Metastatic Melanoma
New therapies and their toxicities

Melissa Eastgate
Deputy Director Medical Oncology
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

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

## AJCC Stage III Stage Groups

<table>
<thead>
<tr>
<th>When T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the pathological stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a/b–T2a</td>
<td>N1a or N2a</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1a/b–T2a</td>
<td>N1b/c or N2b</td>
<td>M0</td>
<td>IIIB</td>
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<tr>
<td>T2b/T3a</td>
<td>N1a–N2b</td>
<td>M0</td>
<td>IIIB</td>
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<tr>
<td>T1a–T3a</td>
<td>N2c or N3a/b/c</td>
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<td>IIIC</td>
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<td>T4b</td>
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<td>IIIC</td>
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<tr>
<td>T0</td>
<td>N1b, N1c</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T0</td>
<td>N2b, N2c, N3b or N3c</td>
<td>M0</td>
<td>IIIC</td>
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### AJCC Eighth Edition
Melanoma Stage III Subgroups

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<thead>
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<th>N Category</th>
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<th>T1b</th>
<th>T2a</th>
<th>T2b</th>
<th>T3a</th>
<th>T3b</th>
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<td>C</td>
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<td>D</td>
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<td>N3c</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

### 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.

**Legend**
- A Stage IIIA
- B Stage IIIB
- C Stage IIIC
- D Stage IIID

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

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Survival in Melanoma by Stage

Stage I (n = 9175)
Stage II (n = 5739)
Stage III (n = 1528)
Stage IV (n = 1158)

Melanoma skin cancer incidence and mortality, 1968 to 2012

![Graph showing incidence and mortality of melanoma skin cancer from 1968 to 2012.](image-url)
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

- DTIC-Dome (dacarbazine)
  - <1990
  - May 1975

- Proleukin (high-dose IL-2)
  - 1970s
  - Jan 1998

- DTIC-Dome (dacarbazine)
  - 1970s

- Yervoy (ipilimumab)
  - Mar 2011

- Zelboraf (vemurafenib)
  - Aug 2011

- Tafinlar (dabrafenib)
  - Sept 2013

- Keytruda (pembrolizumab)
  - July 2015

- Opdivo (nivolumab)
  - June 2015

- Tafinlar + Mekinist (dabrafenib + trametinib)
  - Aug 2015

- Tafinlar + Mekinist dual therapy
  - Aug 2015

- Yervoy (ipilimumab)
  - Jul 2011

- Zelboraf (vemurafenib)
  - Aug 2011

- Tafinlar/Mekinist monotherapies (dabrafenib/trametinib)
  - May 2013

- Proleukin (high-dose IL-2)
  - Jan 1998

- Tafinlar + Mekinist (dabrafenib + trametinib) dual therapy
  - Jan 2014

- Opdivo (nivolumab)
  - Dec 2014

- Keytruda (pembrolizumab)
  - Sep 2014
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

Total N = 5549

Positive SLNB N = 1269

Included 483
Not included 786
Inclusion criteria failed 313
Patient refused rand. 225
n.a. 247
Total 786

Randomized Pat. N = 483

OBS = 241
CLND = 242

Dropouts N = 10
Macro metastases 5
Second. malignoma 1
Age 1
Localization 3

ITT N = 473

OBS = 233
CLND = 240
DECOG 3-years Survival Data

Overall survival

Recurrence-free survival

Leiter et al., The Lancet Oncology 2016;17:757-767
Similar findings – MSLT II

A

Probability of Melanoma-Specific Survival

Years after Randomization

No. at Risk

Dissection

Observation

824 759 654 510 389 275 191 128 83 39 13

931 856 734 564 425 304 217 151 95 55 13

P=0.55

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.
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

1Elia Lemberg 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; 10Sharet 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

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)


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 Sklodowska-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; 12Armada 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.

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
Progression-Free Survival (Intent-to-Treat Population)

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 Chiariion-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,16* Paolo A. Ascierto16*

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 Clinic 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 Toscana 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.
CheckMate 238: Study Design

Patients with:
- High-risk, completely resected stage IIIB/IIIC or stage IV (AJCC 7th edition) melanoma
- No prior systemic therapy
- ECOG 0-1

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

Stratified by:
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

Follow-up
Maximum treatment duration of 1 year

NIVO 3 mg/kg IV Q2W and IPI placebo IV Q3W for 4 doses then Q12W from week 24

IPI 10 mg/kg IV Q3W for 4 doses then Q12W from week 24 and NIVO placebo IV Q2W

n = 453
n = 453

1:1
Primary Endpoint: RFS in All Patients

Events/patients

<table>
<thead>
<tr>
<th></th>
<th>NIVO 453</th>
<th>IPI 453</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
<td>30.8 (30.8, NR)</td>
<td>24.1 (16.6, NR)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.66 (0.54, 0.81)</td>
<td>&lt;0.0001</td>
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</table>

Log-rank P value

aMedian estimate not reliable or stable due to few patients at risk.
Subgroup Analysis of RFS: Disease Stage III and IV

### Stage III

<table>
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<tr>
<th>Events/patients</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>135/368</td>
<td>NR</td>
<td>0.68 (0.54, 0.85)</td>
</tr>
<tr>
<td>174/366</td>
<td>25.5 (16.6, NR)</td>
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### Stage IV

<table>
<thead>
<tr>
<th>Events/patients</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>35/82</td>
<td>30.8 (15.9, NR)</td>
<td>0.68 (0.44, 1.06)</td>
</tr>
<tr>
<td>47/87</td>
<td>15.4 (8.5, NR)</td>
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</tbody>
</table>

*Median estimate not reliable or stable due to few patients at risk.*
Subgroup Analysis of RFS: BRAF Mutation Status

**BRAF Mutant**

<table>
<thead>
<tr>
<th>Events/patients</th>
<th>NIVO</th>
<th>IPI</th>
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</thead>
<tbody>
<tr>
<td>73/187</td>
<td>95/194</td>
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<table>
<thead>
<tr>
<th>Median (95% CI)</th>
<th>NIVO</th>
<th>IPI</th>
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<tbody>
<tr>
<td>30.8 (30.8, NR)</td>
<td>24.6 (14.8, NR)</td>
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<table>
<thead>
<tr>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>0.73 (0.54, 0.99)</td>
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*Median estimate not reliable or stable due to few patients at risk.*

**BRAF Wild type**

<table>
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<tr>
<th>Events/patients</th>
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<table>
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<tr>
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<tbody>
<tr>
<td>NR</td>
<td>16.6 (11.4, NR)</td>
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<tr>
<th>HR (95% CI)</th>
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<tbody>
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<td>0.61 (0.45, 0.82)</td>
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Number of patients at risk

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<table>
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<td>3</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
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</tr>
</tbody>
</table>

RFS (%) vs Months
If not vigilant, may result in more serious immune-related AEs
Kinetics of Appearance of irAEs With Ipilimumab

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


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


Slide credit: clinicaloptions.com
TARGETED THERAPY
BRIM-3: OS with vemurafenib vs DTIC in patients with BRAF V600E-mutant melanoma

<table>
<thead>
<tr>
<th></th>
<th>Vemurafenib (n=295)</th>
<th>DTIC (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>13.3 (11.9–14.9)</td>
<td>10.0 (8.0–14.0)</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.75 (0.60–0.93)</td>
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</table>

Overall survival (%)

HR 0.75 (95% CI 0.60–0.93)
p=0.0085

Number at risk

<table>
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<tr>
<th>Vemurafenib</th>
<th>295</th>
<th>294</th>
<th>293</th>
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<tbody>
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<td>Dacarbazine</td>
<td>303</td>
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</tbody>
</table>

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

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

COMBI-d: PFS and OS<sup>a</sup>  

Progression-Free Survival

- Dabrafenib + Trametinib (n = 211)
  - 2-y PFS, 30%
  - 3-y PFS, 22%

- Dabrafenib + Placebo (n = 212)
  - 2-y PFS, 16%
  - 3-y PFS, 12%

Overall Survival

- Dabrafenib + Trametinib (n = 211)
  - 2-y OS, 52%
  - 3-y OS, 44%

- Dabrafenib + Placebo (n = 212)<sup>b</sup>
  - 2-y OS, 43%
  - 3-y OS, 32%

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

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>D+T</th>
<th>D+Pbo</th>
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<tbody>
<tr>
<td>211</td>
<td>137</td>
<td>110</td>
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<tr>
<td>84</td>
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</table>

<sup>a</sup> Intent-to-treat population; <sup>b</sup> Dabrafenib + placebo includes 26 patients who crossed over to combination arm; +, censored.
COMBI-d: Normal LDH\textsuperscript{a} and < 3 Disease Sites\textsuperscript{b}

**PFS**

- Dabrafenib + Trametinib (n = 76)
- Dabrafenib + Placebo (n = 96)

**OS**

- Dabrafenib + Trametinib (n = 76)
- Dabrafenib + Placebo (n = 96)

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

Presented By Keith Flaherty at 2016 ASCO Annual Meeting
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
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

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<th>Parameter</th>
<th>Value</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Protein</td>
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<td>(60 - 80)</td>
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<tr>
<td>Albumin</td>
<td>34 g/L</td>
<td>(35 - 50)</td>
</tr>
<tr>
<td>Globulin</td>
<td>24 g/L</td>
<td>(25 - 45)</td>
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<tr>
<td>Bilirubin</td>
<td>29 umol/L</td>
<td>(&lt; 20)</td>
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<tr>
<td>Bili(Conj)</td>
<td>10 umol/L</td>
<td>(&lt; 4)</td>
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<tr>
<td>ALP</td>
<td>108 U/L</td>
<td>(30 - 110)</td>
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<tr>
<td>Gamma GT</td>
<td>177 U/L</td>
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<tr>
<td>ALT</td>
<td>1200 U/L</td>
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<td>LD</td>
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<td>Calcium</td>
<td>2.21 mmol/L</td>
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<tr>
<td>Corr Ca</td>
<td>2.33 mmol/L</td>
<td>(2.10 - 2.60)</td>
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</table>

### eGFR

<table>
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<tr>
<th>Parameter</th>
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<tbody>
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<td>Protein</td>
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<td>Globulin</td>
<td>21 L g/L</td>
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<tr>
<td>Bilirubin</td>
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<tr>
<td>AST</td>
<td>16 U/L</td>
<td>(&lt; 35)</td>
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</table>
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%