Metastatic Melanoma New therapies and their toxicities

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Chair, Melanoma MDT RBWH

RBWH

21 July 2018

Question 1:

- How many people die in Australia each year from melanoma?
  a) 300
  b) 1600
  c) 10000

Question 2:

- What is the 2 year survival for someone with metastatic melanoma treated with immunotherapy?
  a) 10%
  b) 30%
  c) 55%

Melanoma Incidence in Australia

- 2015
  - 1675 deaths
  - 12960 new cases
  - 3.6% of cancer deaths

AJCC staging – 8th edition

- T1 measured to 1 decimal place not 2
- Tumour mitotic rate removed

AJCC 8th Edition N-category criteria

N Category	Number of tumor-involved regional lymph node	Presence of in-transit, satellite, and/or microsatellite metastases
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

- Presence of microsatellites, satellites, or in-transit metastases categorized as N1c, N2c, or N3c based on # of tumor-involved regional lymph nodes

Gershenwald, Scolyer, et al. Melanoma. In Amin, M.B., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

AJCC Stage III Stage Groups

When T is…	And N is…	And M is…	Then the pathological stage group is…
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a–N2b	M0	IIIB
T1a–T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a–N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

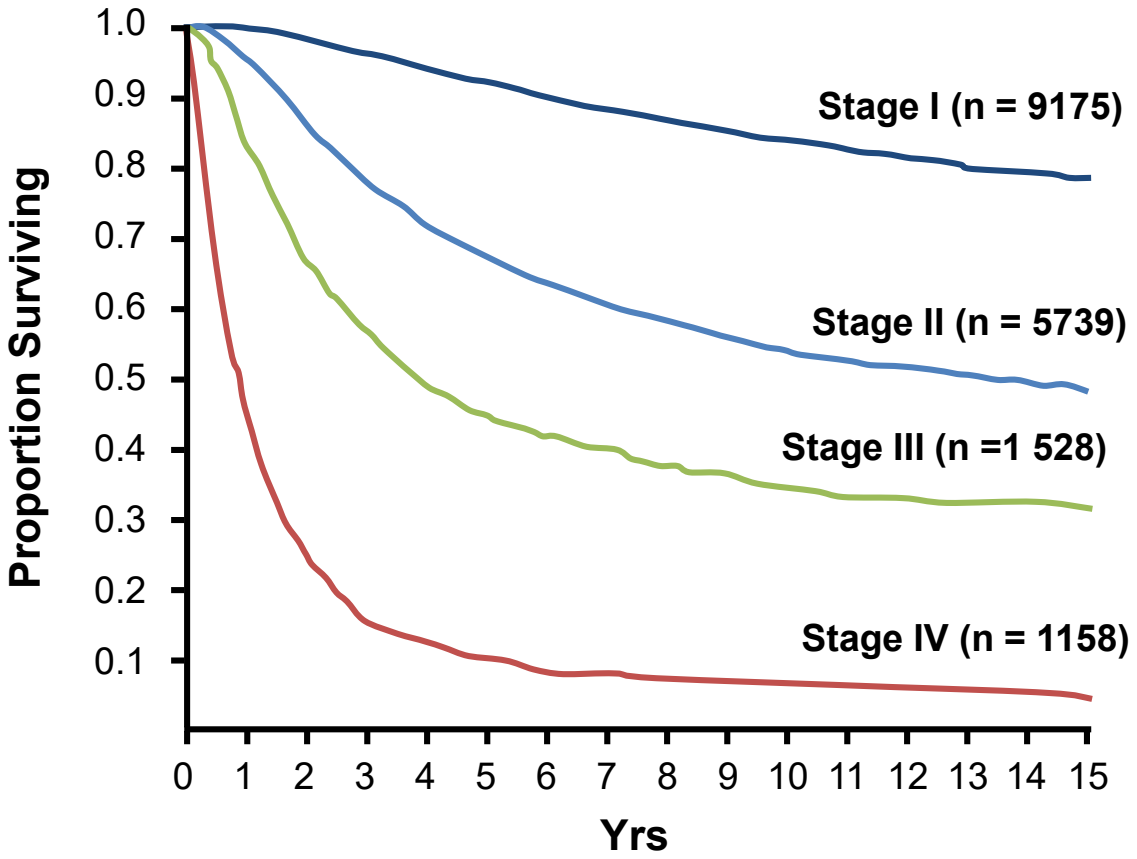
N/A=Not assigned, please see manual for details. [REF]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

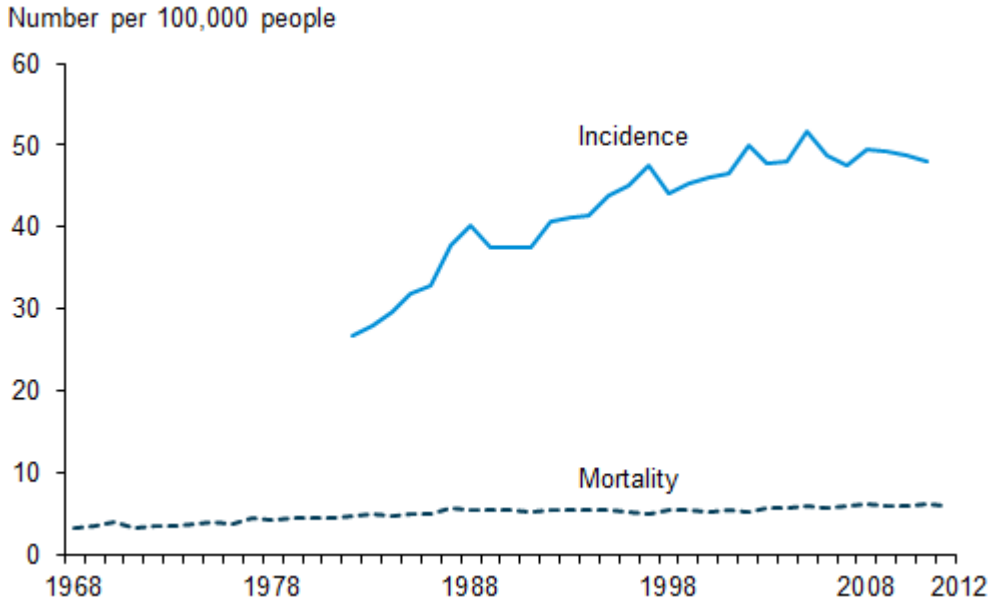
Gershenwald, Scolyer, et al. Melanoma. In Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed., 2017
Gershenwald, Scolyer, Hess, Sondak et al. CA Cancer J Clin. 2017 Oct 13. doi: 10.3322/caac.21409. [Epub ahead of print]

Survival in Melanoma by Stage



Balch CM, et al. J Clin Oncol. 2001;19:3635-3648.

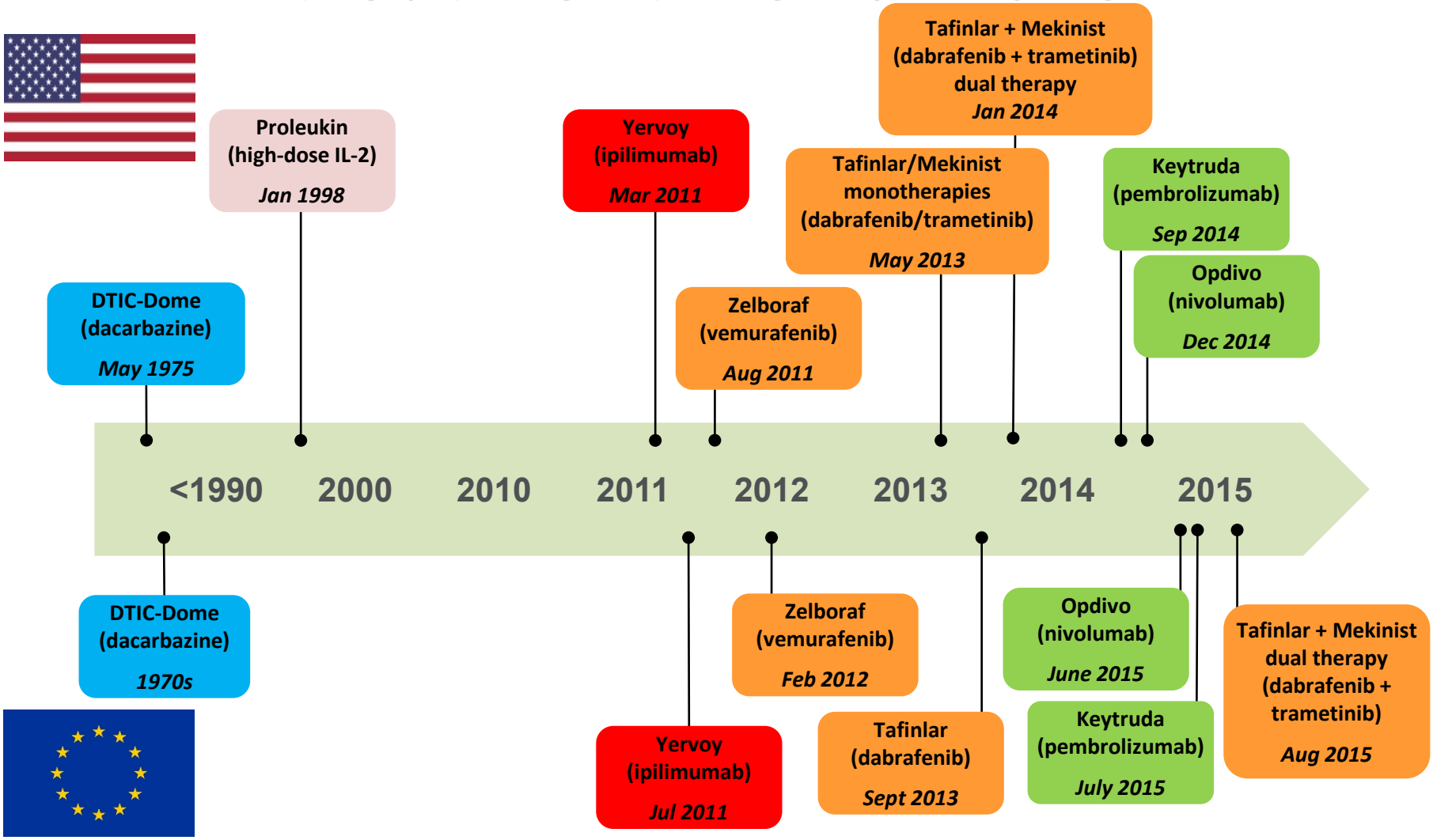
Melanoma skin cancer incidence and mortality, 1968 to 2012



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



Sentinel Lymph Node biopsy

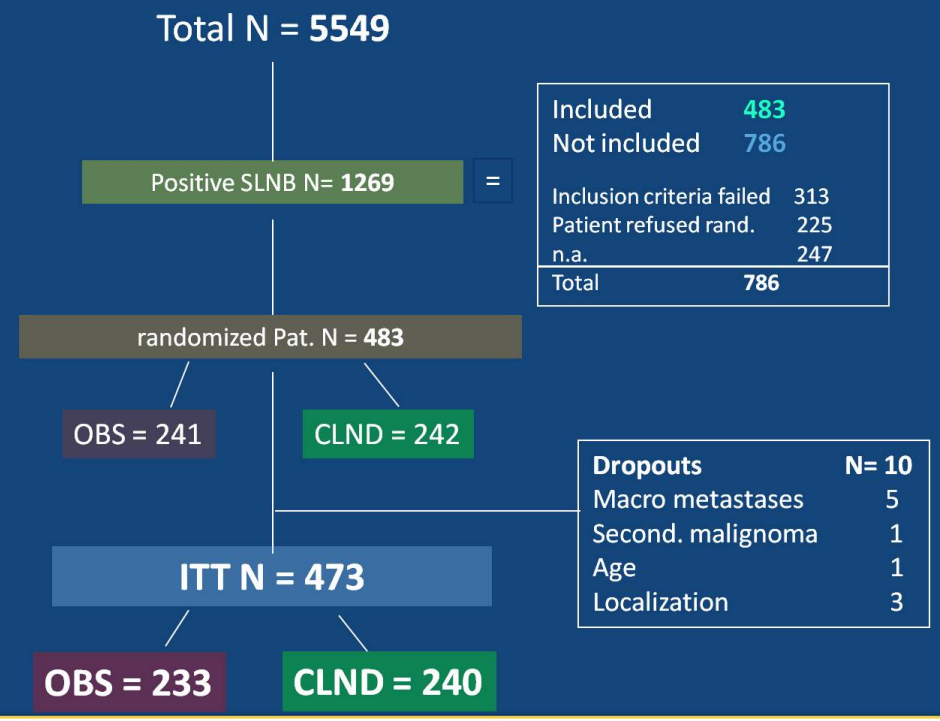
- Very important prognostic factor
- Should be discussed with patients if melanoma is >1mm thick
- Can’t be done after WLE

Surgery for melanoma

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

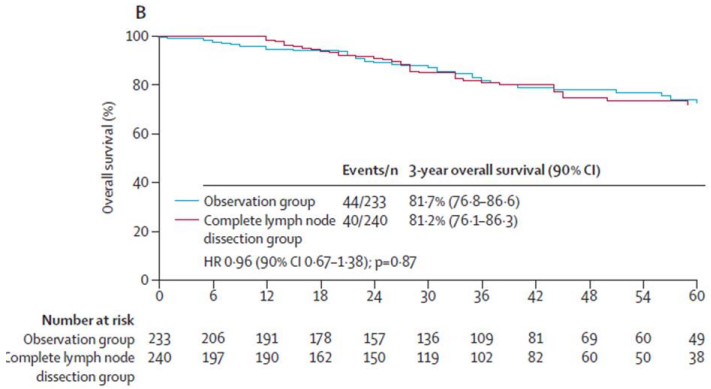
Flow chart

Enrolment was performed from January 2006 to December 2014

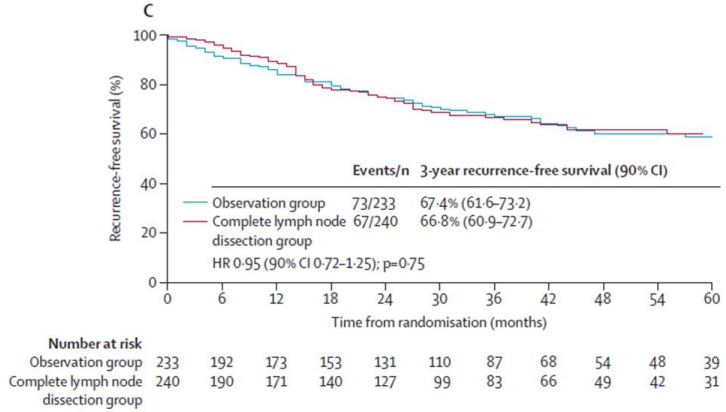


DECOG 3-years Survival Data

Overall survival



Recurrence-free survival

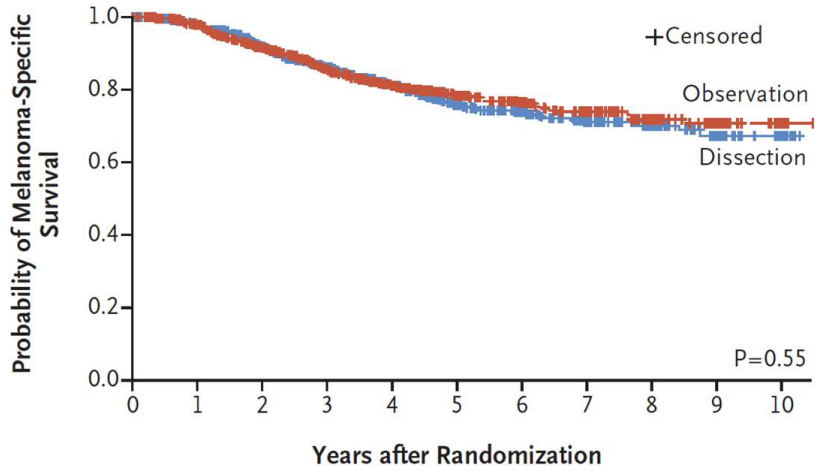


PRESENTED BY: Ulrike Leiter

Leiter et al., The Lancet Oncology 2016;17:757-767

Similar findings – MSLT II

A



No. at Risk

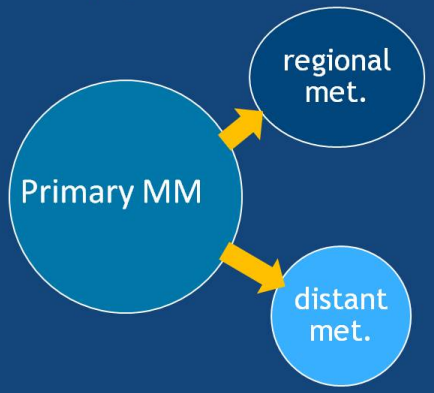
Dissection	824	759	654	510	389	275	191	128	83	39	13
Observation	931	856	734	564	425	304	217	151	95	55	13

Faries et al. NEJM 2017; 376:2211-2222

Discussion of DECOG Results

Halstedian hypothesis (1907):
Stepwise metastasis from the primary through the lymphatics to distant sites

Alternative hypothesis:
Parallel metastasis from the primary to the lymphatics and to distant sites



Only if the Halstedian hypothesis is correct, prophylactic lymph node surgery makes sense.

Halsted WS, Ann. Surg. 1907,
Ackerman and Medalie, Br. J. Dermatol. 2004

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 Robert[18]

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

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Jacob Schachter at 2016 ASCO Annual Meeting

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

PRESENTED AT: ASCO ANNUAL MEETING '16

Final analysis data cutoff date: Dec 3, 2015.

Presented By Jacob Schachter at 2016 ASCO Annual Meeting

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

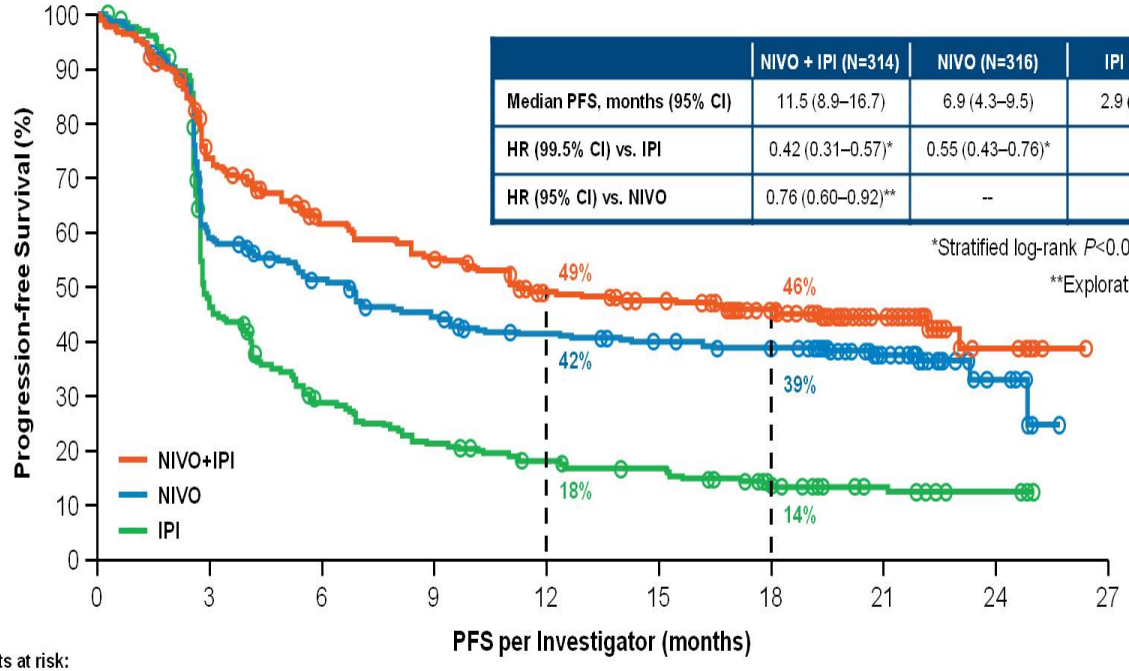
Jedd D. Wolchok,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15]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

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

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

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



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI

**Exploratory endpoint

Number of patients at risk:

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

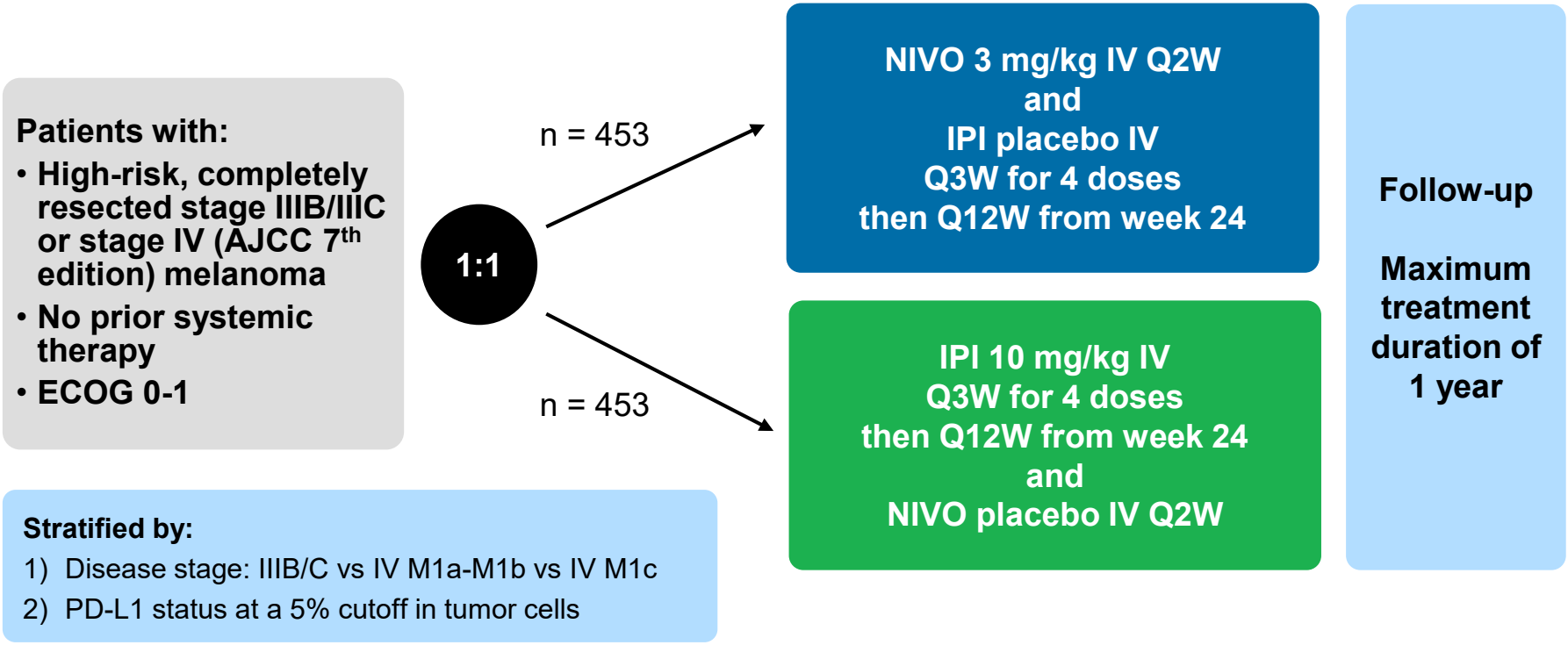
Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

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*]

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

CheckMate 238: Study Design

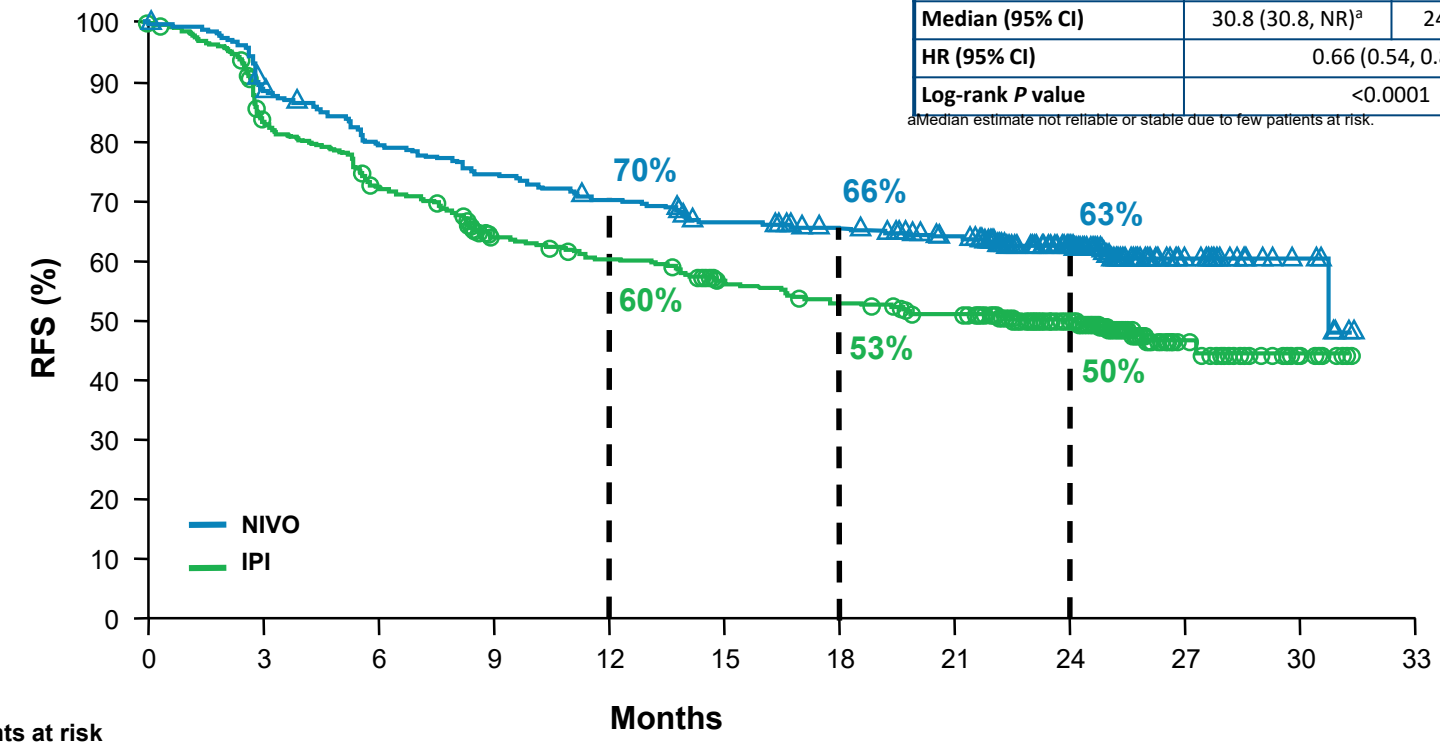


Enrollment period: March 30, 2015 to November 30, 2015

Primary Endpoint: RFS in All Patients

Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.



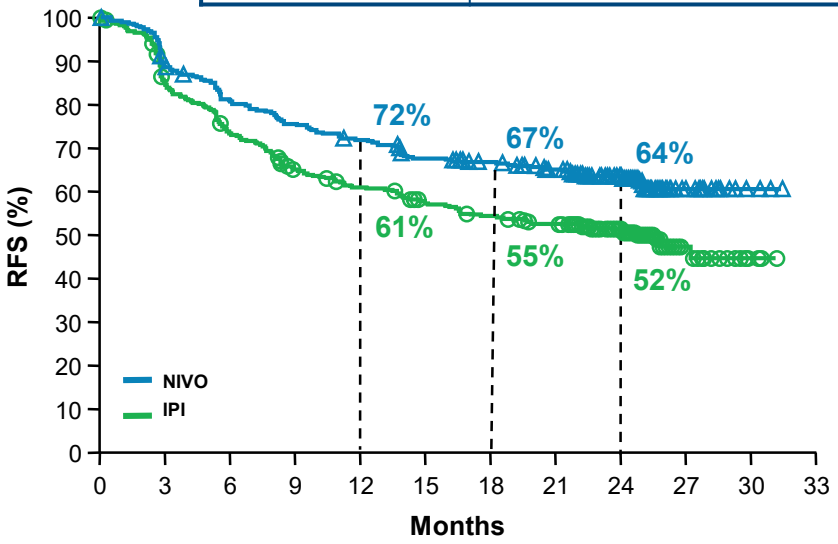
Number of patients at risk

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

Subgroup Analysis of RFS: Disease Stage III and IV

Stage III

Events/patients	135/368	174/366
Median (95% CI)	NR	25.5 (16.6, NR)
HR (95% CI)	0.68 (0.54, 0.85)	



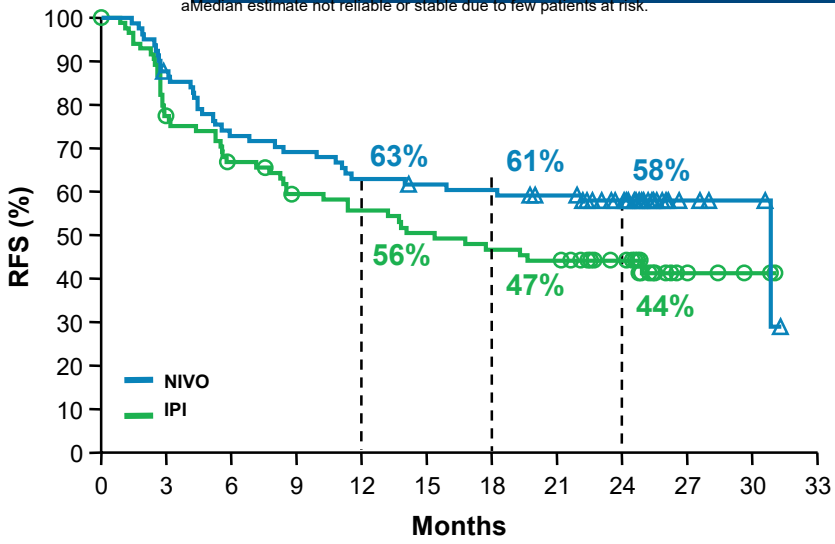
Number of patients at risk

NIVO	368	320	291	272	258	240	230	217	166	22	4	0
IPI	366	298	259	223	207	190	179	169	121	18	3	0

Stage IV

Events/patients	35/82	47/87
Median (95% CI)	30.8 (15.9, NR)[a]	15.4 (8.5, NR)
HR (95% CI)	0.68 (0.44, 1.06)	

[a]Median estimate not reliable or stable due to few patients at risk.



Number of patients at risk

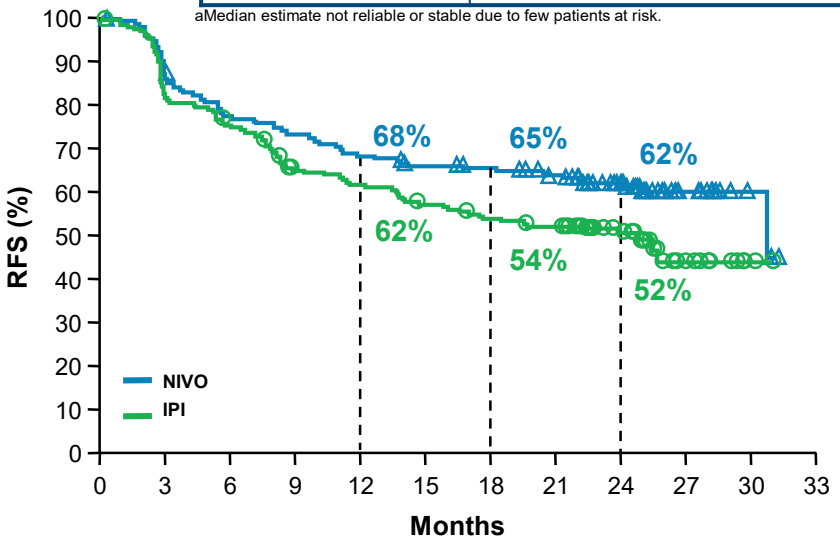
NIVO	82	71	59	56	51	49	48	45	37	6	3	0
IPI	87	65	55	47	44	40	37	35	28	5	2	0

Subgroup Analysis of RFS: *BRAF* Mutation Status

BRAF Mutant

Events/patients	73/187	95/194
Median (95% CI)	30.8 (30.8, NR)[a]	24.6 (14.8, NR)
HR (95% CI)	0.73 (0.54, 0.99)	

aMedian estimate not reliable or stable due to few patients at risk.

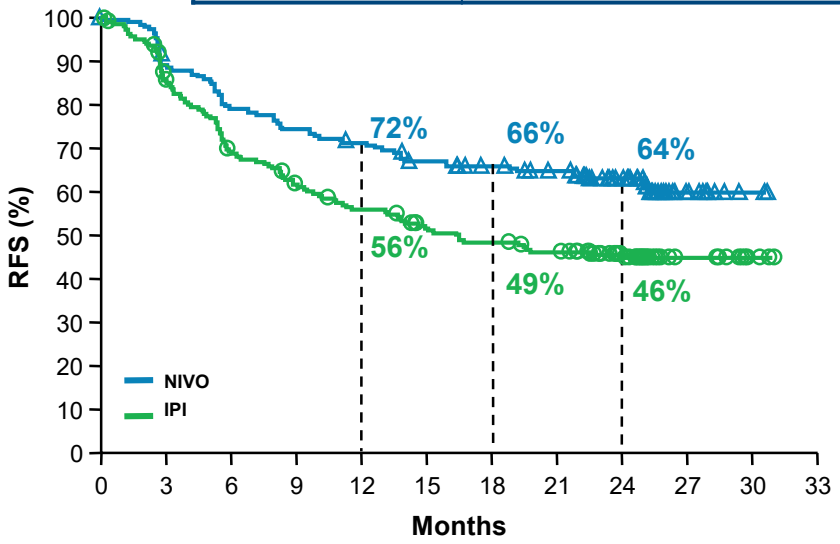


Number of patients at risk

NIVO	187	157	142	135	126	120	117	110	83	16	4	0
IPI	194	155	142	118	112	103	96	91	67	11	2	0

BRAF Wild type

Events/patients	73/197	107/212
Median (95% CI)	NR	16.6 (11.4, NR)
HR (95% CI)	0.61 (0.45, 0.82)	



Number of patients at risk

NIVO	197	172	154	144	137	127	121	115	91	11	2	0
IPI	212	171	138	121	109	97	91	85	62	9	3	0

Immune-Related AEs With Immunotherapy

Skin
- Dermatitis exfoliative
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia

Eye
- Uveitis
- Iritis

Endocrine
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

Hepatic
- Hepatitis, autoimmune

Pulmonary
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

Gastrointestinal
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

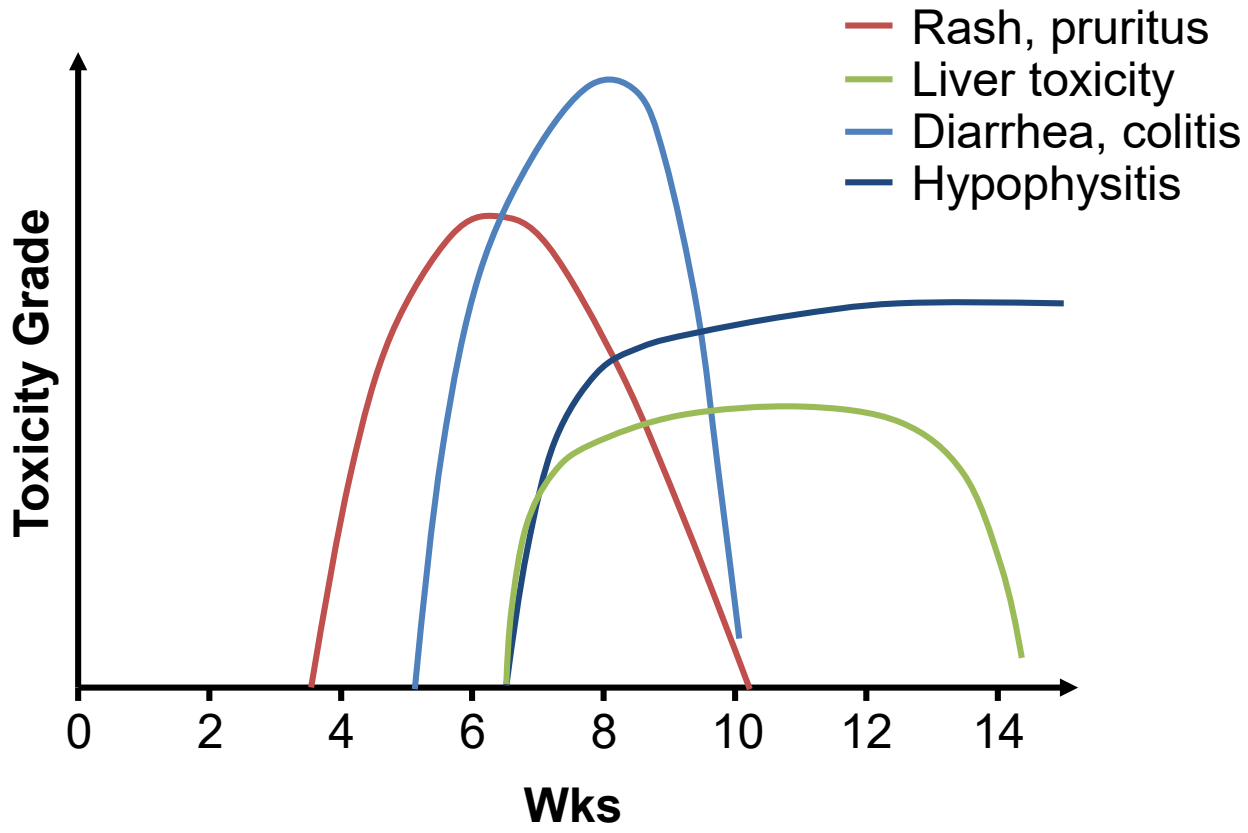
Neurologic
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia gravis–like syndrome

Renal
- Nephritis, autoimmune
- Renal failure

If not vigilant, may result in more serious immune-related AEs

Slide credit: clinicaloptions.com

Kinetics of Appearance of irAEs With Ipilimumab



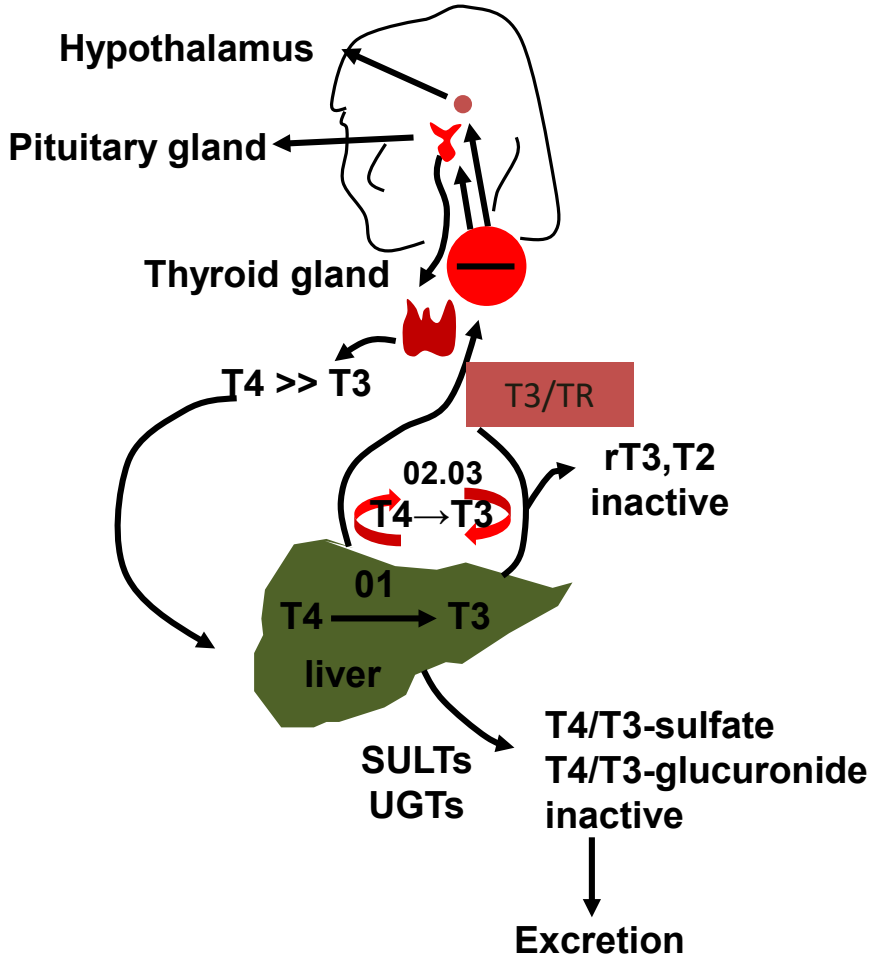
Combined analysis of 325 participants with 10 mg/kg IV q3w x 4

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.

Slide credit: clinicaloptions.com

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



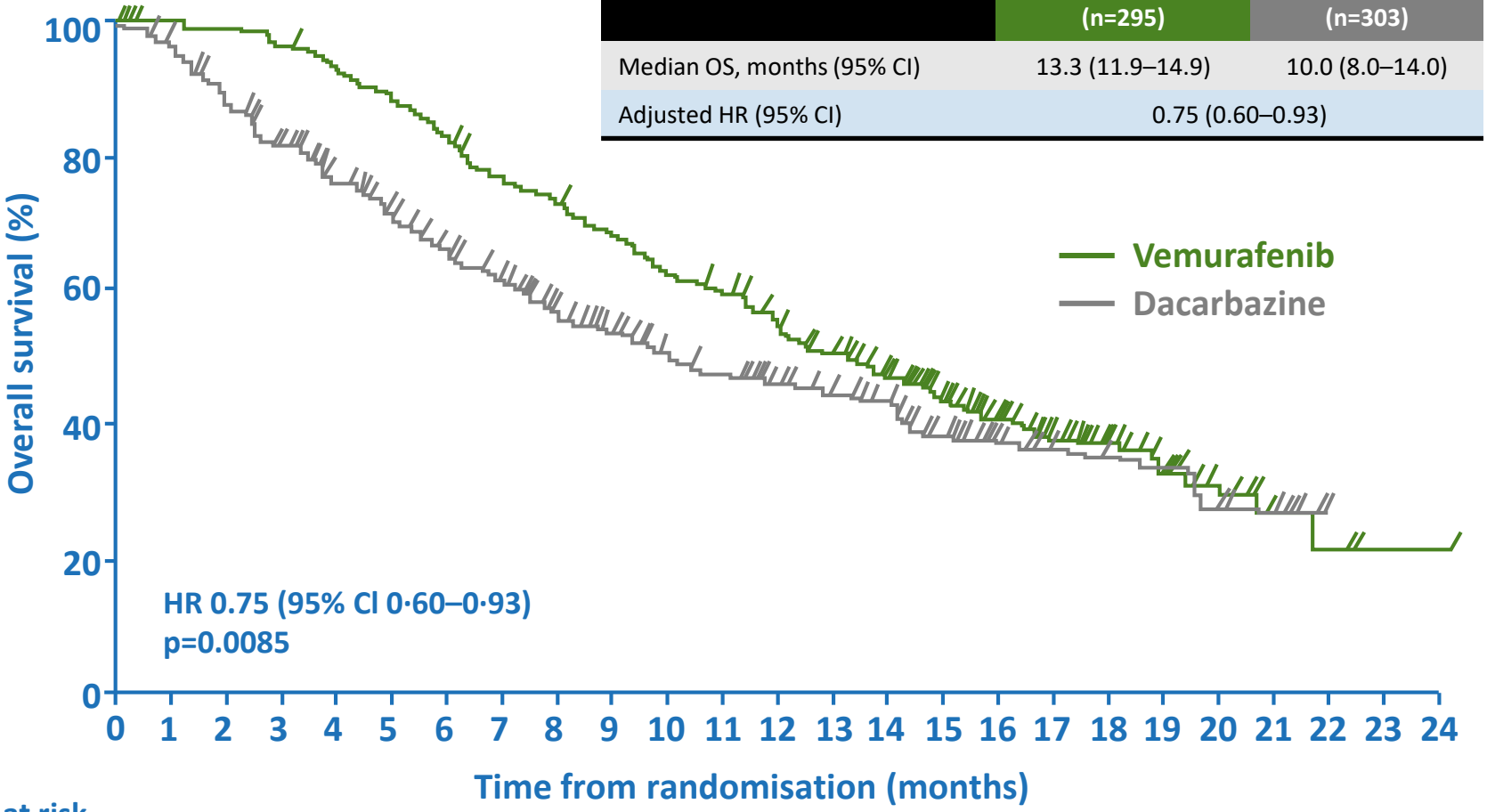
Corsello SM, et al. J Clin Endocrinol Metab. 2013;98:1361-1375.

Slide credit: clinicaloptions.com

TARGETED THERAPY

BRIM-3: OS with vemurafenib *vs* DTIC in patients with BRAF V600E-mutant melanoma

	Vemurafenib (n=295)	DTIC (n=303)
Median OS, months (95% CI)	13.3 (11.9–14.9)	10.0 (8.0–14.0)
Adjusted HR (95% CI)	0.75 (0.60–0.93)	



Number at risk

Vemurafenib	295	294	293	285	274	261	244	223	212	198	181	172	153	138	121	95	75	58	37	25	15	7	3	1	1
Dacarbazine	303	275	251	220	196	175	157	142	118	103	90	84	73	68	59	46	32	27	23	13	7	4	0	0	0

OS=overall survival; CI=confidence interval; HR=hazard ratio.

McArthur GA, *et al. Lancet Oncol* 2014;15:323–32.

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

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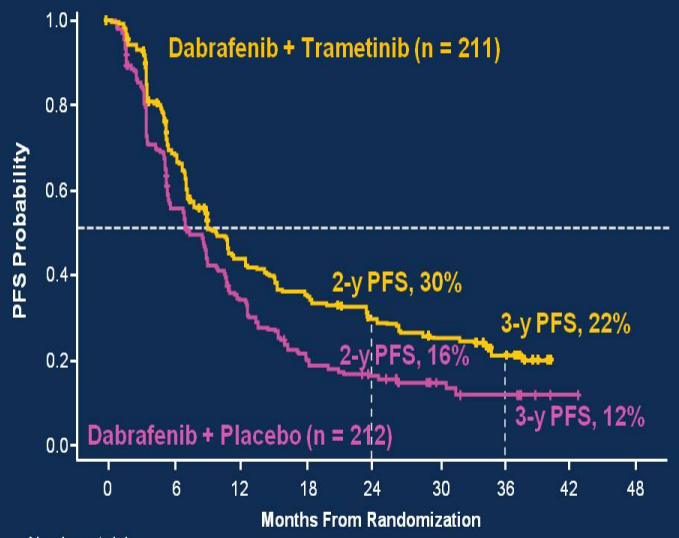
PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Keith Flaherty at 2016 ASCO Annual Meeting

COMBI-d: PFS and OS[a]

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

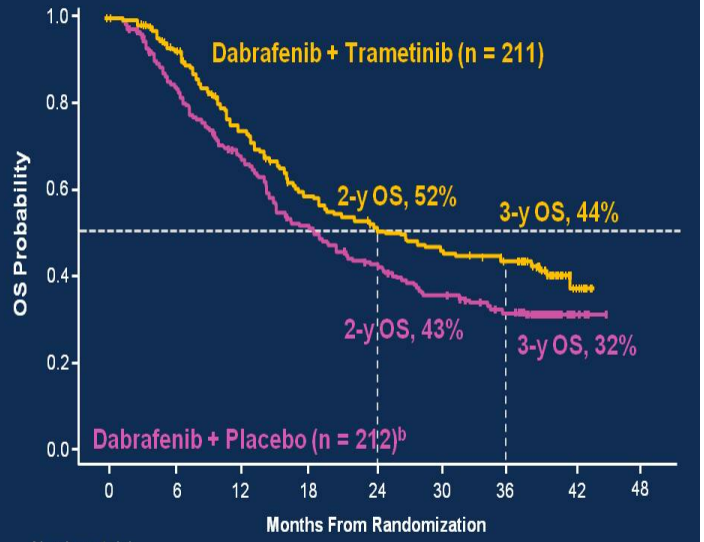
Progression-Free Survival



Number at risk

D+T	211	137	84	69	54	45	31	0	
D+Pbo	212	110	67	41	29	11	7	1	0

Overall Survival



Number at risk

D+T	211	187	143	111	96	86	76	13	0
D+Pbo	212	175	138	104	84	69	57	7	0

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

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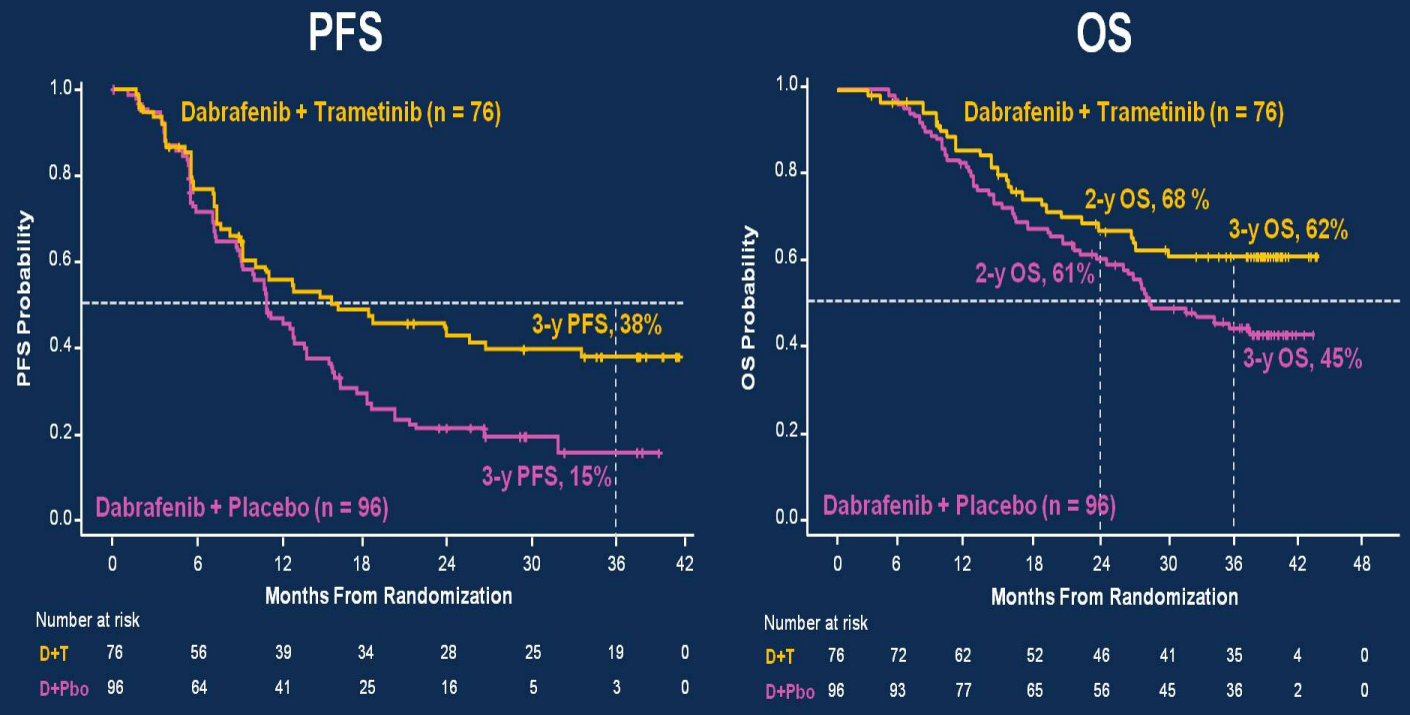
COMBI-d: Normal LDH[a] and < 3 Disease Sites[b]



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

Pyrexia managment

- 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

Australian context

Stage 3/resected stage 4

- Adjuvant therapy currently under consideration by PBAC

Stage 4

- BRAF mutant – dabrafenib/trametinib or vemurafenib/cobimetinib on PBS

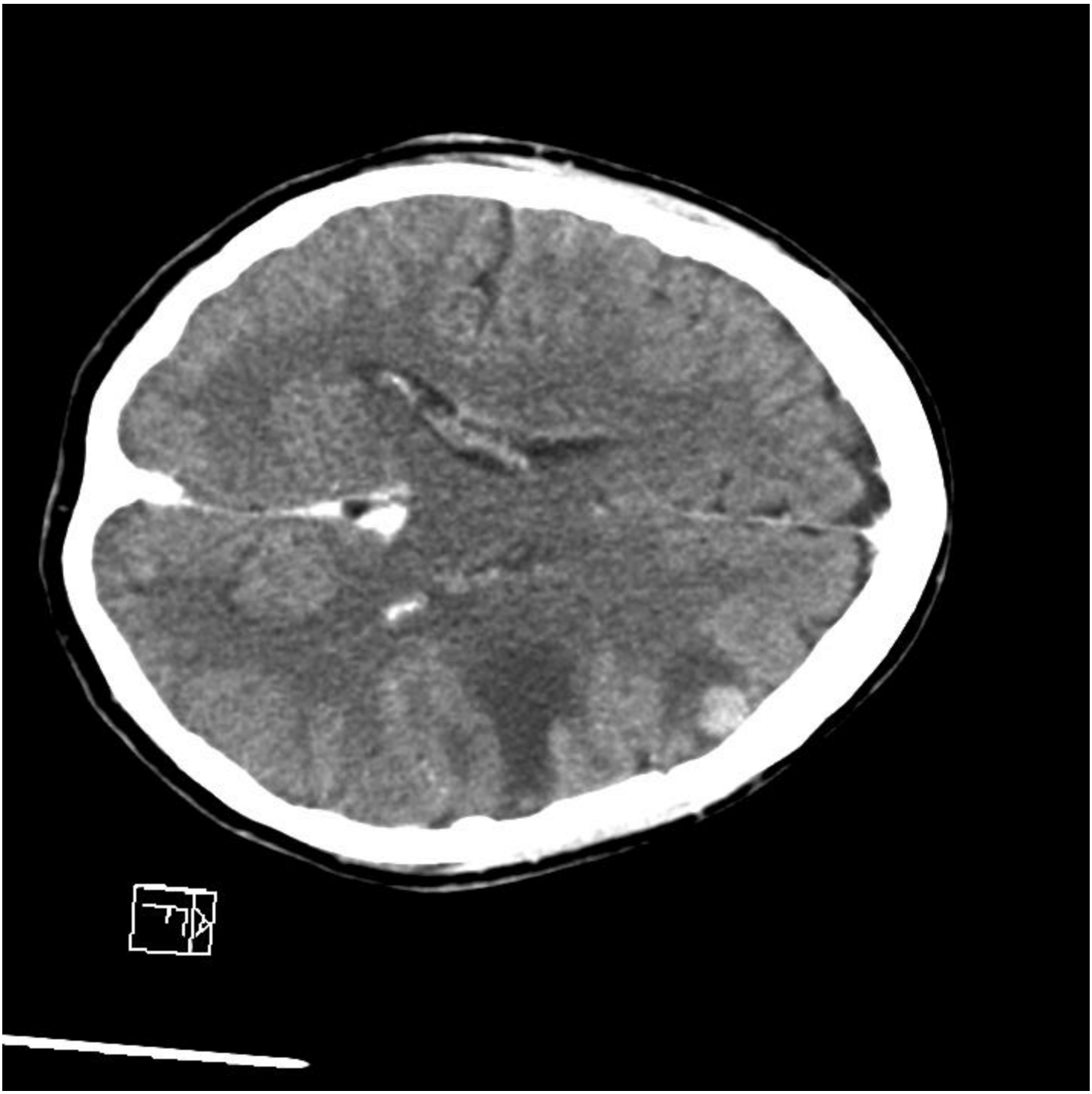
- BRAF wildtype – pembrolizumab/nivolumab on PBS
  - Compassionate access to Ipi/nivo combination

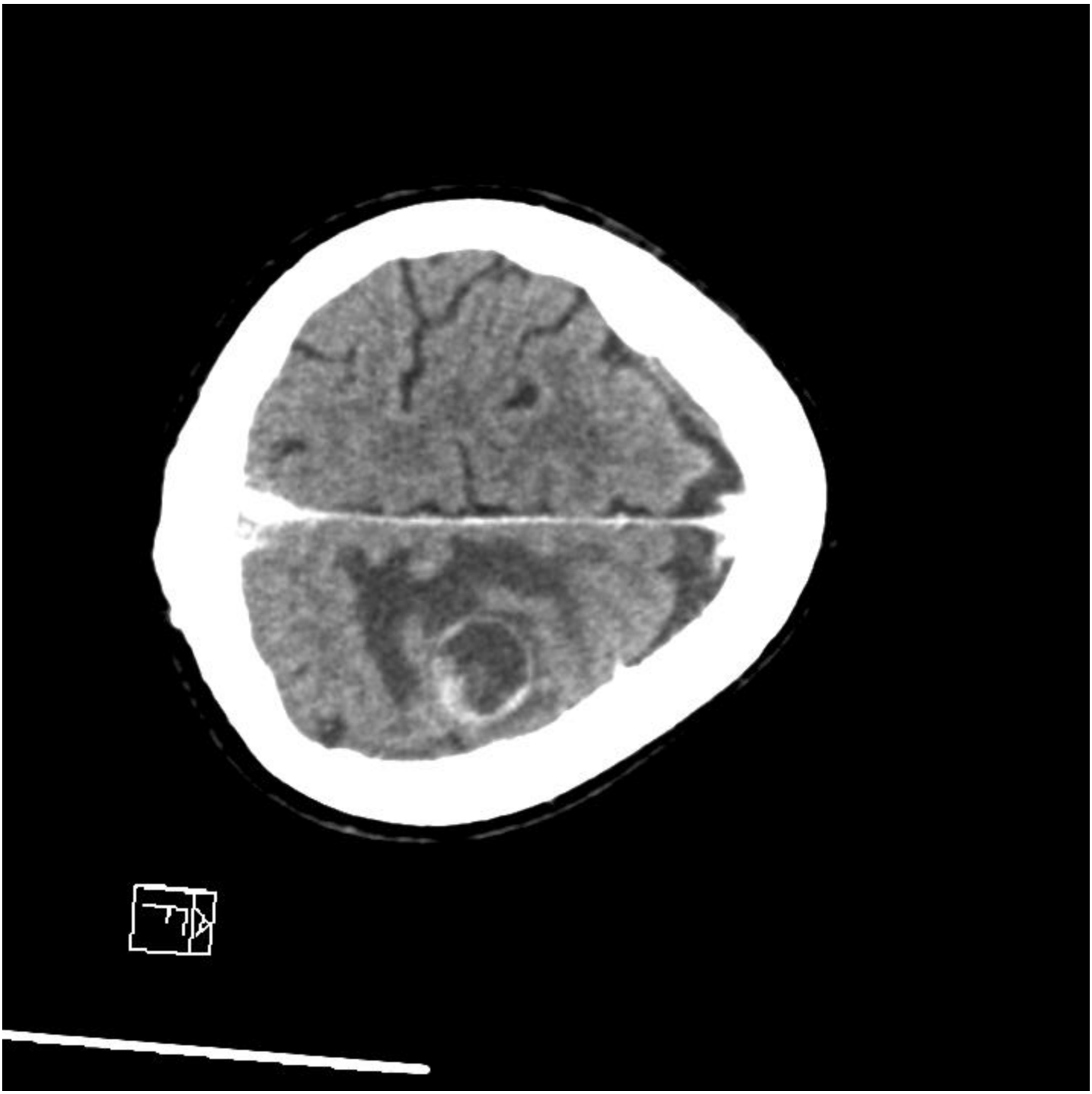
Australian context

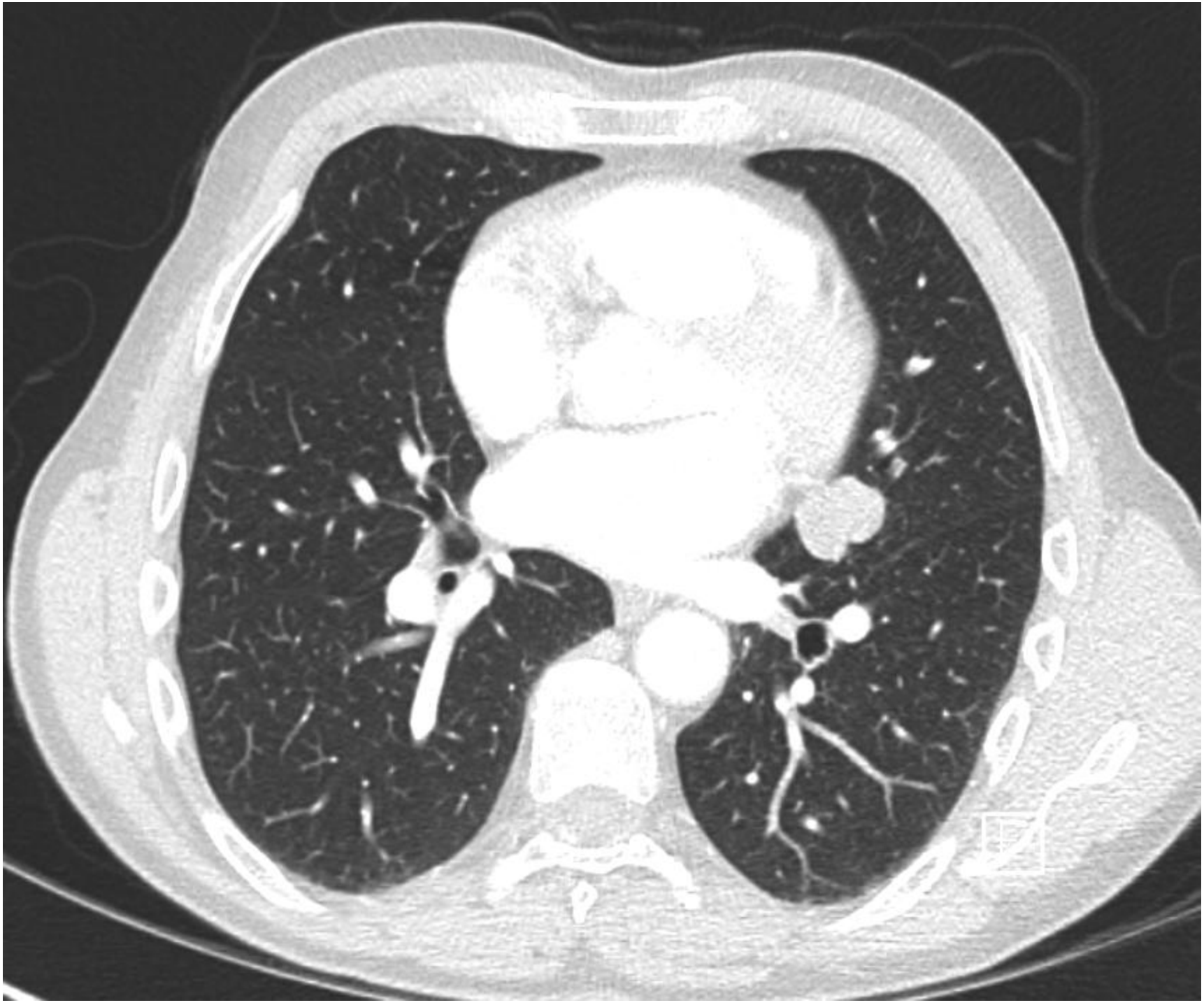
- Ongoing trials – PD1 +CTLA4
  Sequencing
  Combination braf/immunotherapy
  Immunotherapy plus other agents

Case

- 63 year old male
- Melanoma removed from shoulder 2013
- March 2015 presented with R arm weakness then seizures
- Imaging showed multiple brain mets as well as lung and mediastinal disease
- Bronchoscopy and biopsy confirmed metastatic melanoma
- BRAF wild type





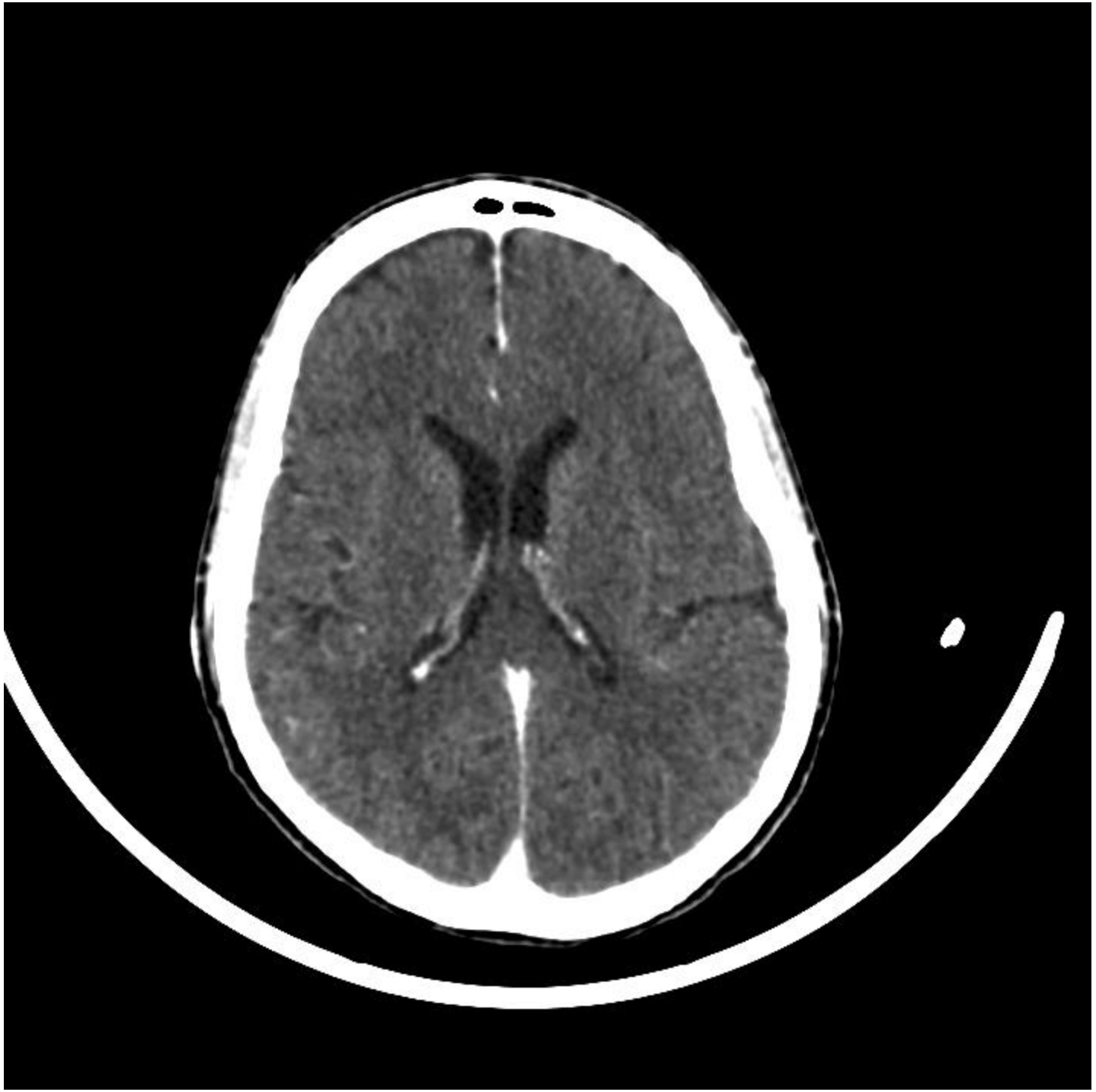


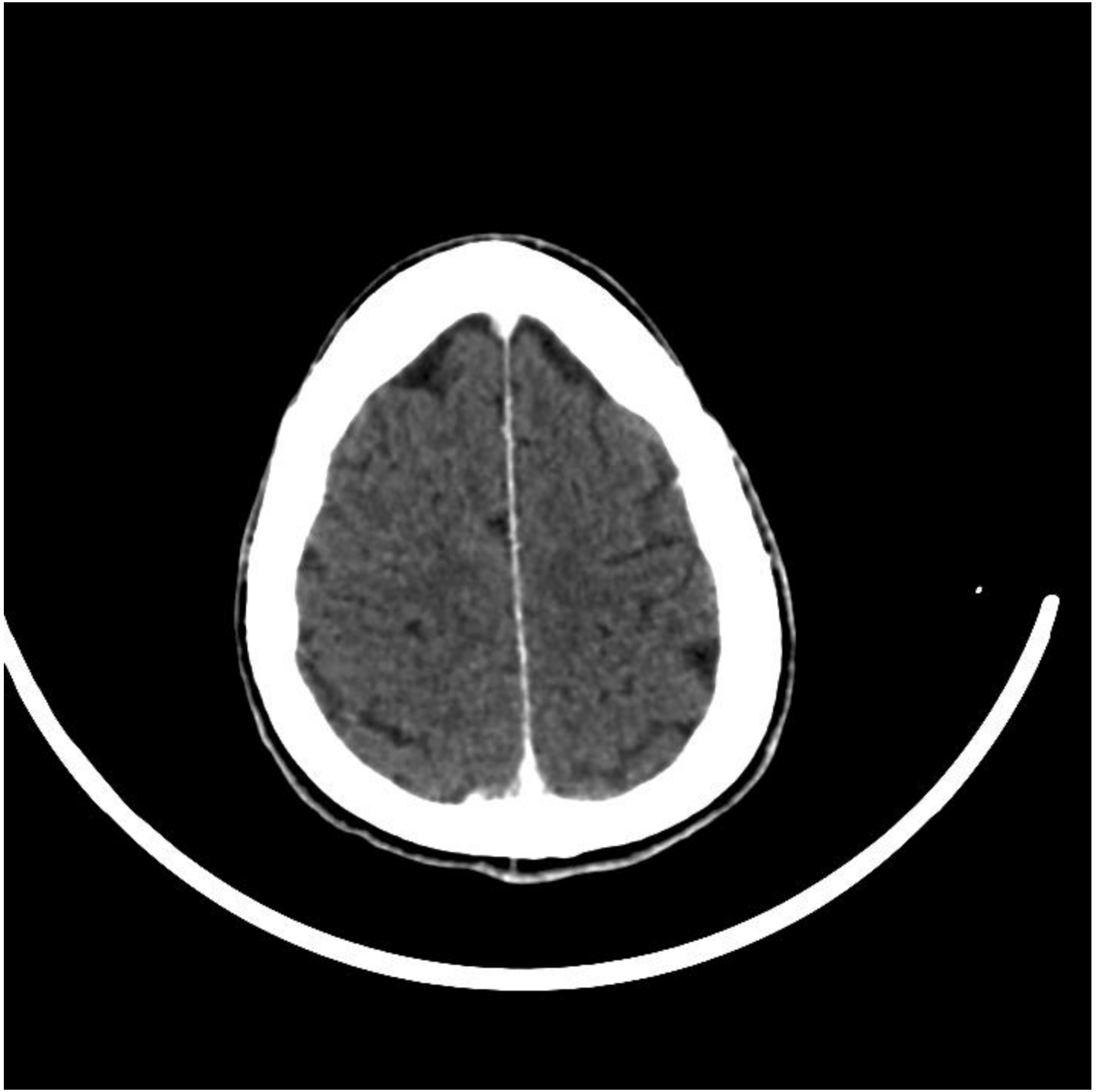
Case 1 cont'd

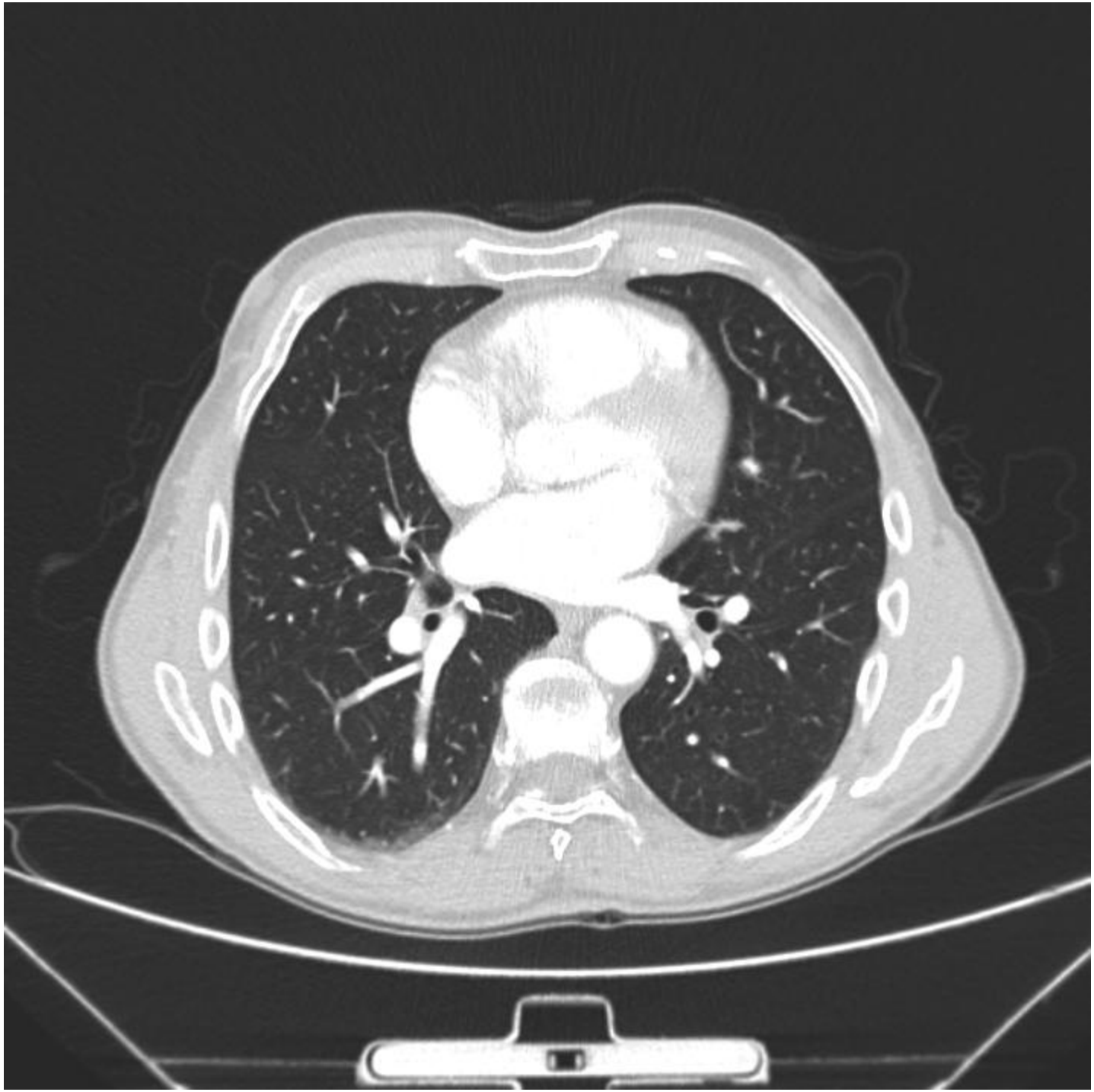
- Seizures controlled on dex/carbamazepine
- Started on pembrolizumab early May 2015
- Early June phone call from family – R arm weakness had worsened, some confusion
- Dexamethasone increased to 4mg bd
- Pembrolizumab continued
- July - arm weakness better, no seizures, dex reduced to 2mg daily then subsequently ceased

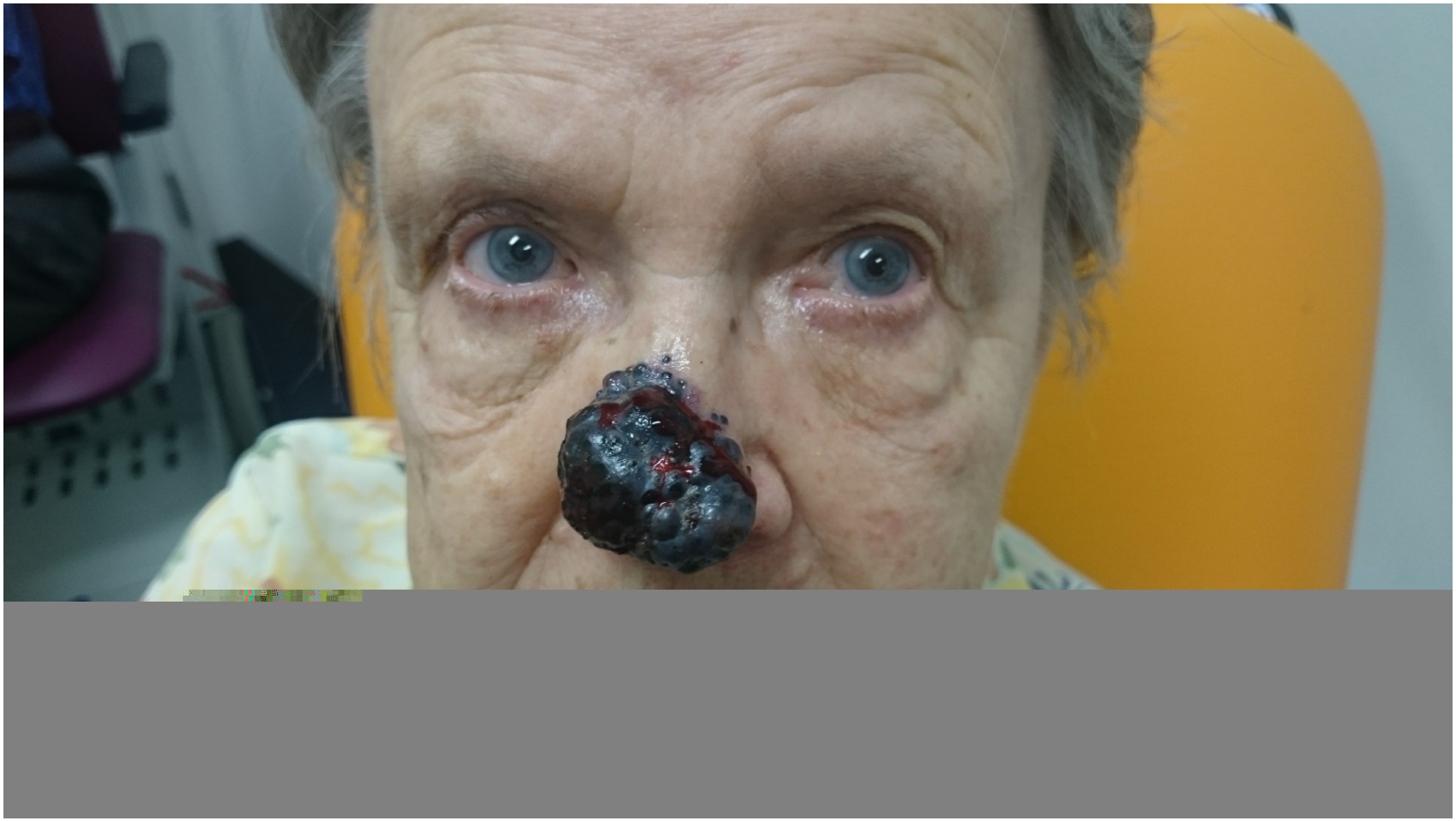
Case 1 cont'd

- Now:
  - Working in son's business
  - No seizures
  - Back driving
  - Near complete response on scans
    - PET no disease
    - MRI not quite normal
  - Toxicity: mild diarrhea
  - Treatment ceased







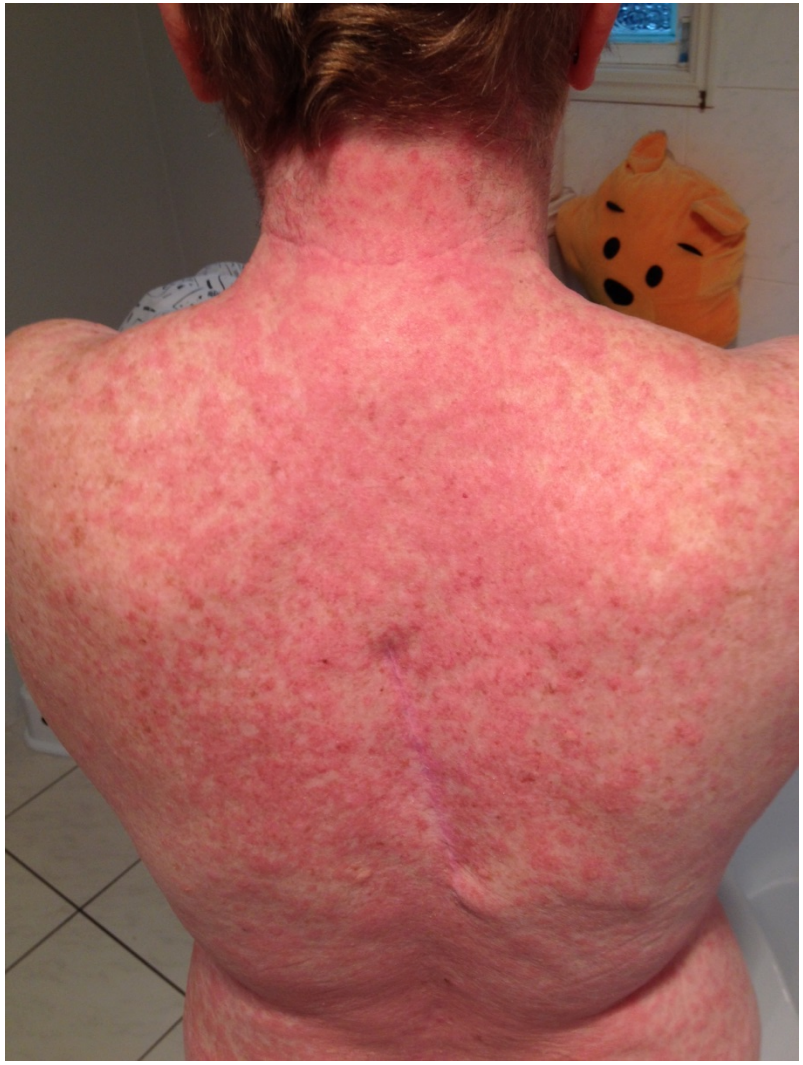


Autoimmune hepatitis

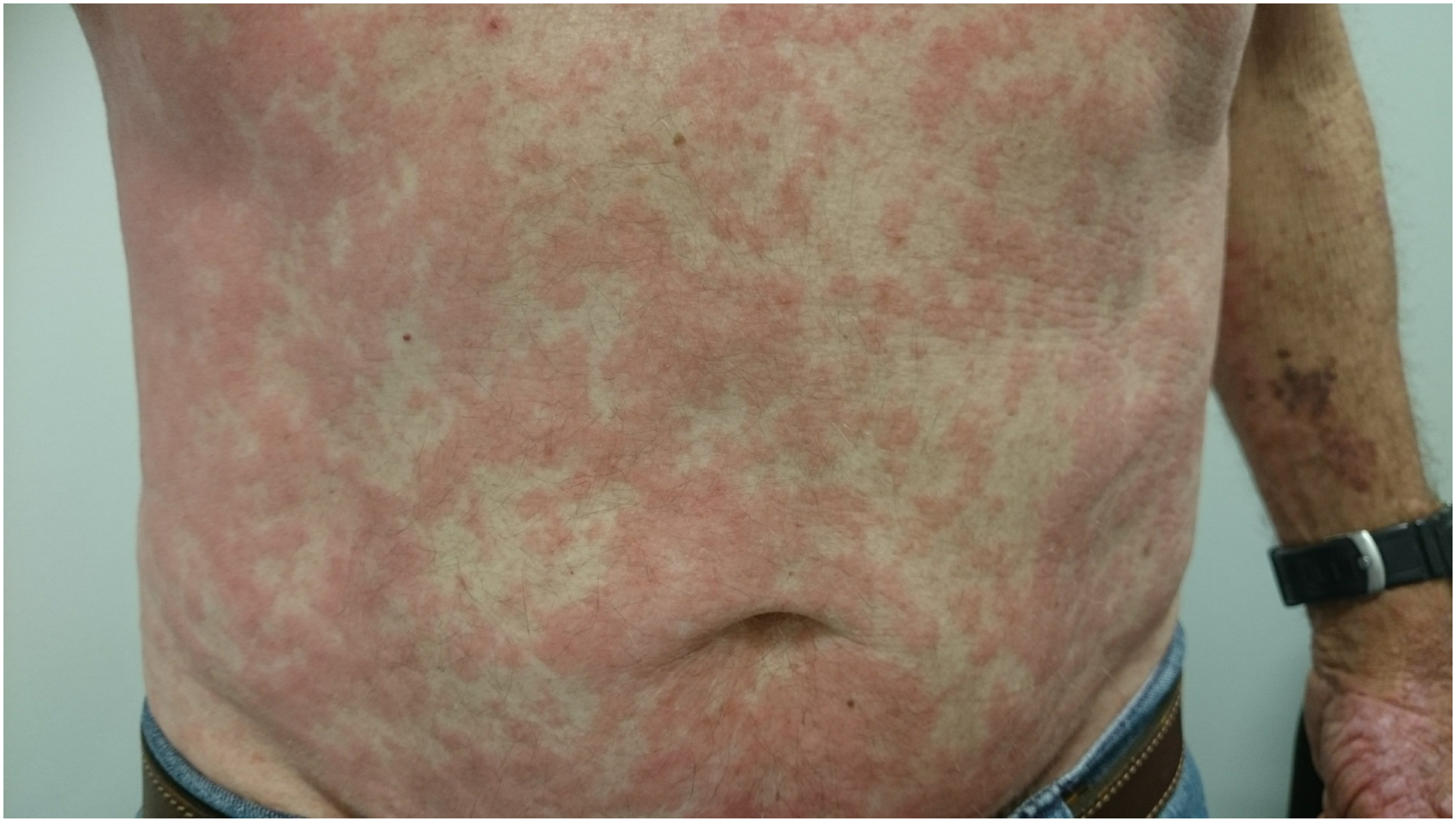
Urate	0.20	mmol/L	(0.15 - 0.50)
Protein	58 L	g/L	(60 - 80)
Albumin	34 L	g/L	(35 - 50)
Globulin	24 L	g/L	(25 - 45)
Bilirubin	29 H	umol/L	(< 20)
Bili(Conj)	10 H	umol/L	(< 4)
ALP	108	U/L	(30 - 110)
Gamma GT	177 H	U/L	(< 55)
ALT	1200 H	U/L	(< 45)
AST	218 H	U/L	(< 35)
LD	551 H	U/L	(120 - 250)
Calcium	2.21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



Question 1:

- How many people die in Australia each year from melanoma?
  a) 300
  b) 1600
  c) 10000

Answer

- 1600

Question 2:

- What is the 2 year survival for someone with metastatic melanoma treated with immunotherapy?
  a) 10%
  b) 30%
  c) 55%

Answer

- 55%