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

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abstract

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.

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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.^{1–3} 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,^{4,5} and the outcome is poor in women who have residual disease after debulking surgery,^{6–8} 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.^{9–12} 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.¹³ The reported frequency of *BRAF* mutations in LGSC varies from 2% to 33%^{11,14-16} and these mutations also are found in up to 46% of serous borderline tumors.^{17,18}

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.^{19,20} 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.²¹⁻²⁶ 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.²⁷⁻²⁹ 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.³⁰ 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.³¹ Patient cases of LGSC were identified from review of diagnostic pathology reports and independent review of hematoxylin and eosin–stained diagnostic slides by expert gynecopathologists. 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.³² 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.³² 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.³³

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 *BRAF*, exon 2 of *KRAS*, exon 20 of *ERBB2*, and exons 2 to 11 of *TP53* were screened by high-resolution melt analysis and validated by direct sequencing, as previously described.^{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.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.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.^{8,36}

Immunohistochemistry. Samples of the ovarian tumor from the primary surgery specimen and in biopsies at disease relapse were stained for mutated *BRAF* V600E with a mutation-specific monoclonal antibody (mouse antihuman *BRAF* V600E monoclonal antibody, clone VE1; Spring Biosciences, Pleasanton, CA) by using the Ventana BenchMark Ultra immunohistochemistry staining module (Ventana Medical Systems, Tucson, AZ) with a 1-in-200 antibody dilution. Results were reviewed by a pathologist (R.L.B.).

RESULTS

Frequency of *BRAF* Mutations in LGSC

BRAF mutation-positive patient cases were identified among an LGSC cohort of 65 patients (by WES/WGS, n = 22; by targeted multigene sequencing, n = 43). Molecular characterization revealed that nine (13.8%) of 65 patients had a *BRAF* mutation. Representative photomicrographs of the *BRAF* mutation-positive tumors are shown in Figure 1. Most (eight [89%] of nine) were *BRAF* V600E mutations, a shared hot-spot mutation locus found in diverse cancer

types; one was a *BRAF* L597R mutation, an uncommon missense variant (Table 1).

In three *BRAF*-mutant tumors, additional variants identified by WES and WGS predicted alteration in the protein sequence (range, 13 to 30 variations per patient case; Table 2) at lower allele frequencies than the *BRAF* mutations, which suggests subclonal events.^{8,37} There was no evidence of additional driver mutations, and no genes with deleterious mutations—other than *BRAF*—were common to the three patient cases.

Clinical Features of *BRAF* Mutation-Positive LGSC Occurrences

Among patients with *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).

All patients with *BRAF*-mutated LGSC had surgery as part of primary treatment, and most tumors (seven [78%] of nine) were optimally debulked to no macroscopic residual disease. The median follow-up time was 61.5 months, and five (56%) of the nine patients remained progression free (Table 1).

Treatment and Clinical Course in Patients With *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 criteria³²; subsequently, the patient received third-line etoposide chemotherapy but experienced disease

Fig 1. Representative histologic sections of *BRAF*-mutated low-grade serous ovarian carcinoma (LGSC) occurrences. Sections (4 μ m) from formalin-fixed, paraffin-embedded tumor tissue blocks were stained with hematoxylin and eosin. (A) Patient case 1, publishing ID 65928; (B) patient case 2, publishing ID 11368; (C) patient case 3, publishing ID 5711; (D) patient case 4, publishing ID 65917; (E) patient case 5, publishing ID 65854; (F) patient case 6, publishing ID 10693; (G) patient case 7, publishing ID 9125; (H) patient case 8, publishing ID 11014; and (I) patient case 9, publishing ID 66198.

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

Table 1. Clinicopathologic Characteristics of *BRAF* Mutation–Positive Low-Grade Serous Ovarian Cancer Occurrences

Characteristic	Patient Case									Summary
	1	2	3	4	5	6	7	8	9	
Publishing ID	65928	11368	5711	65917	65854	10693	9125	11014	66198	N = 9
Age at diagnosis, years	45	77	68	22	40	51	52	31	73	Median, 51; range, 22–77
FIGO stage	IA	IA	IIIA	IIIB	IIIC	IIIC	IIIC	IV	IV	I: 2 of 9 (22%)
										III: 5 of 9 (56%)
										IV: 2 of 9 (22%)
Mutation	<i>BRAF</i> V600E	<i>BRAF</i> V600E	<i>BRAF</i> V600E	<i>BRAF</i> V600E	<i>BRAF</i> V600E	<i>BRAF</i> L597R	<i>BRAF</i> V600E	<i>BRAF</i> V600E	<i>BRAF</i> V600E	<i>BRAF</i> V600E: 8 of 9 (89%)
										<i>BRAF</i> L597R: 1 of 9 (11%)
Method	TS*	WES*	TS*	WES*	TS*	WGS*	TS†	TS	TS	
Preoperative CA-125, U/mL	325	1824	1000	647	161	140	309	245	275	Mean, 547; range 140–1,824
CA-125 normal range, U/mL	< 35	< 35	< 24	< 35	< 35	< 30	< 35	< 35	< 36	Upper limits of normal, 24–35 U/ml
Residual disease after cytoreductive surgery, cm	Nil	Nil	Nil	Nil	Nil	Nil	Nil	≤ 1	> 2	Nil: 7 of 9 (78%)
Primary chemotherapy (carboplatin + paclitaxel)	No	No	No	Yes	Yes	Yes	Yes	Yes‡	Yes‡	Yes: 6 of 9 (67%)
Progression	No	No§	No	Yes	No	Yes	No	Yes	Yes	No: 5 of 9 (56%)
Progression-free survival, months	36.9	> 38‡	11.9	13.8	61.5	8.28	77.1	7.8	1	
Alive	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes: 6 of 9 (67%)
Overall survival, months	36.9	68	11.9	78.6	61.5	23	77.1	8.9	24	

Abbreviations: CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; TS, targeted sequencing; WES, whole-exome sequencing; WGS whole-genome sequencing.

*Etemadmoghadam et al (2017).⁸

†Emmanuel et al (2014).⁹

‡Received neoadjuvant chemotherapy.

§Lost to follow-up after 38 months (ie, no progression information between 38 months and death at 68 months, and cause of death unknown).

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 serous 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 1.1³⁸ during the trial 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,

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

Sample	Mutation Analysis [*]	No. of High-Confidence Mutations	No. of Deleterious Consequences	Driver Gene [†]	Genes With Deleterious Mutation and No Evidence of Mutational Cancer Driver [‡]
11368	WES	110	30	<i>BRAF</i> (c.1799T>A; p.V600E)	<i>ATP2B4, CCHCR1, CD163, CTD-2132N18.3, DCAF8L2, DCHS1, DOC2A, EFHC1, FEAR1, GALNT3, GTF3C2, HLA-C, IFFO1, ITGAV, KAT2A, LCA10, NPY5R, OAS1, PLEC, PRMT10, SECISBP2L, SETDB1, SHOC2, SLC15A1, SYNE2, TEX15, TTN, ZNF710, ZRANB2</i>
65917	WES	20	11	<i>BRAF</i> (c.1799T>A; p.V600E)	<i>BMPI, CA10, CACNA1C, CSMD1, DNMI, IFT172, KCNJ11, MAST2, OR11L1, STAT1</i>
10693 (AOCS-002)	WGS	25	13	<i>BRAF</i> (c.1790T>G; p.L597R)	<i>CC2D2B, CNGB3, DDHD2, ERN1, HPGD, NAPRT1, NPR3, PTPRB, RPGRIP1L, SYT14, TDO2, TLL2</i>

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 *BRAF* V600E mutation by immunohistochemistry (Figs 3B and 3C), and she resumed treatment with dabrafenib via a compassionate access scheme.

Fig 3. Expression of *BRAF* V600E in patient case 4: immunohistochemical staining that used an antibody specific for *BRAF* V600E in formalin-fixed, paraffin-embedded tumor tissue sections of (A) left ovarian tumor from the primary surgical specimen, (B) left supraclavicular fossa lymph node core biopsy before second dabrafenib treatment at 78 months, and (C) left para-aortic lymph node core biopsy before second dabrafenib treatment at 78 months. The bar indicates a 50-µm scale.

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

Fig 4. Positron emission tomography/computed tomography (PET/CT) images for patient case 4. [18F]-fluorodeoxyglucose (¹⁸F-FDG) PET/CT (Siemens Biograph mCT, Knoxville, TN) images (A, B, and C) before and (D, E, and F) after 7 months of second dabrafenib treatment that indicated response to treatment with decrease in size and metabolic activity of lesions. Green arrows, physiologic uptake in heart, kidneys, and bladder. The axial images of the left medial supraclavicular and deep paravertebral lesions (B) before and (E) after 7 months of second treatment with dabrafenib. The right common iliac node (C) before and (F) after 7 months of second treatment with dabrafenib.

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.^{4,5} 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,²¹ and, although some response was observed with decreased 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.⁴³ 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.⁴³ There also is emerging evidence that *BRAF* inhibitors may act in part via an effect on host immunity,^{44,45} 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 al⁴⁶ reported a response in a woman 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.⁴⁶ 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.³⁰ 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 studies^{30,46} 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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