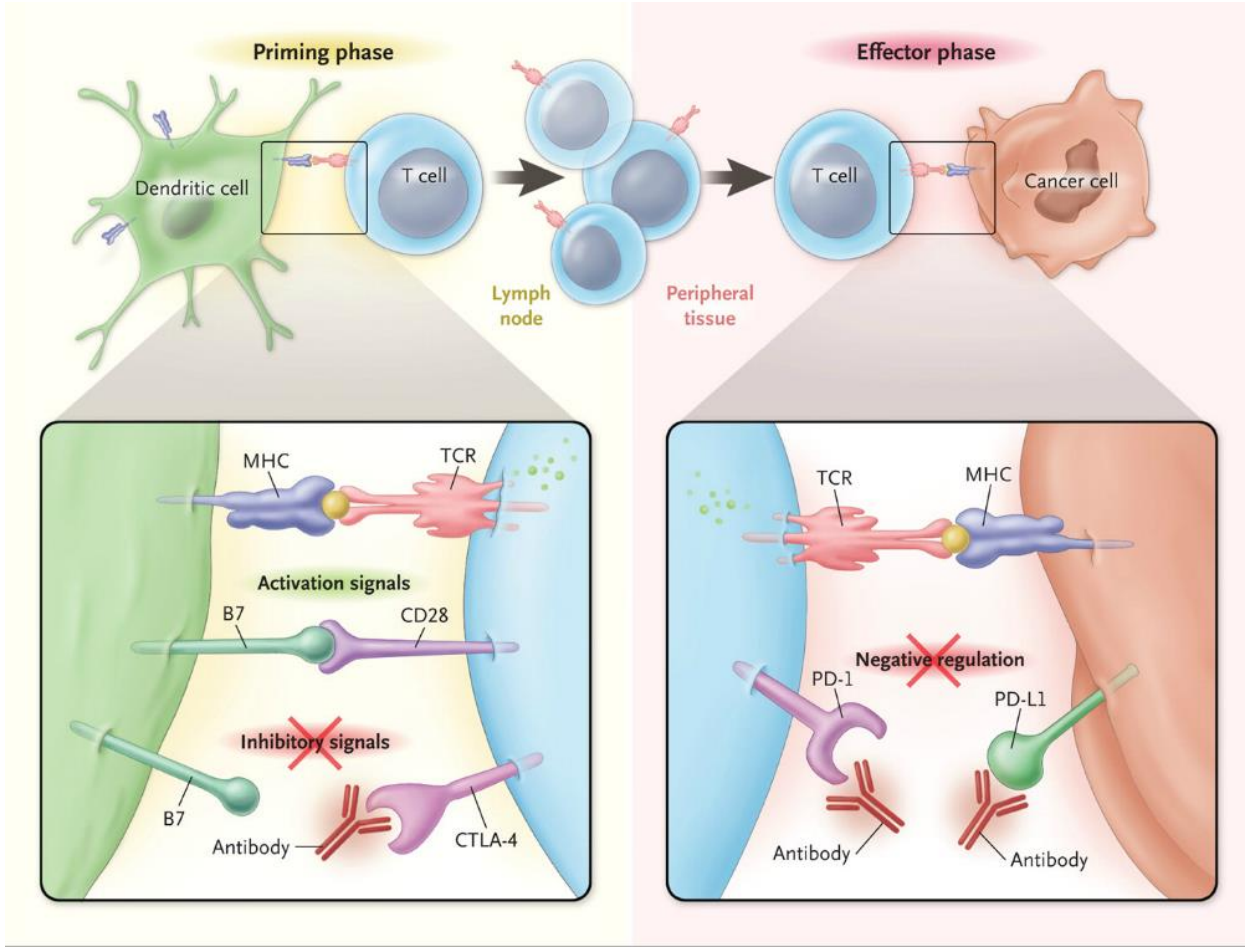
Toxicities of V600E inhibitors



http://dermnetnz.org/treatments/vemurafenib.html

Immunotherapy

Immunotherapy: T-cell priming and evading inhibition



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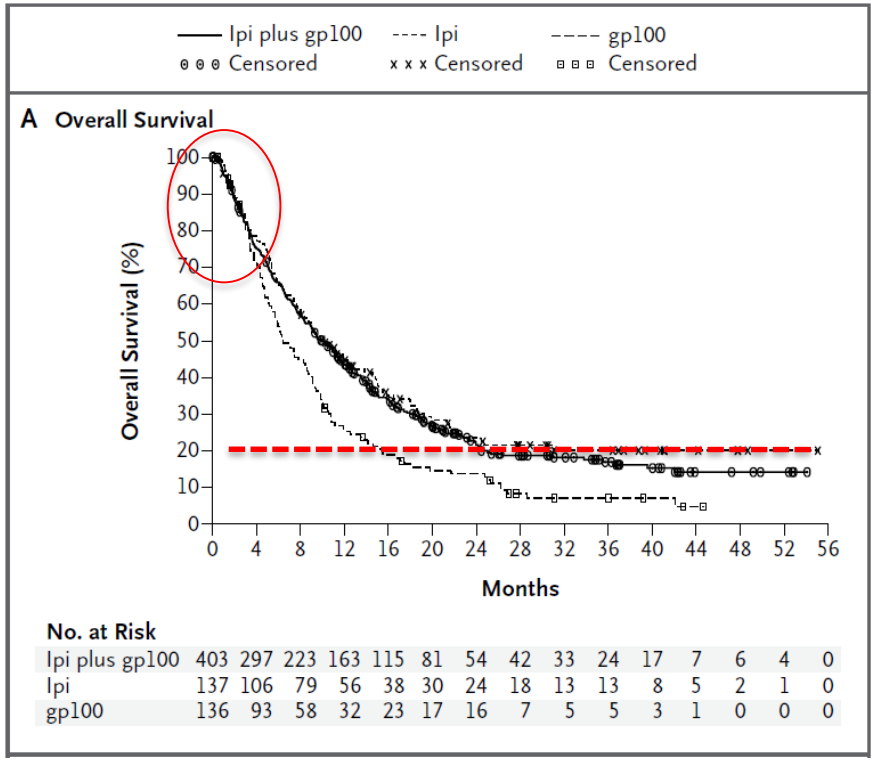
Ipilimumab: first agent to improve OS

Randomise

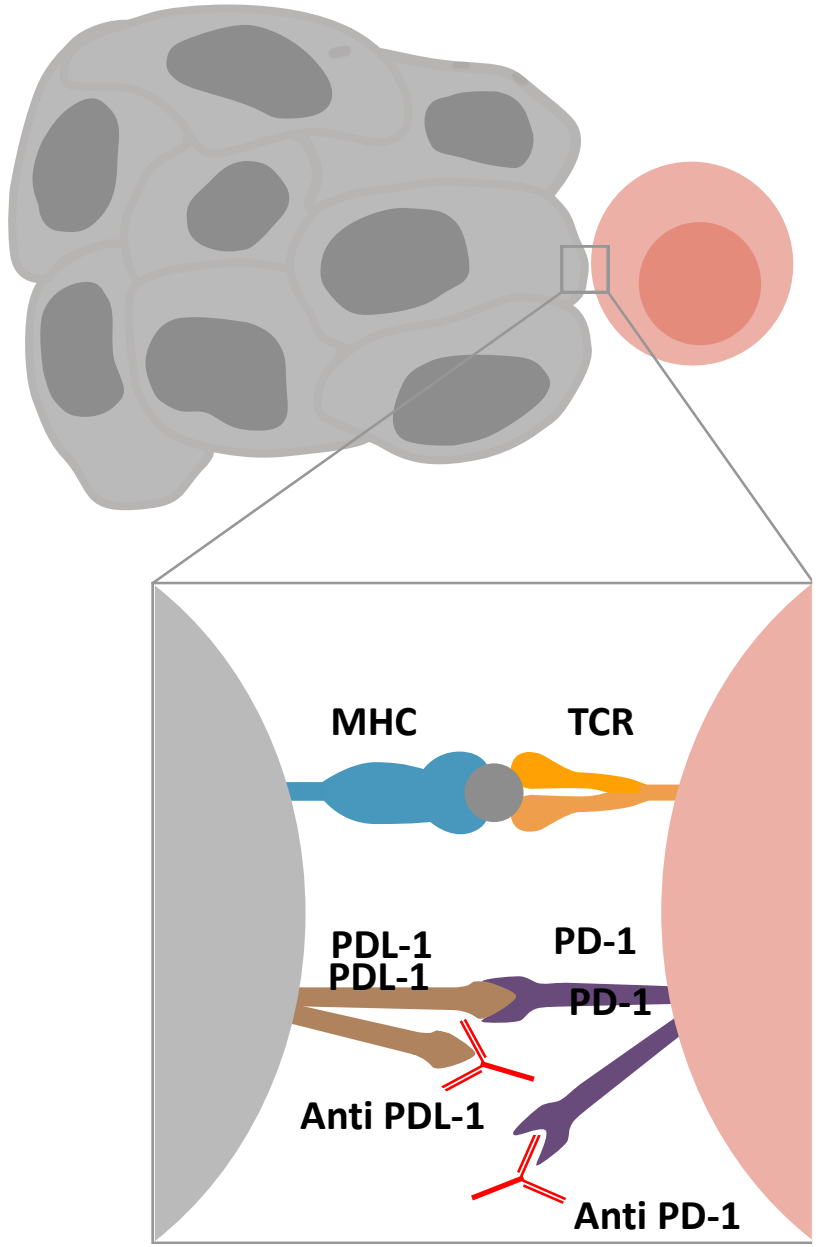
- Gp100 q3w x4
- Ipi 3mg/kg q3w x4
- Ipi + gp100 q3w x4

Unresectable III-IV
Failed prior therapy
N= 676; 3:1:1
"Response rate": 11%
OS 10.0 mo v 6.4mo
HR 0.68 (p<0.001)
Immune adverse events

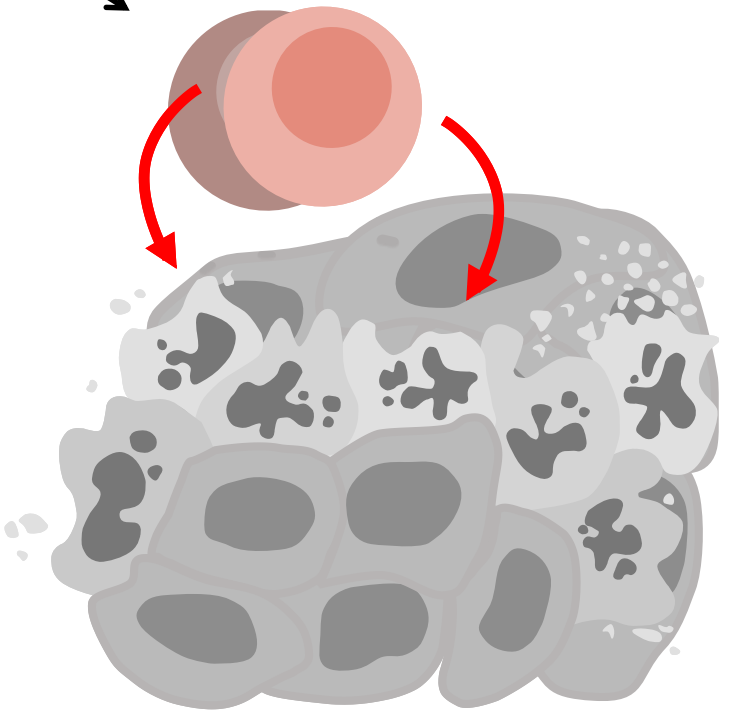


PD-1 like a “fend”

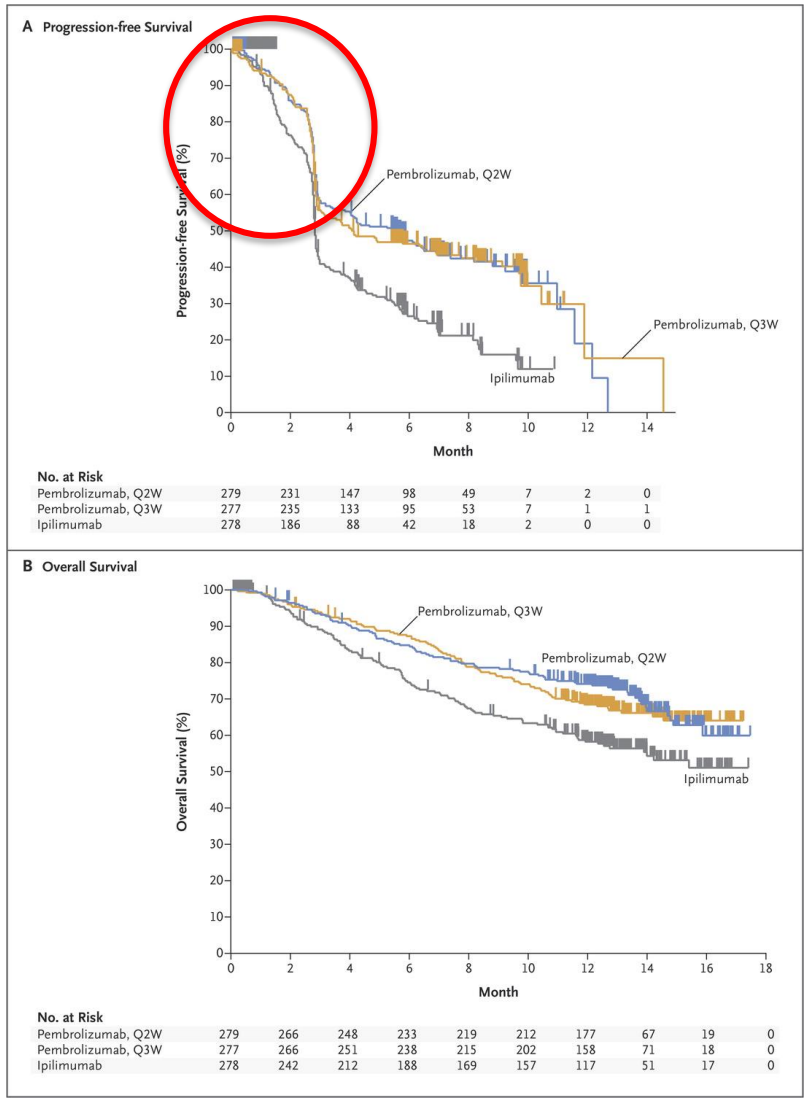
Anti PD-1/PDL-1

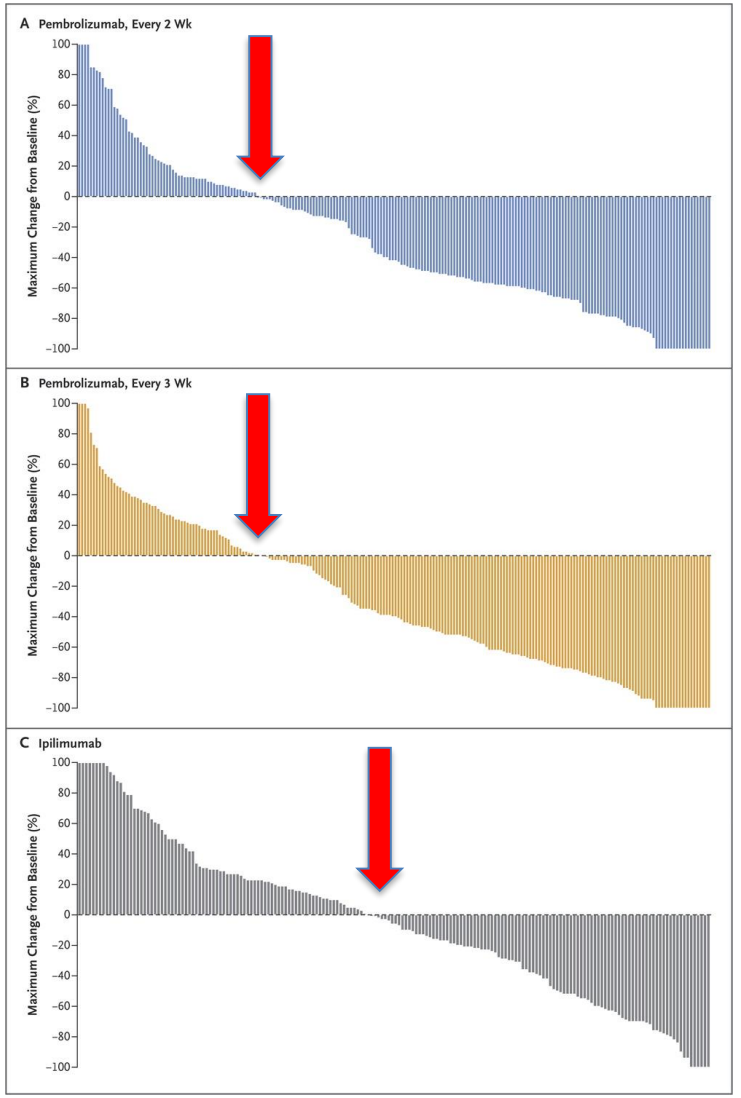


Inhibition of killing response → tumour killing



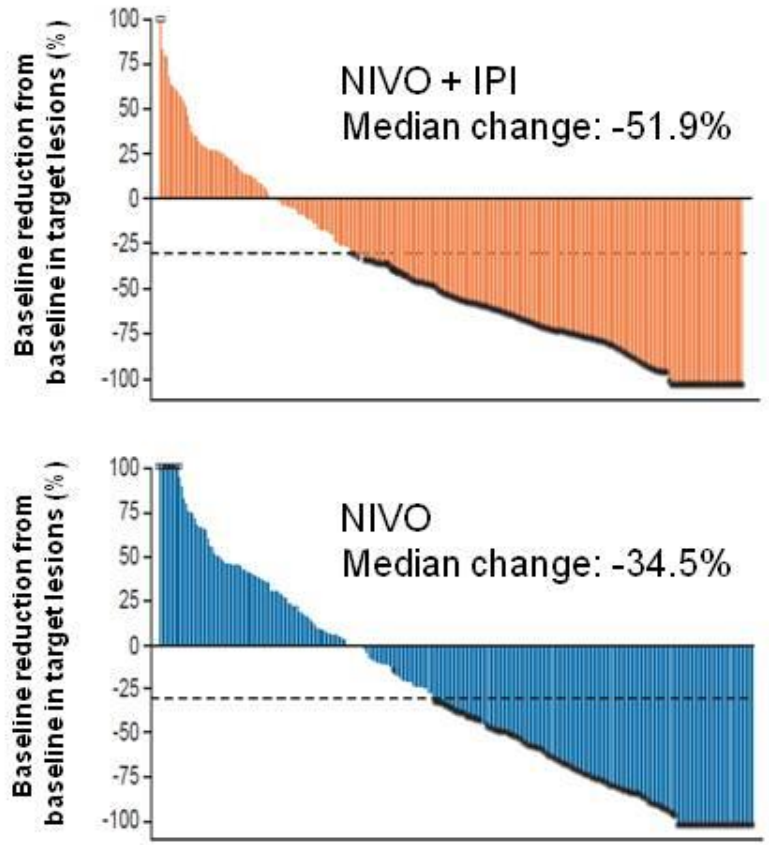
Responses with Pembrolizumab

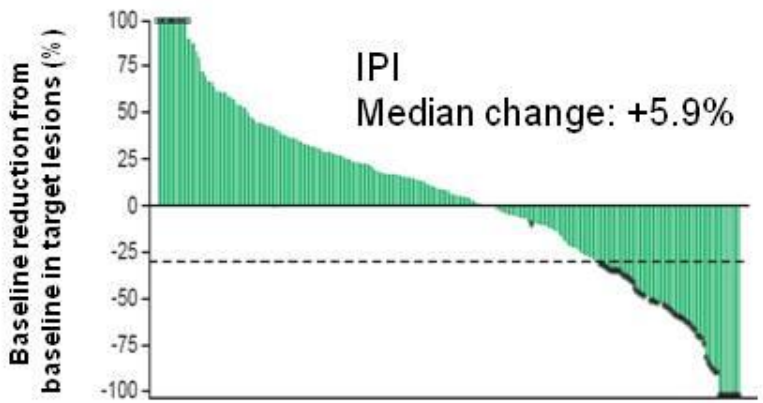




Robert C et al. N Engl J Med 2015;372:2521-2532.

Tumor Burden Change From Baseline





● Confirmed responder

- - - 30% reduction in tumor burden by RECIST v1.1

Nivolumab / Pembrolizumab

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Immune-related adverse events

Gastrointestinal

Monitor for symptoms indicative of immune-related colitis, diarrhoea or GI perforation including:

- Increased frequency of bowel movements
- Diarrhoea
- Abdominal pain
- Blood in stool
- Fever

Hepatic

Monitor for elevations in liver function tests (LFTs) with or without clinical symptoms:

- AST >5 x ULN
- ALT >5 x ULN
- Bilirubin >3 x ULN

NOTE: LFTs must be checked prior to each infusion

Skin

- Pruritus
- Rash
- Erythema
- Vitiligo

Rare reports of fatal toxic epidermal necrolysis, Steven-Johnson Syndrome

Neurological

- Motor neuropathy
- Muscle weakness
- Sensory neuropathy

Rare reports of fatal Guillain-Barré syndrome and myasthenia gravis-like symptoms

Endocrine

May present with non-specific symptoms:

- Headache
- Fatigue
- Visual field defects
- Behavioural changes
- Electrolyte disturbances
- Hypotension
- Adrenal crisis (severe dehydration, hypotension, shock)

Other

YERVOY irAEs can affect any organ or system including the eyes.

Reported but uncommon irAEs include uveitis, eosinophilia, lipase elevation and glomerulonephritis

Bristol-Myers Squibb

BMS. YERVOY (ipilimumab) Approved Product Information. 27 June 2011.

YERVOY (ipilimumab)

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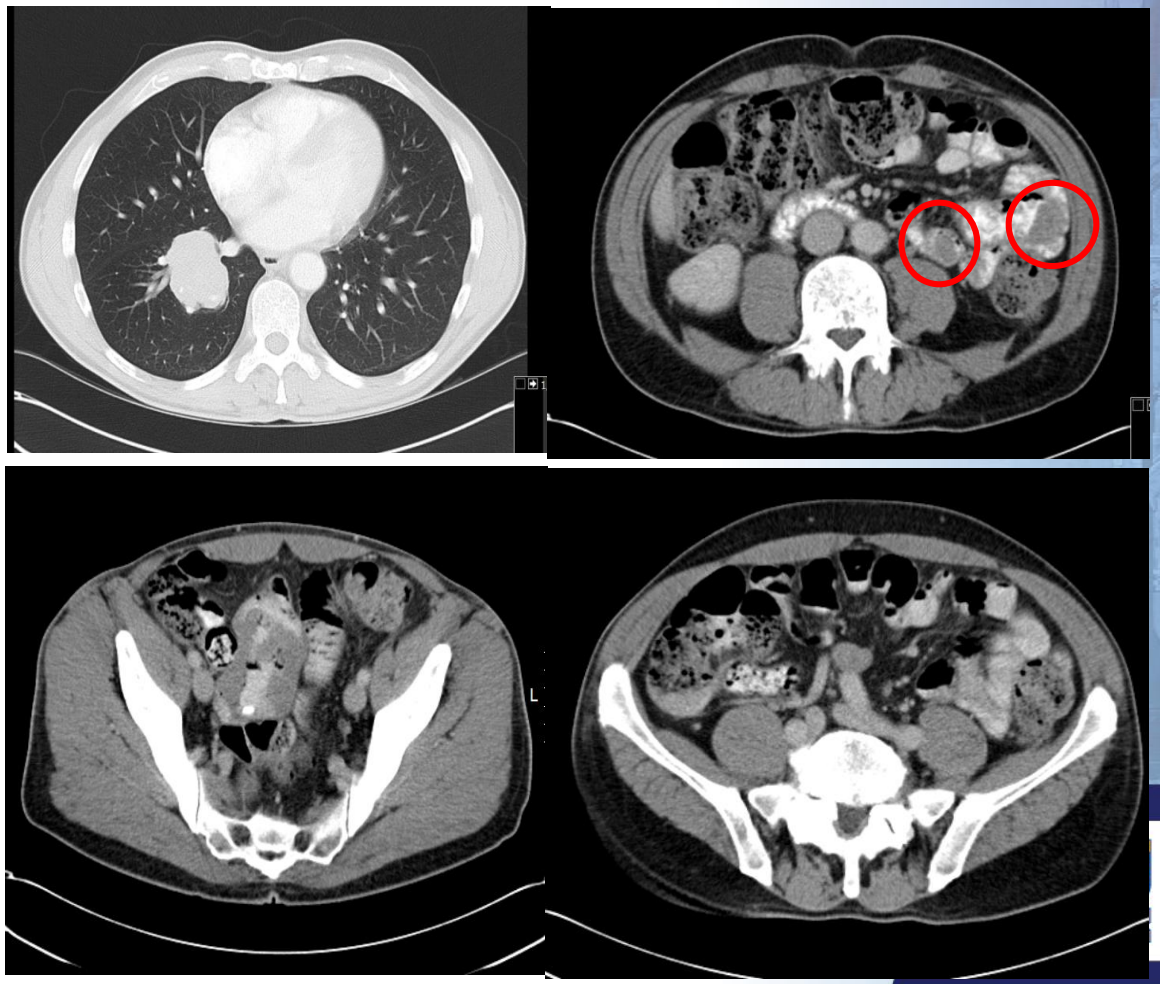
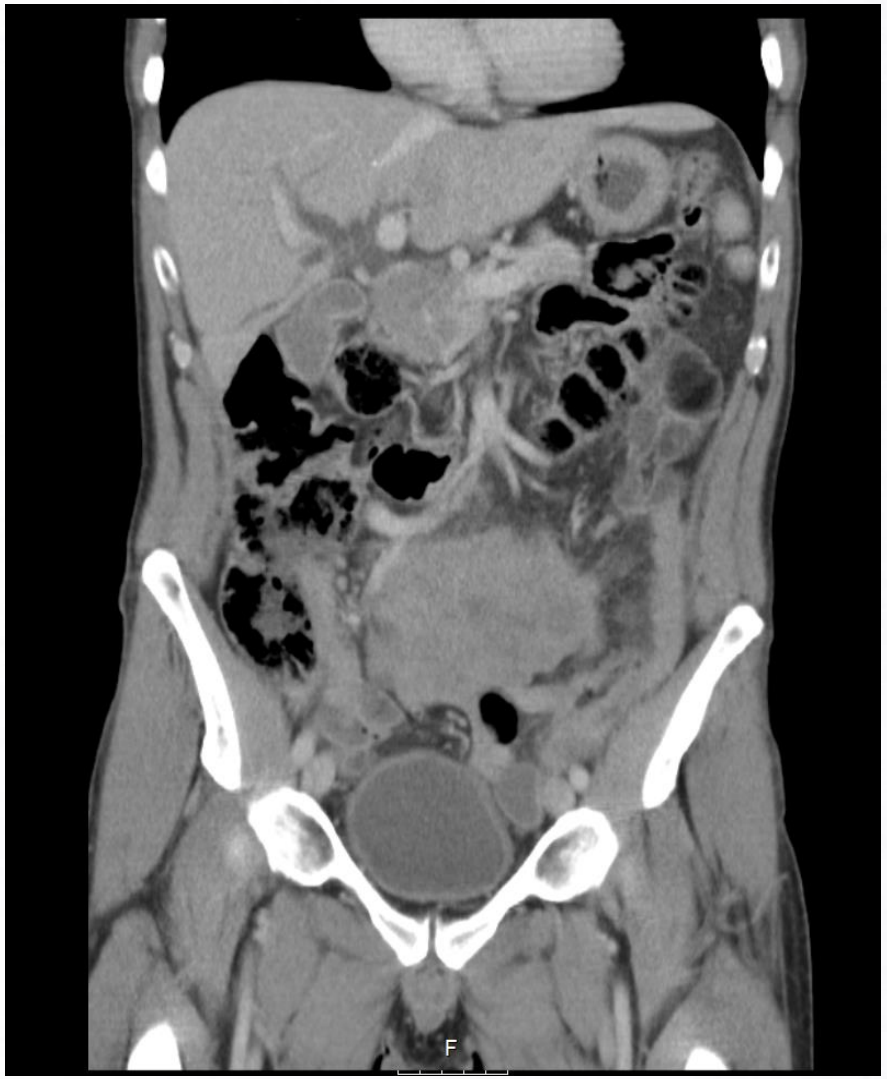
Case: Mr MB

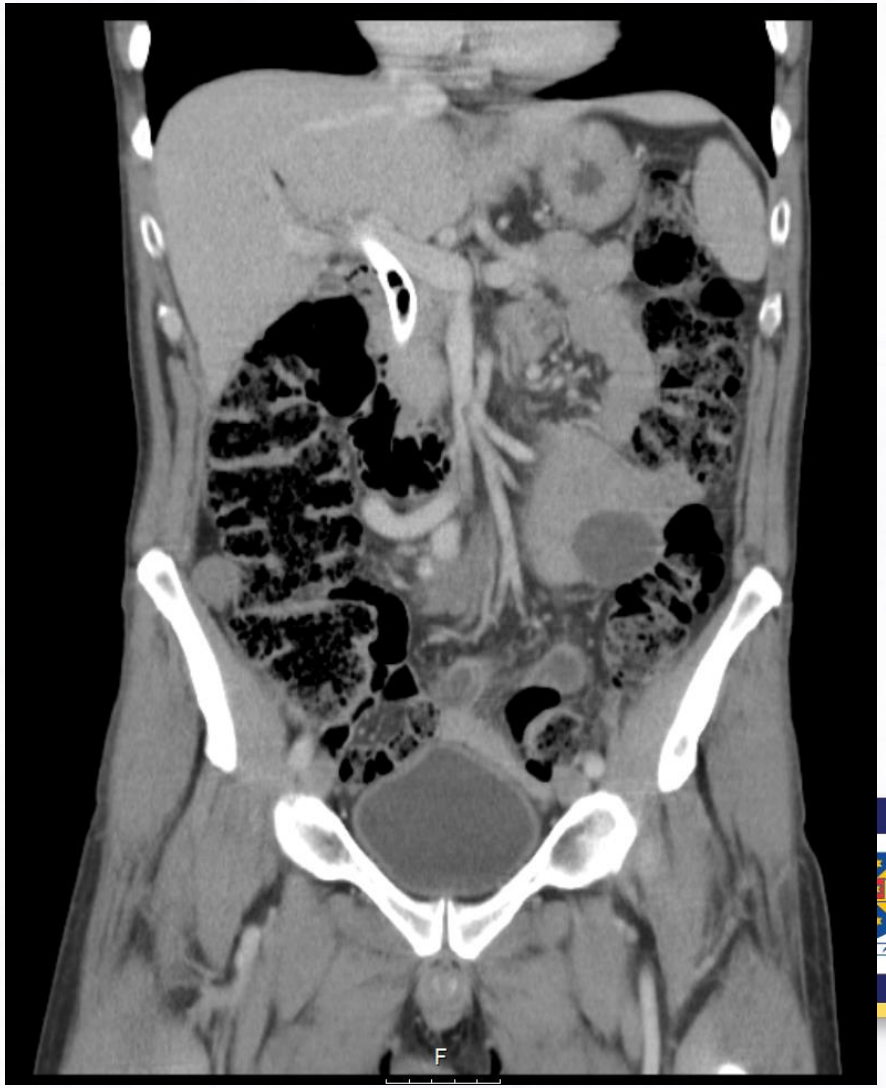
- Diarrhoea – 2/12
- Abdo pain, colicky, intermittent obstructive symptoms
- 8kg weight loss
- Dry cough, worse nocturnally

- LDH 3x upper limit normal
- Biopsy S100 +ve
- BRAF V600E mutation detected



Switched to Pembrolizumab on progression





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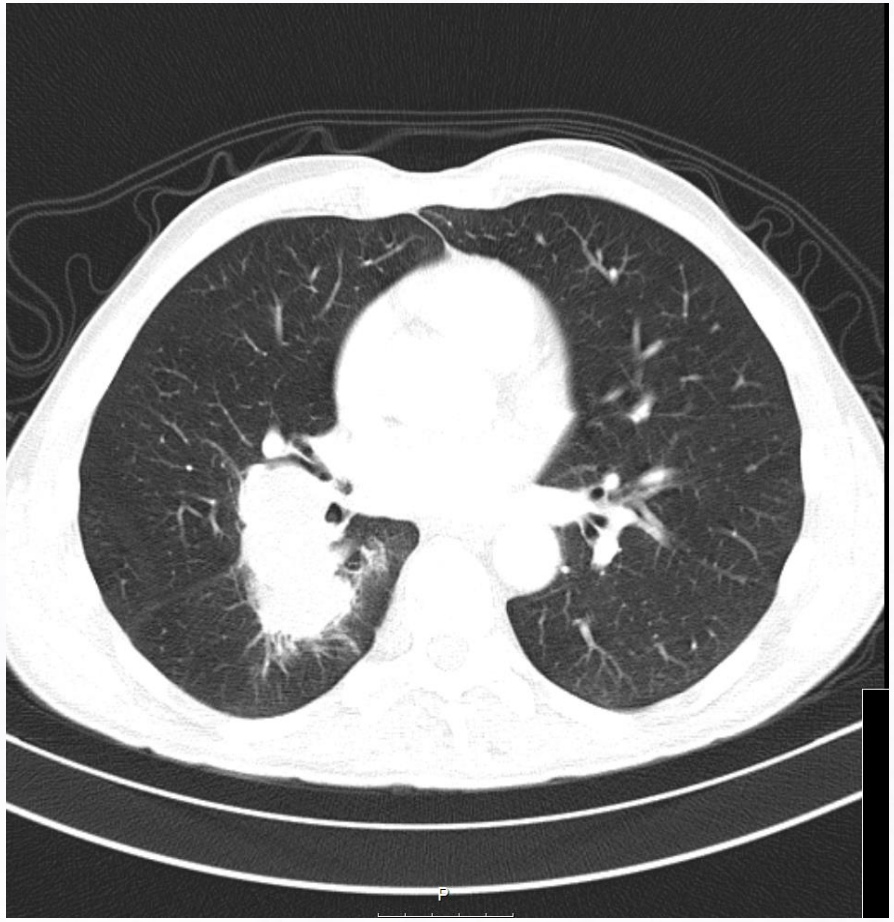
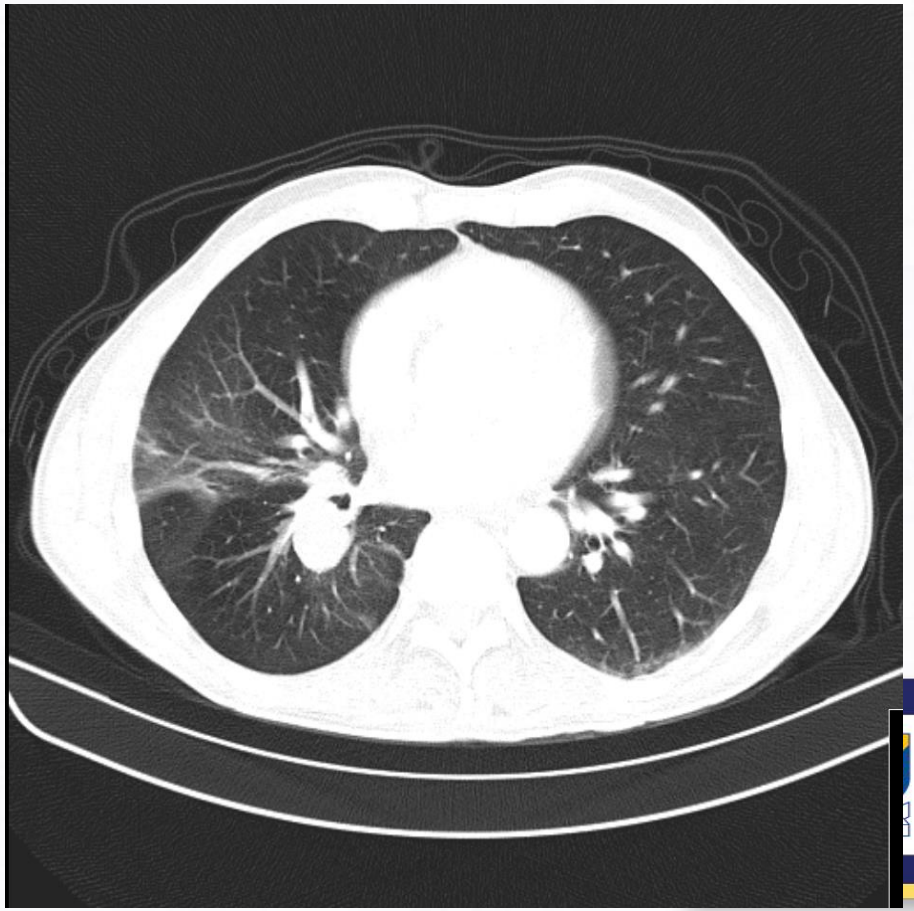
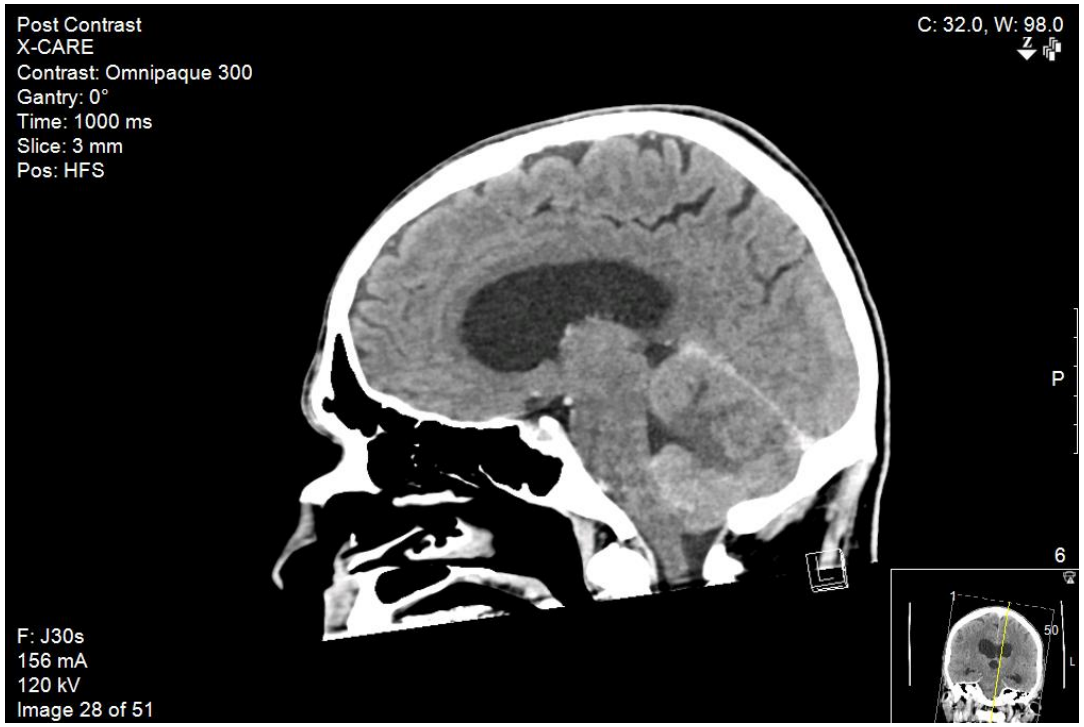
Response to Pembrolizumab





Brain metastases



Risks for brain mets:

- Male gender
- Mucosal
- H+N primary
- High risk primary
- Acral lentiginous or nodular
- 3+ regional LN
- Visceral mets at diagnosis

Ipi has RR 24% if lesions stable

PD-1 drugs: evloving

STEROIDS are a problem

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Financial barriers to access

PHARMAC
Pharmaceutical Management Agency

stuff

If Keytruda keeps melanoma patients alive, why isn't it available free in NZ?

MICHAEL DALY
Last updated 19:20, March 1 2016

How good is it?

According to Pharmac, in the main trial of Keytruda tumours shrank or disappeared in a third of the people taking the drug. For those people the response was maintained at least to the point where data from the trial was analysed.

"There has been strong public interest in this medicine; however, there is a gap between the public's perception of the benefits offered by pembrolizumab and the measured benefits seen in the clinical trials to date," Pharmac said.

"No clinical trial has yet shown that pembrolizumab increases the length of life for melanoma patients compared with other new melanoma treatments or standard chemotherapy."

MSD said its latest clinical trial results showed tumours shrank for 80 per cent of patients who had received no prior treatment, with 14 per cent having no detectable cancer, at a median follow up time of 15 months.

Health Minister Dr Jonathan Coleman said 365 people died of melanoma in New Zealand each year, and with Keytruda working in a third of patients around 120 people could benefit from it.

Petition organiser Leisa Renwick was told in 2015 that she was terminally ill. She paid for a range of drugs, including Keytruda, and the cancer went into remission.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Adva

Jedd D. Wolchok, M.D., Ph.D., Hai
Michael A. Postow, M.D., Naiy
Neil H. Segal, M.D., Ph.D., Charlo
Kathleen Reed, M.S., Matthew I
Stephanie A. Kronenberg, B.A., Bl
Israel Lowy, M.D., Ph.D., Hec
Christine E. Horak, Ph.D.,
Jon M. Wigginton, M.D., Ash

ORIGINAL ARTICLE

urvival with Vemurafenib with BRAF V600E Mutation

ne Robert, M.D., Ph.D.,
mes Larkin, M.D.,
sandro Testori, M.D.,
l Lorigan, M.D.,
Schadendorf, M.D.,
y A. Sosman, M.D.,
mont, M.D., Ph.D.,
Ph.D., Betty Nelson, M.A.,
T. Flaherty, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

l, M.D.,
l, M.D., Ph.D.,
Joseph, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

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ESTABLISHED IN 1812 AUGUST 19, 2010

Improved Survival with Ipilimumab in I with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Rob
Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline
Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. var
Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D.,
Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M
Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D.

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D.,
Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D.,
Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D.,
Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris III, M.D.,
Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D.,
Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I.,
Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H.