# Metastatic Melanoma New therapies and their toxicities

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RBWH

22 July 2017

# Melanoma Incidence in Australia

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

# AJCC Staging System for Cutaneous Melanoma

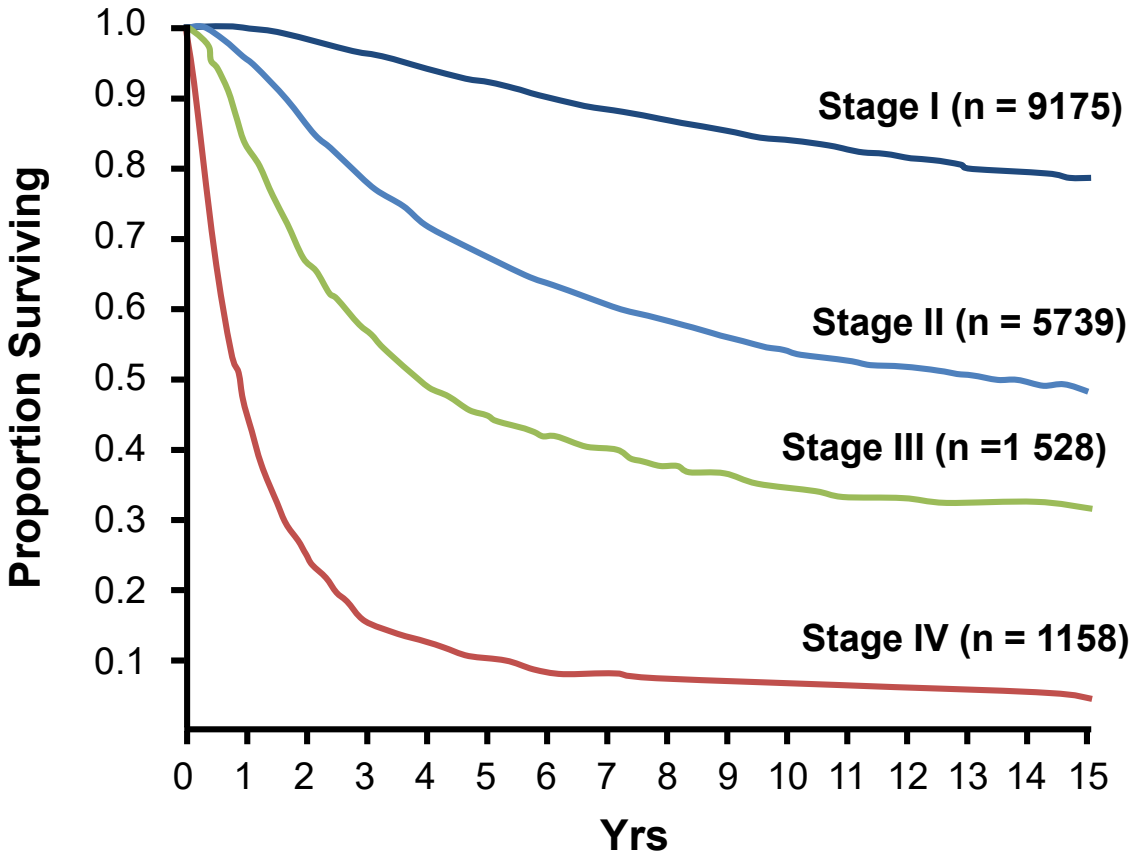
| | Thickness | Ulceration Status/Mitoses |
|---|---|---|
| T1 | ≤ 1.0 mm | a: without + mitosis < 1/mm$^2$, b: with or mitoses ≥ 1/mm$^2$ |
| T2 | 1.01- 2 mm | a: without, b: with |
| T3 | 2.01- 4 mm | a: without, b: with |
| T4 | >4.0 mm | a: without, b: with |

| | 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 |

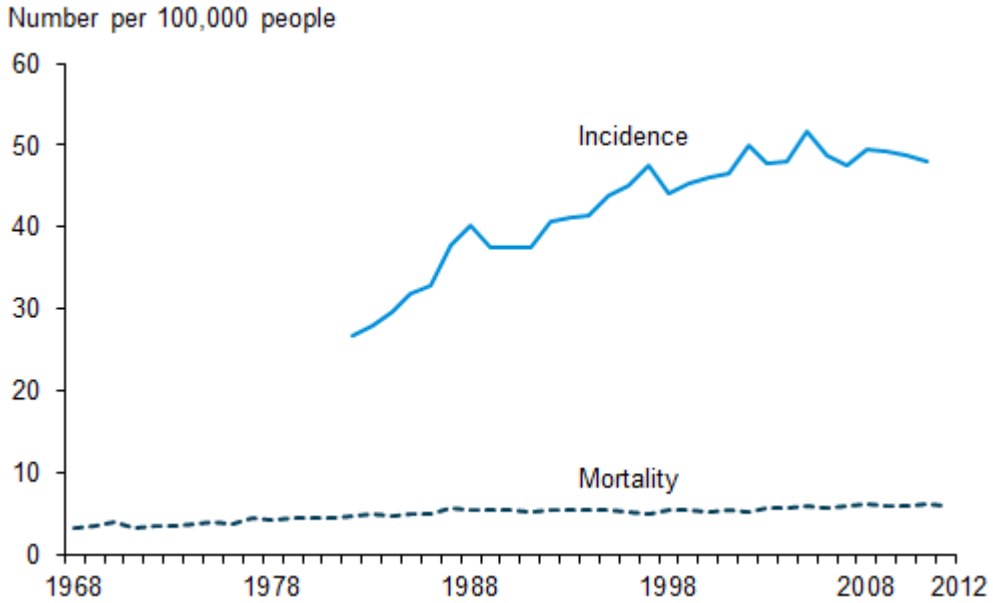
Balch CM, et al. J Clin Oncol. 2009;27:6199-206.

# Survival in Melanoma by Stage




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

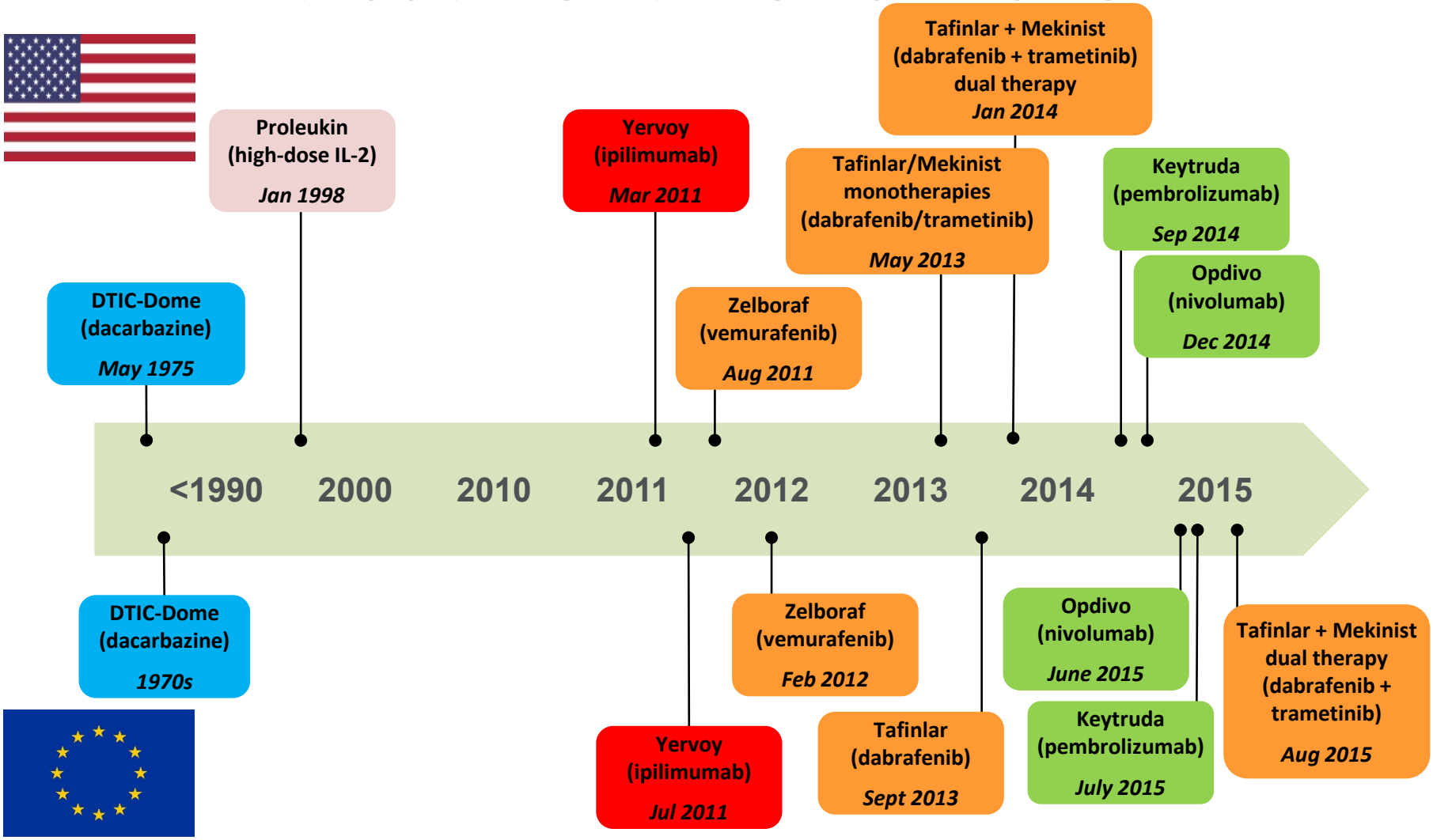
# Melanoma skin cancer incidence and mortality, 1968 to 2012



# Where can we make a difference?

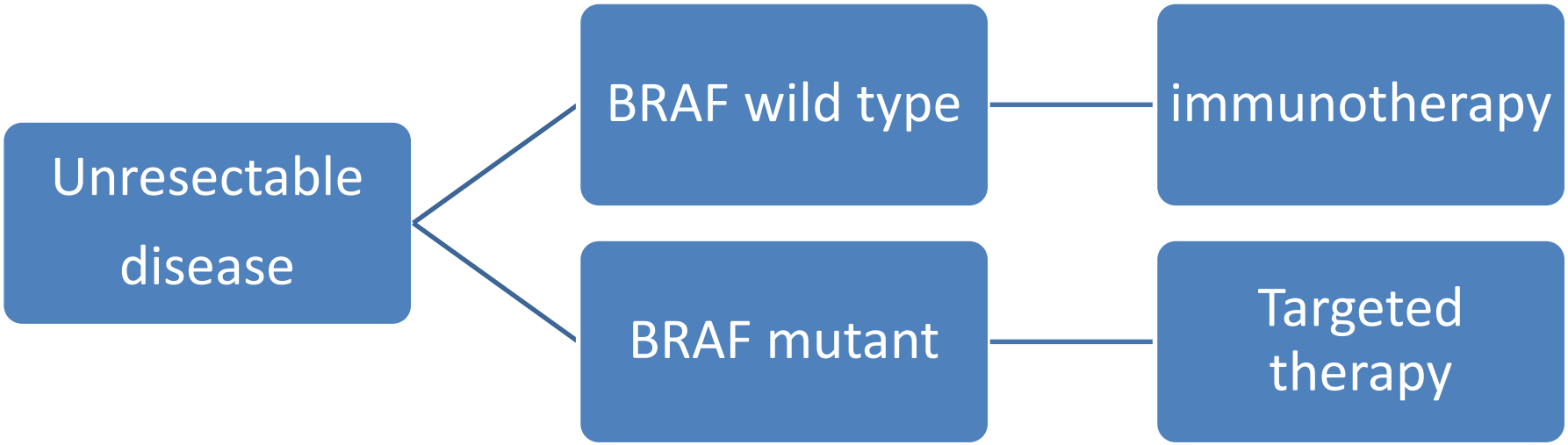
- Prevention/early detection
- Better neo/adjuvant therapy
- Improved treatment in the advanced setting.
  - Downstage to enable curative treatment
  - Picking the right treatment for the right patient
  - Prolong overall survival
- Reduced toxicity of treatment

# Metastatic melanoma available treatment: 1970–2015



# Current paradigm in metastatic melanoma

**50%, Older patients, chronic sun damage**




**50%, Younger patients**

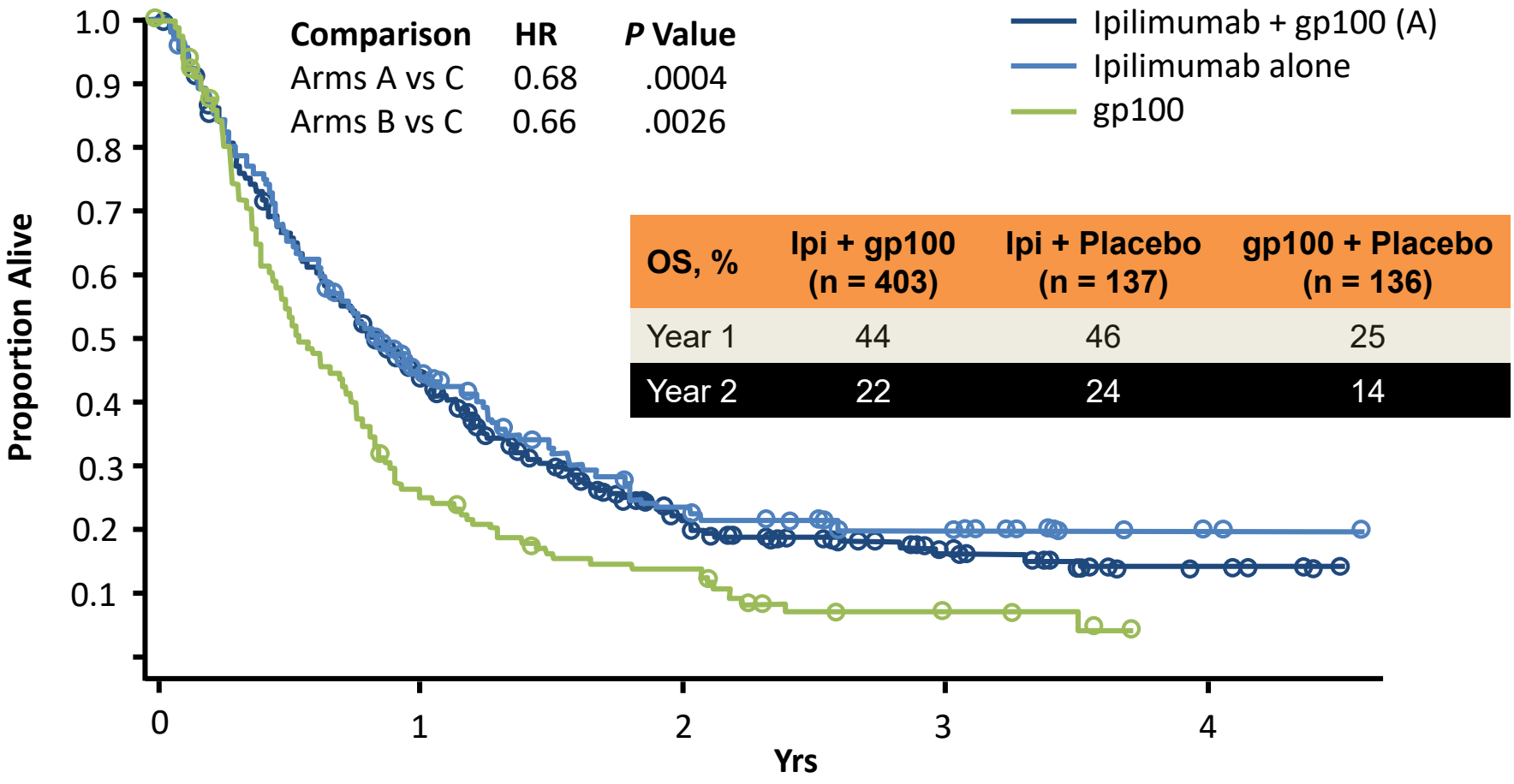
# IMMUNOTHERAPY

# 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



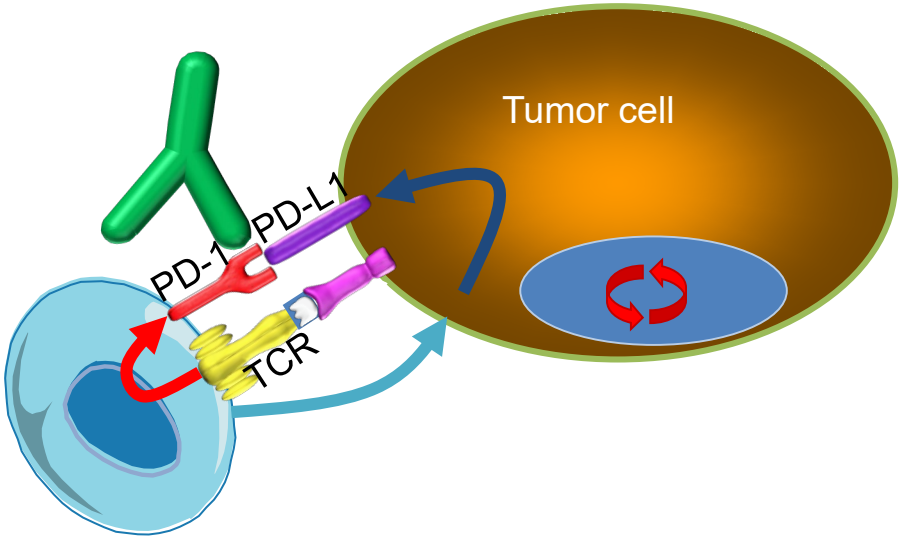

| OS, % | Ipi + gp100 (n = 403) | Ipi + Placebo (n = 137) | gp100 + Placebo (n = 136) |
|---|---|---|---|
| Year 1 | 44 | 46 | 25 |
| Year 2 | 22 | 24 | 14 |

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

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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 |

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Final analysis data cutoff date: Dec 3, 2015.

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# 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

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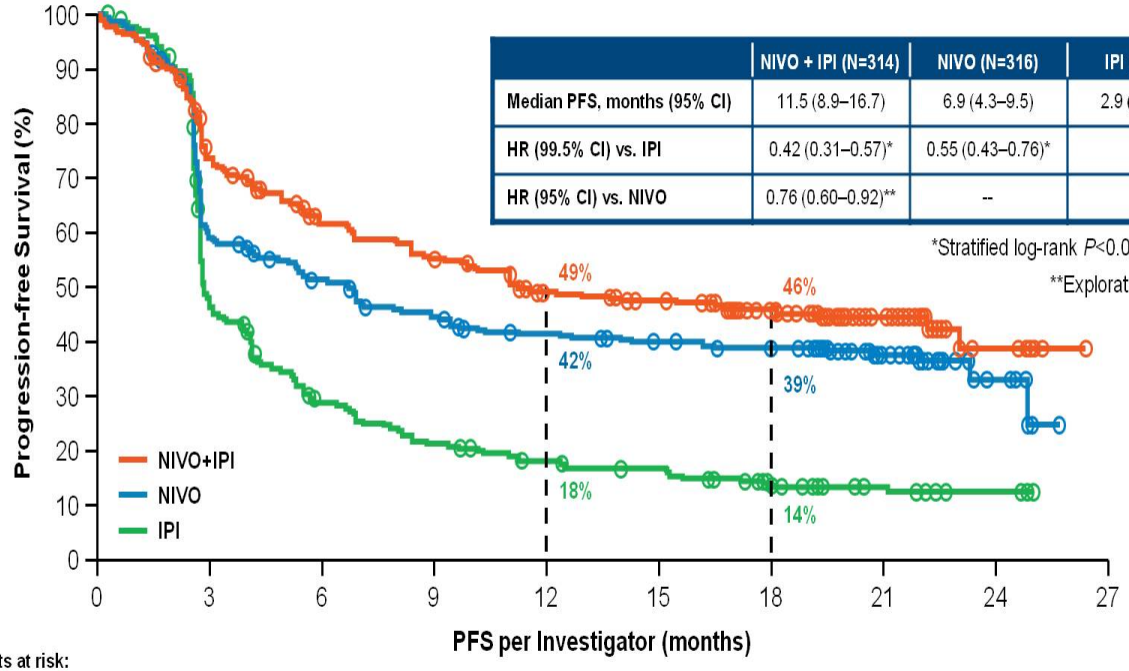
# Progression-Free Survival (Intent-to-Treat Population)




| | 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



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# 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

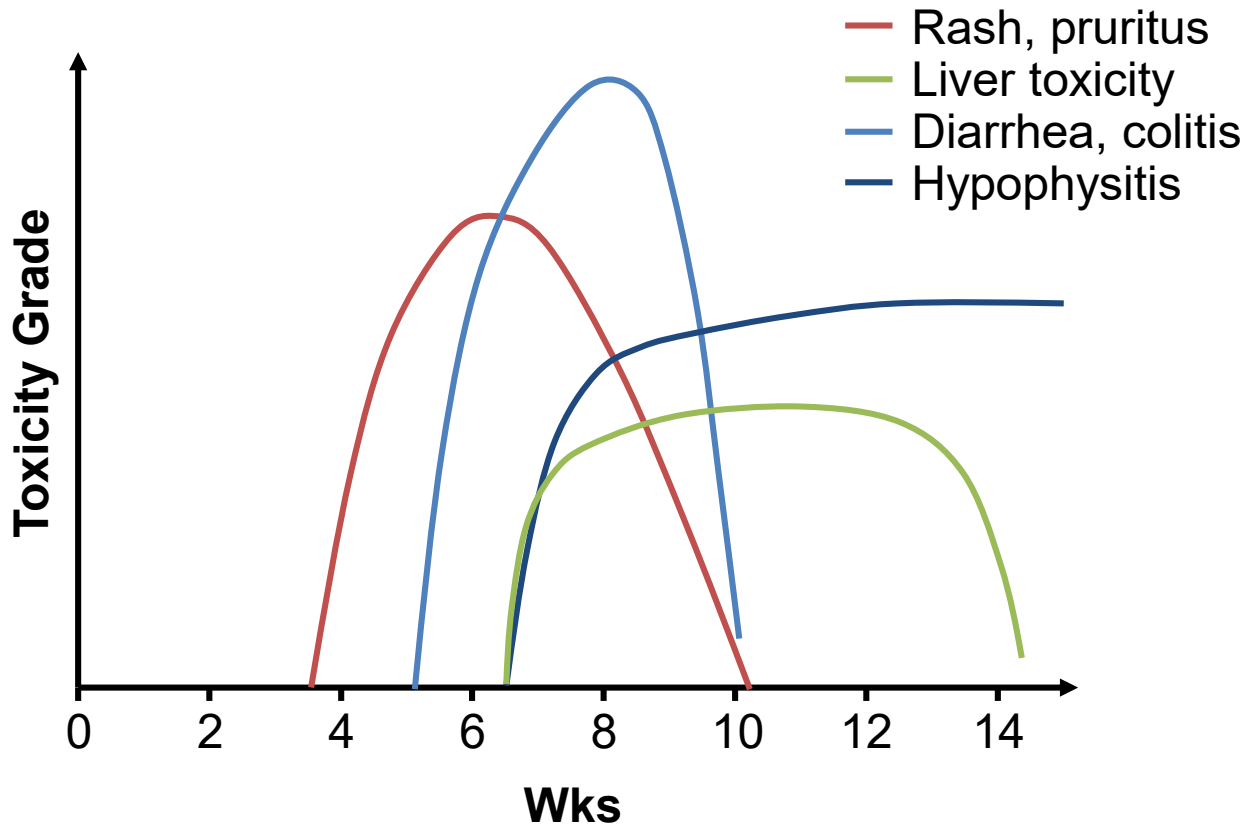
**Neurologic**
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia gravis–like syndrome

**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



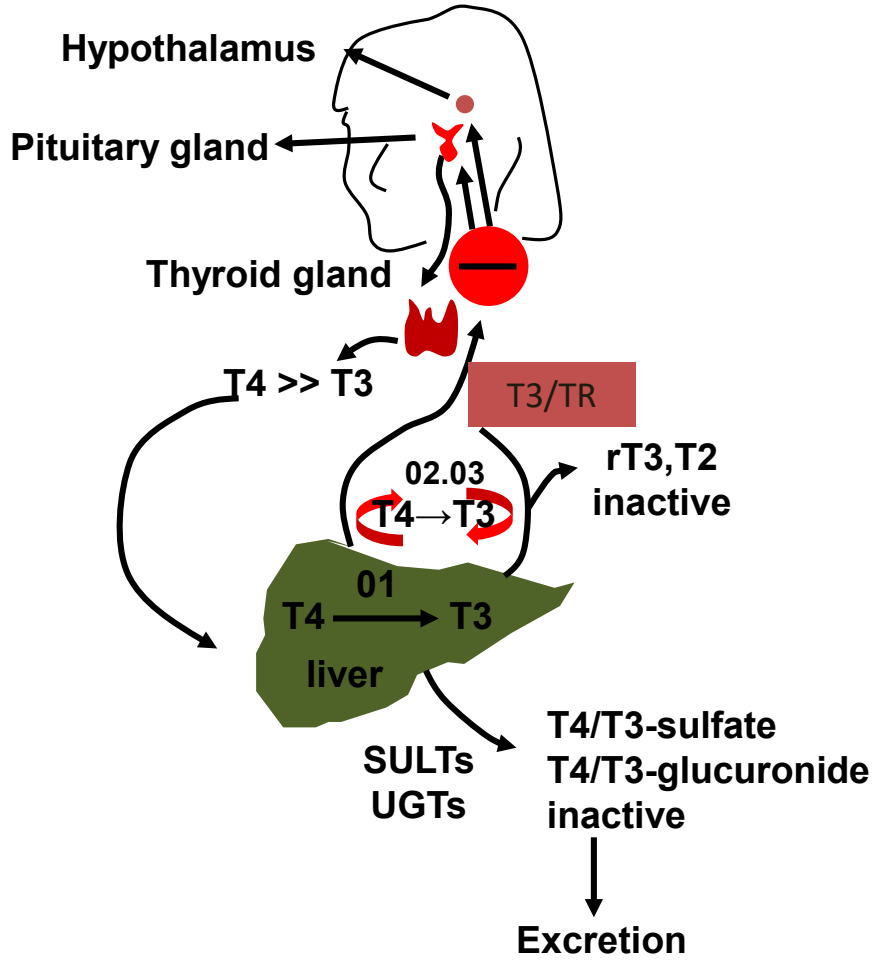

Combined analysis of 325 participants with 10 mg/kg IV q3w x 4

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



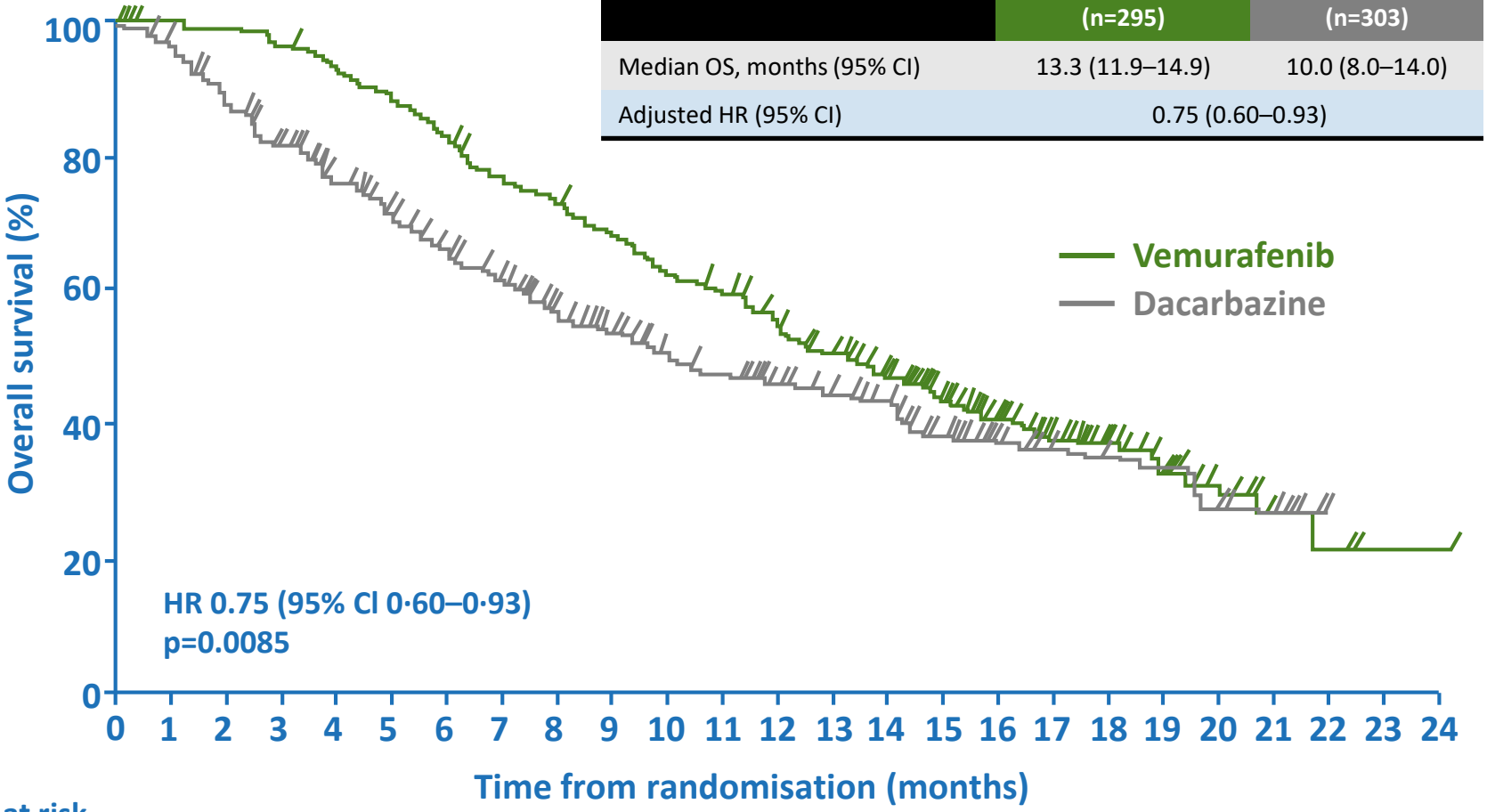

Corsello SM, et al. J Clin Endocrinol Metab. 2013;98:1361-1375.

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

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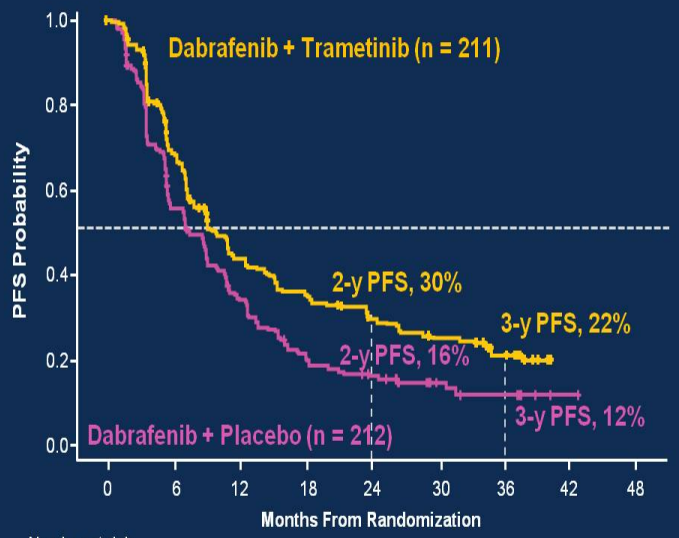
# COMBI-d: PFS and OS[a]

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

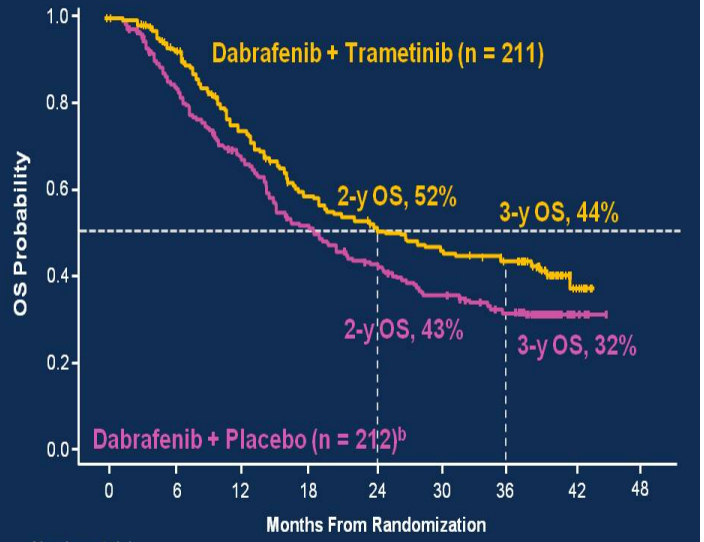
## Progression-Free Survival




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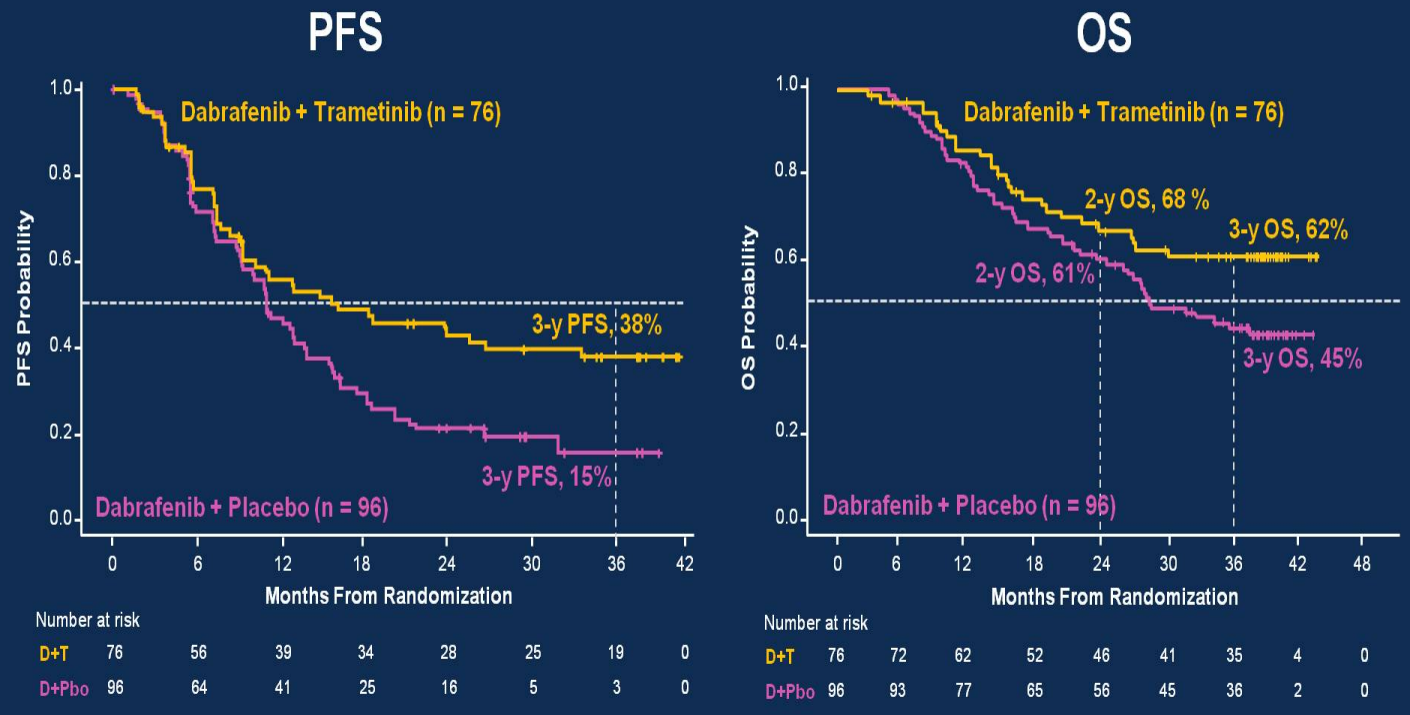
# COMBI-d: Normal LDH[a] and < 3 Disease Sites[b]




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

# 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

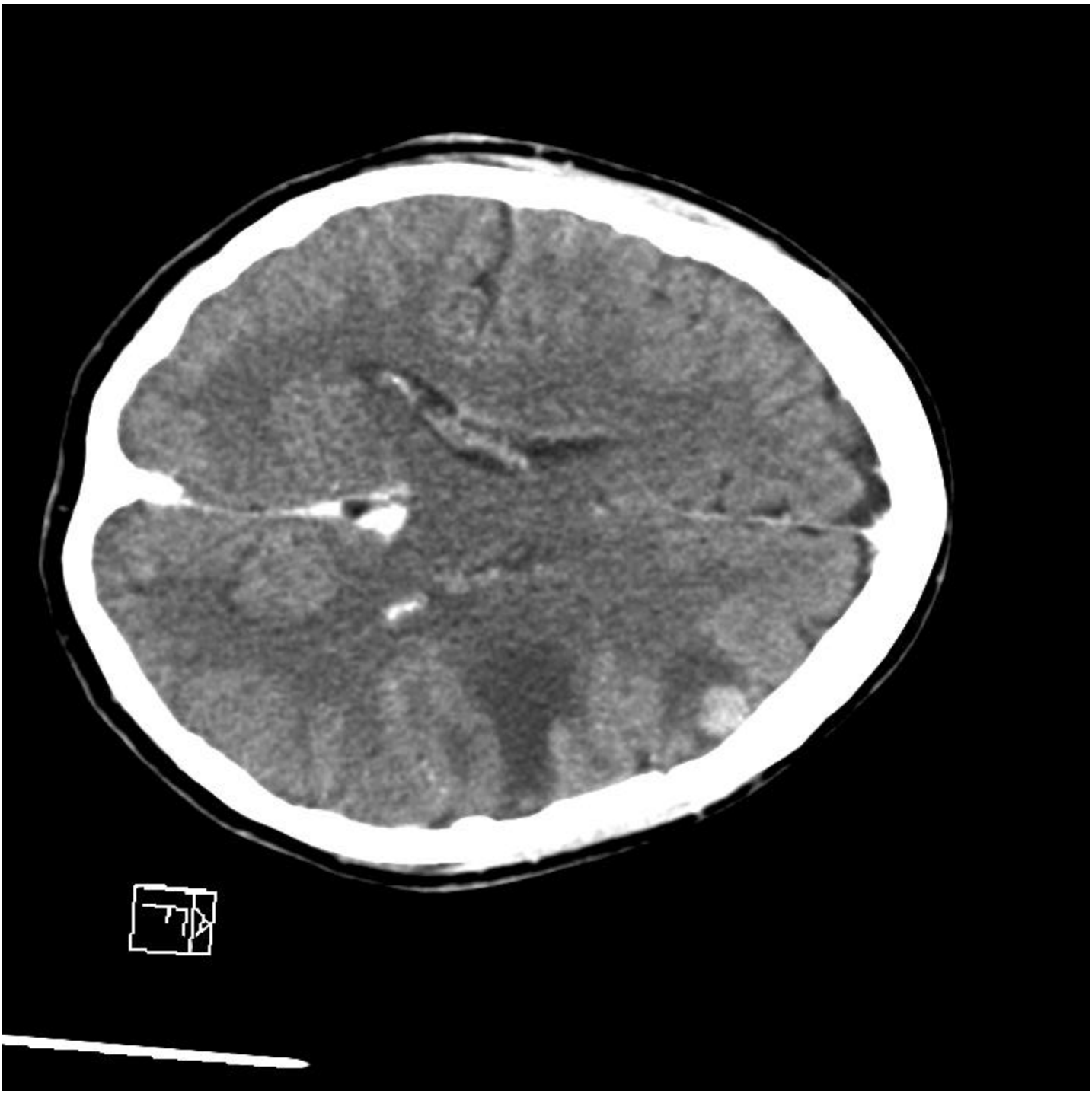
  once resolved can safely restart therapy

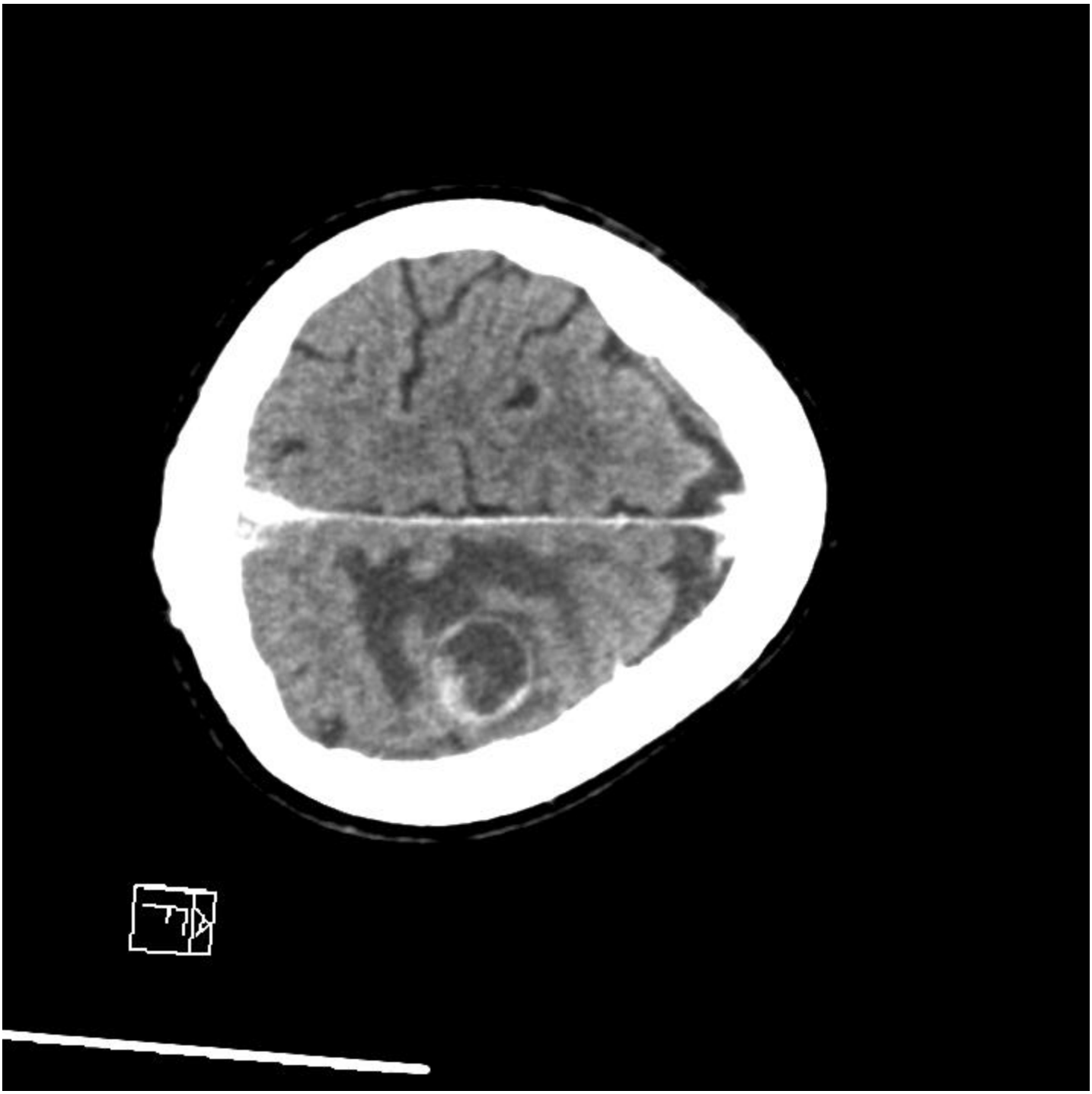
# Australian context

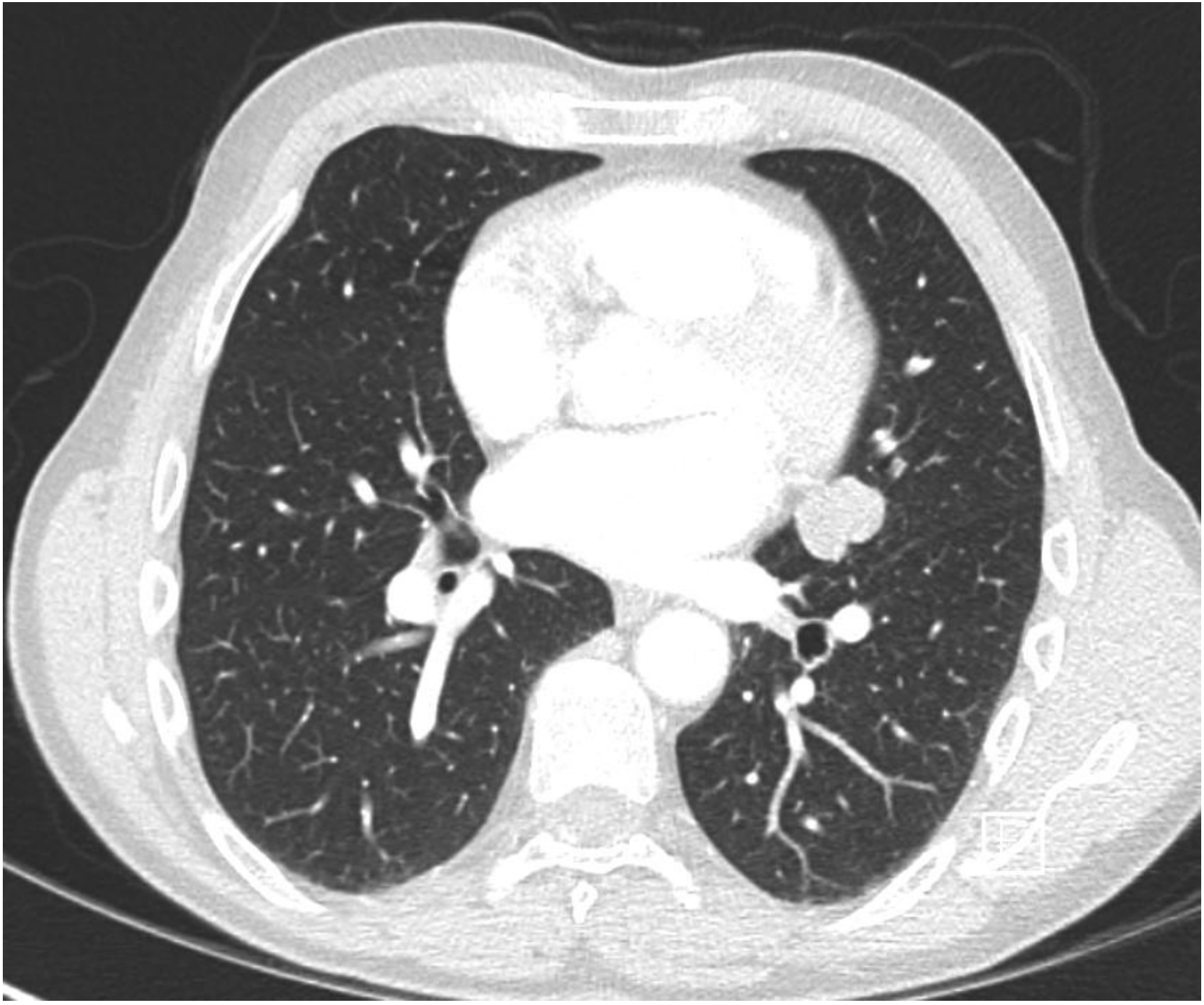
- BRAF mutant – dabrafenib/trametinib or vemurafenib/cobimetinib on PBS
- BRAF wildtype – pembrolizumab/nivolumab on PBS
  - Compassionate access to Ipi/nivo combination
- Ongoing trials – PD1 +CTLA4
  Adjuvant PD1
  Adjuvant CTLA4
  Adjuvant BRAF inhibitor
  Sequencing
  Combination braf/immunotherapy

# 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





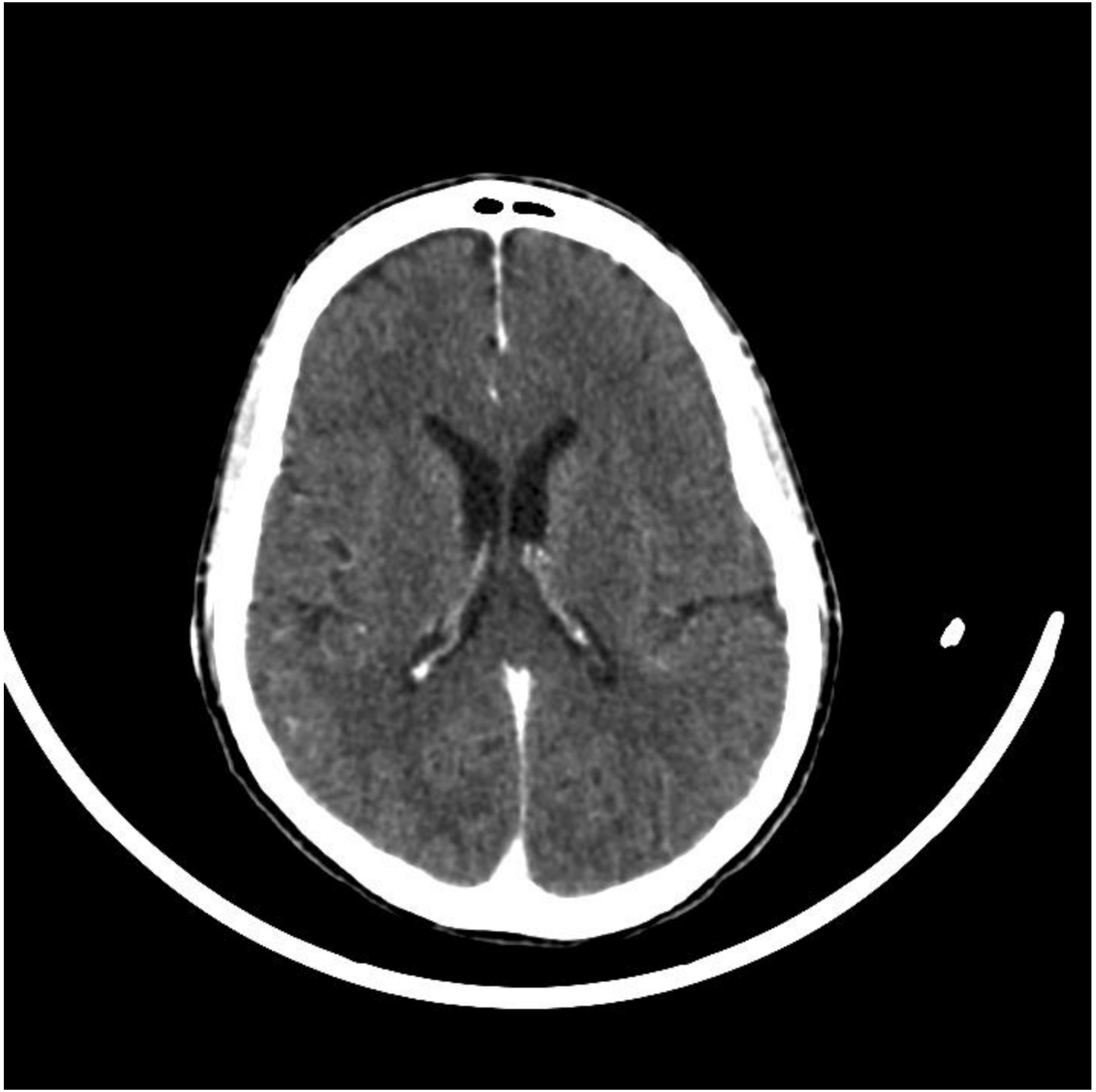


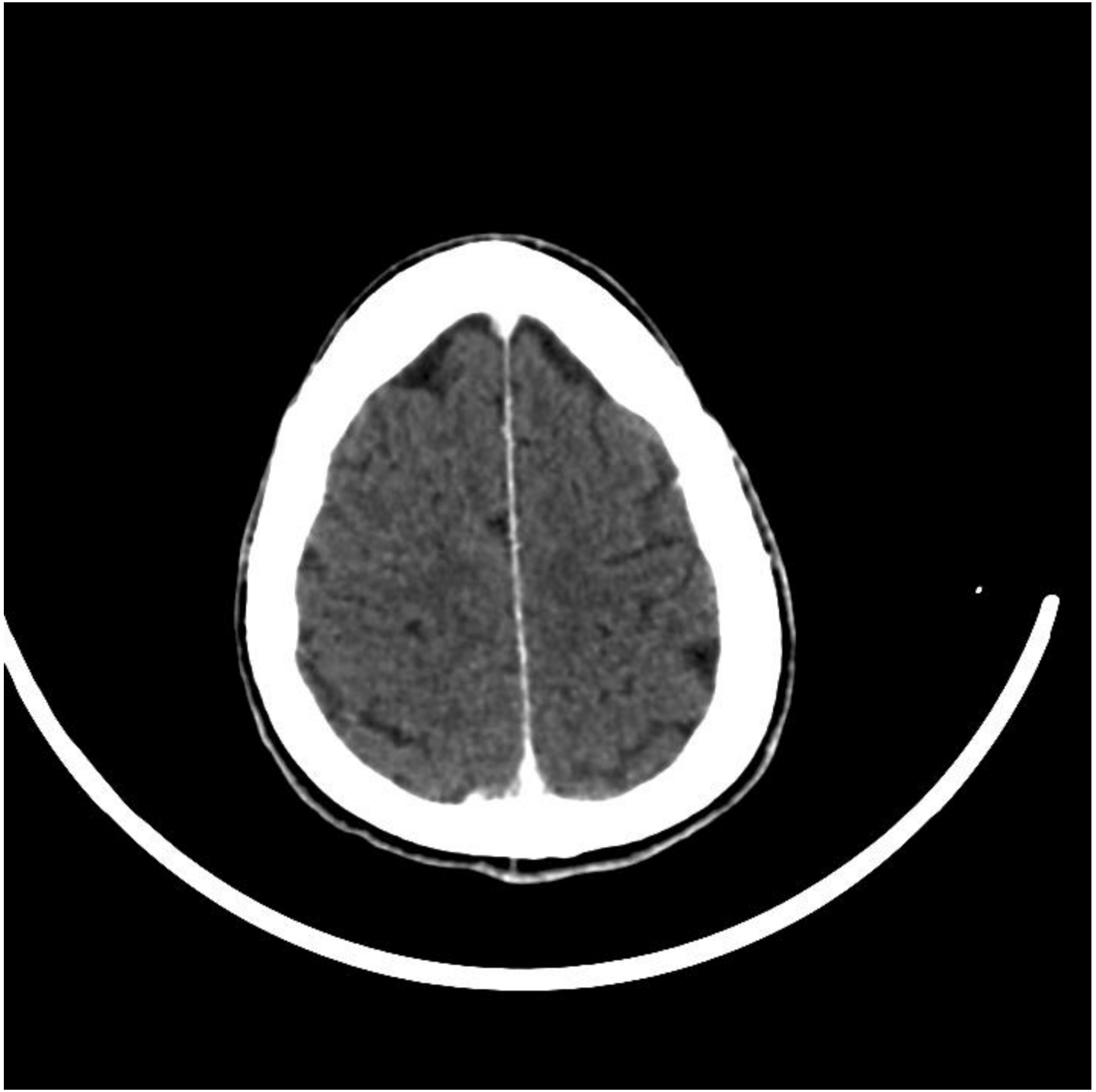
# Case 1 cont'd

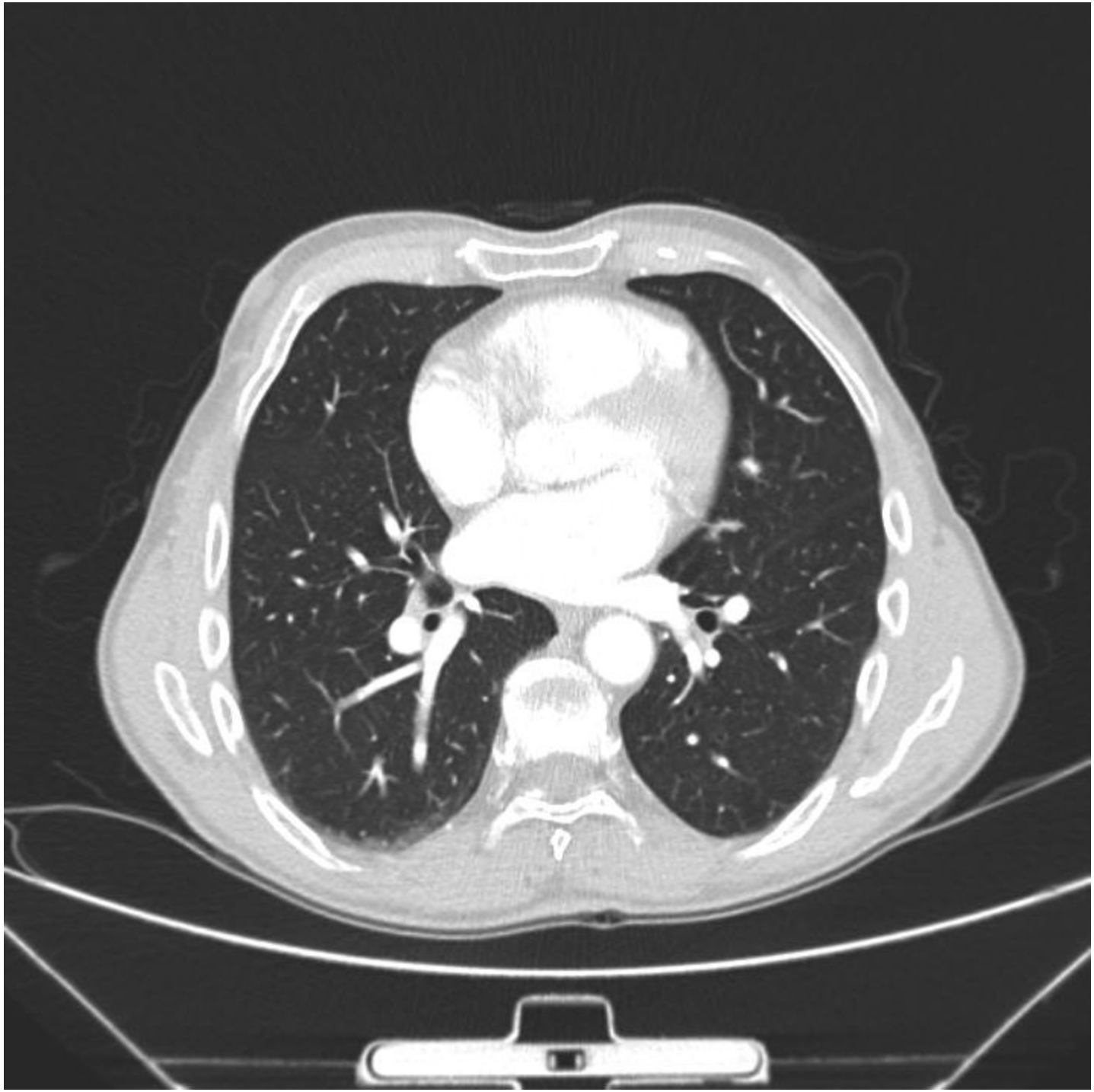
- Seizures controlled on dex/carbamazepine
- Started on pembrolizumab early May 2015
- Early June phone call from family – R arm weakness had worsened, some confusion
- Dexamethasone increased to 4mg bd
- Pembrolizumab continued
- July - arm weakness better, no seizures, dex reduced to 2mg daily then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

# Case 1 cont'd

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



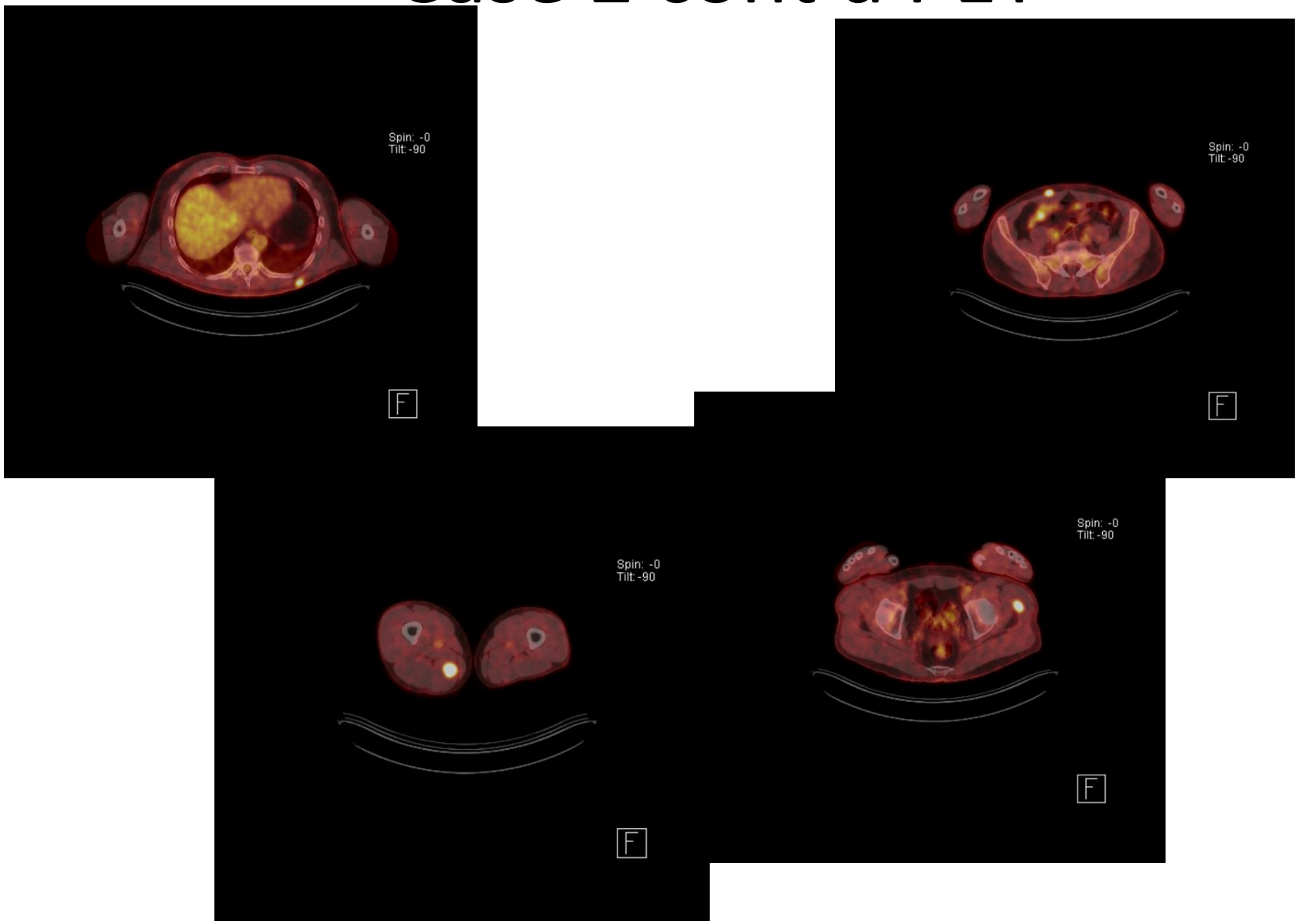




# Case 2 – targeted therapy

- 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

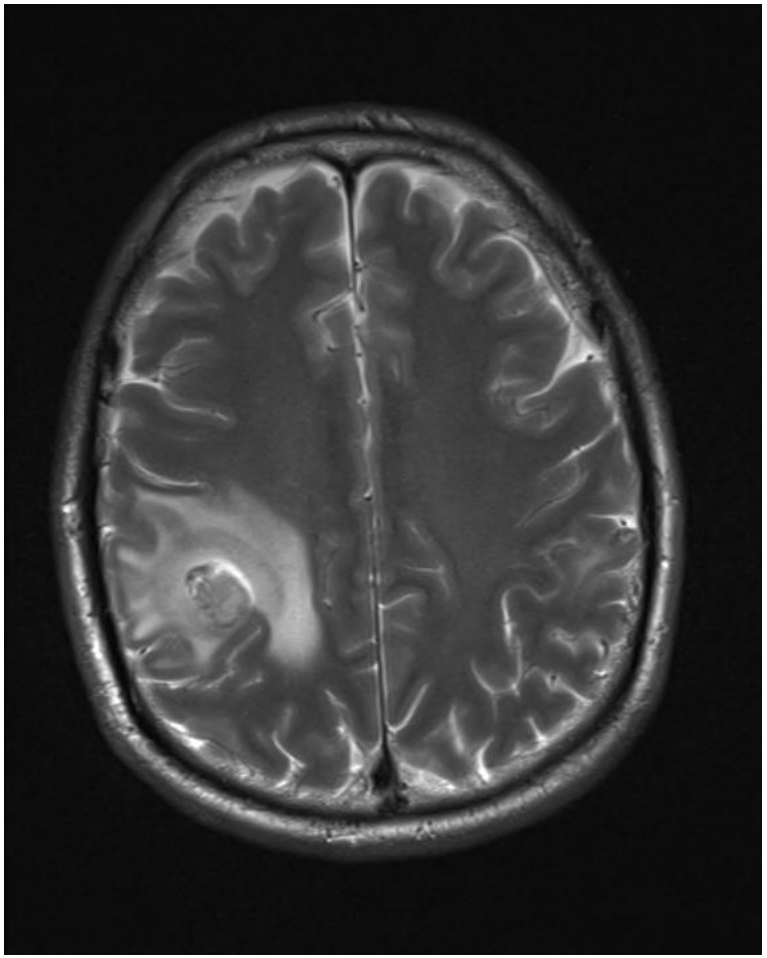
# Case 2 cont'd

- Recommenced full dose dabrafenib/trametinib 3 weeks later
- No further issues with fevers
- PET scan 2/3/16 – complete response

# Case 2 cont’d

- March 2017 developed headaches
- MRI shows multiple brain mets

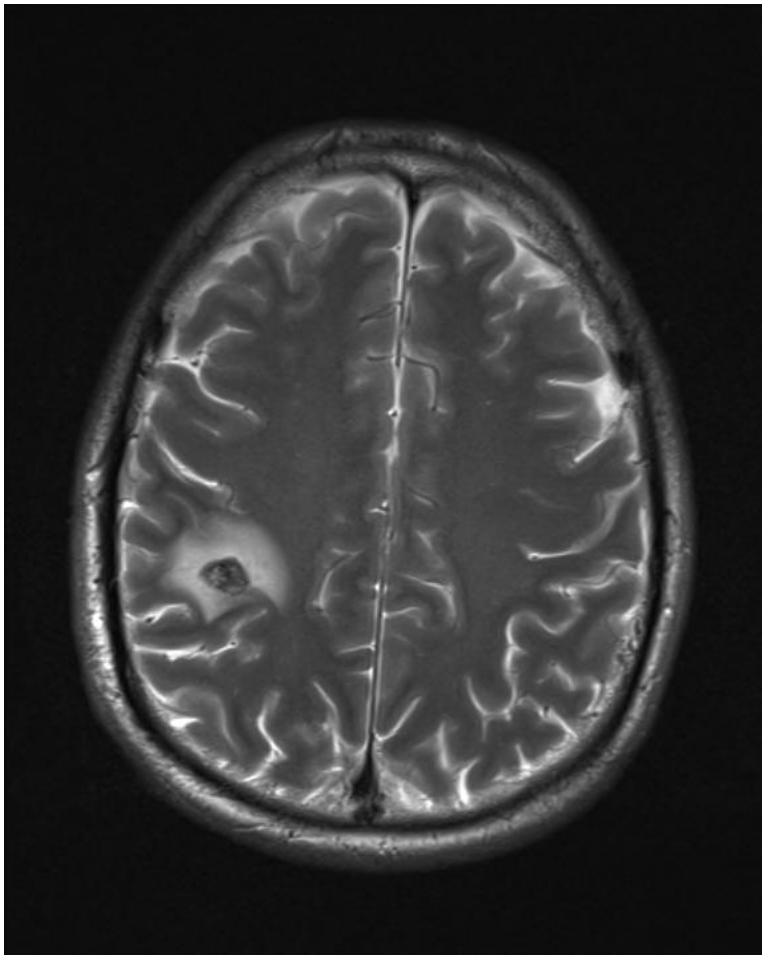
# Case 2 cont’d



# Case 2 cont’d

- Treated with Gamma-knife at PAH
- Systemic therapy changed to pembrolizumab
- Symptoms improved

# Case 2 cont’d

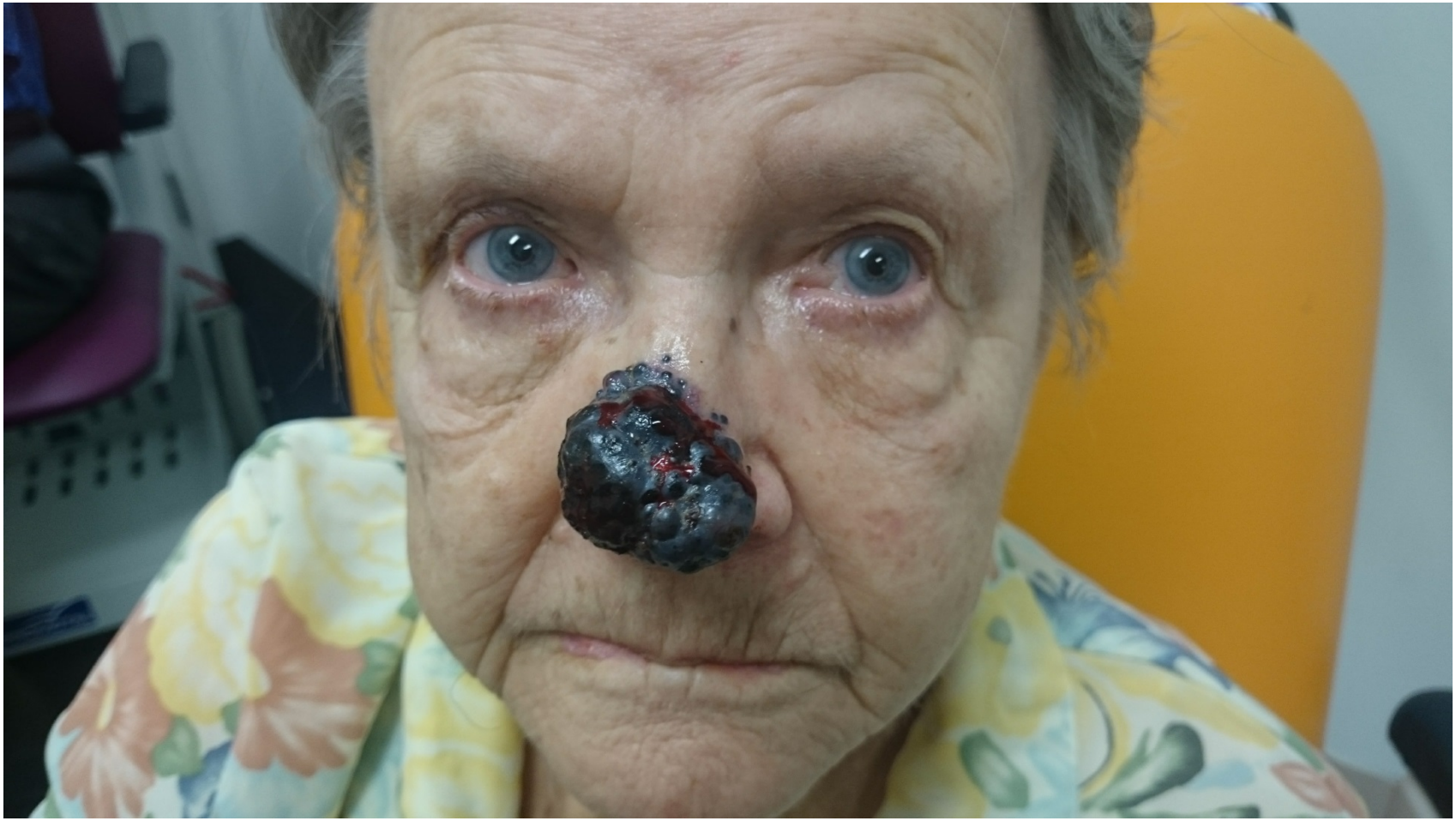


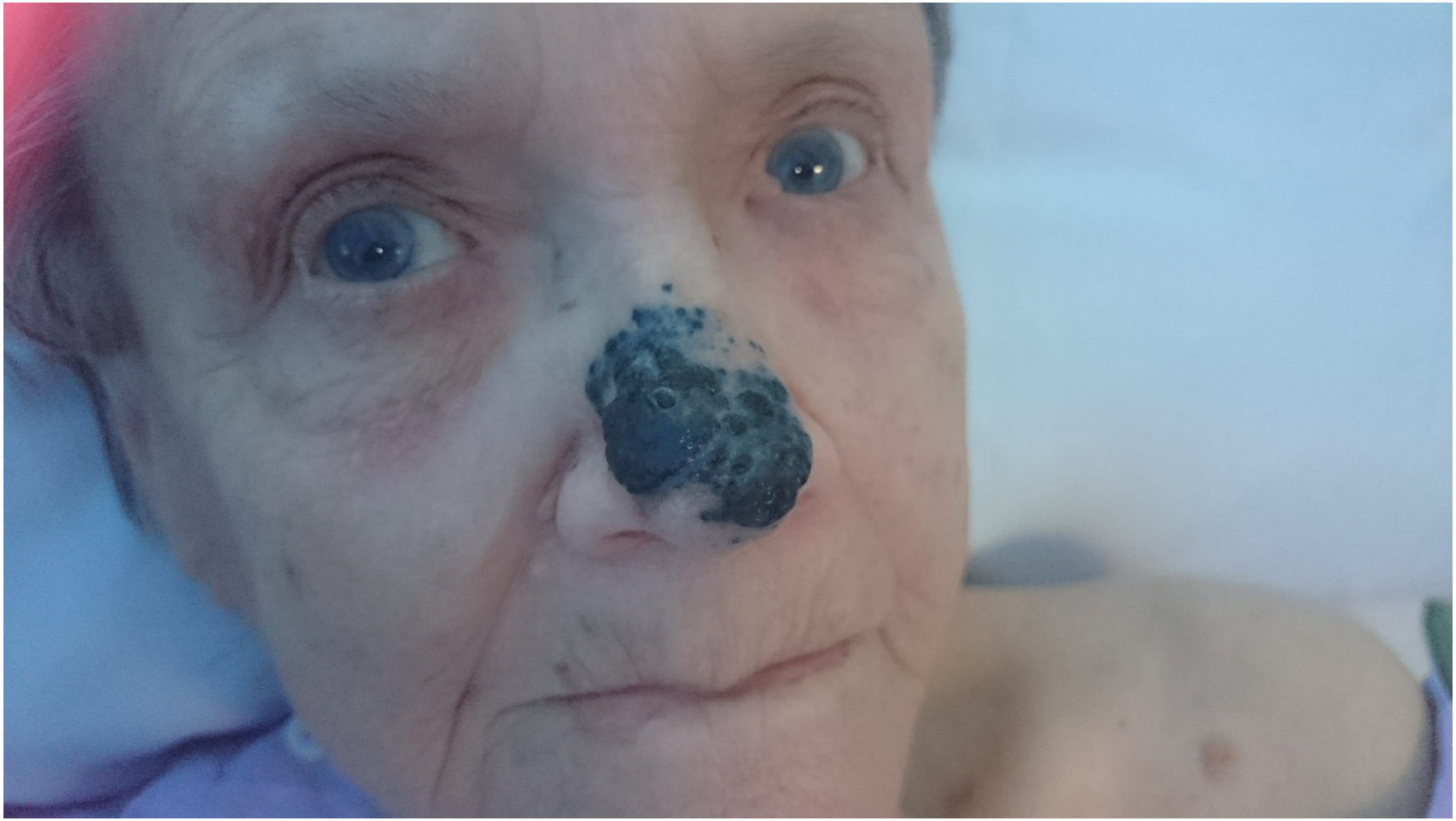
# Case 2 cont’d

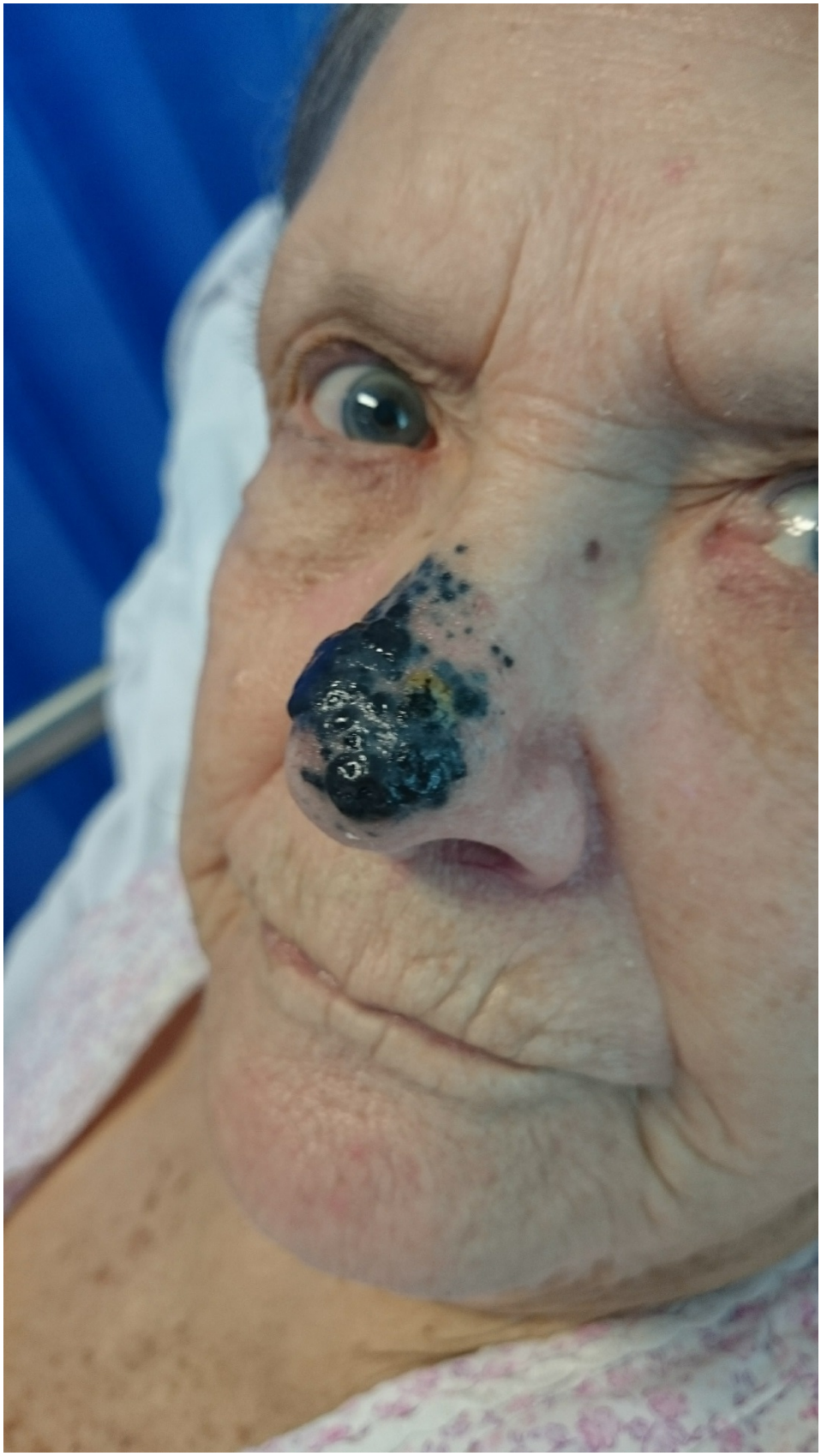
- Currently well
- Remains on pembrolizumab
- No toxicity to date

# Case 3

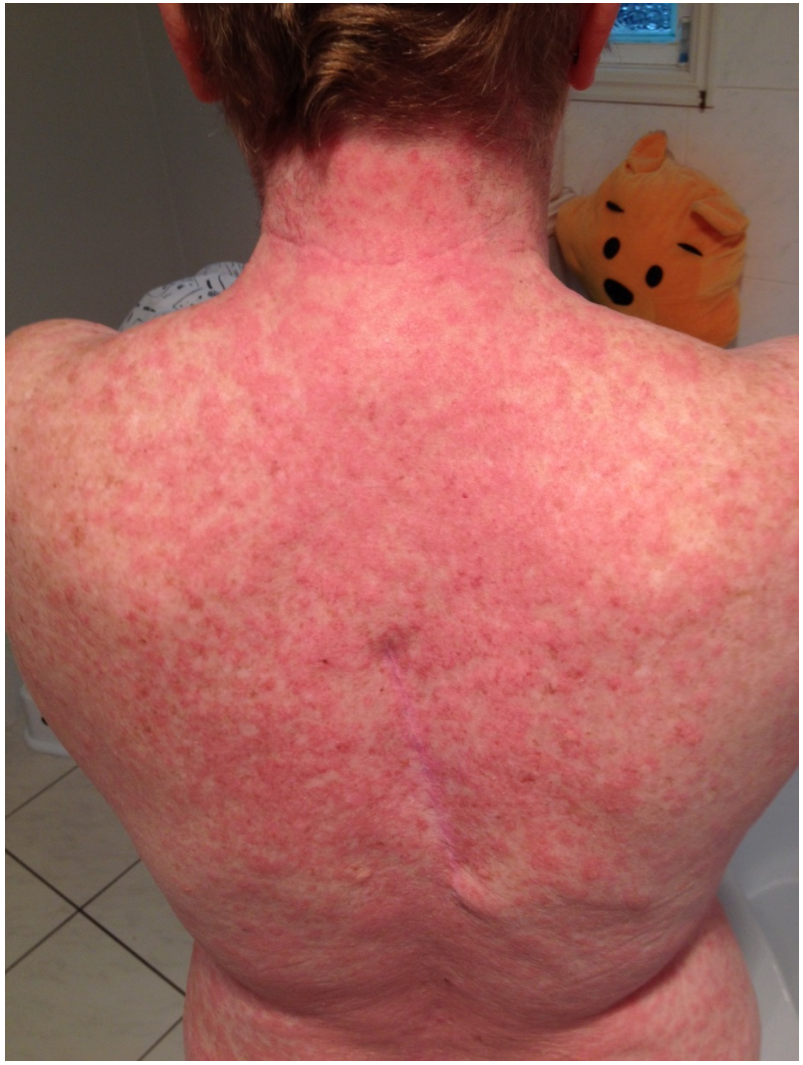
- 84 year old lady referred to plastics with rapidly growing lesion on her nose







# Other toxicities – rash D/T



# Other toxicities – rash pembro