Metastatic Melanoma New therapies and their toxicities

Melissa Eastgate

Deputy Director Medical Oncology

RBWH

23 July 2016

Melanoma Incidence in Australia

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

AJCC Staging System for Cutaneous Melanoma

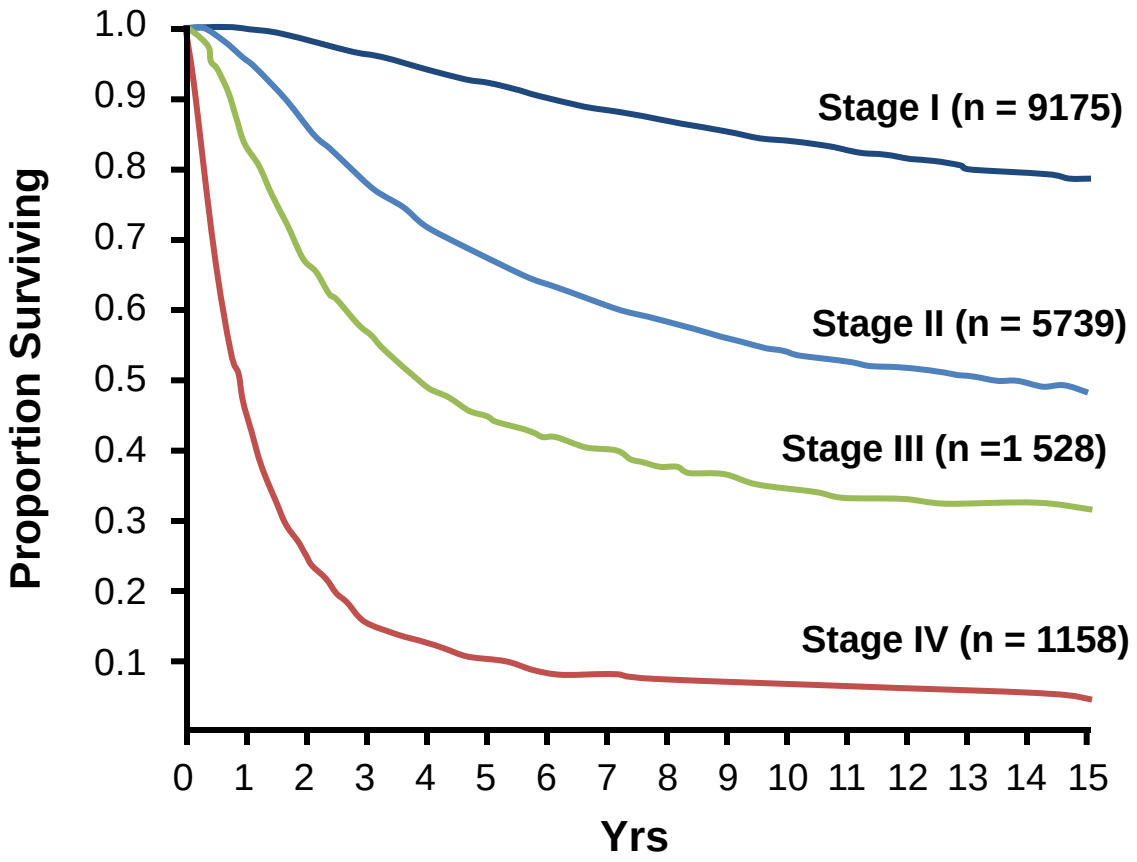
	Thickness	Ulceration Status/Mitoses
T1	≤ 1.0 mm	a: without + mitosis < 1/mm^2, b: with or mitoses ≥ 1/mm^2
T2	1.01- 2 mm	a: without, b: with
T3	2.01- 4 mm	a: without, b: with
T4	>4.0 mm	a: without, b: with

	Met. Nodes, n	Nodal Met. Mass
N1	1 node	a: micro, b: macro
N2	2-3 nodes	a: micro, b: macro, c: in-transit/satellites without metastatic nodes
N3	≥ 4, matted nodes, or in-transit or satellite(s) with metastatic nodes	

	Site	LDH
M1a	Distant skin, SQ, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated

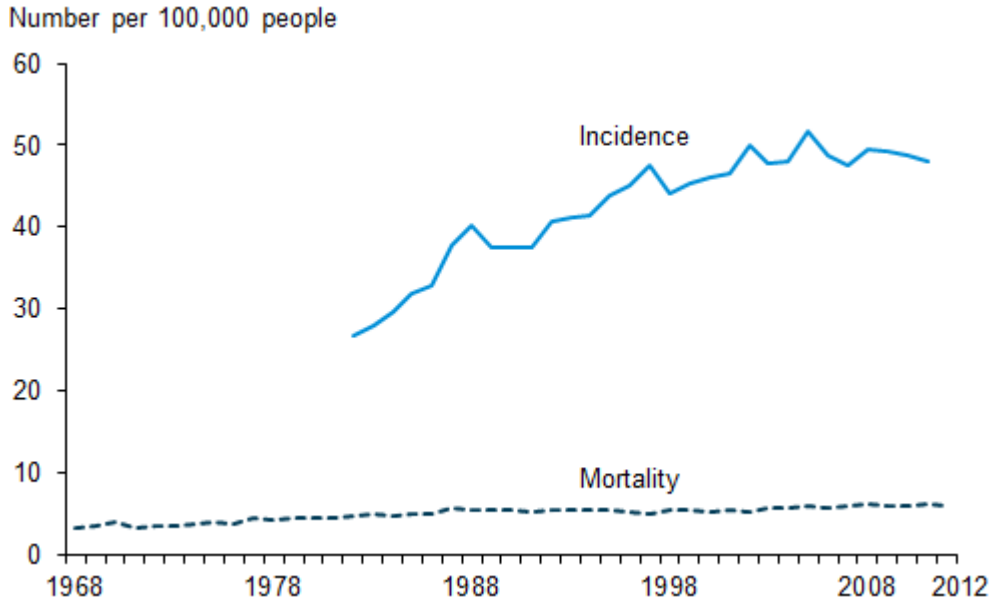
Balch CM, et al. J Clin Oncol. 2009;27:6199-206.

Survival in Melanoma by Stage



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

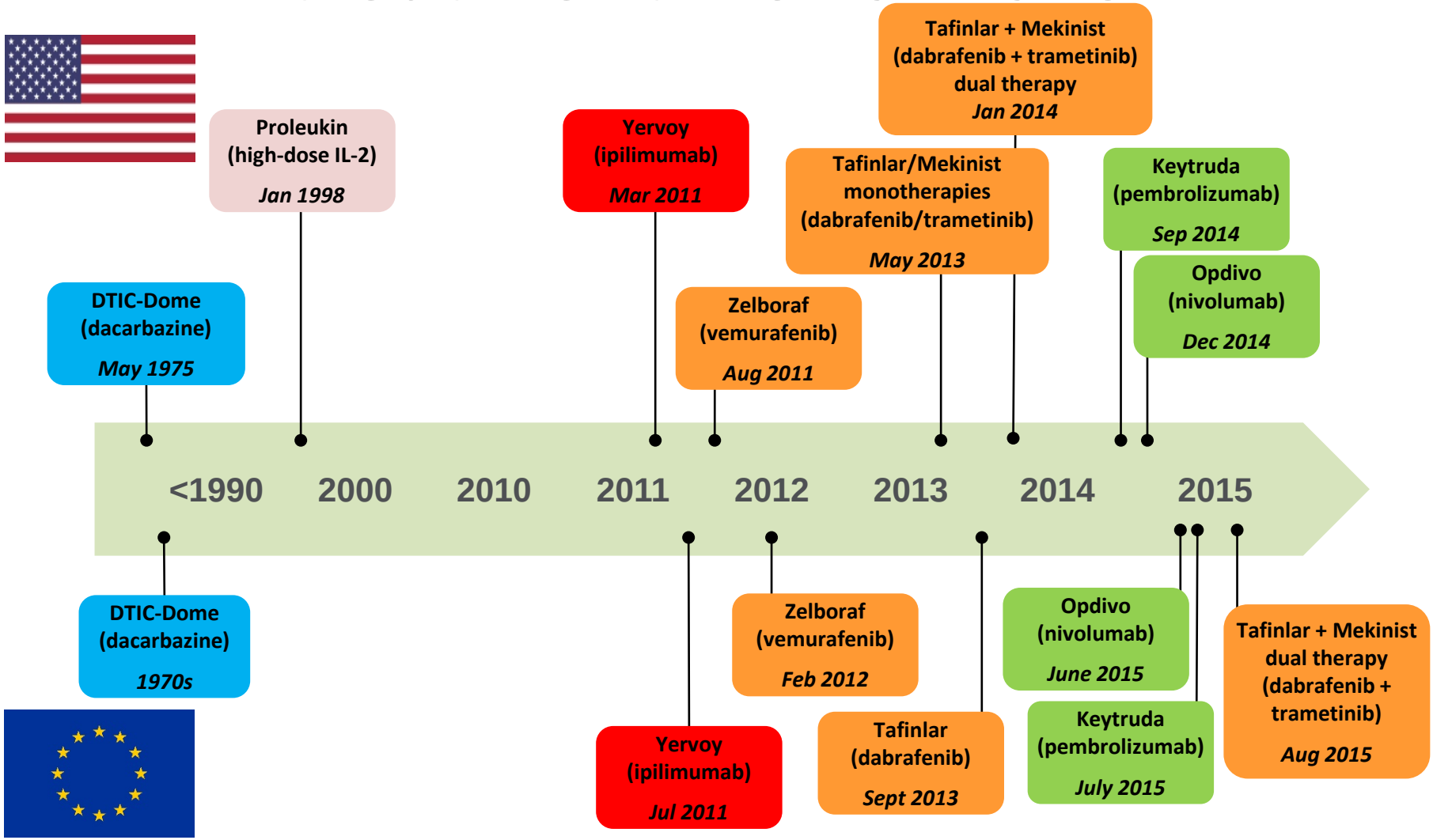
Melanoma skin cancer incidence and mortality, 1968 to 2012



Where can we make a difference?

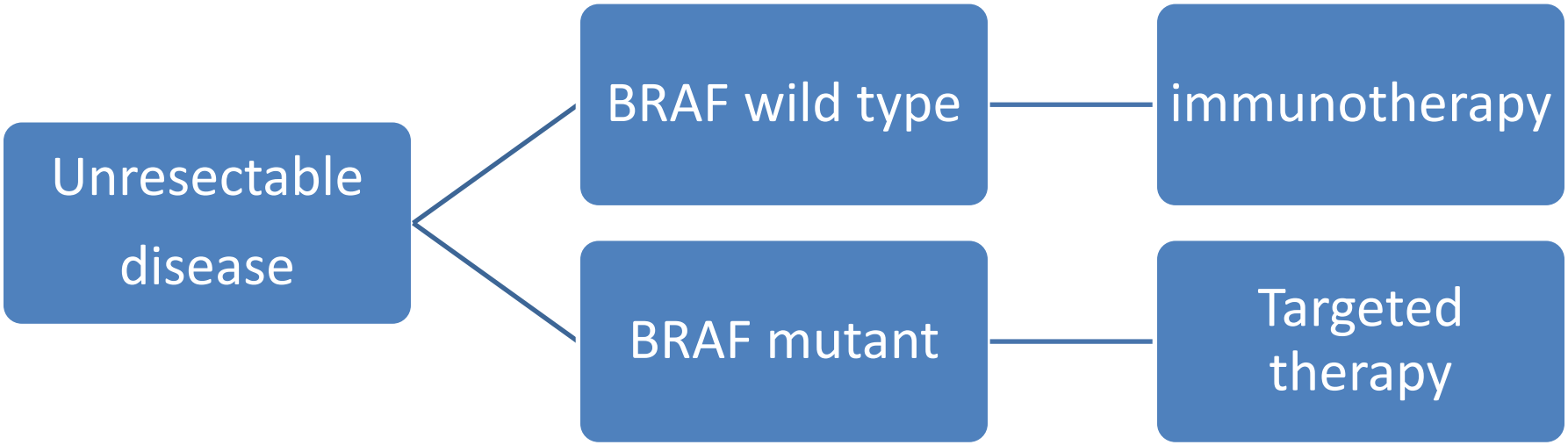
- Prevention/early detection
- Better neo/adjuvant therapy
- Improved treatment in the advanced setting.
  - Downstage to enable curative treatment
  - Picking the right treatment for the right patient
  - Prolong overall survival
- Reduced toxicity of treatment

Metastatic melanoma available treatment: 1970–2015



Current paradigm in metastatic melanoma

50%, Older patients, chronic sun damage



50%, Younger patients

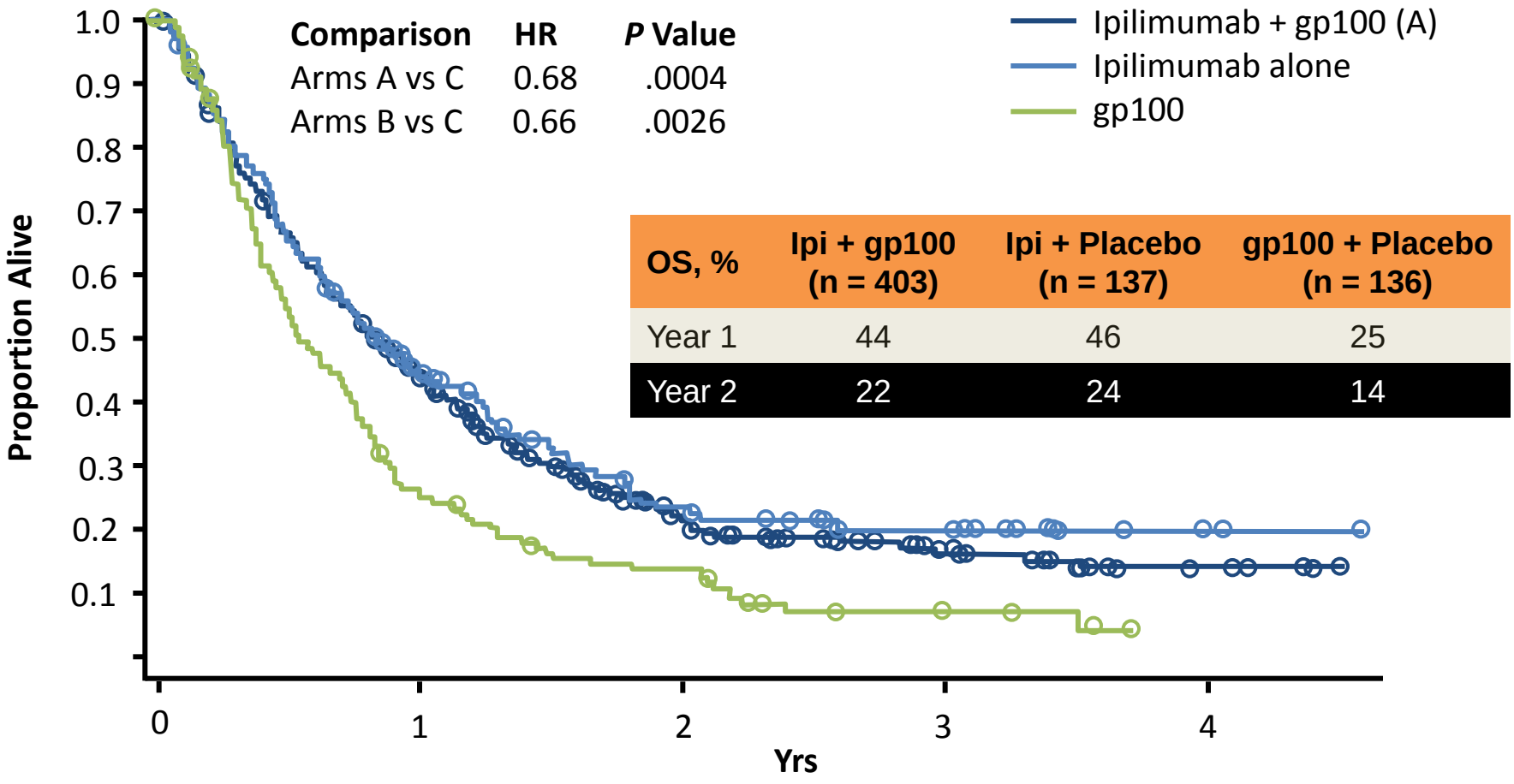
IMMUNOTHERAPY

Tumor-Derived Immune Suppression

- Tumors go to great lengths to evade the immune response
- Systematic studies have identified multiple mechanisms cancers employ to defeat the immune response
  - Immunosuppressive cytokines: TGF-β, IL-4, -6, -10
  - Immunosuppressive immune cells: T-regs, macrophage
  - Disruption of immune activation signaling: loss of MHC receptor, IDO production
- Goal: therapy strategies that "**liberate**" underlying anticancer immune responses
- Immune checkpoints not even in the picture in 2008!

Weiner LM. N Engl J Med. 2008;358:2664-2665.

Ipilimumab, gp100, or Both in Advanced Melanoma (MDX010-20): Survival



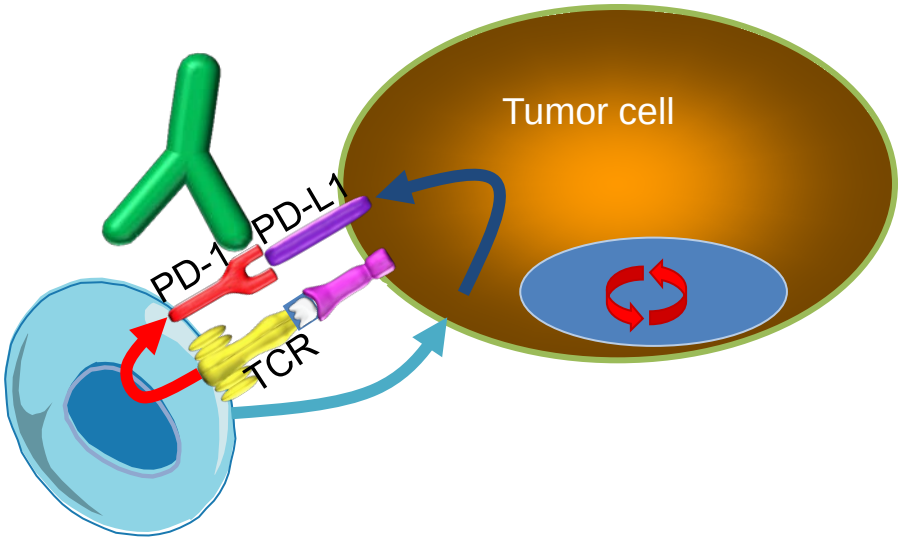
OS, %	Ipi + gp100 (n = 403)	Ipi + Placebo (n = 137)	gp100 + Placebo (n = 136)
Year 1	44	46	25
Year 2	22	24	14

Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Ipilimumab (checkpoint inhibitor)

- Increased long term survival for a small number of patients
- Significant toxicity

PD-1 Adaptive Resistance to Immunotherapy



- PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)[1,2]
  - PD-1:PD-L1 interaction results in T cell suppression (anergy, exhaustion, death)
- In RCC, melanoma, and other tumors, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features, eg, more aggressive disease and shorter survival[3]

1. Topalian SL, et al. Curr Opin Immunol. 2012;24:207-212. 2. Taube JM, et al. Sci Transl Med. 2012;4:127ra37. 3. Thompson RH, et al. Proc Natl Acad Sci USA. 2004;101:17174-17179.

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]

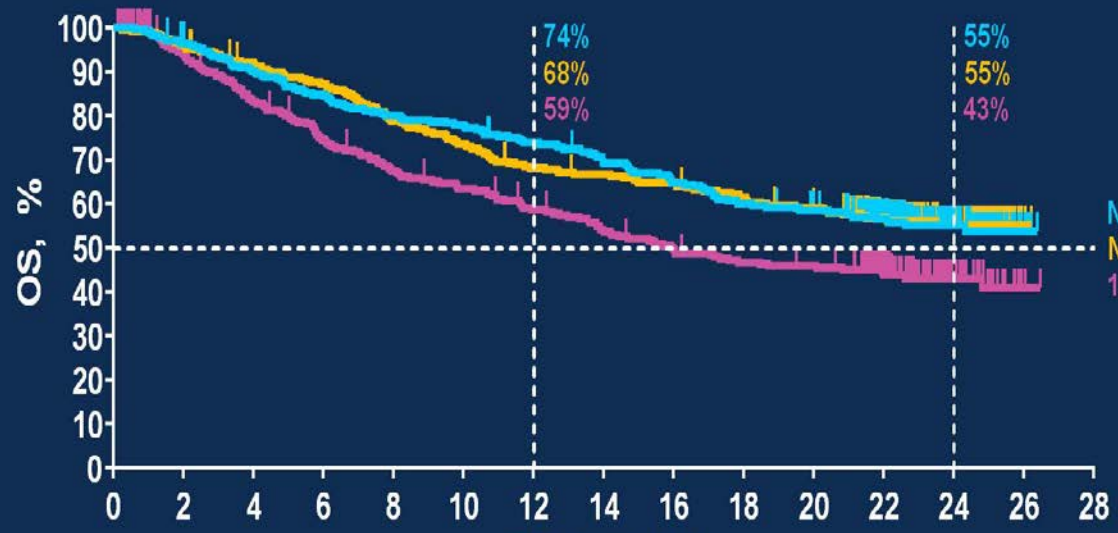
[1]Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer, Israel; [2]University of California, Los Angeles, Los Angeles, CA; [3]Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital, Sydney, Australia; [4]Hospital Clinic de Barcelona, 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	—	—

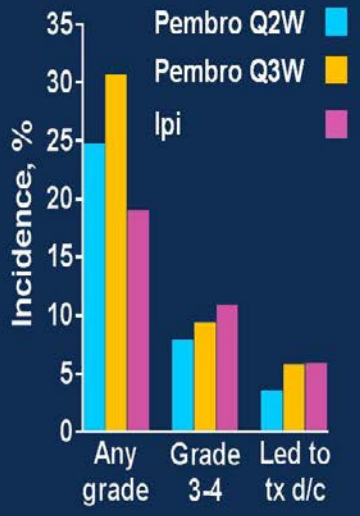


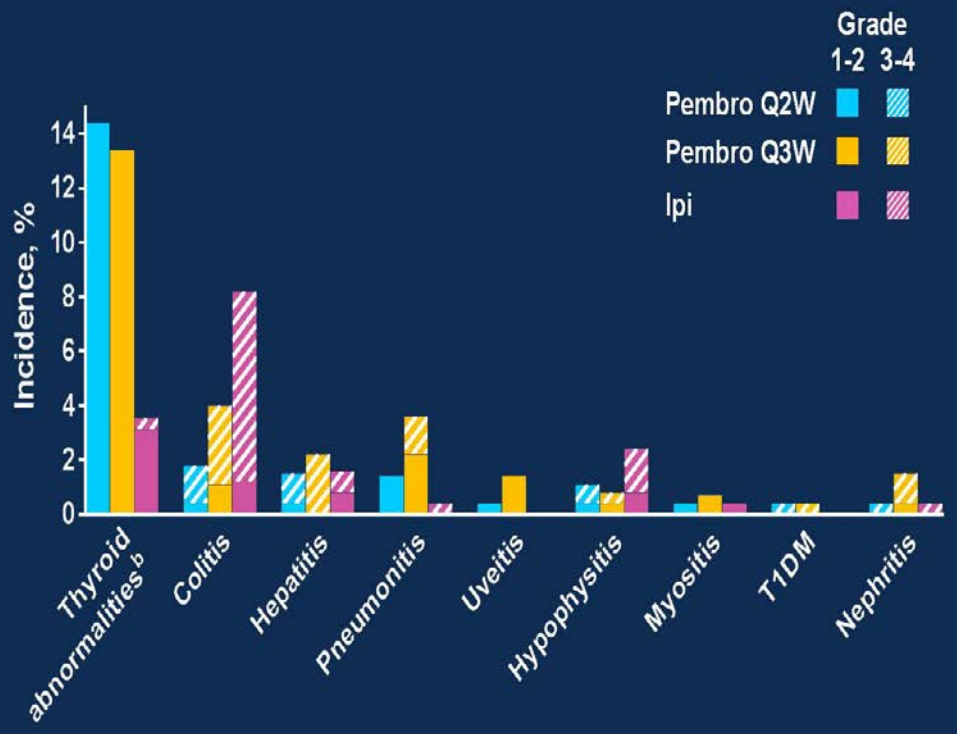
No. at risk

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

Final analysis data cutoff date: Dec 3, 2015.

Incidence of Immune-Mediated AEs[a]





[a]Not adjusted for exposure. Immune-mediated AEs are based on a list of terms specified by the sponsor and were considered regardless of attribution by the investigator. Includes hyper- and hypothyroidism and thyroiditis. Final analysis data cutoff date: Dec 3, 2015.

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

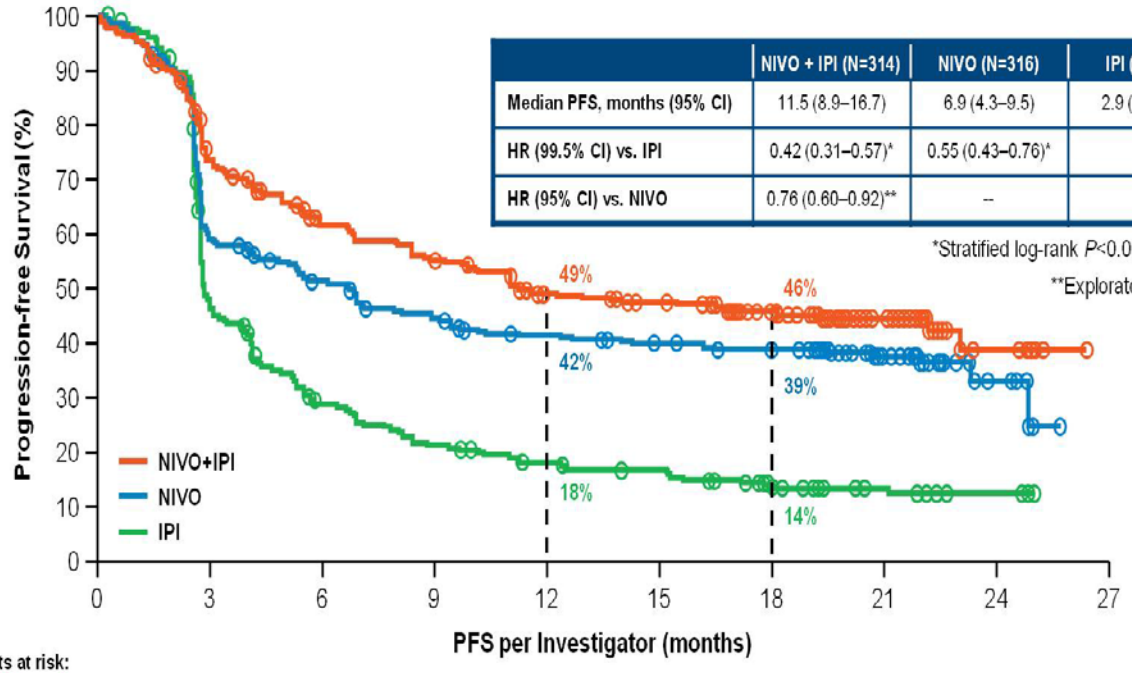
Jedd D. Wolchok,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15] 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

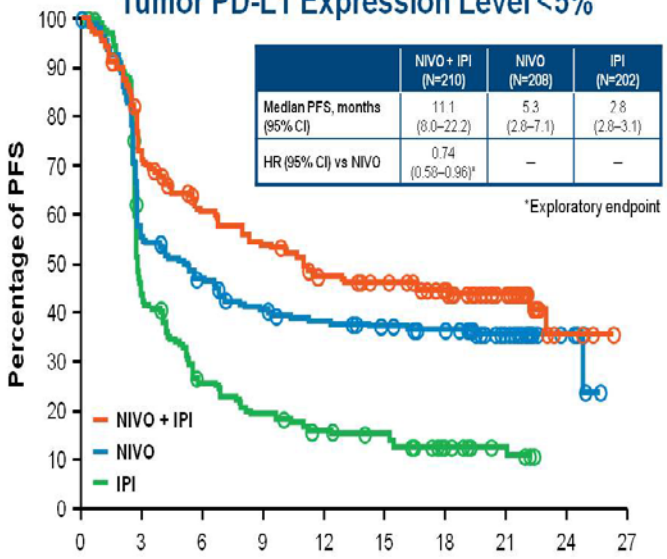
Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

Progression-free Survival by Tumor PD-L1 Expression

Tumor PD-L1 Expression Level <5%

	NIVO + IPI (N=210)	NIVO (N=208)	IPI (N=202)
Median PFS, months (95% CI)	11.1 (8.0–22.2)	5.3 (2.8–7.1)	2.8 (2.8–3.1)
HR (95% CI) vs NIVO	0.74 (0.58–0.96)*	–	–

*Exploratory endpoint

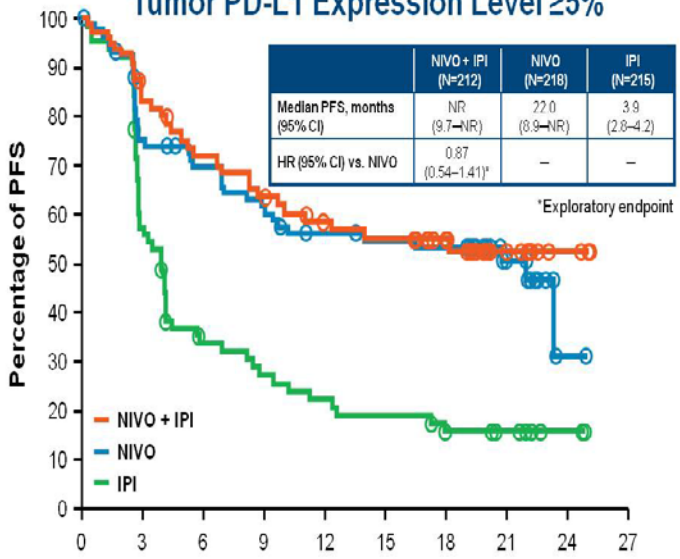


Number of patients at risk:										
NIVO + IPI	210	142	113	101	86	81	69	31	5	0
NIVO	208	108	89	75	69	62	55	29	7	0
IPI	202	82	45	34	26	22	12	7	0	0

Tumor PD-L1 Expression Level ≥5%

	NIVO + IPI (N=212)	NIVO (N=218)	IPI (N=215)
Median PFS, months (95% CI)	NR (9.7–NR)	22.0 (8.9–NR)	3.9 (2.8–4.2)
HR (95% CI) vs. NIVO	0.87 (0.54–1.41)*	–	–

*Exploratory endpoint



Number of patients at risk:										
NIVO + IPI	68	53	44	39	33	31	22	13	3	0
NIVO	80	57	51	45	39	37	36	16	1	0
IPI	75	40	21	17	14	12	8	6	2	0

- For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months)

Database lock Nov 2015

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting

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

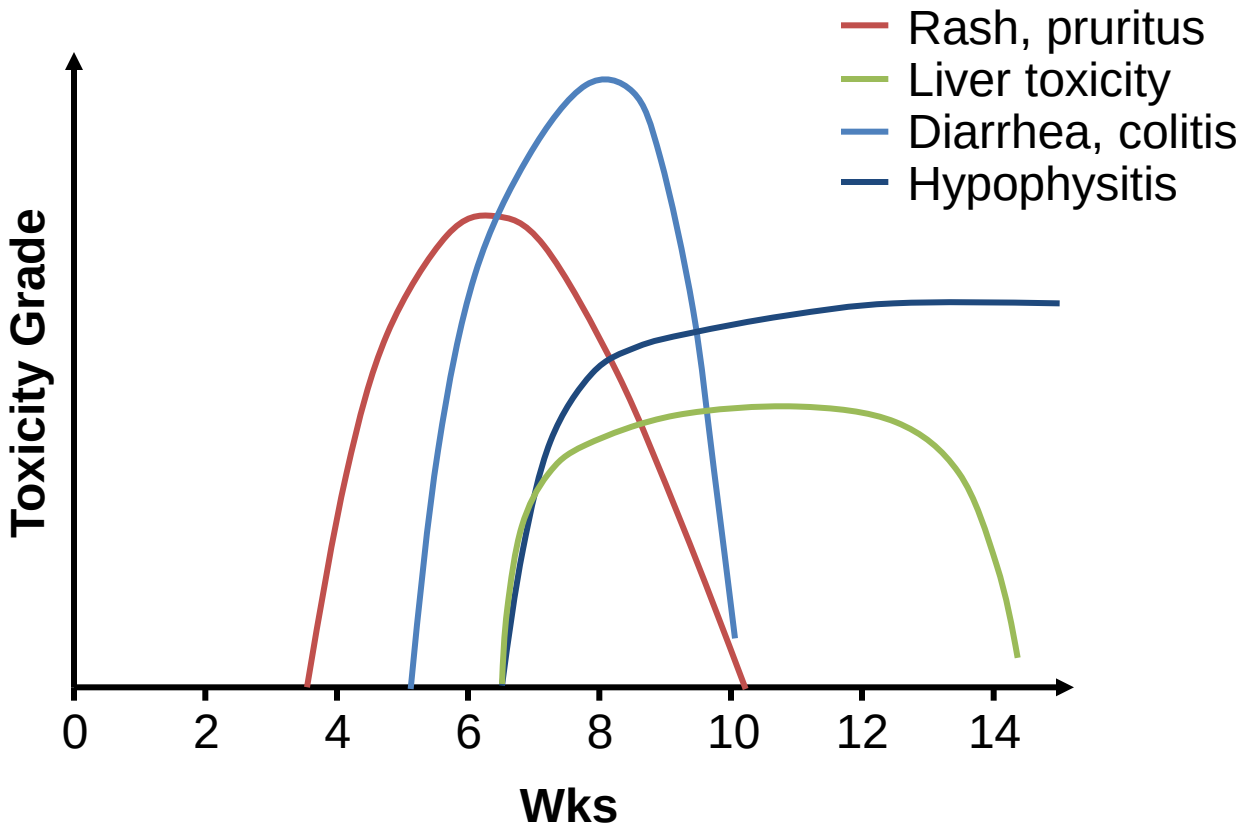
Neurologic
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia gravis–like syndrome

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



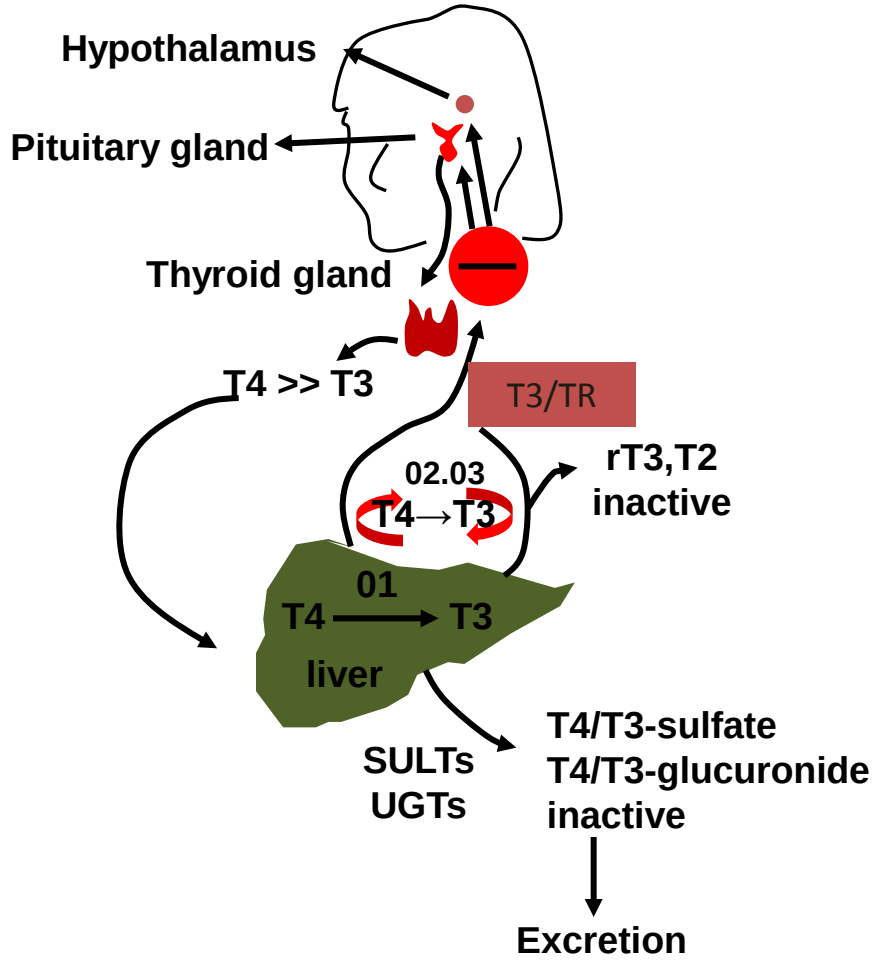
Combined analysis of 325 participants with 10 mg/kg IV q3w x 4

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



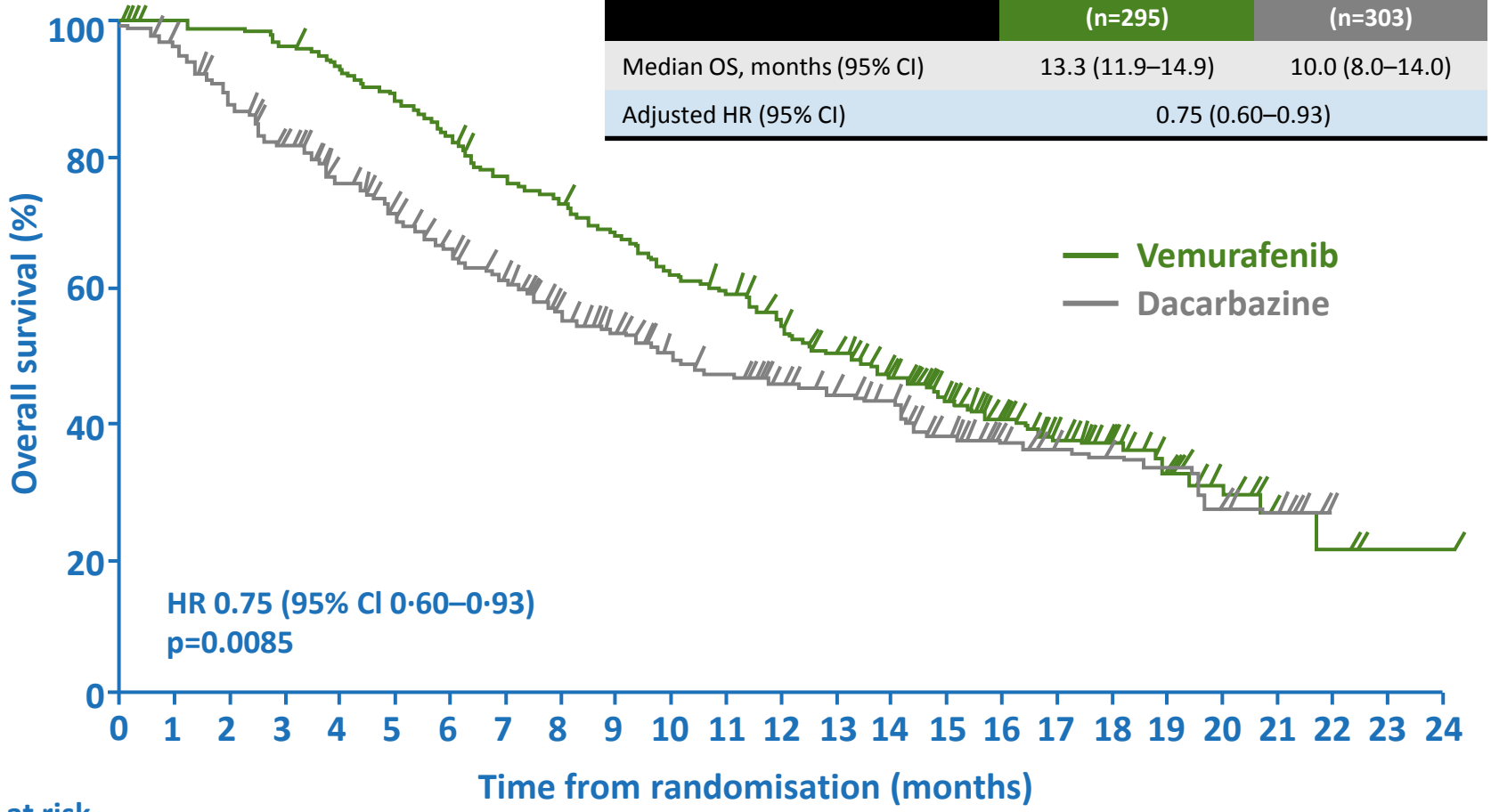
Corsello SM, et al. J Clin Endocrinol Metab. 2013;98:1361-1375.

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

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

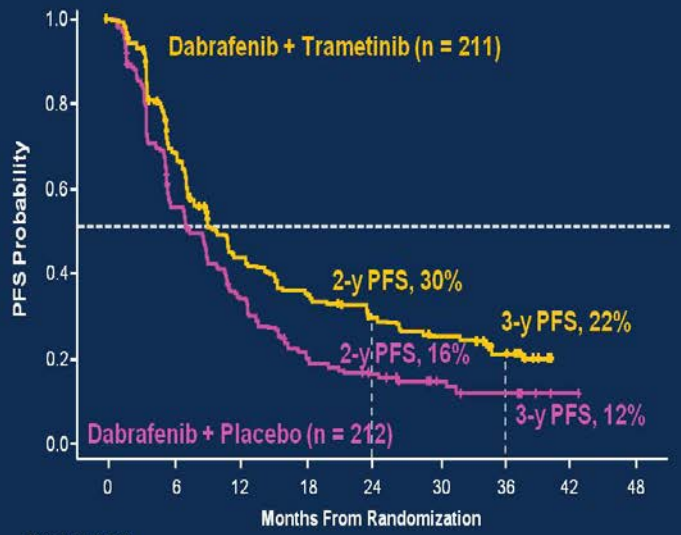
PRESENTED AT: ASCO ANNUAL MEETING '16

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

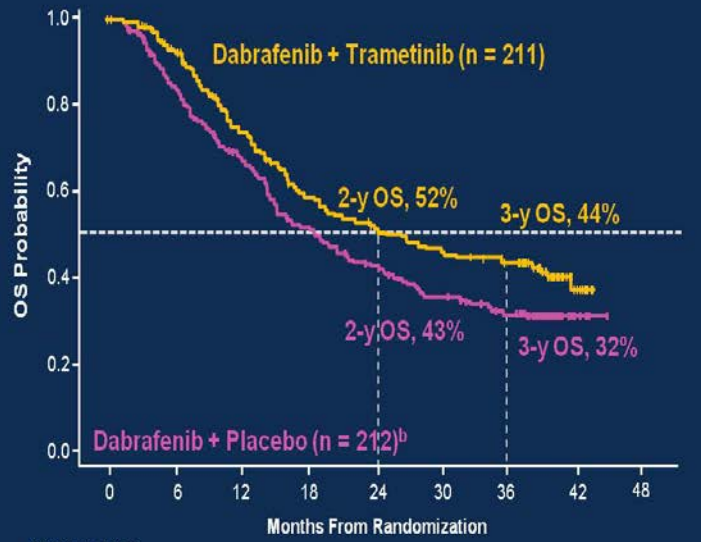
Progression-Free Survival



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

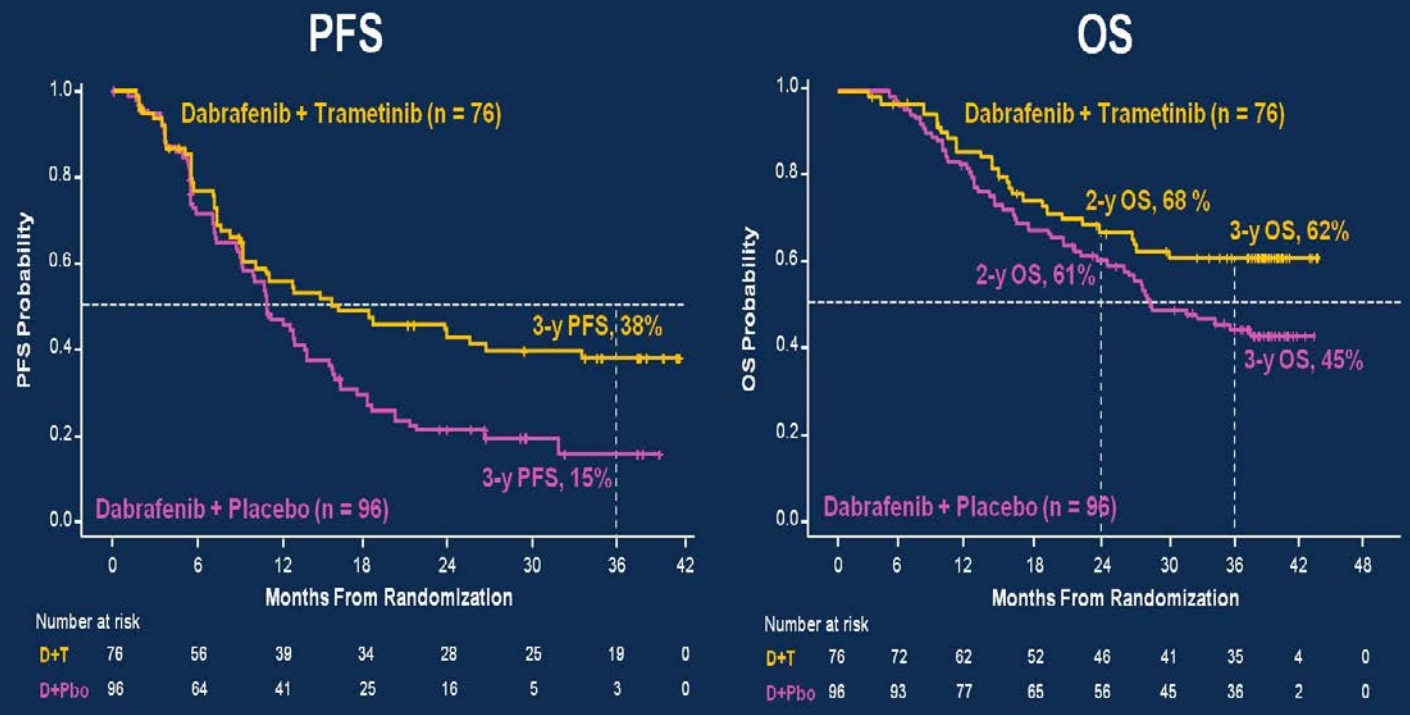


Number at risk

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.

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.

Conclusions

- With additional follow-up, dabrafenib + trametinib continued to show significant benefit over dabrafenib monotherapy despite cross-over
  - 3-year OS, 44% vs 32%
  - 3-year PFS, 22% vs 12%
- Best 3-year outcome with dabrafenib + trametinib was observed in patients with normal LDH and < 3 disease sites
  - 3-year OS, 62%
  - 3-year PFS, 38%
- The safety profile was similar to previous reports for dabrafenib + trametinib, with no unexpected toxicities
- Longest OS follow-up among randomized phase 3 trials evaluating BRAFi + MEKi in patients with *BRAF*-mutant metastatic melanoma

Most Common AEs With Approved Targeted Agents in Advanced Melanoma

AE (≥ Grade 2), %	Vemurafenib[1]	Dabrafenib[2]	Trametinib[3]
Arthralgia	21	5	NR
Rash	18	NR	27
Fatigue	13	6	9
Cutaneous SCC/ keratoacanthoma	12/8	6 (combined)	NR
Hyperkeratosis	6	13	NR
Pyrexia	NR	Pyrexia	NR
Headache	5	5	NR
Photosensitivity (any grade)	12	3	NR
Hypertension	NR	NR	12

1. Chapman PB, et al. N Engl J Med. 2011;364:2507-2516. 2. Hauschild A, et al. Lancet. 2012;380:358-365. 3. Flaherty KT, et al N Engl J Med. 2012;367:107-114.

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

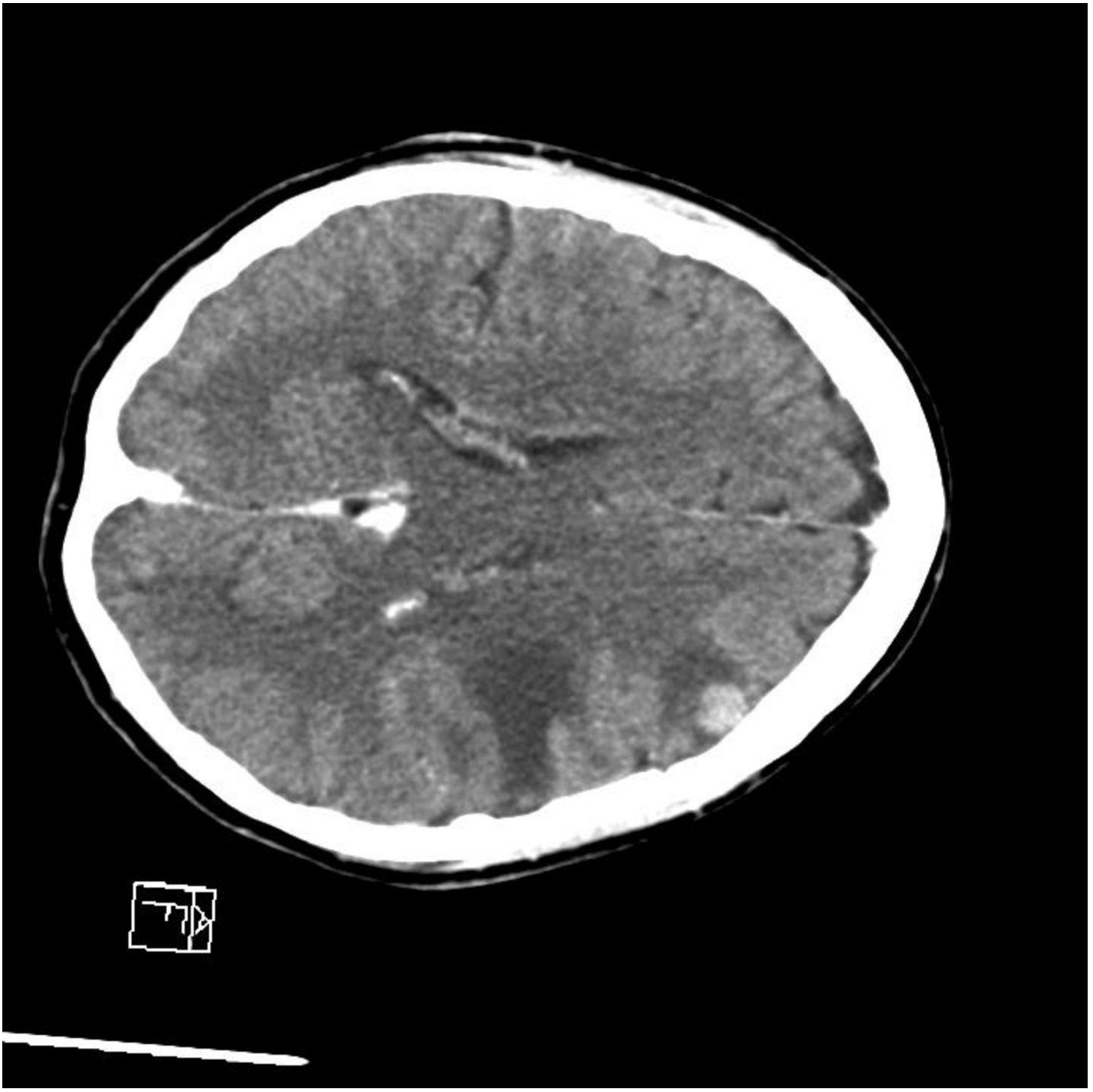
  once resolved can safely restart therapy

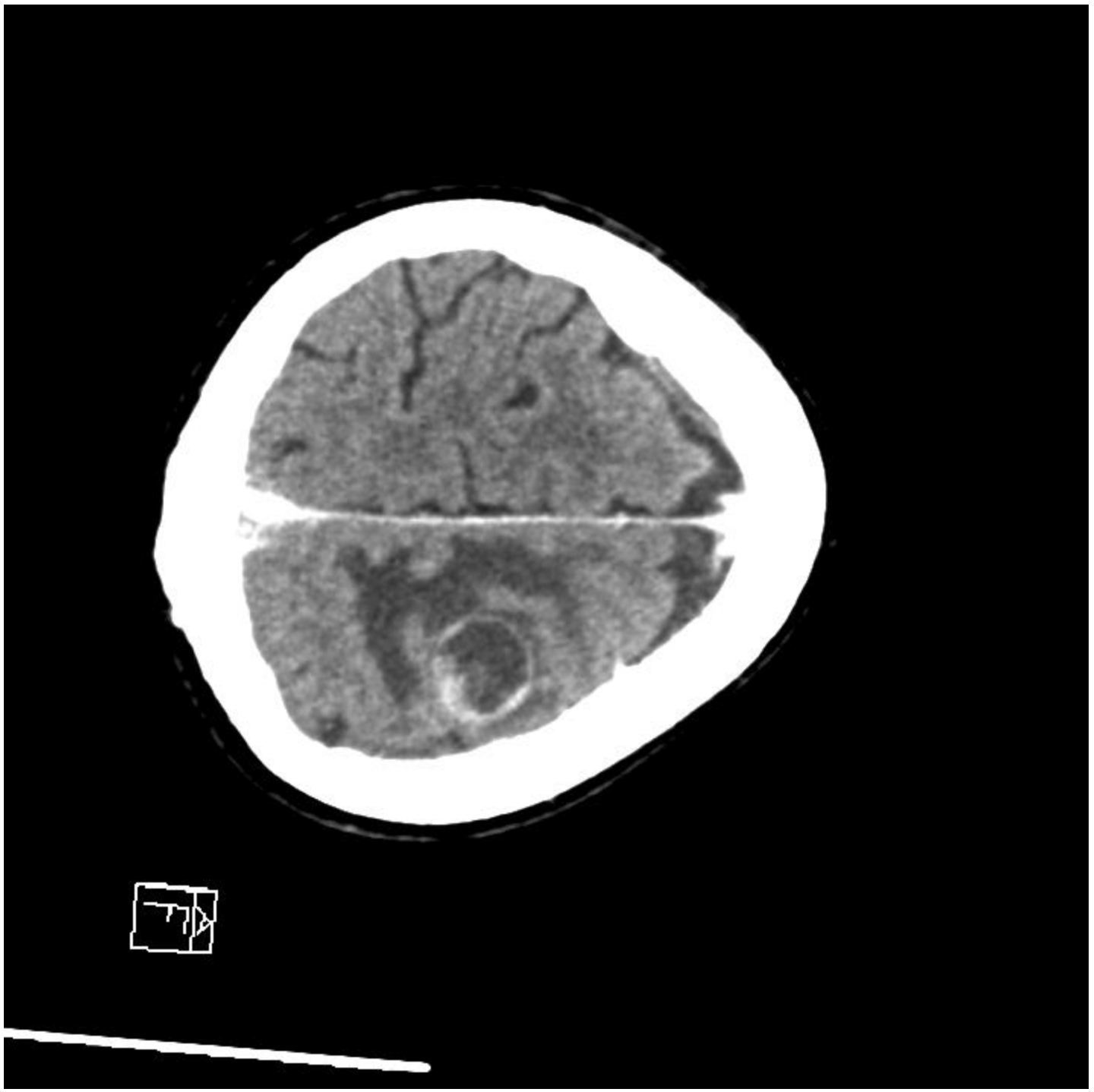
Australian context

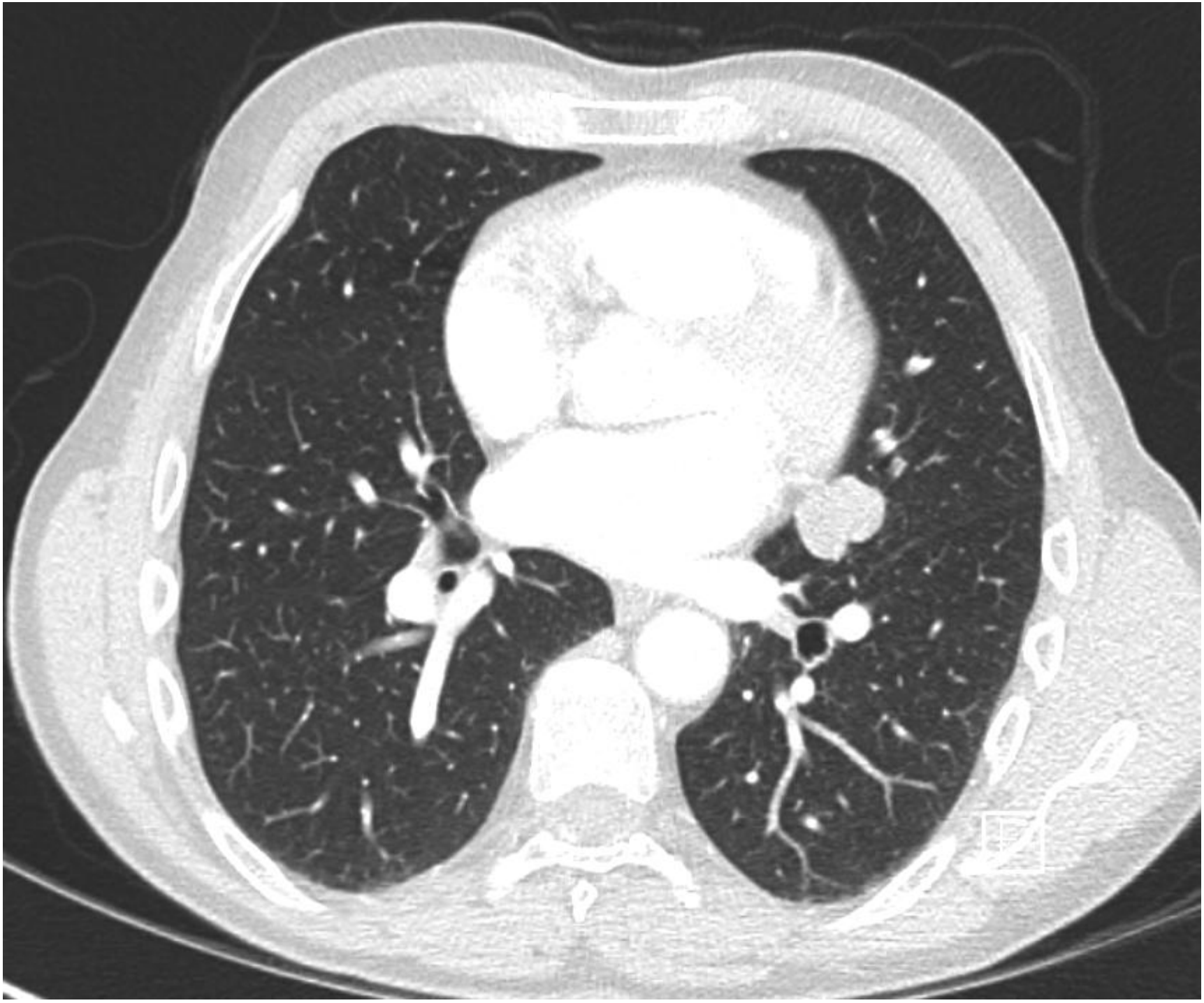
- BRAF mutant – dabrafenib and trametinib on PBS
- BRAF wildtype – pembrolizumab/nivolumab on PBS
- Ongoing trials – PD1 +CTLA4
  Adjuvant PD1
  Adjuvant CTLA4
  Adjuvant BRAF inhibitor
  Sequencing
  Combination braf/immunotherapy

Case 1 - immunotherapy

- 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





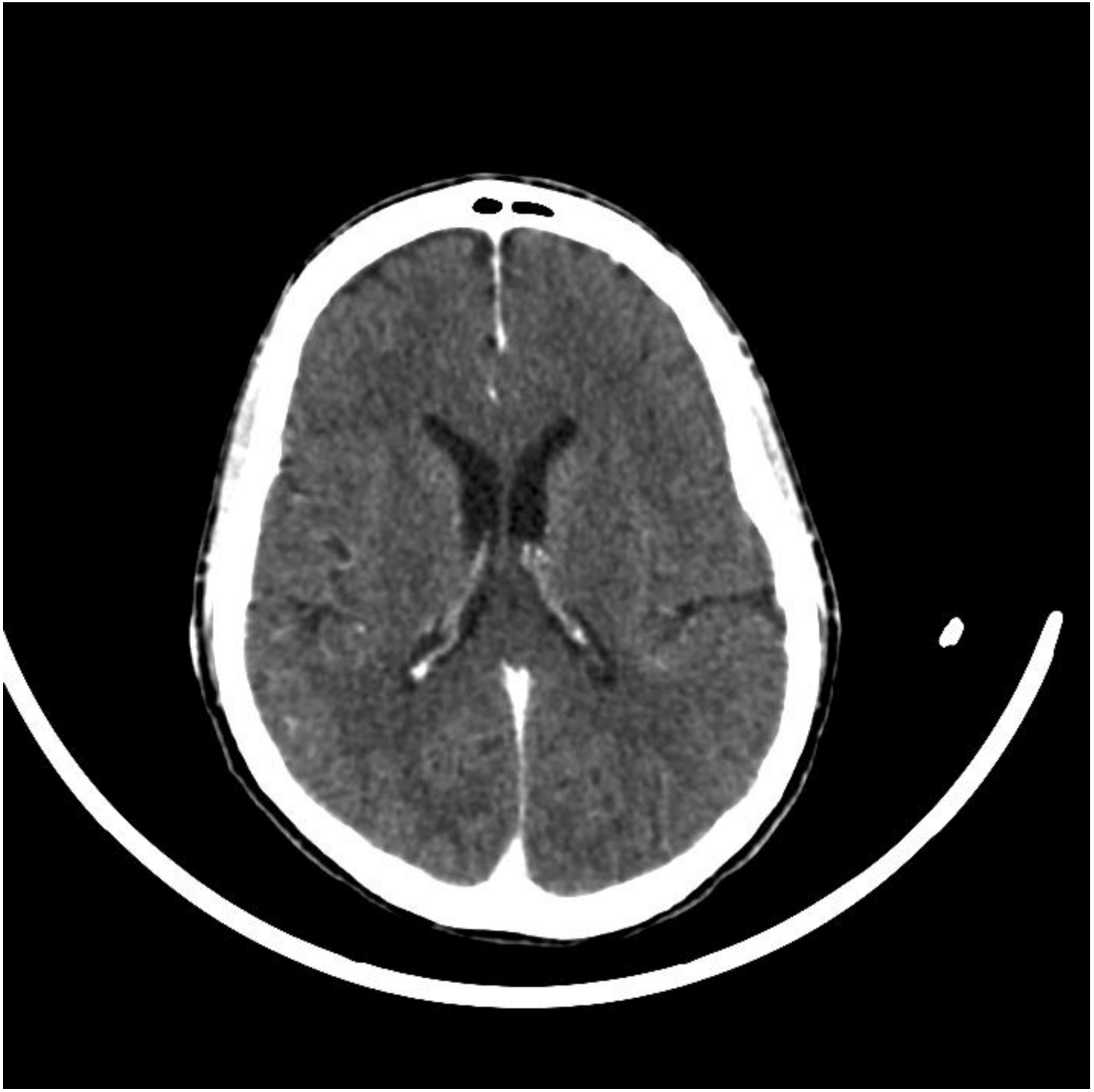


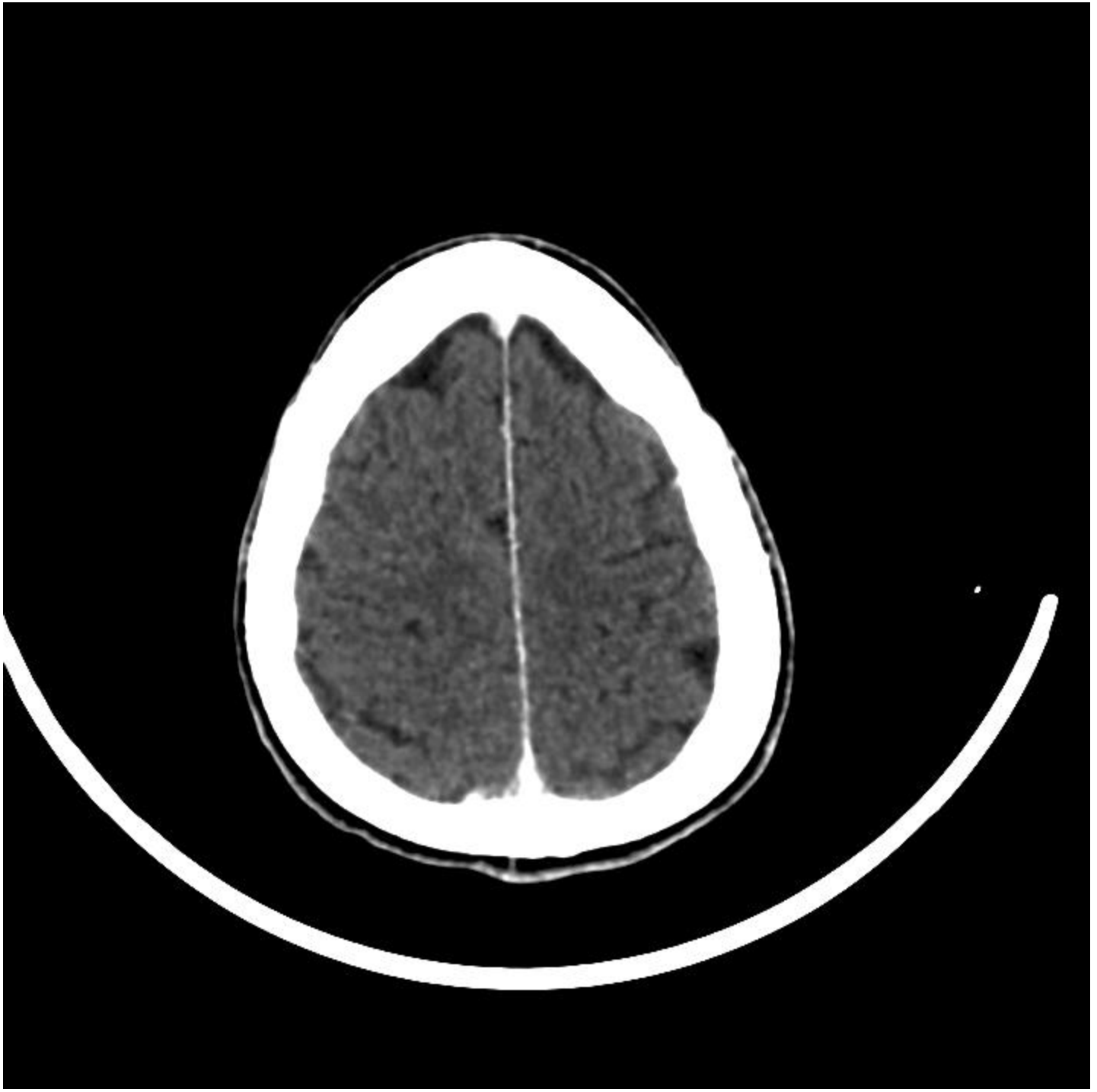
Case 1 cont'd

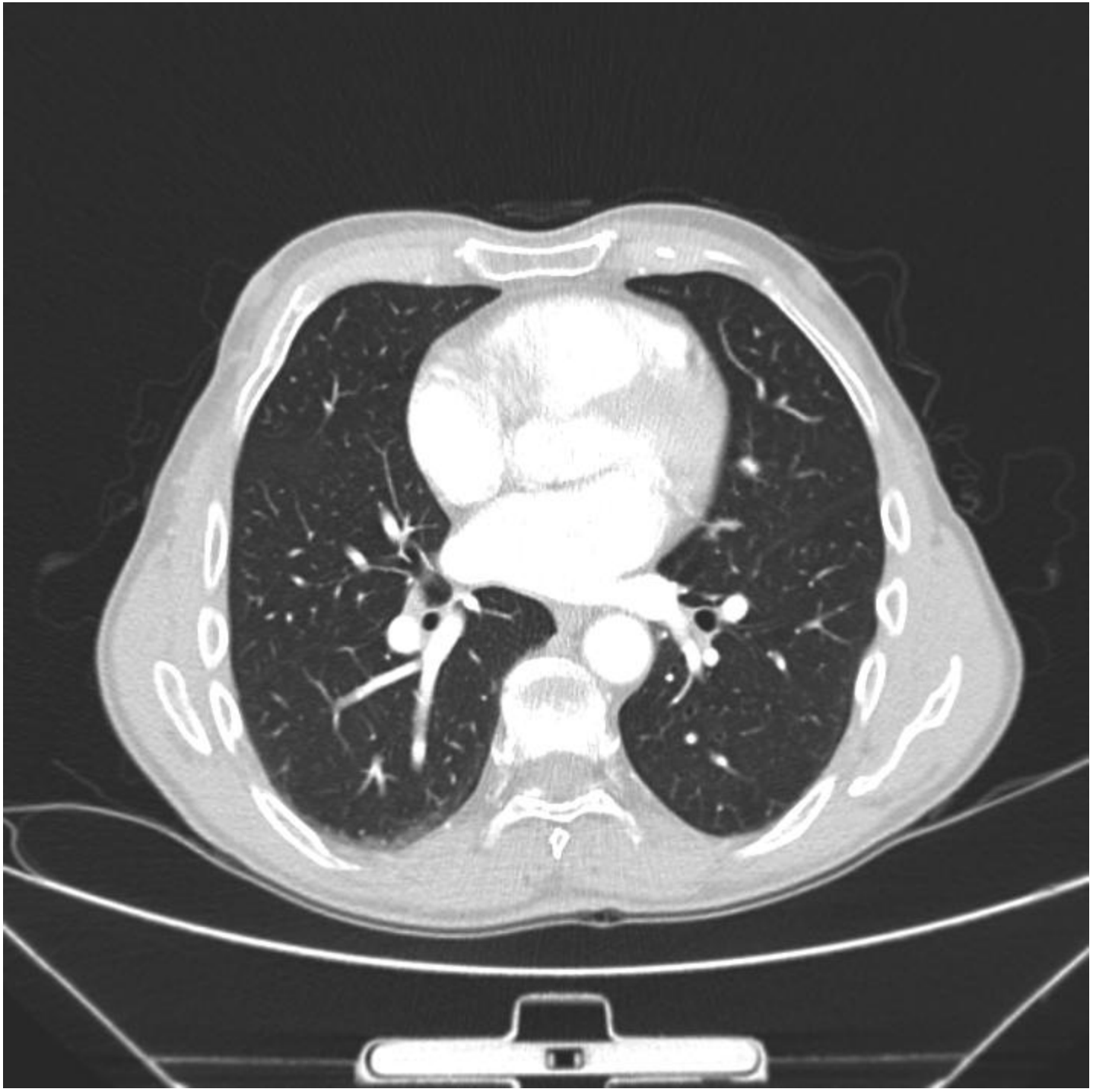
- Seizures controlled on dex/carbamazepine
- Started on pembrolizumab early May 2015
- Early June phone call from family – R arm weakness had worsened, some confusion
- Dexamethasone increased to 4mg bd
- Pembrolizumab continued
- July - arm weakness better, no seizures, dex reduced to 2mg daily then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

Case 1 cont’d

- Now:
  - Working in son’s business
  - Off dex
  - No seizures
  - Back driving
  - Near complete response on scans
  - Considering break from pembrolizumab



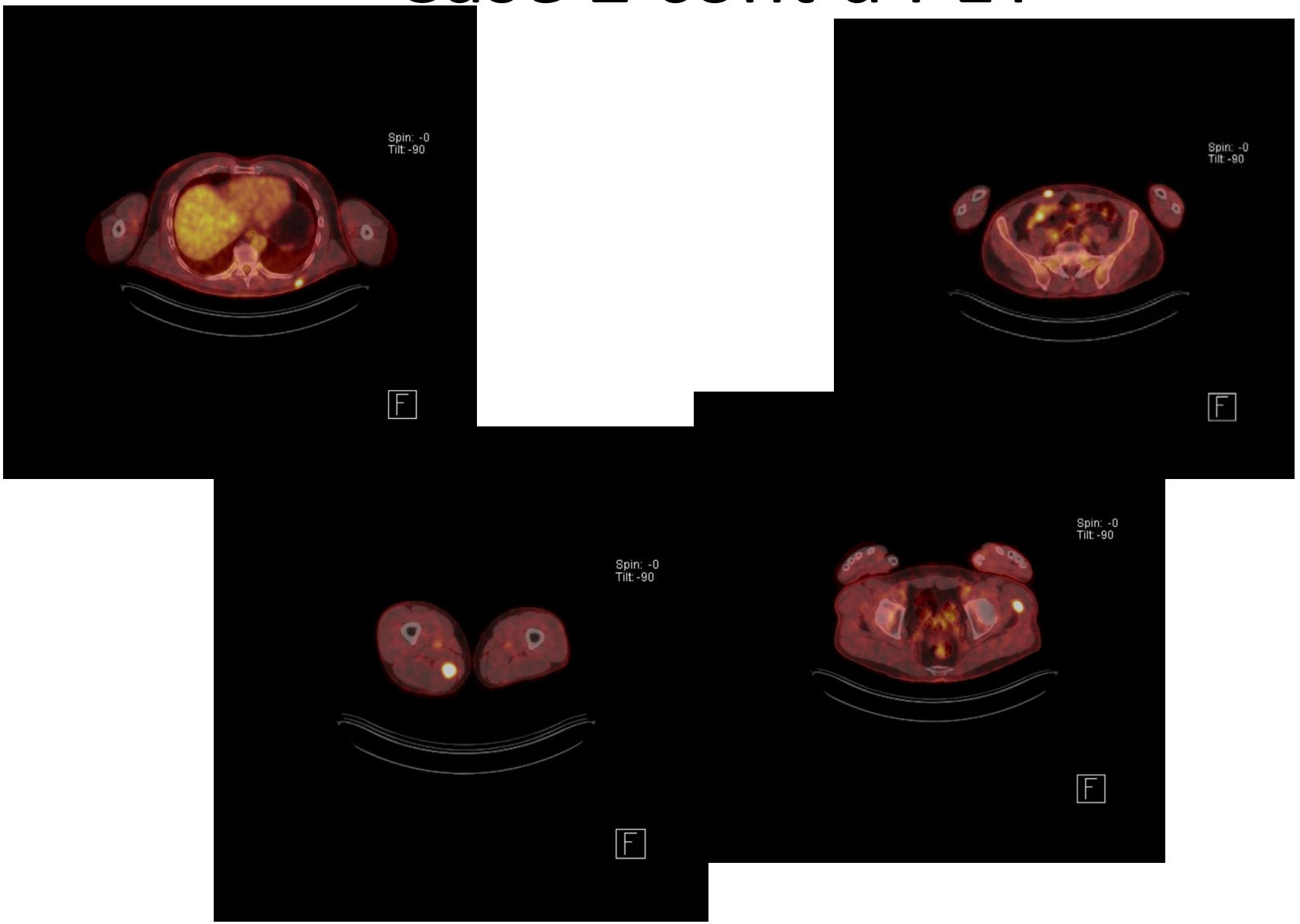




Case 2 – targeted therapy

- 52 year old man
- Sept 2014
- In follow up for NHL
- Incidental finding on imaging of subcutaneous lesion on abdo wall, biopsy – melanoma
- No known skin primary
- BRAF mutant

Case 2 cont’d PET



Case 2 cont’d

- 2 months after starting treatment presented to DEM with 5 days of fevers/rigors/sweats
- SBP 60
- Admitted to ICU, treated with noradrenaline
- EF 48% on echo
- Deranged LFTs
- Dabrafenib/trametinib withheld
- Recovered rapidly

Case 2 cont'd

- Recommenced full dose dabrafenib/trametinib 3 weeks later
- No further issues since then, remains on treatment
- PET scan 2/3/16 – complete response