REVIEW

New therapeutic opportunities for women with low-grade serous ovarian cancer

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Abstract

Low-grade serous ovarian cancer (LGSC) is a morphologically and molecularly distinct subtype of ovarian cancer, accounting for ~10% of serous carcinomas. Women typically present at a younger age and have a protracted clinical course compared with the more common, high-grade serous ovarian cancer. Currently, the primary treatment of LGSC is the same as other epithelial ovarian cancer subtypes, with treatment for most patients comprised of debulking surgery and platinum/taxane chemotherapy. Primary surgical cytoreduction to no visible residual disease remains a key prognostic factor; however, the use of platinum-based chemotherapy in both upfront and relapsed setting is being questioned due to low response rates in LGSC. Most LGSC expresses steroid hormone receptors, and selected patients may benefit from endocrine maintenance therapy following chemotherapy, in particular, those with evidence of residual disease at completion of surgery. In the recurrent setting, while hormonal therapies may offer disease stabilisation with relatively low toxicity, objective response rates remain low. Strategies to increase response rates, including combining with CDK4/6 inhibitors, are being investigated. LGSC has a high prevalence of activating somatic mutations in mitogen-activated protein kinase pathway genes, most commonly in KRAS, BRAF and NRAS. Trametinib, a MEK inhibitor, has shown efficacy over chemotherapy and endocrine therapy. The use of combination targeted therapies, immunotherapy and anti-angiogenic agents, remain active areas of investigation for the treatment of LGSC.

Key Words
- ovarian cancer
- low-grade serous carcinoma
- chemotherapy
- endocrine therapy
- MAPK pathway inhibitors

Introduction

Low-grade serous cancer of the ovary, fallopian tube or peritoneum (LGSC) is a rare subtype of epithelial ovarian carcinoma. Recognised for many years as having distinct histopathologic features, it is only on the basis of more recent molecular characterisation that LGSC has been fully designated as distinct from high-grade serous cancer (HGSC), with different pathogenesis, treatment response and clinical course.

The benefit of this revised classification has been an acceleration in studies of LGSC, and a search for effective treatments that accepts these are different from HGSC. A major challenge is to discern characteristics of LGSC...
from the large body of pre-existing literature that regarded LGSC and HGSC as belonging to a spectrum of disease and variously discriminated by a number of histopathologic grading systems.

**Histopathologic classification of ovarian cancer**

In general, histopathologic grading of cancer is a systematic description of the extent to which cancer tissues resemble their normal tissue counterparts. Until recently, there was no internationally accepted consensus for grading serous ovarian cancer, with two or three-tiered systems variously used. The most widely used included the Shimizu/Silverberg, the International Federation of Gynaecology and Obstetrics (FIGO), World Health Organisation (WHO) and the Gynaecologic Oncology Group (GOG) grading systems (Silverberg 2000). In the Shimizu/Silverberg system, ovarian cancers were graded 1, 2 or 3 based on the dominant architectural pattern, the degree of cytologic atypia as well as the mitotic index. The FIGO system was based on architectural features, with the grade of the tumour depending on the proportion of solid tumour compared with glandular or papillary structures. In this system, grade 1 equated to less than 5% solid tumour; grade 2, 5–50% solid growth and grade 3, greater than 50% solid growth.

A two-tier grading system emerged with Malpica et al. and the MD Anderson Cancer Centre (MDACC) proposing a reproducible two-tier system for histopathologic grading which they had been developing and testing for over 15 years at their centre. This classification differentiated LGSC from HGSC based primarily on nuclear atypia with the secondary feature of mitotic rate (Fig. 1) (Malpica et al. 2004). Another binary classification developed at the Washington Hospital Centre was tested against the MD Anderson version, but the latter was reported to be more promising and clinically meaningful (Seidman et al. 2006). Since the introduction of the ‘Malpica’ or MD Anderson system, other studies have further strengthened the evidence that the binary system is more predictive of outcome than three-tiered grading (Vang et al. 2008, Bodurka et al. 2012, Hannibal et al. 2012).

A change in the WHO guidelines, released in 2014, recommended differentiating LGSC and HGSC. Of note, the recommendation was to use a combination of histopathologic features and p53 immunohistochemical staining patterns associated with underlying TP53 mutations that are characteristic of HGSC (Kurman et al. 2014). Cases with ‘moderate’ differentiation, or grade 2 in a three-tier grading system, can be difficult to classify based on histology alone. The combination of histopathology with molecular features, including TP53 mutation, represents an advance in the accurate separation of LGSC and HGSC (Emmanuel et al. 2014).

**Clinical epidemiology of LGSC**

Historical inconsistency in the definition of LGSC represents a major impediment to understanding the epidemiology and clinical features of this disease from published reports. Notwithstanding this limitation, LGSC is considered to account for under 10% of serous cancers with variation in the proportion depending on the classification system being used. Plaxe reported a rate of 6.3% grade 1 serous cancers among 12,000 ovarian cancer cases in the US Surveillance, Epidemiology and End Results (SEER) registry using the 1–4 grading system where grades 2–4 were considered high grade (Plaxe 2008). Bodurka et al. reported 8.7% of LGSC using the recent two-tier MD Anderson classification (Bodurka et al. 2012).

The same problem of interpretation affects the analysis of other clinical parameters. However, a consistent finding is that LGSC occurs in a younger population than HGSC with median age at diagnosis ranging from 43 to 57 years.

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**Figure 1**

Histopathological features of low-grade serous and high-grade serous ovarian cancer. (A) Low-grade serous cancer showing mild nuclear atypia, compared with high-grade serous cancer (B) which is characterised by marked nuclear pleomorphism and prominent mitoses including atypical forms (arrow). (scale bar: 250 µm).

The majority of women with serous cancers present with advanced disease, regardless of subtype. HGSC is well recognised to present in advanced stages at diagnosis, and recent studies in LGSC have shown similar patterns. In a study that included patients with stages II–IV disease LGSC (MD Anderson two-tier system), 90% of patients presented with stage III disease (Gershenson et al. 2006). Similarly, Fader et al. found that 87% of patients with LGSC (grade 1 used as a surrogate for low grade) presented with stage III disease (Nickles Fader et al. 2013).

In general, overall survival (OS) has been found to be more favourable in LGSC compared to HGSC. In women with LGSC, overall survival and clinical outcome are excellent with surgical excision alone, if the disease is confined to the ovary (stage 1). However, extraovarian spread at diagnosis, the most common presentation, is associated with poor outcome (Ali et al. 2013).

Using a classification consistent with recent guidelines, Gershenshen et al. showed a median OS of 81.8 months in women with stages II–IV LGSC (Gershenson et al. 2006). Plaxe reported mean OS of 99 months in grade 1 cases from the SEER registry, compared with 57 months in grades 2–4 cases (stages I–IV), and median overall survival of 85 months in stages II–IV grade 1 cases, compared with 36 months in the grades 2–4 cases (Plaxe 2008). Borduca et al. reported median OS in LGSC as high as 126 months, although this study had a smaller number of cases ($n = 21$) (Bodurka et al. 2012).

In contrast to the above studies, an analysis by Ali et al. of 32 women with stages II–IV serous ovarian cancers suggested that patients with LGSC had a similar outcome to HGSC with no significant difference in overall survival (Ali et al. 2013). In keeping with these findings, other studies have shown that patients with LGSC who had residual disease following debulking surgery had similar outcomes to their HGSC counterparts (Fader et al. 2014, Etemadmoghadam et al. 2017).

Other clinical associations of LGSC include lower levels of the ovarian cancer serum tumour marker cancer antigen-125 (CA-125) at presentation compared to HGSC (grade 1 vs grades 2–3) and fewer patients with ascites at diagnosis, 63.1% compared to 75.7% in HGSC ($P < 0.001$) (Fader et al. 2014).

## Alternations in cancer driver genes in LGSC

HGSC is characterised by $TP53$ mutations in almost 100% of cases, while LGSC is almost always $TP53$ WT (Table 1) (Singer et al. 2005, Ahmed et al. 2010, Emmanuel et al. 2014). Mutations in $BRCA1$ and $BRCA2$ genes, as well as in other homologous DNA repair-related genes such as $BRIP1$, $CHEK2$ and $RADS1C$ are also frequently identified in HGSC and can be either inherited or somatic (Patch et al. 2015). In contrast, LGSC is characterised by somatic MAPK pathway mutations (Singer et al. 2003a,b, 2005, Kuo et al. 2009, Ahmed et al. 2010, Jones et al. 2012, Emmanuel et al. 2014, Hunter et al. 2015, Etemadmoghadam et al. 2017, Van Nieuwenhuysen et al. 2019).

Abnormalities in MAPK pathway genes are commonly found in cancer and include activating mutations in $KRAS$ and $BRAF$ which promote tumourigenesis through constitutive activation of MAPK/ERK pathway (Fig. 2). Targeting mutations in this pathway, such as the use of BRAF and MEK inhibitors in $BRAF$ mutant melanoma, have resulted in improved clinical outcomes (Chapman et al. 2011). These agents, as well as others

### Table 1  Comparison of characteristics between low-grade and high-grade serous cancer.

<table>
<thead>
<tr>
<th></th>
<th>Low-grade serous cancer</th>
<th>High-grade serous cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Rare (~10% of serous ovarian cancer)</td>
<td>Common (~90% of serous ovarian cancer)</td>
</tr>
<tr>
<td>Histological</td>
<td>Uniform cells with mild to moderate nuclear atypia and a low mitotic index</td>
<td>Pleomorphic cells with marked nuclear atypia and a high mitotic index</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Commonly associated with SBT (60%), progression from SBT</td>
<td>STIC precursor; less commonly associated with SBT (2–12%)</td>
</tr>
<tr>
<td>Molecular profile</td>
<td>Frequent MAPK pathway mutations, $TP53$ wildtype, low-level CNV</td>
<td>Almost ubiquitous mutations in $TP53$, common mutations in HR genes including $BRCA1/2$, high CNV</td>
</tr>
<tr>
<td>IHC staining</td>
<td>$p53$ 'wildtype' staining, high expression of ER and PR</td>
<td>$p53$ ‘overexpressed’ or completely absent, high expression of Ki-67</td>
</tr>
<tr>
<td>Clinical</td>
<td>Younger (median 43–57 years)</td>
<td>Older (median ~62 years)</td>
</tr>
<tr>
<td></td>
<td>Less responsive to chemotherapy (4%)</td>
<td>Responsive to chemotherapy (50–80%)</td>
</tr>
<tr>
<td></td>
<td>Slow progression</td>
<td>Rapid progression</td>
</tr>
</tbody>
</table>

CNV, gene copy number variation; ER, oestrogen receptor; HR, homologous recombination DNA repair; IHC, immunohistochemistry; PR, progesterone receptor; SBT, serous borderline tumour; STIC, serous tubal intraepithelial carcinoma.
targeting MAPK and related pathways, have since been investigated in a number of other tumour types.

The reported frequency of MAPK pathway gene mutations in LGSC varies widely, in part due to differences in histopathologic grading systems, inclusion of serous borderline tumours (SBT) in study cohorts and in the mutation panels and methods of detection.

**KRAS mutations in LGSC**

The frequency of KRAS mutations ranges from 18.6 up to 54.5% (Table 2). An early study by Singer et al. reported the highest frequency of KRAS mutations (54.5%) in a cohort of 22 invasive micropapillary serous carcinomas which likely consists of cases indicative of LGSC. The same group reported KRAS mutations in ~35% of 22 invasive micropapillary serous carcinoma which included some of the same cases as the previous publication (Singer et al. 2002, 2003a). A subsequent study published by Wong et al. reported 18.6% frequency of KRAS mutations in 43 LGSC cases (Wong et al. 2010), while Jones et al. reported 26.7% in 15 cases. More recently, in LGSC cohorts using contemporary classifications, similar frequencies of KRAS mutations have been reported, with 18/79 (22.8%) in...
Table 2  Summary of KRAS, BRAF and NRAS mutation frequencies found in LGSC.

<table>
<thead>
<tr>
<th>Mutated gene</th>
<th>Reference</th>
<th>Cohort</th>
<th>Cases with mutations</th>
<th>Cases tested</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Singer et al. 2002</td>
<td>MPSC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>22</td>
<td>54.5</td>
</tr>
<tr>
<td></td>
<td>Singer et al. 2003a</td>
<td>MPSC</td>
<td>NR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td>Wong et al. 2010</td>
<td>LGSC</td>
<td>8</td>
<td>43</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>Jones et al. 2012</td>
<td>LGSC</td>
<td>4</td>
<td>15</td>
<td>26.7</td>
</tr>
<tr>
<td></td>
<td>Gershenson et al. 2015</td>
<td>LGSC</td>
<td>18</td>
<td>79</td>
<td>22.8</td>
</tr>
<tr>
<td></td>
<td>Hunter et al. 2015</td>
<td>LGSC</td>
<td>4</td>
<td>19</td>
<td>21.1</td>
</tr>
<tr>
<td></td>
<td>Etemadmoghadam et al. 2017</td>
<td>LGSC</td>
<td>15</td>
<td>51</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td>Xing et al. 2017</td>
<td>LGSC</td>
<td>16</td>
<td>56</td>
<td>28.6</td>
</tr>
<tr>
<td></td>
<td>Cheasley et al. 2021</td>
<td>LGSC</td>
<td>20</td>
<td>71</td>
<td>28.2</td>
</tr>
<tr>
<td></td>
<td>Total, %</td>
<td></td>
<td>97</td>
<td>356</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>AACR GENIE Cohort&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>69</td>
<td>210</td>
<td>32.9</td>
</tr>
<tr>
<td>BRAF</td>
<td>Singer et al. 2003a</td>
<td>MPSC</td>
<td>NR</td>
<td>22</td>
<td>33.0</td>
</tr>
<tr>
<td></td>
<td>Wong et al. 2010</td>
<td>LGSC</td>
<td>1</td>
<td>43</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Jones et al. 2012</td>
<td>LGSC</td>
<td>3</td>
<td>15</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>Bossmüller et al. 2013</td>
<td>LGSC</td>
<td>1</td>
<td>7</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>Grisharn et al. 2013</td>
<td>LGSC</td>
<td>1</td>
<td>19</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Gershenson et al. 2015</td>
<td>LGSC</td>
<td>3</td>
<td>79</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Hunter et al. 2015</td>
<td>LGSC</td>
<td>3</td>
<td>19</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Etemadmoghadam et al. 2017</td>
<td>LGSC</td>
<td>6</td>
<td>51</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>Xing et al. 2017</td>
<td>LGSC</td>
<td>10</td>
<td>56</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td>Cheasley et al. 2021</td>
<td>LGSC</td>
<td>9</td>
<td>71</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>Total, %</td>
<td></td>
<td>37</td>
<td>360</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>AACR GENIE Cohort&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>20</td>
<td>210</td>
<td>9.5</td>
</tr>
<tr>
<td>NRAS</td>
<td>Emmanuel et al. 2014</td>
<td>LGSC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5</td>
<td>58</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Hunter et al. 2015</td>
<td>LGSC</td>
<td>5</td>
<td>19</td>
<td>26.3</td>
</tr>
<tr>
<td></td>
<td>Etemadmoghadam et al. 2017</td>
<td>LGSC</td>
<td>6</td>
<td>51</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>Xing et al. 2017</td>
<td>LGSC</td>
<td>2</td>
<td>56</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Cheasley et al. 2021</td>
<td>LGSC</td>
<td>6</td>
<td>71</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Total, %</td>
<td></td>
<td>24</td>
<td>255</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>AACR GENIE Cohort&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>19</td>
<td>210</td>
<td>9.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Micropapillary serous carcinoma (MPSC) has been considered equivalent to LGSC. <sup>b</sup>Data for 210 LGSC cases were downloaded from https://genie.cbioportal.org/. <sup>c</sup>Serous carcinoma with co-existing serous borderline (grades 1 and 2 cases). <sup>d</sup>NR, Not reported, therefore the study was not included in total count.

stages II–IV LGSC (Gershenson et al. 2015), 16/56 (28.6%) ‘invasive’ LGSC, (Xing et al. 2017) and 20/71 (28.2%) LGSC (Cheasley et al. 2021).

In an analysis of publicly available data in the AACR GENIE Cohort (GENIE 2017) (v8.0-public, accessed 2 October 2020), 210 ovarian cancer cases were classified as LGSC, with KRAS mutations being the most common (69/210, 32.9%). The AACR GENIE Cohort represents clinical-grade genomic sequencing data generated in eight CLIA-/ISO-certified laboratories in the USA. The frequency of KRAS mutations in LGSC in the GENIE cohort is very similar to the combined frequencies in cohorts of LGSC published over the last two decades (97/356, 27.2%), suggesting that this is likely to reflect an accurate frequency of KRAS mutations in LGSC (Table 2).

The vast majority of KRAS alterations are in the exon 2, codon 12 ‘hot spot’ region, with most studies reporting KRAS<sup>G12V</sup> and KRAS<sup>G12D</sup> variants to be the most common (Fig. 3 and Table 3). KRAS<sup>G12V</sup> was found in 36.5% of KRAS variants and KRAS<sup>G12D</sup> in 41.7%, combining reported mutations from eight studies representing 540 LGSC cases (Wong et al. 2010, Jones et al. 2012, Gershenson et al. 2015, Hunter et al. 2015, Etemadmoghadam et al. 2017, GENIE 2017, Xing et al. 2017, Cheasley et al. 2021). A smaller proportion of other KRAS variants has been reported (<10% each) including KRAS<sup>G12R/C/A/S</sup>, KRAS<sup>G13C</sup> and NRAS<sup>G126V,R111K</sup> (Fig. 3 and Table 3).

Oncogenic KRAS mutations found in LGSC are similar to those reported in other cancer types including pancreatic, colorectal and small bowel cancer, with exon 2, hot spot mutations, KRAS<sup>G12D</sup> and KRAS<sup>G12V</sup> being the most common (Fig. 4). KRAS<sup>G12C</sup>, the most common variant in lung cancer, is rare in LGSC.

**BRAF mutations in LGSC**

The frequency of BRAF mutations in LGSC is also quite variable in published reports and appears to vary depending on the type of cases included in the cohorts being studied. Frequencies vary from 2 to 33% (Singer et al. 2002, Wong et al. 2010, Jones et al. 2012, Gershenson et al. 2015, Hunter et al. 2015, Etemadmoghadam et al. 2017, GENIE 2017, Xing et al. 2017, Cheasley et al. 2021). A smaller proportion of other BRAF variants has been reported (<10% each) including BRAF<sup>V600E/K</sup>, BRAF<sup>V600L</sup> and BRAF<sup>V600K</sup> (Fig. 3 and Table 3). Oncogenic BRAF mutations found in LGSC are similar to those reported in other cancer types including melanoma, pancreatic, colorectal and small bowel cancer, with exon 2, hot spot mutations, BRAF<sup>V600E/K</sup> and BRAF<sup>V600L</sup> being the most common (Fig. 4). BRAF<sup>V600G</sup>, the most common variant in lung cancer, is rare in LGSC.
et al. 2003a, Wong et al. 2010, Jones et al. 2012, Bosmuller et al. 2013) (Table 2). In the initial study by Singer et al. (2003a), BRAF mutation frequency was reported to be 33% (n = 22 cases). In a study by Wong et al. of stage III disease, only 2% of patients were found to have a BRAF mutation, and the authors suggested that the mutation may be less common in advanced disease (Wong et al. 2010). Another small European study, (n = 7 LGSC), using immunohistochemistry, reported staining consistent with BRAF V600E mutations in 1/7 (14%) of LGSC with the majority of other cases included in the study representing SBT which stained positive in 22/31 (71%) of cases (Bosmuller et al. 2013).

Grisham et al. reported a low frequency of 5.3% and suggested that BRAF mutations were associated with early stage, serous borderline histology and a better outcome (Grisham et al. 2013). In contrast with KRAS analysis, the more recent cohorts estimating BRAF mutations in LGSC remain highly varied with Gershenson et al. (2015) only reporting BRAF mutations in 3.8% (3/79) stages II–IV LGSC cases (Gershenson et al. 2015), Hunter et al. (2015) reporting 15.8% (3/19) while Xing et al. (2017) reported 17.9% (10/56) (Xing et al. 2017).

In the AACR GENIE cohort, BRAF mutations were found in 20/210 LGSC (9.5%), which is similar to the combined proportion of ten studies since 2003 (10.3%, 37/360). The most frequent BRAF mutation found in LGSC is a substitution at the second position of codon 600 of exon 15, BRAF V600E, with a combined variant proportion of 78.2% of BRAF variants overall (Fig. 3 and Table 3). The BRAF V600E mutation is also commonly found in melanoma and thyroid cancer, and although less common, the same amino acid substitution (BRAF V600E) is found in pancreatic, colorectal and non-small cell lung cancer (Fig. 4).

**NRAS mutations in LGSC**

In contrast with BRAF and KRAS mutations which are frequently found in SBT in addition to LGSC, NRAS mutations were only found in invasive disease suggesting that NRAS may be an important oncogenic driver in LGSC (Emmanuel et al. 2014). Subsequent studies identified NRAS mutations in 26% (5/19) of LGSC (Hunter et al. 2015), 11.8% (6/51) (Etemadmoghadam et al. 2017), 8.5% 6/71 (Cheasley et al. 2021) with a lower proportion found by Xing et al. 2/56 (3.6%) cases (Xing et al. 2017).
In the AACR GENIE cohort, NRAS mutations were found in 19/210, 9%, which is very similar to the combined frequencies in published studies of LGSC, 24/255, 9.4% (Table 2). Alterations were almost invariable in codon 61, with the majority being NRAS<sup>Q61R</sup> (81.6%) and NRAS<sup>Q61K</sup> (15.8%) (Fig. 3 and Table 3). NRAS<sup>Q61R</sup> and NRAS<sup>Q61K</sup> are also the most common NRAS alterations found in melanoma and thyroid cancer (Fig. 4).

### Low-frequency gene alterations in LGSC

Mutations in novel candidate genes <i>USP9X</i> and <i>EIF1AX</i> were also more prevalent in low-grade cases compared with SBT; <i>USP9X</i> was detected in 3% of SBT vs 11% of LGSC, and <i>EIF1AX</i> was detected in 2% of SBT vs 15% of LGSC. <i>USP9X</i> and <i>EIF1AX</i> have both been linked to the regulation of mTOR, suggesting that mTOR inhibitors may be a potential companion treatment for targeted therapy trials.

The frequency of non-synonymous mutations outside of the key driver genes is low (Jones et al. 2012). Less common alterations reported in LGSC include MAP2K1, RAS GAP, NF1, ERBB2 and BRAF fusions (Grisham et al. 2015); MACF1, ARID1A, NF2, DOT1L and ASH1L (Cheasley et al. 2021).

Overall, mutations in driver genes have been found in ~50% of LGSC cases. A further understanding of the pathways activated in the remaining <i>BRAF/KRAS/NRAS</i> ‘wild type’ cases is crucial to the tailoring of therapeutic approaches in LGSC.

In addition to point mutations, gene copy number aberrations are a ubiquitous finding in LGSC. However, copy number aberrations in LGSC tend to be low level, with few breakpoints compared with HGSC (Emmanuel et al. 2014). Frequent sites of loss include 9p, at the CDKN2A/2B locus (Hunter et al. 2015), and loss of 1p36.33, found in more than half (54.1%) of LGSC cases (Van Nieuwenhuysen et al. 2019).

### Mutations and clinical characteristics

From the limited literature available, there are suggestions that mutation status may be associated with particular clinical characteristics and outcomes in LGSC. In a cohort of 33 women with LGSC, Wong et al. reported no significant difference in median OS when a <i>BRAF</i> or <i>KRAS</i> mutation was present (77.9 vs 47.3 months, <i>P</i>-value = 0.28) (Wong et al. 2010). In a larger cohort of 79 women with LGSC, Gershenson et al. (2015) reported that women with <i>BRAF</i> and <i>KRAS</i> mutated LGSC had better overall survival (OS) (Gershenson et al. 2015), although the presence of <i>BRAF</i> and <i>KRAS</i> mutations was grouped together and NRAS mutations were not investigated.
Women with NRAS mutation-positive LGSC were reported to be older compared with those KRAS or BRAF mutations; a higher proportion had advanced-stage disease with more residual disease after debulking surgery and lower pre-treatment levels of CA-125. However, the number of NRAS mutation-positive cases in this study was small (n = 5) and these trends did not reach statistical significance (Emmanuel et al. 2014).

McIntyre et al. investigated histopathologic and molecular features that may predict which women with LGSC were more likely to follow an aggressive clinical course based on survival outcomes (McIntyre et al. 2017). Although there were limited case numbers (n = 26), the study concluded that the absence of PR expression and the presence of myometrial lympho-vascular invasion were associated with an unfavourable outcome; however, mutation status did not appear to predict the outcome. Based on the published literature, it remains unclear whether mutation status is associated with differences in clinical outcome.

**Clinical management**

**Optimal primary cytoreductive surgery improves outcome in women with LGSC**

As for all ovarian cancer subtypes, primary bulkling surgery remains the mainstay of treatment for LGSC and retrospective studies specifically focussing on LGSC have shown that optimal debulking surgery is associated with improved outcomes (Nickles Fader et al. 2013, Grabowski et al. 2016).

In the relapse setting, two retrospective reviews suggested improved clinical outcome in women with LGSC who underwent secondary cytoreductive surgery, especially if the surgery resulted in no gross residual disease, and this is recommended in the appropriate clinical setting (Crane et al. 2015). Moreover, in view of the acknowledged chemo-resistance of LGSC, it is arguable that secondary surgery plays an even more significant role than it does in the management of HGSC.

**Low-response rates to platinum-based chemotherapy**

The subsequent recommendation for primary chemotherapy is dependent on staging, and despite LGSC being recognised as more resistant to platinum-based chemotherapy (Schmeler et al. 2008), there is a lack of prospective clinical trial evidence to support a change in standard practice at present.

The recommendations for all forms of epithelial ovarian cancer, including serous cancer, is for chemotherapy to be considered in stage 1C disease following surgery, while for stages II–IV disease, cytoreductive surgery is recommended to be followed by platinum-based chemotherapy. It is important to note that while the use of neoadjuvant chemotherapy in advanced ovarian cancer is becoming
more common (Nicklin et al. 2017), the relative chemoresistance of LGSC argues against the use of neoadjuvant chemotherapy in this subtype (Schmeier et al. 2008, Cobb et al. 2020). In a recent study, of the 36 women with LGSC who received neoadjuvant chemotherapy, matched to patients with HGSC, only 4/36 (11%) women with LGSC had a partial response compared with 27/36 (75%) women with HGSC (Cobb et al. 2020).

A retrospective study by Gershenson et al. examined response to chemotherapy in the relapsed setting. The overall response rate (ORR) to chemotherapy was low at 3.7% with stable disease (SD) rate of 60% and progression-free survival (PFS) of 7 months (Gershenson et al. 2009). The study highlights the high rates of stable disease and whether this is actually due to a response to therapy or the biology of the tumour itself is not certain. Rose et al. assessed the activity of pegylated liposomal doxorubicin in LGSC, a chemotherapy agent commonly used in ovarian cancer, and concluded that it was relatively active in LGSC with 14.3% achieving a complete response (CR) (Rose et al. 2017).

In two recent LGSC clinical trials, the control arm was the physician's choice for chemotherapy. In the MILO/ENGOT-ov1 trial response to chemotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan) was higher than anticipated with PFS 11.5 months and ORR 13% (Monk et al. 2020) (Table 4). However, in GOG 0281, pegylated liposomal doxorubicin or weekly paclitaxel, topotecan, letrozole, PFS was 7.2 months and ORR 6.2%. The reasons for this difference are not entirely clear and may relate to the number of prior lines of treatment allowed, with women in GOG 0281 being more heavily pre-treated (Gershenson et al. 2020b).

**Table 4** Clinical trials in low-grade serous cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>ClinicalTrials.gov ID</th>
<th>Recruitment status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 0239: A phase II trial of selumetinib in women with recurrent low-grade carcinoma of the ovary</td>
<td>NCT00551070</td>
<td>Completed</td>
</tr>
<tr>
<td>Phase II randomised double-blind placebo-controlled trial of combination of pimasertib with SAR245409/placebo in subjects with previously treated unresectable low-grade ovarian cancer</td>
<td>NCT01936363</td>
<td>Completed</td>
</tr>
<tr>
<td>MILO/ENGOT-ov1: phase-3 study of binemetinib vs physician's choice of chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube or peritoneal cancer.</td>
<td>NCT01849874</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>GOG 0281: a randomised phase II/III study to assess the efficacy of trametinib in patients with recurrent or progressive low-grade serous cancer or peritoneal cancer.</td>
<td>NCT02101788</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>GOG 3026: a phase II trial of ribociclib plus letrozole in women with recurrent low-grade serous carcinoma of the ovary or peritoneum</td>
<td>NCT03673124</td>
<td>Recruiting</td>
</tr>
<tr>
<td>A pilot phase II study of neoadjuvant fulvestrant plus abemaciclib in women with advanced low-grade serous carcinoma</td>
<td>NCT03531645</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Basket study of the oral progesterone antagonist onapristone ER (Apristror) in women with progesterone receptor positive (PR+) low-grade serous ovarian cancer.</td>
<td>NCT03909152</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NRG-GY-019: a randomised phase III, two-arm trial of paclitaxel/carboplatin/maintenance letrozole vs letrozole monotherapy in patients with stages II–IV primary low grade serous carcinoma of the ovary or peritoneum</td>
<td>NCT04095364</td>
<td>Recruiting</td>
</tr>
<tr>
<td>A study combining the pimasertib (M3814) pill with standard chemotherapy in patients with ovarian cancer with an expansion in high-grade serous ovarian cancer and low-grade serous ovarian cancer patients</td>
<td>NCT04092270</td>
<td>Recruiting</td>
</tr>
<tr>
<td>A phase II study of VS-6766 (dual RAF/MEK inhibitor) alone and in combination with defactinib (FAK inhibitor) in recurrent low-grade serous ovarian cancer</td>
<td>NCT04625270</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Phase II investigational study of pembrolizumab combination with chemotherapy in platinum-sensitive recurrent low-grade ovarian cancer</td>
<td>NCT04575961</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>

**Therapeutic opportunities**

**Anti-angiogenic agents**

Bevacizumab, a MAB targeting VEGF, has also been approved for ovarian cancer and shows the greatest benefit in those patients at high risk of relapse, which included FIGO stage IV or stage III disease with greater than 1 cm of residual disease (Perren et al. 2011). Retrospective studies focussing on bevacizumab in LGSC, with or without chemotherapy, also suggest activity with both partial and complete responses reported, supporting its use in primary treatment of LGSC in high-risk disease (Grisham et al. 2014, Rose et al. 2016, Dalton et al. 2017).

Bevacizumab may also play a role in relapsed LGSC. A small retrospective study reported high response rates to bevacizumab in recurrent LGSC and SBT with an ORR of 55% in the LGSC subgroup (Grisham et al. 2014) while...
another study similarly reported ORR of 47.5% in 45 patients (Dalton et al. 2017).

Endocrine therapy

Endocrine therapy is often used in the management of women with LGSC, showing activity in multiple clinical settings, including primary adjuvant, primary maintenance and salvage therapies (Gershenson et al. 2012, 2017, Fader et al. 2017, Tang et al. 2019). Most cases of LGSC express hormone receptors, with high ER expression seen in ~70% and high PR expression in ~30%, representing potential treatment targets (Sieh et al. 2013), although, no studies to date have demonstrated an association between receptor expression and response to endocrine therapy (Gershenson et al. 2020a). In a retrospective analysis of 64 women with LGSC, who had received over 80 different hormonal regimens, Gershensen et al. reported a 9% objective response rate and disease stabilisation in 61% (Gershenson et al. 2012). This led to the inclusion of a cohort of women with LGSC in PARAGON, a phase II study of anastrozole, an aromatase inhibitor, in women with potentially hormone responsive recurrent/metastatic gynecologic neoplasms. In women with low-grade ovarian tumours, the majority of which were LGSC, clinical benefit at 6 months was ~60%, and partial responses were reported in 14% (Tang et al. 2019) (Table 5).

Responses to endocrine treatment in the relapse setting led to a retrospective analysis of maintenance in front-line treatment. Gershenson et al. showed that women with stages II–IV LGSC who received maintenance hormonal treatment (primarily letrozole or tamoxifen) following primary chemotherapy had longer progression-free survival (PFS), 65 months, compared with 26 months in women who underwent routine observation (P < 0.001) (Gershenson et al. 2017). Given these results and the low-response rates to chemotherapy, Fader et al. explored hormonal monotherapy alone following cytoreductive surgery in 27 women with stages II–IV LGSC (letrozole, anastrozole or tamoxifen). Although preliminary, survival outcomes were similar to women with LGSC treated with surgery and cytotoxic chemotherapy suggesting that chemotherapy may not be necessary for patients with advanced-stage disease who receive adjuvant hormonal therapy (Fader et al. 2017). This is being followed up in a phase III trial (NRG GY-019, NCT04095364), initiated in 2019, comparing chemotherapy (paclitaxel/carboplatin) and letrozole with letrozole alone in stages II–IV LGSC (Table 4).

Endocrine therapy combined with CDK4/6 inhibitors

Strategies to increase the effectiveness of endocrine treatment in LGSC are being tested, including the addition of cyclin-dependent kinase (CDK) 4/6 inhibitors

Table 5 Low-grade serous ovarian cancer: case reports and basket trials.

<table>
<thead>
<tr>
<th>Case studies</th>
<th>Intervention</th>
<th>Response, duration of treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRA5G12V mutant LGSC</td>
<td>Seluminitib</td>
<td>PR, 7 years</td>
<td>Takekuma et al. 2016</td>
</tr>
<tr>
<td>KRA5G12D mutant LGSC</td>
<td>Trametinib</td>
<td>PR, &gt;10 months</td>
<td>Pejovic et al. 2015</td>
</tr>
<tr>
<td>KRA5G12V mutant LGSC</td>
<td>Binimetinib</td>
<td>PR, 31 months</td>
<td>Han et al. 2018</td>
</tr>
<tr>
<td>KRA5G12D mutant LGSC</td>
<td>Vemurafenib</td>
<td>PR, 21 months</td>
<td>Combe et al. 2015</td>
</tr>
<tr>
<td>BRAFV600E mutant LGSC</td>
<td>Dabrafenib and trametinib; encorafenib and binimetinib</td>
<td>Dabrafenib/trametinib – CR, 12 months; Encorafenib/binimetinib – SD, 3.5 years</td>
<td>Tholander et al. 2020</td>
</tr>
<tr>
<td>BRAFV600E mutant LGSC</td>
<td>Dabrafenib, BG283 trial</td>
<td>Dabrafenib – PR, &gt;11 months; BG283 – PR, &gt; 2 years</td>
<td>Moujaber et al. 2018, Desai et al. 2020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basket trials</th>
<th>Intervention</th>
<th>Response, duration of treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS/RAF-mutant solid tumours. One BRAFV600E and one KRA5G12D LGSC</td>
<td>CH5126766/VS-6766</td>
<td>PR, 15 and 31 weeks</td>
<td>Guo et al. 2020</td>
</tr>
<tr>
<td>BRAF mutant tumours. One BRAFV600E mutant LGSC</td>
<td>Vemurafenib</td>
<td>PR, &gt;12 months</td>
<td>Hyman et al. 2015</td>
</tr>
<tr>
<td>Advanced BRAF mutated cancer. Two BRAFV600E LGSC</td>
<td>Dabrafenib and pazopanib</td>
<td>PR, 5 months and 37 months</td>
<td>Haraldsdottir et al. 2018</td>
</tr>
<tr>
<td>ER-positive gynaecological cancers</td>
<td>Anastrazole</td>
<td>ORR, 13.9%</td>
<td>Tang et al. 2019</td>
</tr>
<tr>
<td>ER-positive ovarian cancers</td>
<td>Ribociclib and letrozole</td>
<td>1 CR and 2 PR, &gt; 27 months</td>
<td>Colon-Otero et al. 2020</td>
</tr>
</tbody>
</table>

*One patient also in a basket trial; †CH5126766/VS-6766 is a MEK inhibitor that has functional RAF inhibitory activity; ‡PR, partial response; CR, complete response; SD, stable disease; ORR, objective response rate.
CDK 4/6, in conjunction with the ER-regulated cyclin D1, plays a critical role in regulating transition from G1 to S phase, and inhibition of this axis is an effective therapeutic strategy in ER-positive, advanced breast cancer. CDK inhibitors (palbociclib, ribociclib and abemaciclib) have been shown to improve survival in women with metastatic ER-positive breast cancer when combined with aromatase inhibitors (letrozole and anastrozole) or fulvestrant (Finet et al. 2016, Hortobagyi et al. 2016, Goetz et al. 2017). Based on these findings in breast cancer, the efficacy of ribociclib and letrozole was tested in a small phase II trial in ovarian and endometrial cancer (n = 40) (Table 5). LGSC patients were among those showing the most significant benefit, with all three women achieving durable responses (one CR and two with partial responses over 2 years) (Colon-Otero et al. 2020). GOG 3026 (NCT03673124), a phase II trial of ribociclib and letrozole; and NCT03531645, a phase II trial of fulvestrant and abemaciclib in LGSC, are currently recruiting, and the results will provide important information on the potential for this approach (Table 4).

In studies of aromatase inhibitors in relapsed LGSC to date, response rates have been similar at ~13%. In Gershenson’s retrospective analysis, in 54 women managed with aromatase inhibitors, the response rate was 13.0% (letrozole, 6/33; anastrozole, 1/21) (Gershenson et al. 2012), in PARAGON the objective response rate to anastrozole was 13.9% (36 patients) (Arend et al. 2020) and in the GOG 0281 trial, 6/44 (13.6%) patients responded to letrozole (Gershenson et al. 2020a). Combining aromatase inhibitors with CDK4/6 inhibitors has the potential to increase response rates, and an increased understanding of hormone signalling in LGSC has the potential to lead to more effective endocrine combination therapies (Tables 4 and 5).

### Targeting the MAPK pathway

Selumetinib, a potent selective small molecule inhibitor of MEK1/2 was trialled in a single arm, phase II study enrolling 52 patients with relapsed LGSC (Farley et al. 2013) (Table 4). The study reported an ORR of 15.4%, which included one patient who had a CR and seven patients with a partial response (PR). SD was reported in 34 patients (65%). One patient continued to respond for more than 7 years (Takekuma et al. 2016) (Table 5). Response did not correlate with mutation status, although the number of cases was small and only KRAS and BRAF were assessed. NRAS mutations were not investigated which may contribute to at least part of this result.

The promising selumetinib results led to further trials investigating single agent or combination MEK inhibitor studies. The MILO Study (MEK inhibitor in low-grade serous ovarian cancer) investigated MEK162 (binimetinib) vs chemotherapy in patients with recurrent or persistent LGSC (Monk et al. 2020). One of the published case reports, a woman with a KRAS<sup>G12V</sup> mutated LGSC had a durable response with binimetinib (Han et al. 2018) as part of this trial (Table 5). Unfortunately, despite individual reports of response to MEK inhibitors, the MILO study was discontinued due to interim analysis suggesting futility of treatment. Median PFS was 9.1 months (95% CI, 7.3–11.3) for binimetinib and 10.6 months (95% CI, 9.2–14.5) for the chemotherapy arm. Secondary endpoints were also similar with ORR 16% vs 13% and median duration of response 8.1 months vs 6.7 months for binimetinib and physician choice of chemotherapy. A higher than expected rate of response to chemotherapy was observed, and the need for predictive biomarkers for response to treatment was highlighted (Monk et al. 2020).

Another early phase trial investigated the effect of the MEK inhibitor, pimasertib, in combination with a PI3K inhibitor (SAR245409) in women with LGSC (Arend et al. 2020); however, again following interim analysis, the trial was permanently discontinued on the basis of futility. Median PFS was 7.23 months (80% CI, 5.06 to N/A) and 9.99 months (80% CI, 7.39–10.35) for pimasertib alone and pimasertib + SAR245409, respectively, with ORR of 9.4% in the combination arm and 12.1% in the pimasertib alone arm (Arend et al. 2020).

GOG 0281, a phase II/III trial comparing the MEK inhibitor trametinib with the physician’s choice of standard of care therapy (pegylated liposomal doxorubicin, weekly paclitaxel, topotecan, letrozole or tamoxifen) was the first clinical trial of targeted agents to show improved outcome for women with LGSC (Table 4). GOG 0281 met its primary end point, with a median PFS of 13.0 months for trametinib and 7.2 months for standard of care (HR, 0.48; P < .001). ORRs were 26 and 6.2% for trametinib and standard therapy, respectively, demonstrating the potential for targeted therapy in LGSC (Gershenson et al. 2019).

There have been case reports of response of BRAF mutation-positive LGSC to BRAF inhibitors monotherapy or in combination with other agents (Combe et al. 2015, Hyman et al. 2015, Haraldsdottir et al. 2018, Moujaber et al. 2018, Tholander et al. 2020).

Combined BRAF and MEK inhibition improved ORR, PFS and quality of life with reduced adverse effects, compared to BRAF inhibition alone, in BRAF mutated melanoma (Flaherty et al. 2012). However, there were...
no synergistic effects of first-generation BRAF inhibitor, vemurafenib with MEK inhibitors in KRAS mutant cell lines, probably due to paradoxical MAPK pathway activations (Yuan et al. 2020). Lefirafenib is a second-generation BRAF inhibitor with little to no paradoxical increase in MAPK signalling (Desai et al. 2020). It showed antitumour activity in both BRAF and KRAS mutated cancers (Desai et al. 2020). The combination of Lefirafenib and MEK inhibition has shown enhanced efficacy in KRAS-mutated non-small cell lung cancer cell lines (Desai et al. 2020), and clinical trials are currently underway to assess the efficacy of the combination in MAPK pathway-mutated cancers including LGSC (NCT03905148, clinicaltrials.gov).

Several early phase clinical trials combining MEK inhibition with diverse targets including FAK inhibition (defactinib) (Shinde et al. 2020) and BCL-2/XL (navitoclax) (Iavarone et al. 2019) (Table 4) and RAF-MEK inhibitor (CHS126766/VS-6766b) (Guo et al. 2020) (Table 5) have shown activity in LGSC and studies are ongoing.

While questions remain regarding the optimal RAS/RAF pathway inhibitors and combinations that are effective in LGSC, MEK and BRAF inhibition have resulted in disease control in a significant number of women, in clinical trials, basket trials and in individual case reports (Pejovic 2015) (Table 5). It is clear that some LGSC has oncogene ‘addiction’ and are reliant on activation of the MAPK pathway, with some women demonstrating profound and sustained response to MEK and BRAF inhibitors. However, the relationship between mutation status and treatment response is not straightforward, and reliable predictive biomarkers are yet to be identified.

### Immunotherapy and CAR-T cell therapy

LGSC has a low mutational burden (Jones et al. 2012, Etemadmoghadam et al. 2017) and tends to have fewer tumour-infiltrating lymphocytes (TIL) (Webb et al. 2015) and may therefore not appear to be an ideal candidate for immune-checkpoint inhibition. However, BRAF and MEK inhibition has been shown to promote a favourable immune microenvironment in melanoma by decreasing immunosuppressive signals leading to increased intra-tumoural CD4+ and CD8+ T cells, and animal studies have demonstrated improved survival with BRAF/MEK inhibitors when combined with anti-PD1 therapy (Hu-Lieskovan et al. 2015). More research is needed to determine whether immune-checkpoint inhibition will play a role in LGSC treatment. A trial investigating pembrolizumab in combination with chemotherapy in platinum-sensitive recurrent low-grade ovarian cancer is yet to start recruiting (NCT04575961, Table 4).

Targeting driver mutations is attractive for adoptive T-cell therapy, as they are tumour-specific and likely to be expressed in most cells in a given tumour. An example of this approach is a case report of HLA-restricted adoptive T-cell therapy specifically targeting KRASG12D in a patient with colorectal cancer, who had substantial tumour regression after the infusion of autologous T cells. The T cells reacted specifically with an HLA-C allele that was bar-coded with the mutant KRASG12D peptide (Tran et al. 2016). KRAS is the most commonly mutated gene in LGSC; however, whether adoptive T-cell therapy would be effective in LGSC is yet to be determined.

### Conclusions and management approaches for LGSC

Acceptance of a binary histopathological classification dividing serous ovarian cancer into LGSC and HGSC coupled with increased tumour mutation testing and understanding of the molecular drivers in LGSC is transforming the clinical landscape for LGSC and increasing potential treatment options including endocrine therapy, molecularly targeted agents and anti-angiogenesis inhibitors.

A critical point for routine clinical practice is to ensure that LGSC is accurately diagnosed, which may rely on adequate tissue sampling, expert histopathology, immunohistochemistry and molecular studies if possible. An immediate impact of a LGSC diagnosis is that upfront debulking surgery is indicated rather than carboplatin-based neoadjuvant treatment; the latter having poor response and detrimental effect on outcome.

Besides standard chemotherapy and endocrine agents, which have low response rates, there is no approved effective treatment for women with LGSC. In this circumstance, prospective clinical trials become an important option for patients and clinicians, even in the primary treatment setting. Key outstanding questions include investigation of the relative efficacy and toxicity profiles of endocrine treatments compared with platinum-based primary chemotherapy, and whether or when non-platinum chemotherapy agents should preferentially be used.

Targeting the RAS-MAPK pathway shows promise in LGSC, but fine-tuning the approach is necessary. Progress in this area will rely on increased experience with tumour mutation profiling at diagnosis, or for relapsed
or progressive LGSC. Based on current knowledge, the presence of activating \textit{BRAF} mutations, such as V600E, will guide the use of BRAF inhibitors, with or without MEK inhibitors. In non-BRAF mutant LGSC, single-agent MEK inhibitors may be considered. Clinical trials designed to commence single-agent MEK inhibitors with the addition of a second agent on progression would have the advantage of supporting identification of single-agent predictive biomarkers and cancers requiring additional blockade while avoiding the toxicity of combined therapy in patients where it is not needed.

The prospect of improving outcomes for women with LGSC has been advanced by a specific diagnosis of this disease. Thoughtful clinical trial design for LGSC, including follow-up of promising findings from early phase trials; rational molecular profiling; novel adaptive platform approaches and inclusion of LGSC patients in basket trials of targeted agents, is now key to improving clinical practice in this area.

\section*{Declaration of interest}

Tania Moujaber, Rosemary Balleine, Paul Harnett, Ida Madsen and Bo Gao have no conflicts of interest to declare. Anna DeFazio has received research grants and speaker's fees from AstraZeneca.

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\section*{Author contribution statement}

Anna DeFazio, Tania Moujaber and Ida Madsen contributed to analysis of published and publicly available data, and all authors contributed to writing of the manuscript.

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