

RBWH Cancer Care Melanoma update

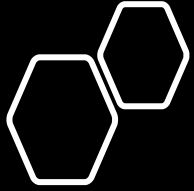
- Melissa Eastgate
- Deputy Director Medical Oncology
- Chair, Melanoma MDT RBWH
- July 2021



Faculty of
Medicine

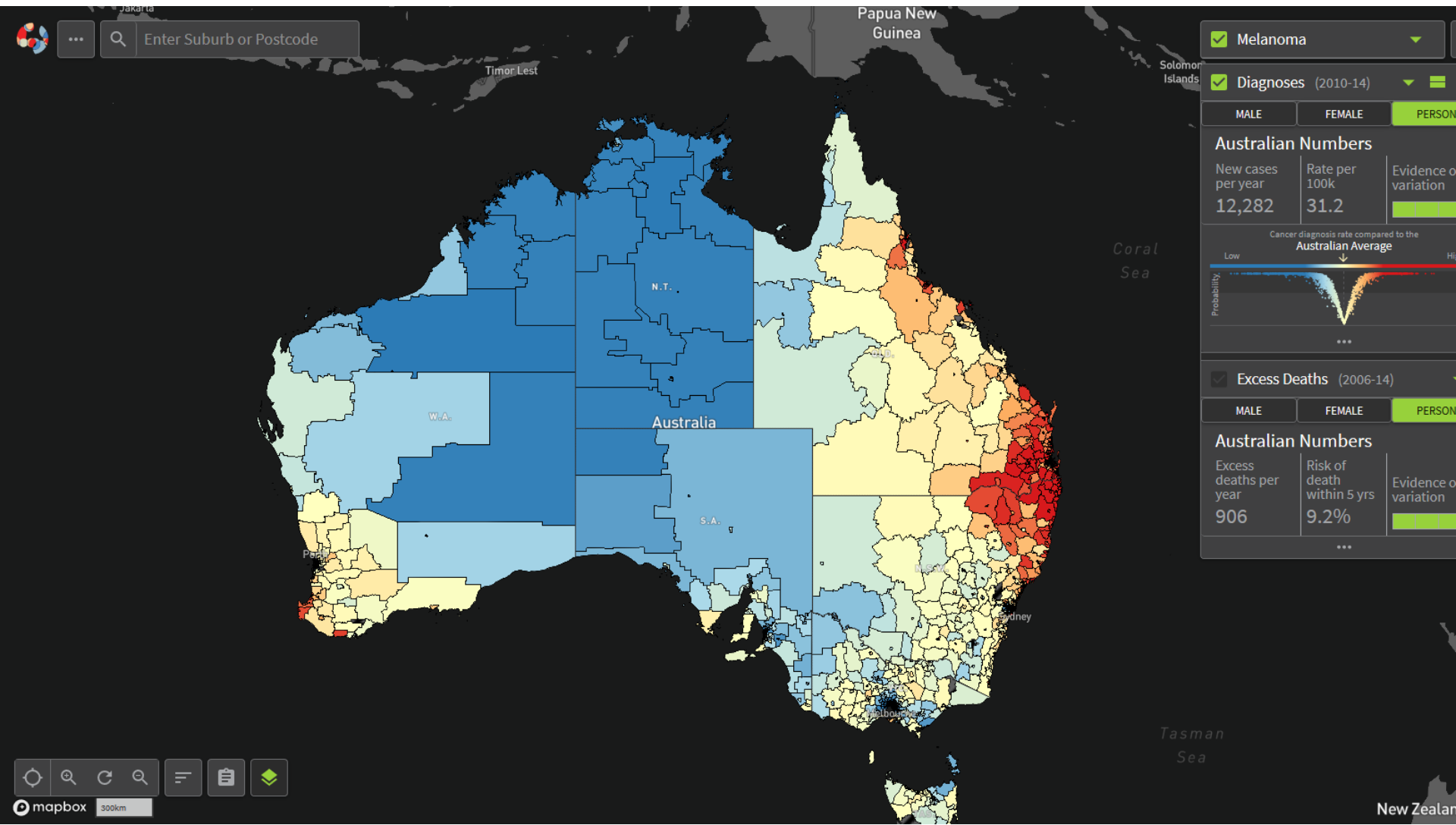


Queensland
Government



Melanoma Incidence in Australia

- 2015
 - 1675 deaths
 - 12960 new cases
 - 3.6% of cancer deaths
 - Most common cancer in 15-39 yr olds
 - Most common cause of cancer death in 20-39 yr olds



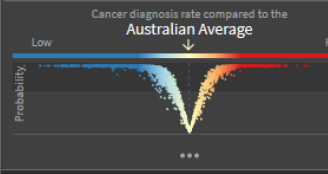
Melanoma

Diagnoses (2010-14)

MALE FEMALE **PERSON**

Australian Numbers

New cases per year	Rate per 100k	Evidence of variation
12,282	31.2	



Excess Deaths (2006-14)

MALE FEMALE **PERSON**

Australian Numbers

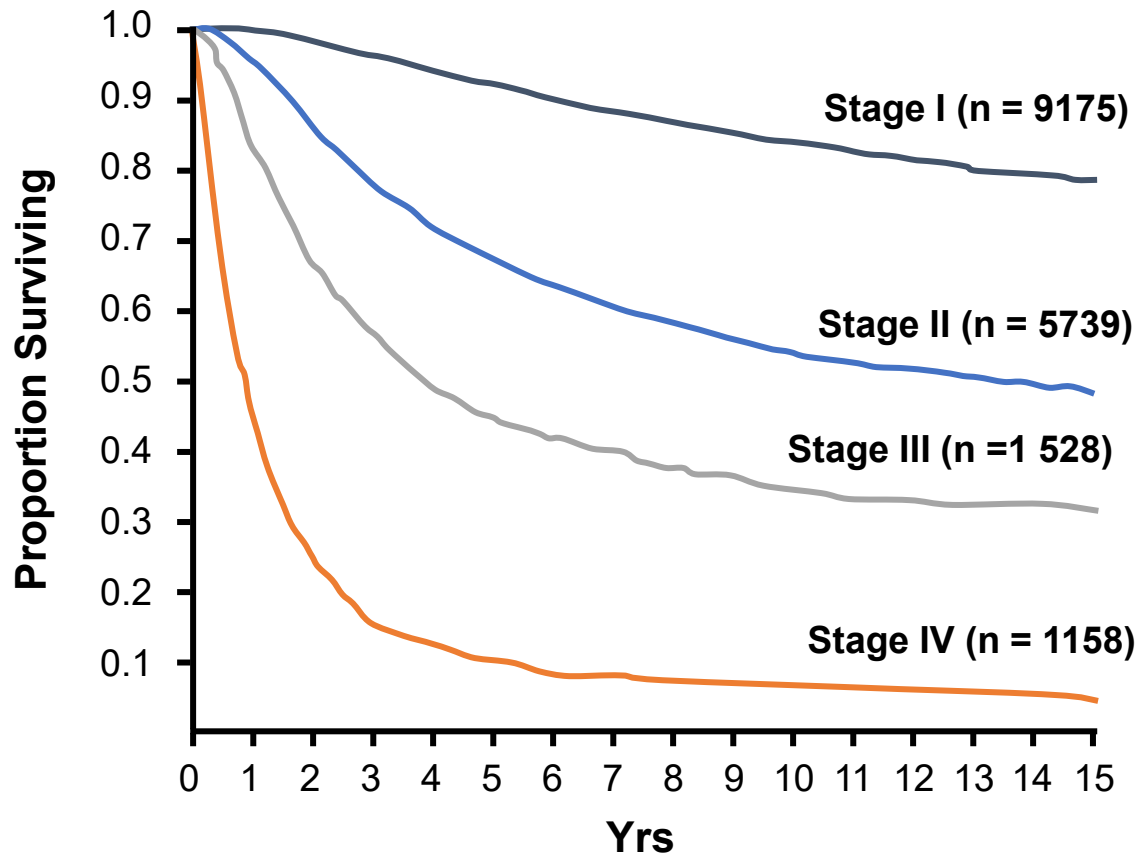
Excess deaths per year	Risk of death within 5 yrs	Evidence of variation
906	9.2%	

Map navigation controls: Home, Search, Refresh, Zoom In, Zoom Out, Full Screen, Print, and a green checkmark icon.

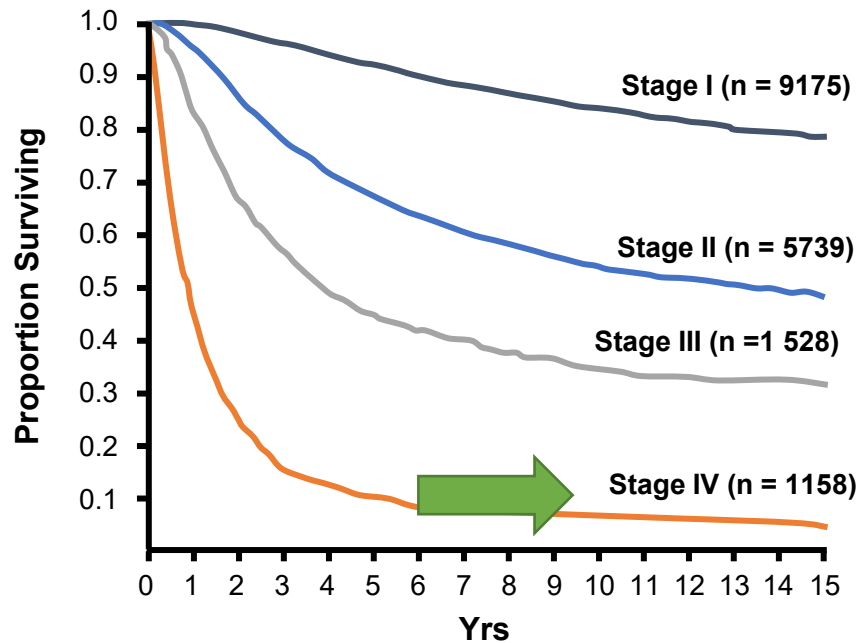
mapbox 300km

New Zealand

Historical Survival in Melanoma by Stage

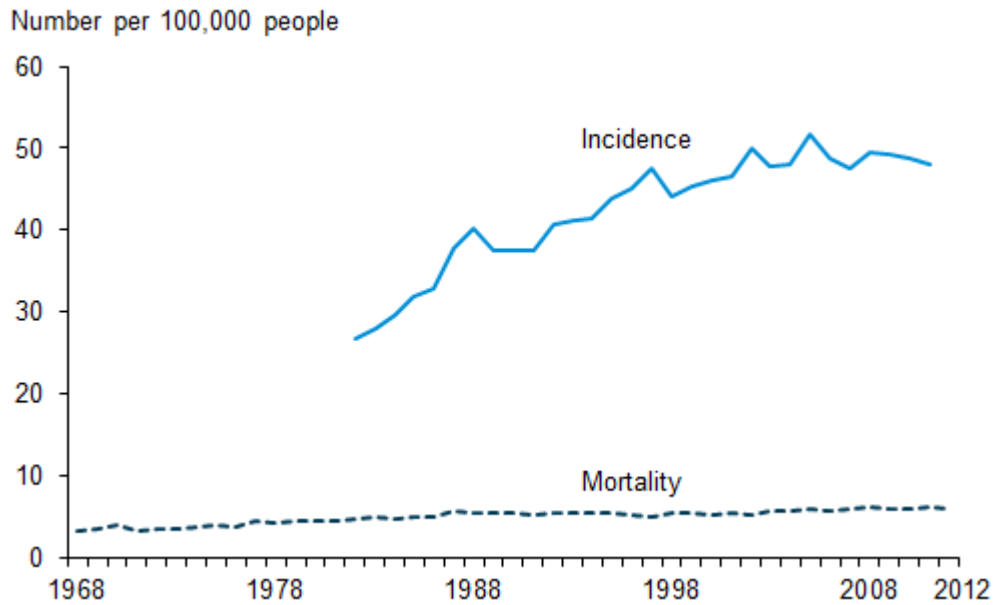


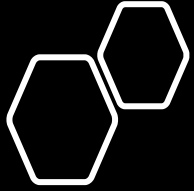
Historical Survival in Melanoma by Stage



Median survival 6-9 months

Melanoma skin cancer incidence and mortality, 1968 to 2012

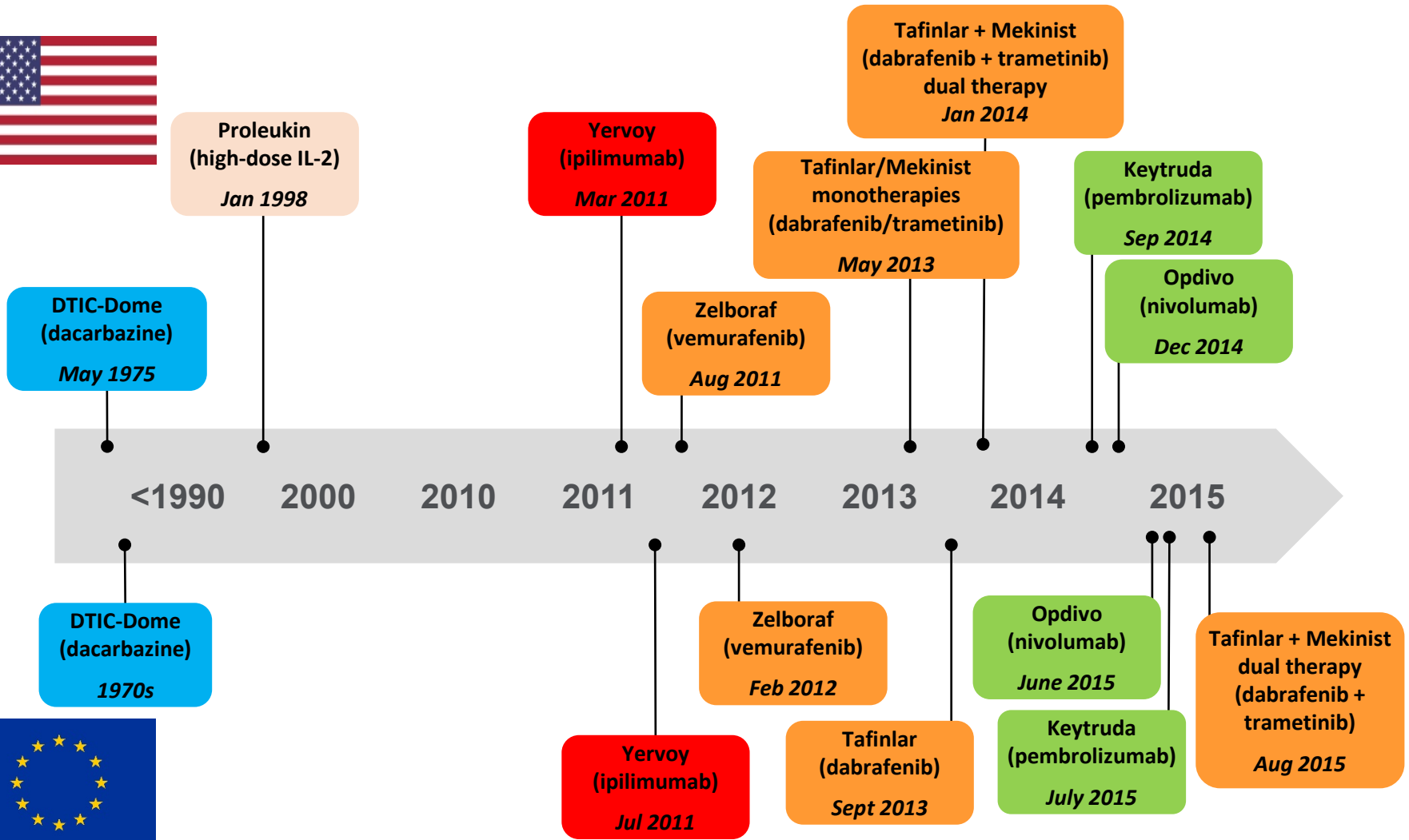


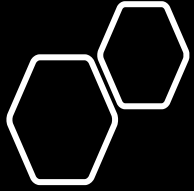


Where can we make a difference?

- Prevention/early detection
- Better neo/adjuvant therapy
- Improved treatment in the advanced setting.
 - Downstage to enable curative treatment
 - Picking the right treatment for the right patient
 - Prolong overall survival
- Reduced toxicity of treatment

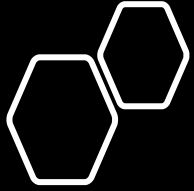
Metastatic melanoma available treatment: 1970–2015





RBWH Melanoma MDT

- Initiated in February 2016 – no coordinated service prior to this
- Interest from general surgery/plastics/neurosurgery
- 2018 fundraiser “Million Metres for Melanoma”
 - Med Onc Fellow 0.5 FTE
 - Admin support
 - Research grants



Melanoma MDT participants

- Medical Oncology
- Radiation Oncology
- CCC
- MDT administrator
- Plastic surgery
- General surgery
- Neurosurgery

Role of surgery in early stage melanoma

Sentinel lymph node biopsy:

- Very important prognostic factor
- Should be discussed with patients if melanoma is >1mm thick
- Technically difficult if after WLE

- NO benefit for completion LN dissection in patients with a positive sentinel node now confirmed in 2 studies

Immunotherapy

Drug classes

- Anti CTLA4 antibody
 - Ipilimumab
- PD1/PDL1 inhibitors
 - Pembrolizumab
 - Nivolumab

Pembrolizumab Versus Ipilimumab For Advanced Melanoma: Final Overall Survival Analysis of KEYNOTE-006

Jacob Schachter,¹ Antoni Ribas,² Georgina V. Long,³ Ana Arance,⁴ Jean-Jacques Grob,⁵
Laurent Mortier,⁶ Adil Daud,⁷ Matteo S. Carlino,⁸ Catriona McNeil,⁹ Michal Lotem,¹⁰
James Larkin,¹¹ Paul Lorigan,¹² Bart Neyns,¹³ Christian Blank,¹⁴ Teresa M. Petrella,¹⁵
Omid Hamid,¹⁶ Honghong Zhou,¹⁷ Scot Ebbinghaus,¹⁷ Nageatte Ibrahim,¹⁷ Caroline Robert¹⁸

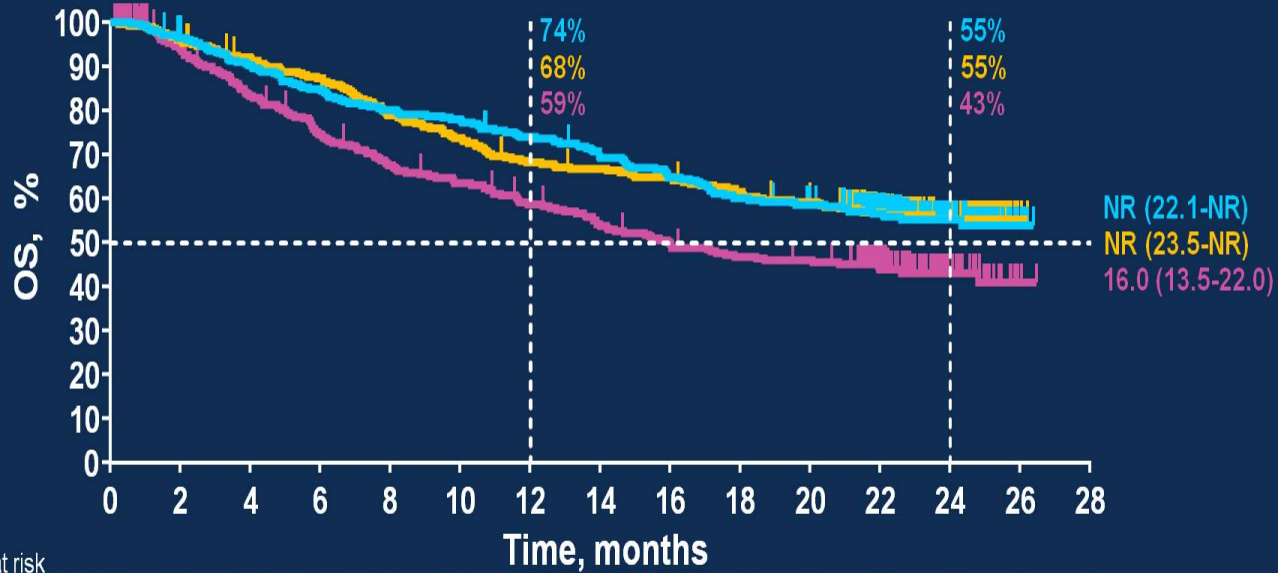
¹Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel; ²University of California, Los Angeles, Los Angeles, CA; ³Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital, Sydney, Australia; ⁴Hospital Clinic de Barcelona, Barcelona, Spain; ⁵Aix Marseille University, Hôpital de la Timone, Marseille, France; ⁶Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France; ⁷University of California, San Francisco, San Francisco, CA; ⁸Westmead and Blacktown Hospitals, Melanoma Institute Australia, and The University of Sydney, Sydney, Australia; ⁹Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, and Melanoma Institute Australia, Camperdown, Australia; ¹⁰Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; ¹¹Royal Marsden Hospital, London, UK; ¹²University of Manchester and the Christie NHS Foundation Trust, Manchester, UK; ¹³Universitair Ziekenhuis Brussel, Brussels, Belgium; ¹⁴Netherlands Cancer Institute, Amsterdam, Netherlands; ¹⁵Sunnybrook Health Sciences Center, Toronto, ON; ¹⁶The Angeles Clinic and Research Institute, Los Angeles, CA; ¹⁷Merck & Co., Inc., Kenilworth, NJ; ¹⁸Gustave Roussy and Paris-Sud University, Villejuif, France

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Overall Survival

Arm	Events, n	HR (95% CI)	P
Pembro Q2W	122	0.68 (0.53-0.87)	0.00085
Pembro Q3W	119	0.68 (0.53-0.86)	0.00083
Ipi	142	—	—



No. at risk

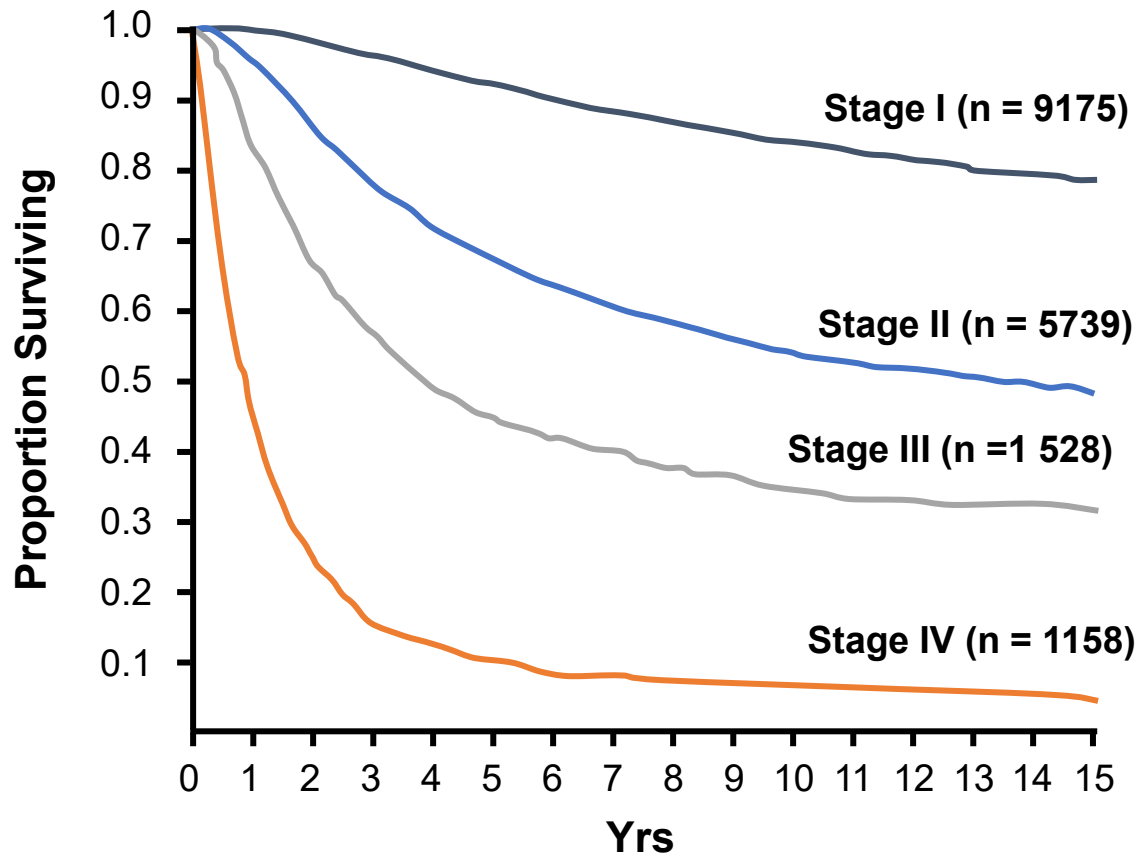
Pembro Q2W	279	266	249	234	221	215	202	188	176	163	156	96	44	4	0
Pembro Q3W	277	266	251	238	215	201	184	179	174	164	156	93	43	1	0
Ipi	278	242	213	189	170	159	145	132	122	113	110	69	28	1	0

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Final analysis data cutoff date: Dec 3, 2015.

Historical Survival in Melanoma by Stage



Updated Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (Checkmate 067)

Jedd D. Wolchok,¹ Vanna Chiarion-Sileni,² Rene Gonzalez,³ Piotr Rutkowski,⁴ Jean-Jacques Grob,⁵ C. Lance Cowey,⁶ Christopher D. Lao,⁷ Dirk Schadendorf,⁸ Pier Francesco Ferrucci,⁹ Michael Smylie,¹⁰ Reinhard Dummer,¹¹ Andrew Hill,¹² John Haanen,¹³ Michele Maio,¹⁴ Grant McArthur,¹⁵ Dana Walker,¹⁶ Joel Jiang,¹⁶ Christine Horak,¹⁶ James Larkin,^{17*} F. Stephen Hodi^{18*}

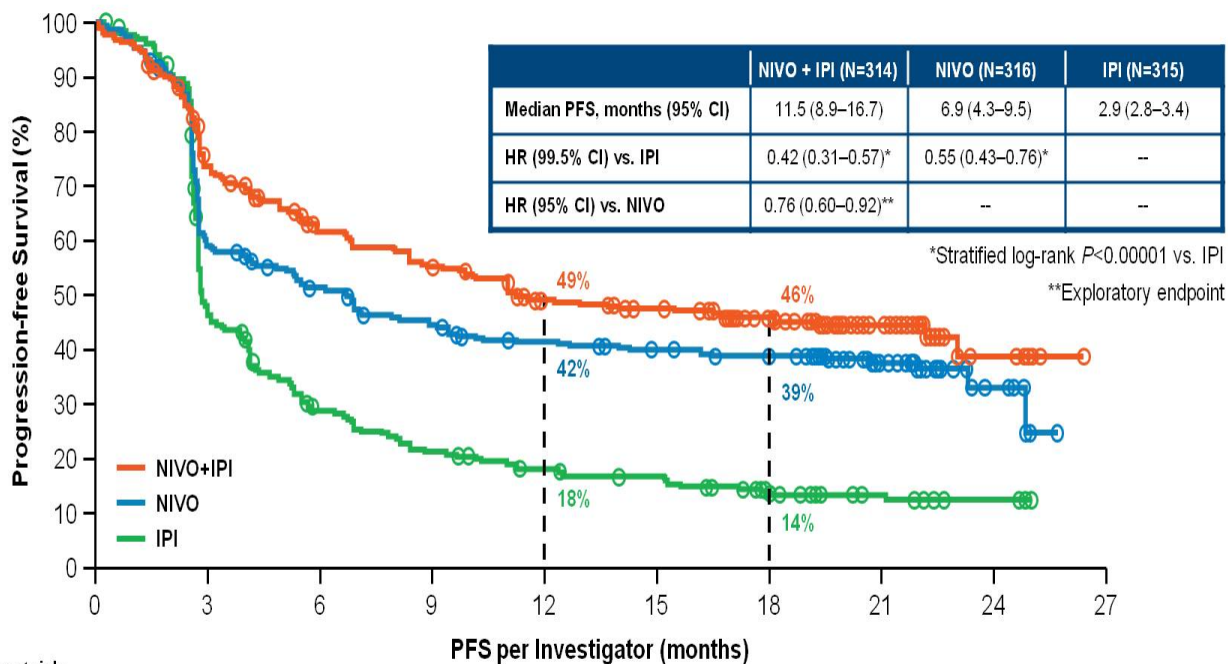
¹Memorial Sloan Kettering Cancer Center, Ludwig Institute for Cancer Research and Weill Cornell Medical College, New York, NY, USA; ²Oncology Institute of Veneto IRCCS, Padua, Italy; ³University of Colorado Cancer Center, Denver, CO, USA; ⁴Maria Skłodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland; ⁵Hospital de la Timone, Marseille, France; ⁶Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology Research, Dallas, TX, USA; ⁷University of Michigan, Ann Arbor, MI, USA; ⁸Department of Dermatology, University of Essen, Essen, Germany; ⁹European Institute of Oncology, Milan, Italy; ¹⁰Cross Cancer Institute, Edmonton, Alberta, Canada; ¹¹Universitäts Spital, Zurich, Switzerland; ¹²Tasman Oncology Research, QLD, Australia; ¹³Netherlands Cancer Institute, Amsterdam, The Netherlands; ¹⁴University Hospital of Siena, Siena, Italy; ¹⁵Peter MacCallum Cancer Centre, Victoria, Australia; ¹⁶Bristol-Myers Squibb, Princeton, NJ, USA; ¹⁷Royal Marsden Hospital, London, UK; ¹⁸Dana-Farber Cancer Institute, Boston, MA, USA. *Contributed equally to the study

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Progression-Free Survival (Intent-to-Treat Population)



Number of patients at risk:

	0	3	6	9	12	15	18	21	24	27
Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

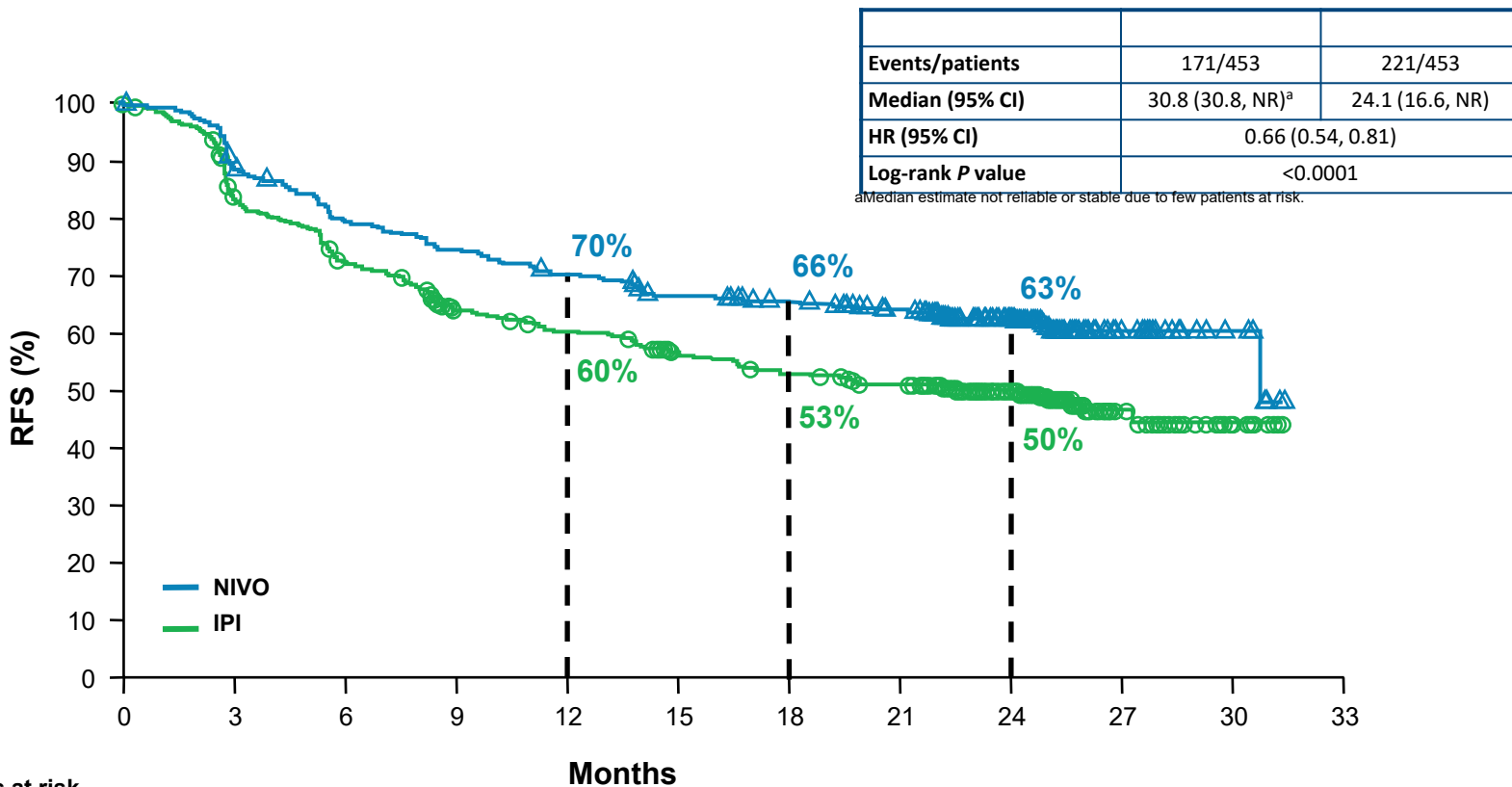
Database lock Nov 2015

Adjuvant Therapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage III/IV Melanoma: Updated Results from a Phase 3 Trial (CheckMate 238)

Jeffrey Weber,¹ Mario Mandala,² Michele Del Vecchio,³ Helen Gogas,⁴ Ana M. Arance,⁵
C. Lance Cowey,⁶ Stéphane Dalle,⁷ Michael Schenker,⁸ Vanna Chiarion-Sileni,⁹ Ivan Marquez-Rodas,¹⁰
Jean-Jacques Grob,¹¹ Marcus Butler,¹² Mark R. Middleton,¹³ Michele Maio,¹⁴ Victoria Atkinson,¹⁵
Reinhard Dummer,¹⁶ Veerle de Pril,¹⁷ Anila Qureshi,¹⁷ Abdel Saci,¹⁷ James Larkin,^{18*} Paolo A. Ascierto^{19*}

¹NYU Perlmutter Cancer Center, New York, New York, USA; ²Papa Giovanni XIII Hospital, Bergamo, Italy; ³Medical Oncology, National Cancer Institute, Milan, Italy; ⁴University of Athens, Athens, Greece; ⁵Hospital Clínic de Barcelona, Barcelona, Spain; ⁶Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, Texas, USA; ⁷Hospices Civils de Lyon, Pierre Bénite, France; ⁸Oncology Center Sf Nectarie Ltd., Craiova, Romania; ⁹Oncology Institute of Veneto IRCCS, Padua, Italy; ¹⁰General University Hospital Gregorio Marañón, Madrid, Spain; ¹¹Hôpital de la Timone, Marseille, France; ¹²Princess Margaret Cancer Centre, Toronto, Ontario, Canada; ¹³Churchill Hospital, Oxford, United Kingdom; ¹⁴Center for Immuno-Oncology, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; ¹⁵Gallipoli Medical Research Foundation and University of Queensland, Brisbane, Australia; ¹⁶University Hospital Zurich, Switzerland; ¹⁷Bristol-Myers Squibb, Princeton, New Jersey, USA; ¹⁸Royal Marsden NHS Foundation Trust, London, UK; ¹⁹Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; *Contributed equally to this study.

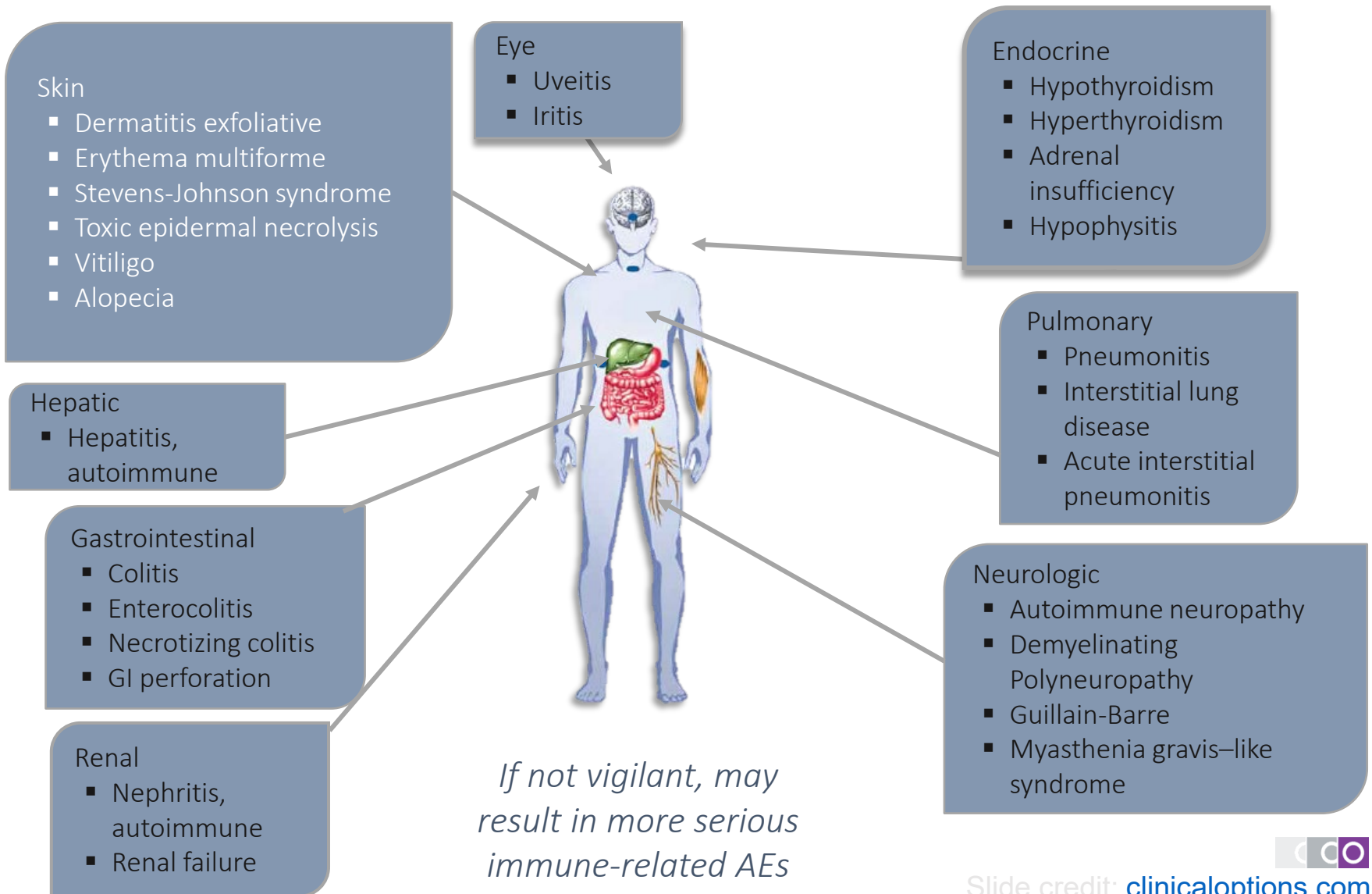
Primary Endpoint: RFS in All Patients



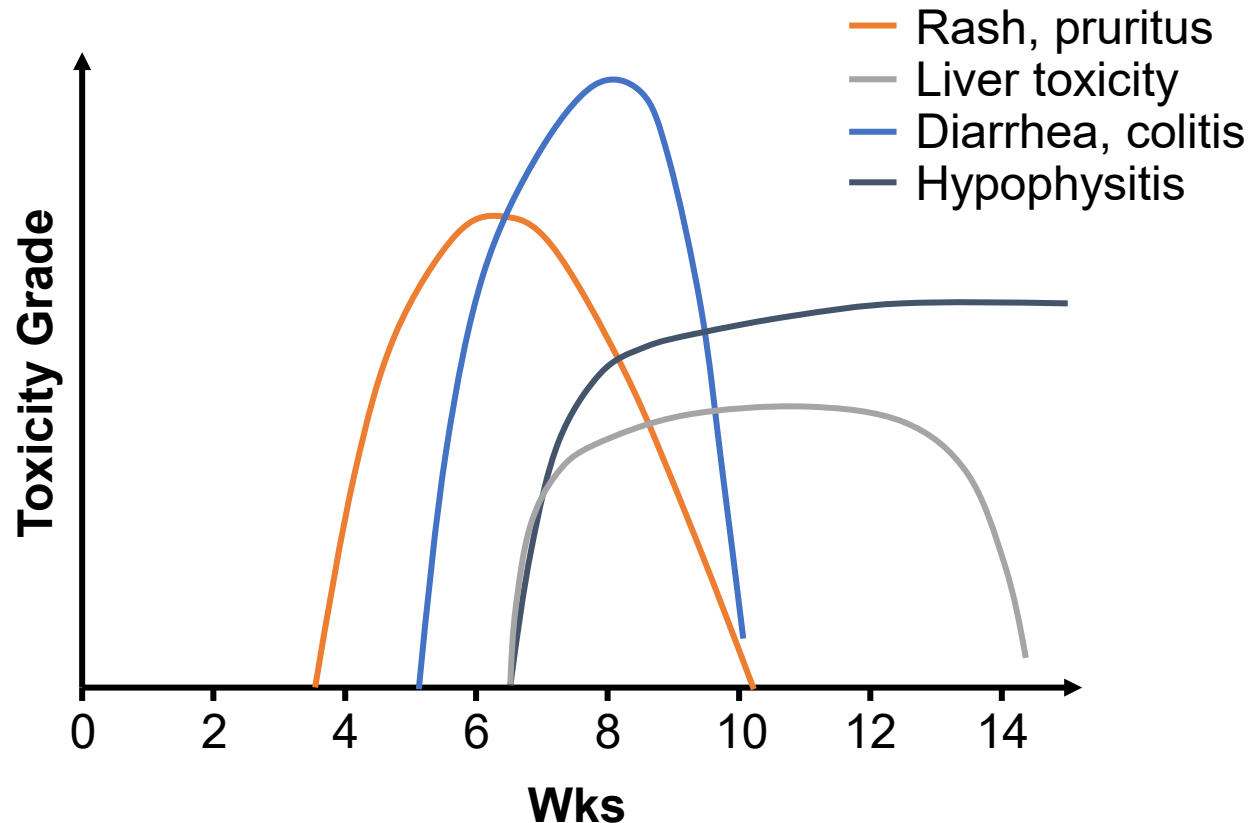
Number of patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33
NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

Immune-Related AEs With Immunotherapy



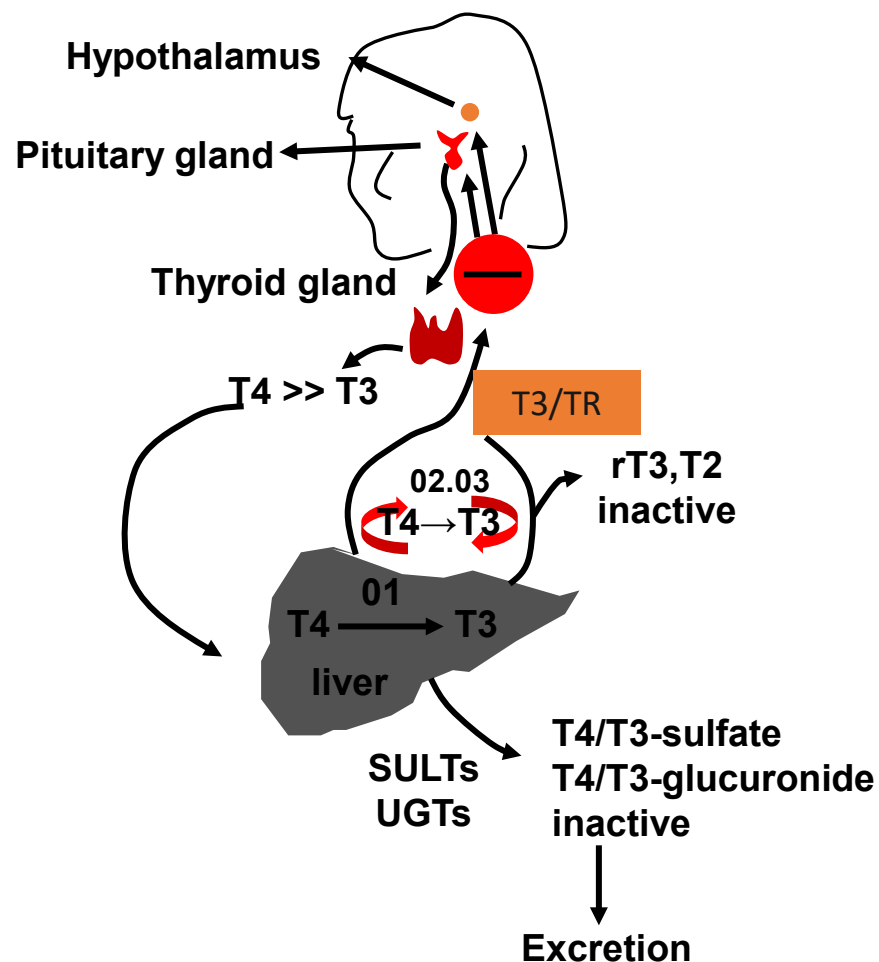
Kinetics of Appearance of irAEs With Ipilimumab



Combined analysis of 325 participants with 10 mg/kg IV q3w x 4

Immune-Mediated Endocrinopathies

- Can be serious or fatal if not managed correctly
- Hypophysitis, thyroid disease, and primary adrenal insufficiency have all been reported
- Mechanism of injury not fully understood
- Monitor pt for pituitary, thyroid, or adrenal disease
- Check TFTs at baseline and prior to each dose
- Time to onset may be much later; median 11 wks



Targeted therapy

Genomic Analysis and 3-Year Efficacy and Safety Update of COMBI-d

A phase 3 study of dabrafenib + trametinib vs dabrafenib monotherapy in patients with unresectable or metastatic *BRAF* V600E/K–mutant cutaneous melanoma

K.T. Flaherty, M.A. Davies, J. Grob, G.V. Long, P. Nathan, A. Ribas, C. Robert, D. Schadendorf, D.T. Frederick, M.R. Hammond, J. Jane-Valbuena, X.J. Mu, M. Squires, S.A. Jaeger, S.R. Lane, B. Mookerjee, L.A. Garraway

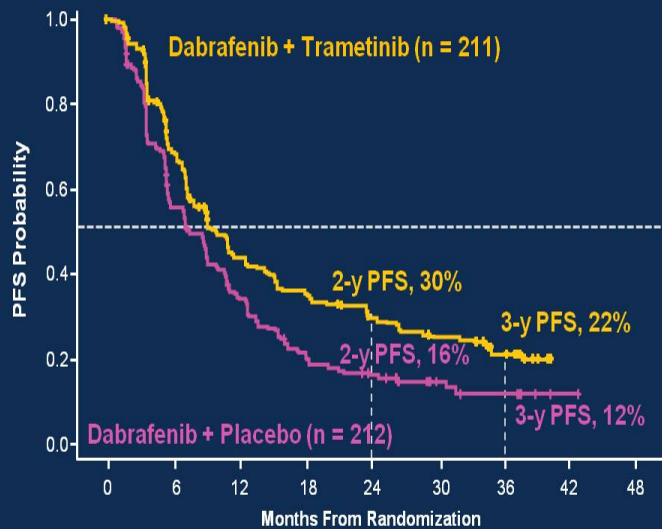
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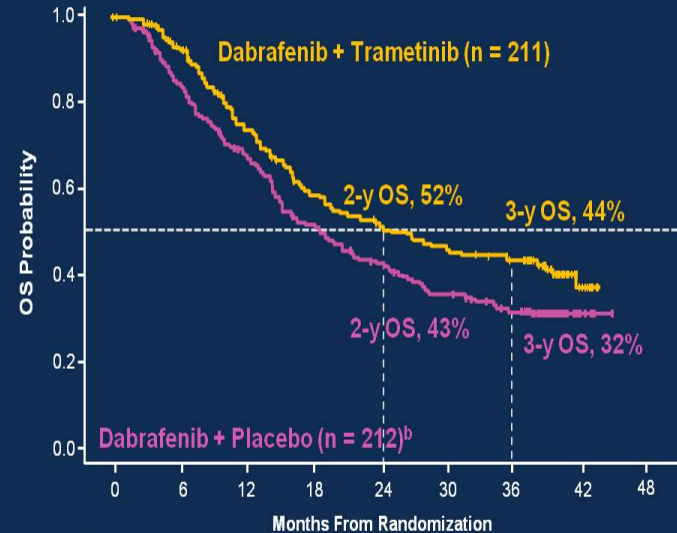
COMBI-d: PFS and OS^a

58% of D+T patients alive at 3 years still on D+T

Progression-Free Survival



Overall Survival



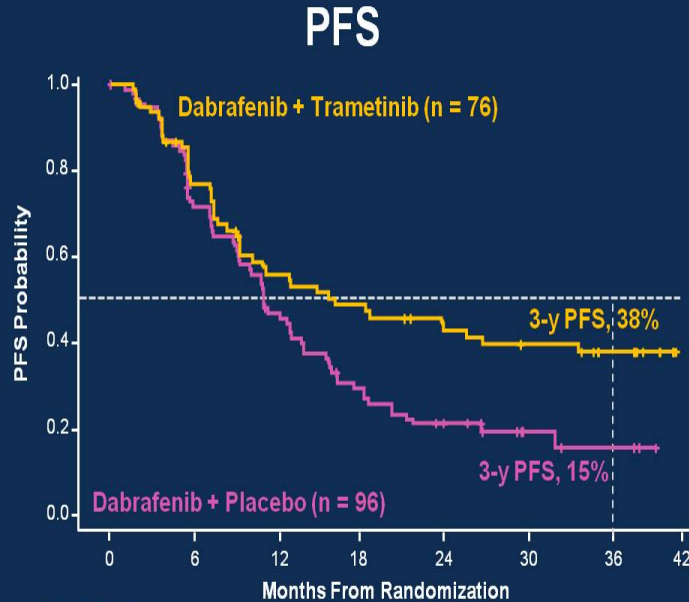
^a Intent-to-treat population; ^b Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.

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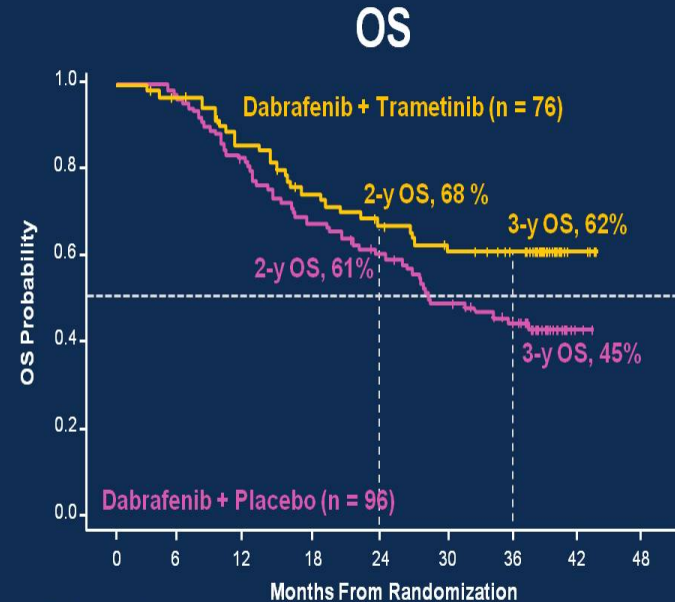
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Presented by: Keith T. Flaherty, MD

COMBI-d: Normal LDH^a and < 3 Disease Sites^b



Number at risk	0	6	12	18	24	30	36	42
D+T	76	56	39	34	28	25	19	0
D+Pbo	96	64	41	25	16	5	3	0



Number at risk	0	6	12	18	24	30	36	42	48
D+T	76	72	62	52	46	41	35	4	0
D+Pbo	96	93	77	65	56	45	36	2	0

^a Baseline LDH ≤ ULN; ^b Any organ at baseline with ≥ 1 metastasis could be counted as a single disease site; +, censored.

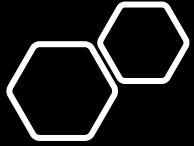
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Presented by: Keith T. Flaherty, MD

Pyrexia management

- Mild – paracetamol, NSAIDs
- Moderate or associated with rigors, dehydration – withhold dabrafenib/trametinib until resolves
- Severe, involving hypotension, renal failure –
 - withhold dabrafenib/trametinib
 - steroids
 - once resolved can safely restart therapy



Audit: Melanoma brain metastases

Shu Lee, Lindy Jeffree,
Melissa Eastgate

- 3rd most common cause of brain metastasis
- Brain metastasis occurs in 40-50% of patients with metastatic melanoma
- Autopsy series up to 75%
- Cause of death in 95% of patients
- Historically excluded from clinical trials of systemic therapy

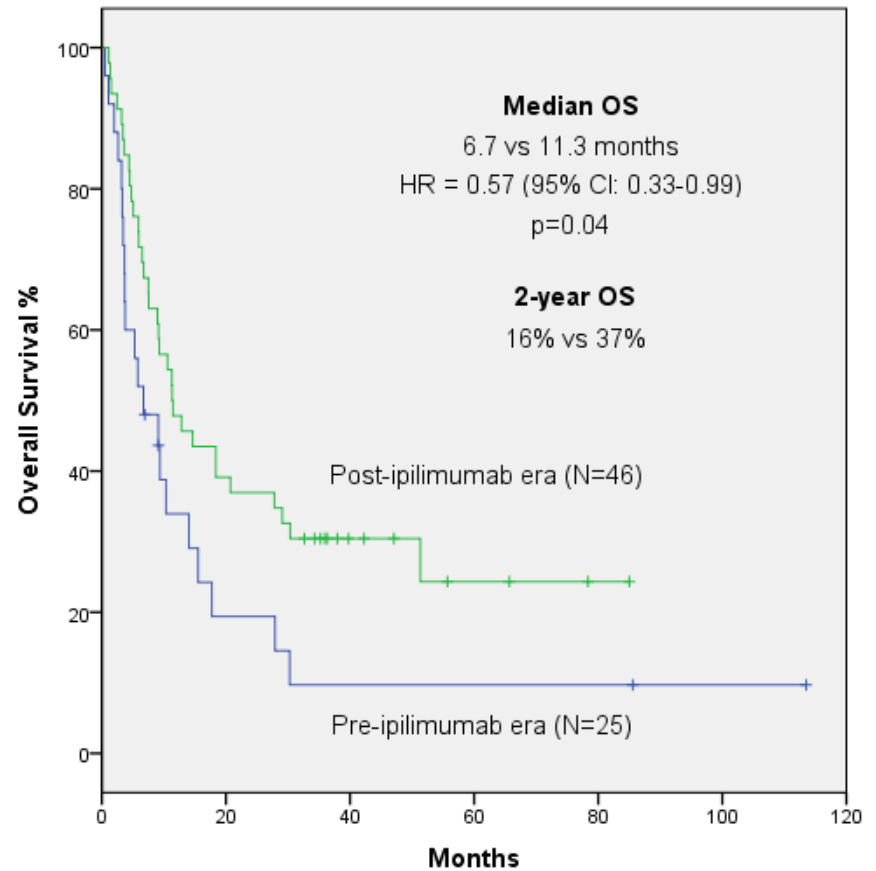
Methods

- Melanoma patients with brain metastases who underwent neurosurgery at RBWH between July 2007 and October 2015 were retrospectively identified. (71 patients)
- Clinical and follow-up information were collected from medical records.
- Survival was analysed using Kaplan-Meier estimates.
- Univariate and multivariate analyses to determine independent predictors of survival were undertaken using a Cox proportional hazard regression model.

Results

- 93% were successfully discharged home post-operatively but 11% required inpatient rehabilitation prior to discharge.
- There was no procedure-related mortality
- 1 patient died within 30 days of surgery

Survival outcomes after resection of brain metastasis



Australian context

Stage 2

- trial open for high risk patients, over 2mm with ulceration or over 4mm without ulceration

Stage 3/resected stage 4

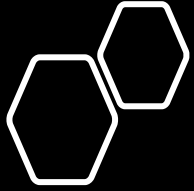
- Adjuvant therapy PBS funded – targeted and immunotherapy

Australian context

Stage 4

- BRAF mutant – dabrafenib/trametinib or vemurafenib/cobimetinib on PBS
- BRAF wildtype –
 - Single agent pembrolizumab/nivolumab
 - Double agent ipilimumab/nivolumab

All patients – clinical trials ongoing



Prevention is better than cure

- Daily sunscreen use could reduce melanoma rates by 75%
- Broad brimmed hats
- Protective clothing
- Sunglasses

**SLIP! SLOP! SLAP!
SEEK! SLIDE!**

like Sid Seagull!

SHADE

HAT

SHIRT

SUNGLASSES

SUNSCREEN
SPF30 OR HIGHER

SUNSMART

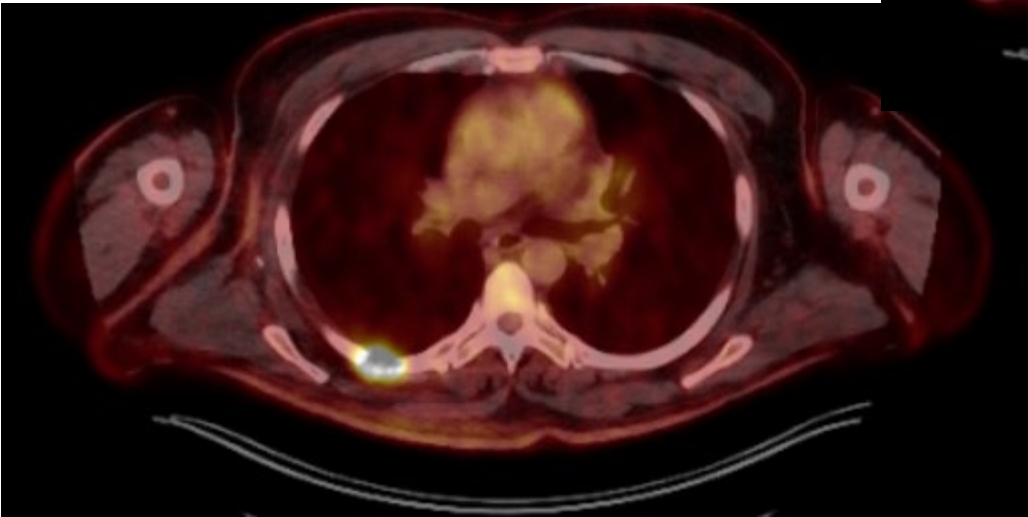
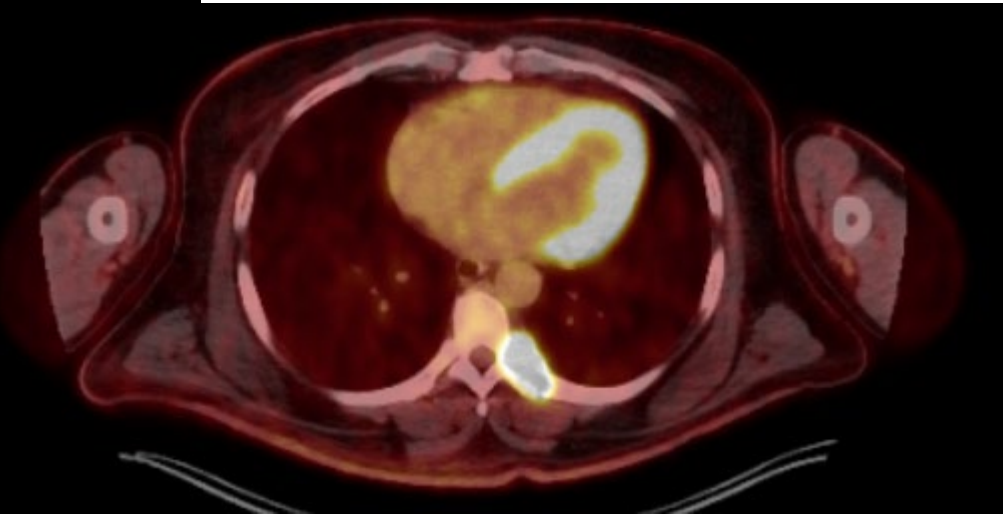
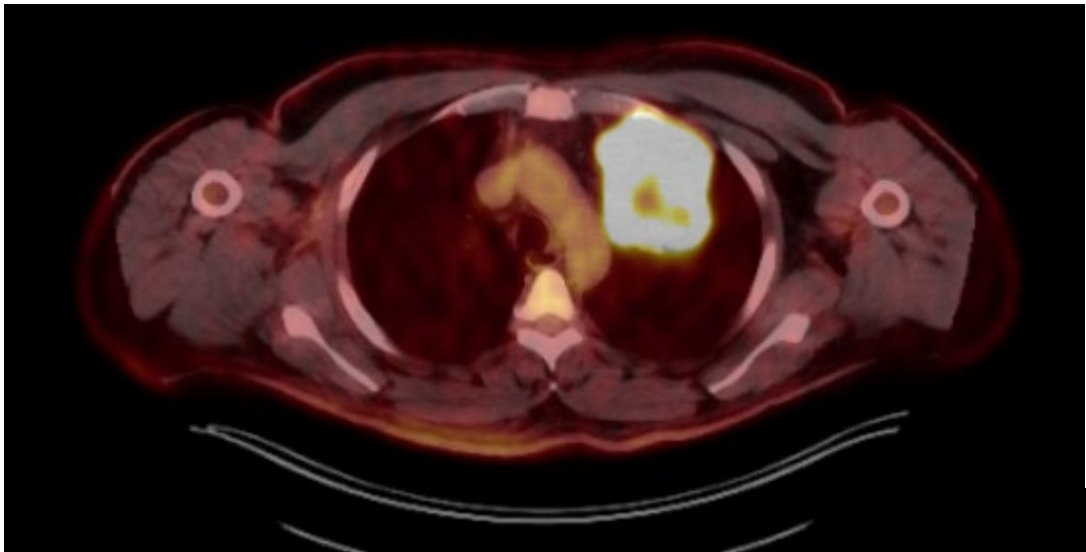
Cancer Council Hépline
13 11 20
cancerqld.org.au

Questions?



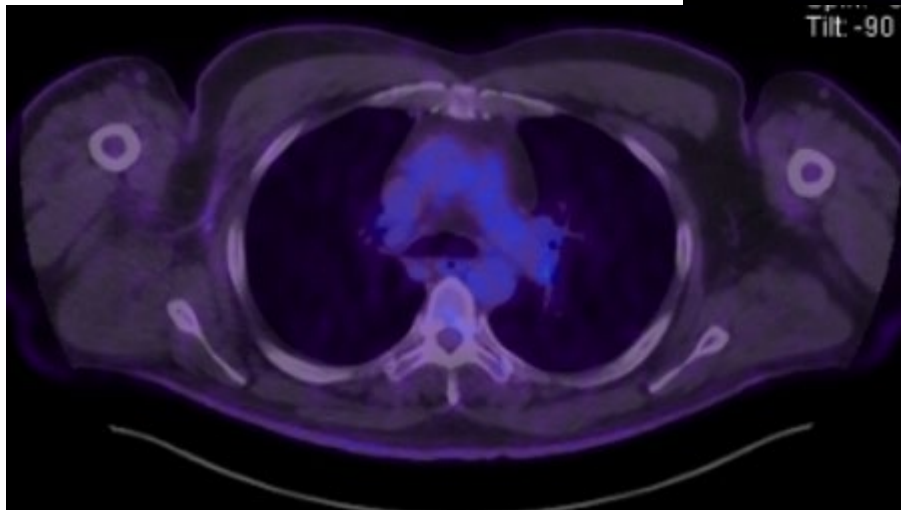
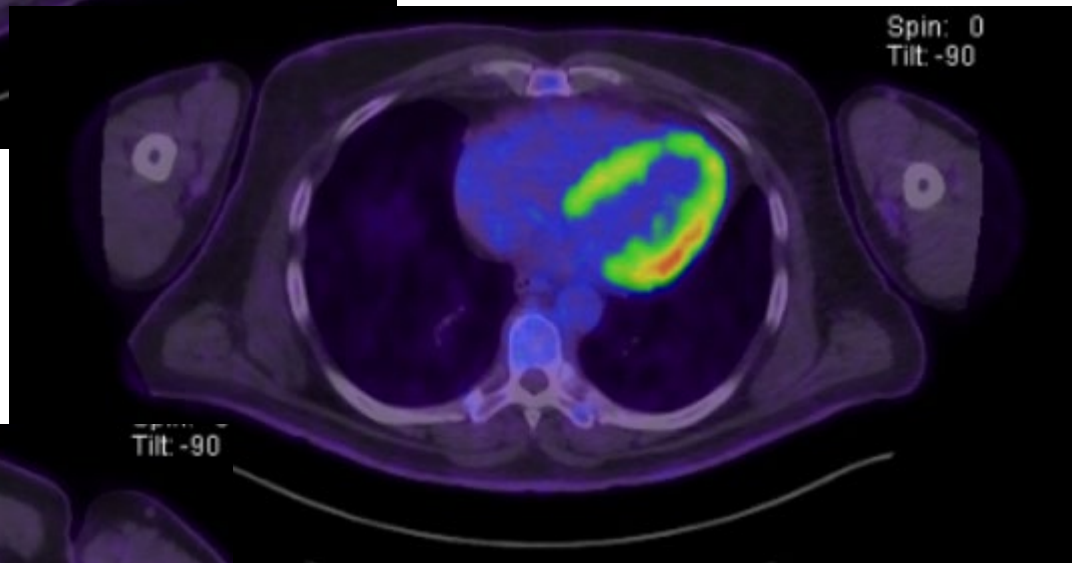
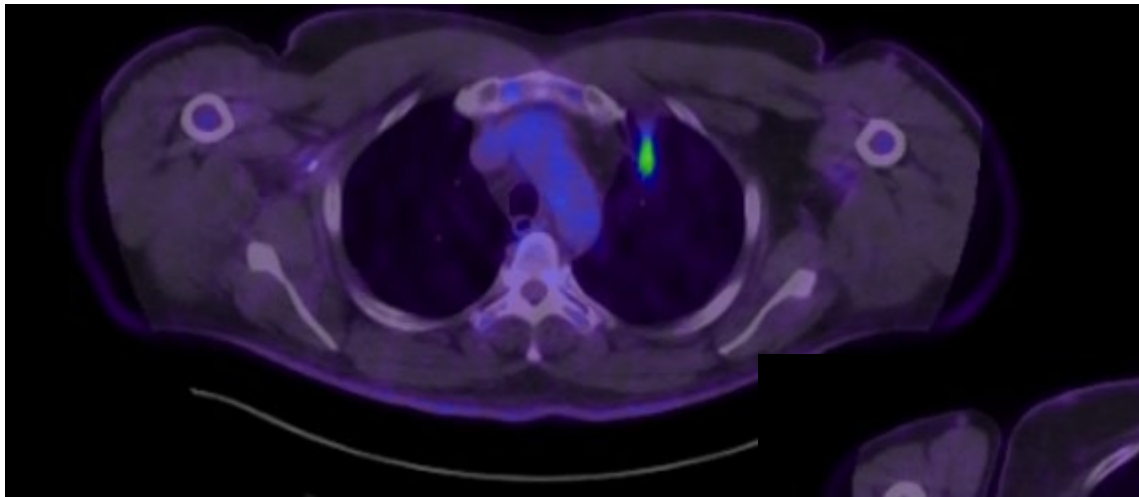
Case:

- 62 yr old male
- Stage 3 disease 2014
 - Treated with axillary clearance
 - Unknown primary
- 2016 developed wt loss, fatigue
 - Imaging showed metastatic disease



Case cont'd

- Treated on a clinical trial
 - Pembrolizumab and IMP 321 (lag 3 protein)
- Side effects
 - Diarrhea started after 6 months on treatment
 - Prednisone
- Remained on treatment to 2018
 - PET showing all lesions had resolved apart from residual small lesion in lung



Case cont'd

- Feb 2019 – wedge resection
- Pathology – no melanoma
- Now off treatment

Autoimmune hepatitis

Urate	0.20	mmol/L	(0.15 - 0.50)
Protein	58	L g/L	(60 - 80)
Albumin	34	L g/L	(35 - 50)
Globulin	24	L g/L	(25 - 45)
Bilirubin	29	H umol/L	(< 20)
Bili(Conj)	10	H umol/L	(< 4)
ALP	108	U/L	(30 - 110)
Gamma GT	177	H U/L	(< 55)
ALT	1200	H U/L	(< 45)
AST	218	H U/L	(< 35)
LD	551	H U/L	(120 - 250)
Calcium	2.21	mmol/L	(2.10 - 2.60)
Corr Ca	2.33	mmol/L	(2.10 - 2.60)

eGFR	82	mL/min/1.73m ²	(> 60)
Urate	0.32	mmol/L	(0.15 - 0.50)
Protein	61	g/L	(60 - 80)
Albumin	40	g/L	(35 - 50)
Globulin	21	L g/L	(25 - 45)
Bilirubin	12	umol/L	(< 20)
Bili(Conj)	< 4	umol/L	(< 4)
ALP	66	U/L	(30 - 110)
Gamma GT	19	U/L	(< 55)
ALT	21	U/L	(< 45)
AST	16	U/L	(< 35)

Other toxicities – rash D/T



Other toxicities – rash pembro

