**BRAF Mutations in Low-Grade Serous Ovarian Cancer and Response to BRAF Inhibition**

**Purpose** Low-grade serous ovarian carcinoma (LGSC) responds poorly to chemotherapy and is characterized by activating mutations in the Ras sarcoma–mitogen-activated protein kinase (RAS-MAPK) pathway, including oncogenic BRAF. However, response to BRAF inhibitors is tumor-type specific. Significant improvement in survival is seen in patients with BRAF-mutant melanoma, but other cancer types, such as colorectal cancers, are generally less sensitive. We examined the frequency and characteristics of BRAF-mutated LGSC and described the response to treatment with BRAF inhibitors.

**Patients and Methods** Mutations were assessed in LGSC (N = 65) by using targeted, exome, and whole-genome sequencing. Patient characteristics, treatment, and clinical outcome were assessed, and the median follow-up time was more than 5 years. BRAF inhibitors were trialed in two patients with a somatic BRAF V600E mutation: one patient received dabrafenib monotherapy and was monitored clinically, biochemically (cancer antigen [CA]-125 levels), and with positron emission tomography (PET) imaging. Expression of the BRAF V600E protein in this patient was assessed by immunohistochemistry.

**Results** Among patients with LGSC, nine (13.8%) of 65 had a somatic BRAF mutation. Of the nine patients with BRAF mutation–positive LGSC, four experienced progressive disease that did not respond to conventional chemotherapy. Two of the patients experienced progression quickly and died as a result of disease progression, and two received targeted treatment. Two patients with BRAF V600E mutation received BRAF inhibitors at relapse and both achieved durable responses.

**Conclusion** BRAF mutations are not uncommon in patients with LGSC and should be routinely tested, because BRAF inhibitors can be an effective treatment for these patients. The results highlight the need for targeted treatment in this rare tumor type, and a prospective study is needed to formally assess the response rate and clinical benefit.

**INTRODUCTION**

Epithelial ovarian cancer (EOC) is a heterogeneous disease composed of several histologic and molecular subtypes, and emerging molecular analyses are challenging longstanding clinical treatment paradigms. EOC subtypes are characterized by different gene expression and somatic mutation patterns and by varying degrees of sensitivity to current standard carboplatin-paclitaxel combination chemotherapy. The predominant type of EOC is serous carcinoma, which accounts for approximately 80% of occurrences. Serous carcinoma is then classified into two main subtypes: the more common and better characterized high-grade serous carcinoma, and the less common low-grade serous carcinoma (LGSC). LGSC generally is not responsive to standard platinum-based chemotherapy, and the outcome is poor in women who have residual disease after debulking surgery, which underscores the need for alternative therapeutic options.

LGSC is molecularly distinct from high-grade serous carcinoma and is characterized by activating mutations of the Ras sarcoma–mitogen-activated protein kinase (RAS-MAPK) pathway. It displays few genomic changes and is typically TP53 wild type. Oncogenic BRAF mutations, such as V600E, lead to constitutive activation of
the MAPK pathway and can be found in several cancer types, most often in melanoma. The reported frequency of BRAF mutations in LGSC varies from 2% to 33%, and these mutations also are found in up to 46% of serous borderline tumors. Clinical trials have shown impressive response rates to BRAF inhibitors in BRAF-mutant melanoma, and BRAF inhibitor use in metastatic melanoma is now considered standard of care. Responses in other tumor types, including gastrointestinal stromal tumor, thyroid papillary cancer, hairy cell leukemia, and high-grade colorectal neuroendocrine tumors, also have been reported. However, some cancer types, such as colorectal adenocarcinoma, have much lower response rates to BRAF inhibitors despite the presence of the same somatic BRAF mutations. Thus, although oncogenic BRAF represents a potential therapeutic target, responses vary according to tumor type, and clinical benefit is not always achieved. This inconsistency has led to large basket trials that assess the response to BRAF inhibitors in multiple BRAF-mutant cancers. However, definitive conclusions from assessment of response in rare tumor types remains difficult because of small patient numbers.

We present the characterization of BRAF mutations in patients with LGSC, including two patients with BRAF V600E mutation whose diseases demonstrated substantial clinical, biochemical, and radiologic responses after treatment with BRAF inhibitors.

PATIENTS AND METHODS

The study population consisted of women diagnosed with LGSC between 1992 and 2015 (N = 65). The women were identified in the Australian Ovarian Cancer Study (AOCS) or the Gynecologic Oncology Biobank at Westmead Hospital (GynBiobank, Sydney, NSW). We incorporated the shift from a three-tier grading system to a two-tier grading system, as recommended in the 2014 WHO classification of ovarian tumors. Patient cases of LGSC were identified from review of diagnostic pathology reports and independent review of hematoxylin and eosin–stained diagnostic slides by expert gynepathologists. In addition, grade 2 occurrences were screened for TP53 mutations, and only those that were wild type, consistent with a molecular classification of LGSC, were included in the LGSC cohort.

Clinical Definitions

Progression-free survival was calculated as the time interval from date of histologic or cytologic diagnosis to the date of first progression based on Gynecologic Cancer Intergroup (GCIG) criteria. Overall survival was calculated from date of diagnosis to date of death as a result of any cause. Treatment response was assigned according to GCIG cancer antigen (CA)–125 criteria. Briefly, 50% or greater reduction in serum CA-125 from an elevated pretreatment level, confirmed and maintained for at least 28 days, was considered a response. The reverse Kaplan-Meier method was used to quantify the follow-up time.

Study Oversight

Women recruited to AOCS and the GynBiobank provided written consent. The AOCS was approved by the human research ethics committee at the Peter MacCallum Cancer Centre, Queensland Institute of Medical Research, Westmead Hospital, and at all other participating hospitals. The GynBiobank and this study were approved by the Western Sydney Local Health District Human Research Ethics Committee.

Written informed consent was obtained from the patient treated with dabrafenib to include clinical information and imaging. This process also was approved by the Western Sydney Local Health District Human Research Ethics Committee.

Sequencing and Immunohistochemistry

Frozen or fixed tumor samples were sectioned, and hematoxylin and eosin stains were used to assess tumor content before and after serial sectioning for nucleic acid extraction. For samples that contained 70% or more tumor, 1 × 100 μm sections were used for DNA extractions. For samples that contained less than 70% tumor, needle dissection of tumor cells was performed on sections of up to 50 × 10 μm. Extractions were performed using the DNeasy blood and tissue kit or QIAamp DNA mini kit (Qiagen, Hilden, Germany). DNA was quantified with the Qubit dsDNA BR assay (Invitrogen, Carlsbad, CA).
Targeted multigene sequencing. Mutations in exon 15 of \textit{BRAF}, exon 2 of \textit{KRAS}, exon 20 of \textit{ERBB2}, and exons 2 to 11 of \textit{TP53} were screened by high-resolution melt analysis and validated by direct sequencing, as previously described.\textsuperscript{8,9} A subset of cases was screened by next-generation sequencing. Target enrichment of the DNA samples was performed according to the manufacturer's protocol.\textsuperscript{34} The polymerase chain reactions for each sample were pooled, and target enriched DNA samples were purified with Agencourt AMPure XP beads (Beckman Coulter, Indianapolis, IN). The DNA libraries were prepared according to Qiagen protocols.\textsuperscript{35} DNA libraries (> 4 nM) were sequenced on a MiSeq (Illumina, San Diego, CA) at the Australian Genome Research Facility (Melbourne, Victoria, Australia), with a read length of 2 × 150 base pairs. A sequencing coverage read depth of ×1,200 was achieved for each sample.

Exome and whole-genome sequencing. Whole-genome sequencing (WGS) and whole-exome sequencing (WES) data and analysis were obtained for 22 patient cases by using snap-frozen tumor tissue and matched normal DNA from peripheral blood lymphocytes, as previously described.\textsuperscript{8,36} Among patients with \textit{BRAF}-mutation positive LGSC, age at diagnosis ranged from 22 to 77 years (median, 51 years; Table 1). The majority had International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease at diagnosis (seven [78\%] of nine patients).

Clinical Features of \textit{BRAF} Mutation–Positive LGSC Occurrences

Treatment and Clinical Course in Patients With \textit{BRAF} Mutation–Positive LGSC After Disease Progression

Four patients experienced progression, and all four had relatively short progression-free survival (Table 1; Fig 2). None of these four patients responded to chemotherapy in the relapsed setting. The first two patients, patient case 6 and 8 (Table 1), received treatment with conventional chemotherapy and had poor overall survival (Figs 2A and 2B) compared with the two patients who received targeted treatment (Figs 2C and 2D).

Patient case 6 was a 51-year-old woman diagnosed with stage IIIC LGSC whose tumor was optimally debulked to no residual macroscopic disease (Fig 2A). The patient experienced disease progression within 5 months of completion of primary carboplatin and paclitaxel chemotherapy, and she began second-line chemotherapy with pegylated liposomal doxorubicin. There was no response by CA-125 criteria\textsuperscript{32}; subsequently, the patient received third-line etoposide chemotherapy but experienced disease progression within 5 months.
progression and died 2 months after the completion of treatment. Overall survival was less than 2 years from her initial diagnosis.

Patient case 8 was diagnosed with stage IV ovarian cancer at age 31 years (Fig 2B). She received three cycles of neoadjuvant chemotherapy (carboplatin plus paclitaxel) with no significant response by CA-125 criteria. She proceeded to surgery, and the tumor was debulked to ≤ 1 cm of residual disease; pathology confirmed grade 1 serous carcinoma that developed from borderline serous cystadenoma. After an additional five cycles of carboplatin and paclitaxel, her CA-125 measure decreased (51 U/mL) but did not normalize. Disease progression was evident within...
2 months of completion of chemotherapy: the CA-125 level increased to 502 U/mL, and the patient died a month later, less than a year from diagnosis.

Patient case 4 was a 22-year-old woman who presented with abdominal pain. Pelvic ultrasound revealed a complex ovarian mass, and the serum CA-125 level was significantly elevated (647 U/mL; normal range, < 35 U/mL). Surgery identified widespread peritoneal disease, and histopathology revealed a serious borderline tumor with invasive implants throughout the peritoneum, which reflected a FIGO stage of IIIB. The tumor was debulked to no macroscopic residual disease. Despite six cycles of chemotherapy with carboplatin and paclitaxel, her CA-125 level remained elevated (38 U/mL) at the end of primary treatment (Fig 2C), indicative of chemotherapy-resistant residual disease.

Eleven months later, imaging confirmed progressive LGSC that led to a secondary debulking surgery and additional chemotherapy. At additional disease progression, the patient entered a phase I trial of the BRAF inhibitor dabrafenib21 (GlaxoSmithKline, Sydney, Australia) and received 100 mg twice daily. Her best response according to RECIST 1.1 was stable disease and a 28% decrease of the target lesion.

During the study, an interruption in dabrafenib for toxicity resulted in a CA-125 spike to 238 U/mL, ascopubs.org/journal/po JCO™ Precision Oncology 5
which promptly decreased after resumption of dabrafenib. After 10 months of dabrafenib therapy, the patient stopped study participation because of a combination of toxicity and progressive disease.

After subsequent disease progression, the patient received chemotherapy with carboplatin plus gemcitabine and liposomal doxorubicin, but there was no response by CA-125 criteria. At the time of disease progression after chemotherapy, biopsy of supraclavicular and para-aortic lymph nodes confirmed the continued presence of \( \text{BRAF}^{V600E} \) mutation by immunohistochemistry (Figs 3B and 3C), and she resumed treatment with dabrafenib via a compassionate access scheme.

Table 2. Summary of Single Nucleotide Variants and Insertions or Deletions by Sample

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mutation Analysis†</th>
<th>No. of High-Confidence Mutations</th>
<th>No. of Deleterious Consequences</th>
<th>Driver Gene‡</th>
<th>Genes With Deleterious Mutation and No Evidence of Mutational Cancer Driver§</th>
</tr>
</thead>
<tbody>
<tr>
<td>11368</td>
<td>WES</td>
<td>110</td>
<td>30</td>
<td>( \text{BRAF}^{V600E} )</td>
<td>( \text{ATP2B4, CCHCR1, CD163, CTD-2132N18.3, DCAF8L2, DCHS1, DOCA2A, EPHIC1, FE4R1, GALNT3, GTF2C2, HLA-C, IFPO1, ITGA5, KLF2A, LCA10, NPY1R, OAS1, PLEC, PRMT10, SECISBP2L, SETDB1, SHOC2, SLC15A1, SYNE2, TEX15, TTN, ZNF710, ZRANB2} )</td>
</tr>
<tr>
<td>65917</td>
<td>WES</td>
<td>20</td>
<td>11</td>
<td>( \text{BRAF}^{V600E} )</td>
<td>( \text{BMP1, CA10, CACNA1C, CSMD1, DNM1, IFT172, KCNJ11, MAST2, OR1H1, STAT1} )</td>
</tr>
<tr>
<td>10693 (AOCS-002)</td>
<td>WGS</td>
<td>25</td>
<td>13</td>
<td>( \text{BRAF}^{V600E} )</td>
<td>( \text{CC2D2B, CNGB3, DDHD2, ERN1, HPGD, NAPRT1, NPR3, PTPRB, RPGRIP1L, SYT14, TDO2, TLL2} )</td>
</tr>
</tbody>
</table>

Abbreviations: AOCS, Australian Ovarian Cancer Study; WES, whole-exome sequencing; WGS, whole-genome sequencing.

*Published in Etemadmoghadam et al (2017).8
†Coding mutation; amino acid change.
‡Source: Integrative Oncogenomics.37

**Fig 2.** The serum cancer antigen (CA)-125 levels and treatment throughout the clinical course of patients: (A) patient case 6, publishing ID 10693; (B) patient case 8, publishing ID 11014; (C) patient case 4, publishing ID 65917; and (D) patient case 9, publishing ID 66198; which promptly decreased after resumption of dabrafenib. After 10 months of dabrafenib therapy, the patient stopped study participation because of a combination of toxicity and progressive disease.

After subsequent disease progression, the patient received chemotherapy with carboplatin plus gemcitabine and liposomal doxorubicin, but there was no response by CA-125 criteria. At the time of disease progression after chemotherapy, biopsy of supraclavicular and para-aortic lymph nodes confirmed the continued presence of \( \text{BRAF}^{V600E} \) mutation by immunohistochemistry (Figs 3B and 3C), and she resumed treatment with dabrafenib via a compassionate access scheme.
During treatment with dabrafenib 150 mg twice daily (50% higher than her previous dose), there was an impressive clinical response, which included reduced analgesic requirements, improved well-being, and marked reduction in the palpable supraclavicular lymph node. After 7 months of therapy, her CA-125 level decreased to within the normal range for the first time since diagnosis. A positron emission tomography/computed tomography scan confirmed a significant partial radiologic response to treatment (63% decrease in sum of diameters of measured lesions) and significantly fewer metabolically active lesions throughout almost all nodal regions and pulmonary nodules (Fig 4).

At the time of censoring, the patient continued to receive dabrafenib, and her CA125 had remained within normal range for 4 months. These data confirmed a complete response according to GCIG CA-125 criteria.32

The final patient, patient case 9, was a 71-year-old woman who was diagnosed with stage IV disease at diagnosis; she had a pleural effusion, and her CA-125 level was elevated to 275 U/mL (normal, < 36 U/mL). She received one cycle of neoadjuvant carboplatin and paclitaxel before hospital admission with a bowel obstruction, and she underwent debulking surgery. Histopathology confirmed LGSC, and mutation testing revealed a BRAF V600E mutation. With disease progression, she was enrolled into a BRAF inhibitor basket trial (Desai et al, manuscript in preparation) and has received treatment for more than 12 months. This patient experienced a partial radiologic response (Bo Gao, personal communication, December 2017) and normalization of her CA-125 level with treatment with a BRAF inhibitor (Fig 2D).

DISCUSSION

Here, we report clinical outcomes in, to our knowledge, one of the largest series of patients with BRAF mutation–positive LGSC reported to date. We also report the first, to our knowledge, response to the BRAF inhibitor dabrafenib in a patient who has LGSC with a somatic BRAF V600E mutation.

LGSC typically is TP53 wild type and commonly harbors RAS and RAF pathway mutations.9,14,18 This finding has led to clinical trials to evaluate MAPK/ERK kinase (MEK) inhibitor activity. A phase II trial to evaluate the response to the MEK inhibitor selumetinib in LGSC reported a promising response rate of 15%.39 Response was not associated with known BRAF/KRAS mutation status, although this may be due to the small number of cases with known mutations in the trial. It is unclear whether all mutation subtypes of LGSC respond similarly to MEK inhibition.

We found BRAF mutations in 13.8% (nine of 65) of patients with LGSC, which falls within the broad range reported previously (2% to 33%).11,14-16,40 This was similar to the 17.9% rate (10 of 56 patients) reported by Xing et al40 in a similarly sized cohort and was slightly higher than rate in the American Association for Cancer Research GENIE Project database, for which the frequency of patients with BRAF mutations in LGSC was four (7%) of 56 patients.41 The GENIE Project contains genomic records generated in CLIA/ISO–certified laboratories obtained at multiple tertiary referral centers41 and may be enriched for patients with late-stage disease who seek biomarker–driven clinical trials, whereas patients enrolled in this study were prospectively recruited from clinics.

Some studies have suggested that BRAF V600E mutations in LGSC are rare and are associated with early-stage disease and improved prognosis.15,16,42 However, we found that most women with a BRAF mutation–positive carcinoma were diagnosed at an advanced stage. In our cohort, most tumors were able to be debulked
to no residual disease, which is associated with improved prognosis. However, in the relapse setting, *BRAF* V600E mutation–positive LGSC was not responsive to chemotherapy. Four of the nine patients with *BRAF* mutation–positive disease experienced progression soon after primary treatment. Disease in all four responded poorly to chemotherapy, which is characteristic of LGSC. Two patients received conventional treatment and died within 2 years of diagnosis. Two others received BRAF inhibitors, and both achieved sustained response.

Patient case 4 initially received dabrafenib as part of a dose-finding phase I trial, and, although some response was observed with deceased serum CA-125 levels, a much more profound response was seen when the patient was retreated with dabrafenib 46 months later. The explanation for the improved response with subsequent dabrafenib treatment is potentially multifactorial and may include the increased dosage, in line with current melanoma dosing guidelines, which suggests that her original dose was subtherapeutic. The patient also had a 25-kg weight loss between dabrafenib treatment periods, although there is no evidence to date that the dabrafenib dose requires adjustment for weight. There also is emerging evidence that BRAF inhibitors may act in part via an effect on host immunity, and it is possible that an uncharacterized immunologic component contributed to the response in this patient.

Consistent with our findings, responses to another BRAF inhibitor, vemurafenib, have been reported in LGSC. Combe et al reported a response in a women who, similar to our patient, was heavily pretreated; she achieved a durable partial response to vemurafenib according to RECIST and CA-125 criteria for more than 21 months. Similarly, in a large basket trial of vemurafenib in multiple cancer types, the one patient with LGSC also showed a sustained (> 12 months) partial response to vemurafenib. Patient case 9 in this study also was
the only patient with LGSC in a basket trial of a novel BRAF inhibitor (Desai et al, manuscript in preparation); her disease has shown a sustained response, which provides additional evidence that BRAF V600E mutation–positive tumors in LGSC are broadly responsive to BRAF inhibition.

In conclusion, recurrent LGSC is relatively chemotherapy resistant, and targeted treatment may play an important role in improvement of patient outcomes. Our results are consistent with recent reports of response to BRAF inhibition in at least two other studies30,46 and suggest that BRAF inhibitors may be an effective option in patients with relapsed, BRAF mutation–positive LGSC.

Moreover, the frequency in which these mutations were detected indicates the importance of routine molecular testing for BRAF V600E mutations in all patients with advanced LGSC. The results also highlight the importance of novel clinical trial designs, such as platform and basket trials, because traditional clinical trials are unlikely to be successfully identify effective treatments for rare ovarian cancer subtypes.

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AUTHOR CONTRIBUTIONS
Conception and design: Tanja Moujaber, Paul R. Harnett, Anna deFazio
Collection and assembly of data: Tanja Moujaber, Dariush Etemadmoghadam, Catherine J. Kennedy, Yoke-Eng Chiew, Catherine Saunders, Casina Kan, Sian Fereday, Nadia Traficante, Sean M. Grimmond, Alexander Dobrovic, Paul R. Harnett, Anna deFazio
Provision of study material or patients: Tanja Moujaber, Catherine J. Kennedy, Gerard V. Wain, Russell Hogg, Sian Fereday, Nadia Traficante, Alexander Dobrovic, Anna deFazio
Administrative support: Sian Fereday, Anna deFazio
Financial support: Anna deFazio
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Tania Moujaber
No relationship to disclose

Dariush Etemadmoghadam
No relationship to disclose

Catherine J. Kennedy
No relationship to disclose

Yoke-Eng Chiew
No relationship to disclose

Rosemary L. Balleine
No relationship to disclose

Catherine Saunders
Employment: Macquarie Medical Imaging

Gerard V. Wain
No relationship to disclose

Bo Gao
No relationship to disclose

Russell Hogg
No relationship to disclose

Sivatharsny Sirangan
No relationship to disclose

Casina Kan
No relationship to disclose

Sian Fereday
Research Funding: AstraZeneca (Inst)

Nadia Traficante
Research Funding: AstraZeneca (Inst)

Ann-Marie Patch
No relationship to disclose

John V. Pearson
Stock and Other Ownership Interests: Genomioa
Research Funding: BGI

Nicola Waddell
No relationship to disclose

Sean M. Grimmond
Honoraria: Angen
REFERENCES


Appendix

Australian Ovarian Cancer Study Group

Management group.

D. Bowtell, Peter MacCallum Cancer Centre, East Melbourne and University of Melbourne, Parkville, Victoria, Australia; and Imperial College London, London, England, United Kingdom; G. Chenevix-Trench, A. Green, and P. Webb, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; A. DeFazio, Westmead Institute for Medical Research, University of Sydney and Westmead Hospital, Sydney, New South Wales, Australia; and D. Gertig, University of Melbourne, Parkville, Victoria, Australia

Project and Data Managers.

N. Traficante and S. Fereday, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; S. Moore, K. Harrap, T. Sadkowsky, and N. Pandeya, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; J. Hung, Westmead Hospital, Westmead, Sydney, New South Wales, Australia

Research nurses and assistants.

M. Malt, B. Alexander, P. Ashover, S. Brown, T. Corrish, L. Green, L. Jackman, K. Ferguson, K. Martin, A. Martyn, and B. Ranieri, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; A. Mellon and R. Robertson, John Hunter Hospital, New Lambton, New South Wales, Australia; T. Vanden Bergh, M. Jones, and P. Mackenzie, Royal Hospital for Women, Randwick, New South Wales, Australia; J. Maidens, Royal North Shore Hospital, St Leonards, New South Wales, Australia; K. Nattress, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia; Y.E. Chiew, A. Stenlake, and H. Sullivan, Westmead Hospital, Westmead, Sydney, New South Wales, Australia; J. White, Royal Adelaide Hospital, Adelaide, South Australia, Australia; V. Jayde, Royal Hobart Hospital, Hobart, Tasmania, Australia; P. Mamers, Monash Medical Centre, Clayton, Victoria, Australia; L. Bowes, L. Galletta, D. Giles, J. Hendley, and K. Alsop, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; C. Ball and C. Young, King Edward Memorial Hospital, Subiaco, Western Australia, Australia; T. Schmidt, H. Shirley, S. Viduka, Hoa Tran, Sanela Bilic, and Lydia Glavinas, St John of God Pathology, Osborne Park, Western Australia, Australia; and Julia Brooks, St John of God Hospital, Subiaco, Western Australia, Australia
Clinical and scientific collaborators.

R. Stuart-Harris, Canberra Hospital, Garran, Australian Capitol Territory, Australia; F. Kirsten, Bankstown Hospital, Bankstown, New South Wales, Australia; J. Rutovitz, Integrated Cancer Centre, Wahroonga, New South Wales, Australia; P. Clingan and A. Glasgow, Wollongong Hospital, Wollongong, New South Wales, Australia; A. Proietto, S. Byrne, and G. Otton, John Hunter Hospital, New Lambton, New South Wales, Australia; J. Shannon, Nepean Hospital, Kingswood, New South Wales, Australia; T. Bonaventura and J. Stewart, Newcastle Mater Misericordiae Hospital, Waratah, New South Wales, Australia; S. Begbie, Port Macquarie Base Hospital, Port Macquarie, New South Wales, Australia; D. Bell, S. Baron-Hay, A. Ferrier (deceased), G. Gard, D. Nevell, N. Pavlakis, S. Valmadre, and B. Young, Royal North Shore Hospital, St Leonards, New South Wales, Australia; C. Camaris, R. Crouch, L. Edwards, N. Hacker, D. Marsden, and G. Robertson, Royal Hospital for Women, Randwick, New South Wales, Australia; P. Beale, J. Beith, J. Carter, C. Dalrymple, R. Houghton, and P. Russell, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia; M. Links, St George Hospital, Kogarah, New South Wales, Australia; J. Grygiel, St Vincent’s Hospital, Darlinghurst, New South Wales, Australia; J. Hill, Wagga Wagga Base Hospital, Wagga Wagga, New South Wales, Australia; A. Brand, K. Byth, R. Jaszewski, R. Sharma, P. Harnett, and G. Wain, Westmead Hospital, Westmead, Sydney, New South Wales, Australia; M. Friedlander, Prince of Wales Hospital, Sydney, Australia; B. Ward and D. Papadimos, Mater Misericordiae Hospital, South Brisbane, Queensland, Australia; A. Crandon, M. Cummings, K. Horwood, A. Obermair, L. Perrin, D. Wyld, and J. Nicklin, The Royal Brisbane and Women’s Hospital, Herston, Queensland, Australia; J. Nicklin, Wesley Hospital, Auchenflower, Queensland, Australia; M. Davy, M.K. Oehler, C. Hall, and T. Dodd, Royal Adelaide Hospital, Adelaide, South Australia, Australia; T. Healy and K. Pittman, Burnside Hospital, Toorak Gardens, South Australia, Australia; D. Henderson, Flinders Medical Centre, Bedford Park, South Australia, Australia; J. Miller and J. Pierdes, Queen Elizabeth Hospital, Woodville South, South Australia, Australia; P. Blomfield, D. Chaliss, R. McIntosh, and A. Parker, Royal Hobart Hospital, Hobart, Tasmania, Australia; B. Brown and R. Rome, Freemasons Hospital, East Melbourne, Victoria, Australia; D. Allen, P. Grant, S. Hyde, R. Laurie, and M. Robbie, Mercy Hospital for Women, Heidelberg, Victoria, Australia; D. Healy, T. Jobling, T. Manolitsas, J. McNealage, P. Rogers, B. Susil, E. Sumithran, and I. Simpson, Monash Medical Centre, Clayton, Victoria, Australia; K. Phillips, D. Rischin, S. Fox, D. Johnson, S. Lade, M. Loughrey, N. O’Callaghan, and W. Murray, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; P. Waring, University of Melbourne, Parkville, Victoria, Australia; V. Billson, J. Pyman, D. Neesham, and M. Quinn, The Royal Women’s Hospital, Parkville, Victoria, Australia; C. Underhill, Border Medical Oncology, Wodonga, Victoria, Australia; R. Bell, Andrew Love Cancer Centre, Geelong, Victoria, Australia; L.F. Ng, Ballarat Base Hospital, Ballarat, Victoria, Australia; R. Blum, Bendigo Health Care Group, Bendigo, Victoria, Australia; V. Ganju, Peninsula Health, Frankston, Victoria, Australia; I. Hammond, Y. Leung, and A. McCartney (deceased), King Edward Memorial Hospital, Subiaco, Western Australia, Australia; M. Buck, Mount Hospital, Perth, Western Australia, Australia; I. Havis; Bar-Ilan University, Safed, Israel; D. Purdie, D. Whiteman, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia; and N. Zeps, St John of God Pathology, Osborne Park, Western Australia, Australia.