Record of the Cancer Treatment Subcommittee of PTAC Meeting held on 15 February 2021

Cancer Treatment Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Cancer Treatment Subcommittee meeting; only the relevant portions of the meeting record relating to Cancer Treatment Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Cancer Treatment Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its May 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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Present from the Cancer Treatment Subcommittee:
Marius Rademaker (Chair)
Allanah Kilfoyle
Chris Frampton
Lochie Teague
Michelle Wilson
Peter Ganly
Richard Isaacs
Robert Matthew Strother
Scott Babington
Tim Hawkins

Apologies:
Anne O'Donnell

Summary of recommendations

The following recommendation summary is an order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• Rituximab for the treatment of adult patients with acute lymphoblastic leukaemia/lymphoma	Low Priority
• Rituximab for the treatment of adult patients with acute lymphoblastic leukaemia/lymphoma with CD20 expression	Medium priority
• Olaparib for the first-line maintenance treatment of high-grade ovarian cancers with a germline mutation in breast cancer susceptibility gene 1 or 2 (BRCAm)	High Priority

1. The role of PTAC Subcommittees and records of meetings

1.1. This meeting record of the Cancer Treatment Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. The Cancer Treatment Subcommittee is a Subcommittee of PTAC. The Cancer Treatment Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Cancer Treatment Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for malignancy that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for malignancy that differ from the Cancer Treatment Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

1.5. PHARMAC considers the recommendations provided by both the Cancer Treatment Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for malignancy.

2. Record of Subcommittee meeting held Friday, October 16, 2020

2.1. The Subcommittee reviewed the records of the PTAC meeting held on 16 October 2020 and agreed that the minutes be accepted.

3. Correspondence and Matters Arising

Gastrointestinal cancers special interest group (GISIG) correspondence

3.1. Subcommittee reviewed correspondence from the gastrointestinal cancers special interest group (GISIG).

3.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Discussion

3.3. The Subcommittee noted the November 2020 letter from the GISIG, and previous correspondence between PHARMAC and the GISIG. The Subcommittee considered the letter highlighted valid concerns, and that funding for gastrointestinal cancer treatments remains an ongoing challenge, as does funding for treatments in other therapeutic areas.

3.4. The Subcommittee considered each of the pharmaceuticals raised in the correspondence, and made the following comments regarding the relative priority for review of these pharmaceuticals;

3.4.1. The Subcommittee considered there to be an unmet need for nab-paclitaxel and noted that the proposal for nab-paclitaxel for the first line treatment of metastatic pancreatic cancer had last been reviewed by PTAC in August 2015. The Subcommittee considered that it should review any updated evidence for this pharmaceutical as the first priority of the pharmaceuticals listed by the GISIG, and that it would welcome an updated funding application from the GISIG to support this review.

3.4.2. The Subcommittee noted that it last reviewed trastuzumab for the treatment of gastric cancer at its meeting in August 2011, and that this application had been formally declined by PHARMAC in July 2019. The Subcommittee considered there may be updated evidence that, together with any improved pricing of trastuzumab which may be achieved through future biosimilar market entry, could improve the relative priority for funding of trastuzumab for this indication. The Subcommittee considered it should review any updated evidence for this as the second priority of the pharmaceuticals listed by the GISIG, and that it would welcome an updated funding application from the GISIG.

3.4.3. The Subcommittee noted that a funding application for pembrolizumab for the treatment of microsatellite instability-high (MSI-high) or mismatch repair deficient (dMMR) cancers had been made by a consumer. The Subcommittee noted that PHARMAC staff were in conversations with the pharmaceutical supplier for further information that could support this funding application. The Subcommittee considered this to be the third priority of the pharmaceuticals listed by the GISIG for its review and noted that this would be included on the agenda at an upcoming clinical advice meeting.

3.4.4. The Subcommittee noted that a funding application for atezolizumab in combination with bevacizumab for the treatment of unresectable hepatocellular carcinoma had been made by a pharmaceutical supplier. The Subcommittee noted this application would be included on the agenda at an upcoming CaTSoP meeting.

3.4.5. The Subcommittee considered that cetuximab, bevacizumab and raltitrexed had been reviewed relatively recently, and therefore did not consider these would be good candidates for further clinical advice at this time, in the absence of updated evidence; however, the Subcommittee would welcome submission of any new clinical trial data, when available, for consideration.

3.5. The Subcommittee considered that correspondence from cancer special interest groups, such as the GISIG, is helpful to inform an assessment of current unmet needs and for horizon scanning for different tumour streams. The Subcommittee suggested that PHARMAC staff engage with Te Aho o te Kahu (the Cancer Control Agency) and the Ministry of Health's Medical Oncology Working Group (MOWG) to further explore how the groups could align when working on matters of common interest such as treatment landscape analysis, gap analysis, and horizon scanning.

3.6. The Subcommittee considered there are a number of other special interest groups that have had varying degrees of engagement with PHARMAC and CaTSoP and considered engagement with these would be beneficial to provide balanced representation and advocacy for new medicines. The Subcommittee considered that this includes SIGs for breast, genitourinary, gynaecological, and lung cancers, lymphoma, melanoma, myeloma and sarcoma, as well as a bone marrow transplant interest group.

4. Rituximab for precursor B-cell acute lymphoblastic leukaemia

Application

4.1. The Subcommittee reviewed the application for rituximab in the treatment of adult patients with B-cell acute lymphoblastic leukaemia.

4.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

4.3. The Subcommittee **recommended** that rituximab for the treatment of adult patients with acute lymphoblastic leukaemia/lymphoma be listed with a low priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** - (B-cell acute lymphoblastic leukaemia/lymphoma) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:
> All of the following:
> 1. Patient has newly diagnosed B-cell acute lymphoblastic leukaemia/lymphoma; and
> 2. Treatment must be in combination with an intensive chemotherapy protocol with curative intent; and
> 3. The total rituximab dose would not exceed the equivalent of 375 mg/m^2 per dose for a maximum of 18 doses.

4.4. The Subcommittee **recommended** that rituximab for the treatment of adult patients with acute lymphoblastic leukaemia/lymphoma with CD20 expression be listed with a medium priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** - (CD20 +ve B-cell acute lymphoblastic leukaemia/lymphoma) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:
> All of the following:
> 1. Patient has newly diagnosed B-cell acute lymphoblastic leukaemia/lymphoma; and
> 2. Tumour is CD20 positive, defined as at least 20% CD20 expression; and
> 3. Treatment must be in combination with an intensive chemotherapy protocol with curative intent; and
> 4. The total rituximab dose would not exceed the equivalent of 375 mg/m^2 per dose for a maximum of 18 doses.

4.5. In making this recommendation, the Subcommittee noted that:

- adult patients with B-cell acute lymphoblastic leukaemia/lymphoma have a very high health need with a high risk of treatment failure
- a more pronounced effect of rituximab was observed in patients with higher CD20 expression in the GRAALL-2005 trial, although this difference was not significant.
- There was a lack of interaction between the addition of rituximab to chemotherapy and cytogenetics or CD20 expression in the UKALL14 trial, which suggests that the GRAALL-2005 results may be generalizable to all patients with B-cell ALL and not just those patients with CD20 expression greater than 20%.
- it is unlikely that more evidence for rituximab in this patient group will become available.

Discussion

4.6. The Subcommittee noted that adult patients with B-cell acute lymphoblastic leukaemia/lymphoma have a very high health need and undergo treatment for many months, mostly as inpatients with a high risk of treatment failure. The Subcommittee noted that fit, younger B-cell acute lymphoblastic leukaemia (ALL) /lymphoma patients are treated with intensive multiagent chemotherapy and allograft if eligible and that there were fewer older patients with B-cell acute lymphoblastic leukaemia/lymphoma. The Subcommittee noted that treatment is sustained and toxic and considered that less than 50% of patients are cured. The Subcommittee noted that relapse in B-cell ALL is significant, that most relapses cannot be salvaged, and that salvage treatment

is highly resource intensive. The Subcommittee considered that preventing relapse in B-cell ALL patients is an important treatment outcome.

4.7. The Subcommittee noted that there are approximately 20 incident adult patients with B-cell ALL/lymphoma per year in New Zealand. The Subcommittee previously considered that up to 10 of these patients would have CD20 expression greater than 20%.

4.8. The Subcommittee noted that rituximab is a monoclonal antibody targeting the CD20 surface antigen. The Subcommittee noted that approximately 30% of B-cell ALL patients have CD20 positivity at over 20% expression (ie 20% of B-cells have measurable CD20). The Subcommittee noted that CD20 is widely expressed on B-cells. The Subcommittee noted that CD20 expression is an adverse prognostic factor and that expression increases as B-cells mature. The Subcommittee noted that the 3-year overall survival for CD20 positive B-cell ALL patients with expression greater than 20% is 27%, compared to 40% for patients with B-cell CD20 expression less than 20% (Thomas et al. Blood. 2009;113:6330-7).

4.9. The Subcommittee noted an update to a previously considered clinician application for the use of rituximab in the treatment of adult patients with B-cell ALL. The Subcommittee noted that this application was reviewed in August 2017 where the Subcommittee deferred making a recommendation pending the results of the Phase III UKALL14 trial which was ongoing at the time of the 2017 meeting.

4.10. The Subcommittee noted that at the August 2017 meeting, it reviewed the results of the GRAALL-2005 study in which patients received 16-20 doses of rituximab versus no rituximab with conventional B-cell ALL therapy for two years (Maury et al N Engl J Med 2016;375:1044-53). The Subcommittee noted that the response rate was the same for both treatment arms, but that the event free survival was improved in the rituximab arm driven by a decrease in relapse rate (HR 0.52; 95% CI 0.31 to 0.89). The Subcommittee noted that there was a trend towards improvement in overall survival in the rituximab treatment arm, but that this was not statistically significant (4-year overall survival with rituximab 61%; 95% CI 52% to 72% vs 50% without rituximab; 95% CI 41% to 62%).

4.11. The Subcommittee previously considered that this study provided weak strength but good quality evidence to suggest a benefit of adding rituximab, with no significant increase in adverse events compared with standard precursor B-cell ALL therapy. However, the Subcommittee noted the small number of patients included in the GRAALL-2005 and considered that this raised questions about the potential benefit of a large number of rituximab doses given over a prolonged period.

4.12. At the August 2017 meeting, the Subcommittee also noted that the Phase III UKALL14 trial (NCT01085617), which had closed for recruitment but was not yet published at the time of the meeting, was seeking to determine if the addition of four doses of rituximab to standard Phase 1 induction chemotherapy resulted in improved event-free survival in patients with B-cell ALL, regardless of baseline CD20 status. The Subcommittee noted that the GRAALL-2005 trial was limited to adult CD20 positive, Philadelphia (Ph) chromosome negative B-cell ALL patients, whereas the UKALL14 trial included CD20 positive and negative patients as well as Ph positive patients. The Subcommittee at the time considered the UKALL14 confirmatory trial may resolve any residual uncertainty from the GRAALL-2005 trial, and thus deferred making a formal recommendation until the results of the UKALL14 trial were available.

4.13. The Subcommittee noted that interim results from the UKALL14 trial have since been published in November 2019 (Marks et al., Blood, 2019. 134(Supplement_1):739-739). The Subcommittee noted that response rates, including minimal residual disease negative responses, mortality, and adverse events were the same in both rituximab and non-rituximab treatment arms. The Subcommittee noted that the 3-year event free survival for standard treatment was 42%, compared with 49% with standard care plus rituximab, and was not significantly different between the two groups (HR 0.88; 95% CI 0.71 to 1.11). The Subcommittee considered that the primary endpoint of event free survival provides very similar information to overall survival but omits the minority of people who relapse and are salvaged. The Subcommittee noted that salvage therapy is unsatisfactory even if patients do survive and is expensive, and therefore considered that event free survival is a clinically relevant endpoint in ALL.

4.14. The Subcommittee noted that the UKALL14 trial reported no interaction between the addition of rituximab to chemotherapy and cytogenetics or CD20 expression. The Subcommittee considered that this may have been limited by the relatively small number of rituximab doses (four) administered in UKALL14. The Subcommittee noted that, as previously reported in other studies, survival was poorest in those patients who had higher expression of CD20. The Subcommittee noted that high risk younger (less than 40-years of age) patients who received myeloablative transplant had better outcomes if they had received rituximab. The Subcommittee noted that the event free survival at 3 years for this group was 72% compared to 51% for standard care alone (HR 0.47; 95% CI 0.23 to 0.95) (Marks et al., Blood, 2019. 134(Supplement_1):739-739).

4.15. The Subcommittee considered the evidence for the use of rituximab in the treatment of adults with B-cell ALL to be of weak strength due to the low patient numbers, the differing dosing regimens used and the variation in populations included in the two studies (GRAALL-2005 and UKALL14). The Subcommittee considered that this made comparison of the two trials difficult. However, the Subcommittee considered that the evidence for the use of rituximab in the treatment of adults with B-cell ALL to be of good quality and considered that the evidence was applicable to the New Zealand patient population as this evidence pre-dates the new forms of immunotherapy that target other relevant surface antigens (eg, CD19 and CD22).

4.16. The Subcommittee considered that given the development of novel treatments with different mechanisms of action in the treatment of B-cell ALL, it is unlikely that more evidence for rituximab in this patient group will become available.

4.17. The Subcommittee noted that CD20 is upregulated during treatment and considered that 4 doses of rituximab at the onset of B-cell ALL therapy may not be a sufficient treatment duration for the CD20 expression level to be clinically relevant. The Subcommittee considered that the non-significant trend to a better outcome with the addition of rituximab in the UKALL14 trial indicates that in order to obtain the full benefit of adding rituximab to existing chemotherapy protocols, the dosing regimen used in the GRAALL-2005 trial would be required.

4.18. The Subcommittee noted that a more pronounced effect of rituximab was observed in patients with higher CD20 expression GRAALL-2005 trial, although this difference was not significant. The Subcommittee also noted that initially the study recruited patients irrespective of CD20 expression. The Subcommittee considered that the lack of interaction between the addition of rituximab to chemotherapy and cytogenetics or CD20 expression in the UKALL14 trial suggests that the GRAALL-2005 results may be generalizable to all patients with B-cell ALL and not just those patients with CD20 expression greater than 20%.

4.19. The Subcommittee considered there to be no issues with the use of rituximab outside of its Medsafe approved indications for this patient group.

4.20. The Subcommittee considered that B-cell acute lymphoblastic leukaemia and lymphoma are overlapping clinical presentations of the same disease, and that the diagnosis and management of these disease presentations are the same. The Subcommittee noted that the incidence of B-cell lymphoblastic lymphoma was rare and therefore would not sufficiently affect the estimate of patient numbers.

4.21. The Subcommittee considered that if rituximab were funded, it would be reasonable to assume that there may be a reduction in the use of other, more expensive agents such as pegylated-asparaginase or other treatment options via PHARMAC's exceptional circumstances framework, which can incur a significant cost to the health system.

5. Olaparib for ovarian, fallopian tube or primary peritoneal cancer, newly diagnosed, BRCA-mutated, platinum sensitive – maintenance

Application

5.1. The Subcommittee considered the application for olaparib for first-line maintenance for newly diagnosed, BRCA-mutated, platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer, following review of this application by PTAC in August 2020.

5.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

5.3. The Subcommittee **recommended** that access to olaparib be widened for the first-line maintenance treatment of high-grade ovarian cancers with a germline mutation in breast cancer susceptibility gene 1 or 2 (BRCAm) with a high priority, within the context of treatment of malignancy, subject to the following Special Authority criteria that would allow for once-per-patient-lifetime access to olaparib:

> **Initial application** only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has a high-grade serous* epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
> 2. There is documentation confirming pathogenic germline BRCA1 or BRCA2 gene mutation; and
> 3. Either:
> 3.1. All of the following:
> 3.1.1. Patient has newly diagnosed, advanced disease; and
> 3.1.2. Patient has received one line of previous treatment with platinum-based chemotherapy; and
> 3.1.3. Patient's disease must have experienced a partial or complete response to the first-line platinum-based regimen; or
> 3.2. All of the following:
> 3.2.1. Patient has received at least two lines of previous treatment with platinum-based chemotherapy; and

3.2.2. Patient has platinum sensitive disease defined as disease progression occurring at least 6 months after the last dose of the penultimate line of platinum-based chemotherapy; and
3.2.3. Patient's disease must have experienced a partial or complete response to treatment with the immediately preceding platinum-based regimen; and
3.2.4. Patient has not previously received funded olaparib treatment; and
4. Treatment will be commenced within 8 weeks of the patient's last dose of the immediately preceding platinum-based regimen; and
5. Treatment to be administered as maintenance treatment; and
6. Treatment not to be administered in combination with other chemotherapy.

Renewal only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Treatment remains clinically appropriate and patient is benefitting from treatment; and
2. Either:
2.1. No evidence of progressive disease; or
2.2. Evidence of residual (not progressive) disease and the patient would continue to benefit from treatment in the clinician's opinion; and
3. Treatment to be administered as maintenance treatment; and
4. Treatment not to be administered in combination with other chemotherapy; and
5. Either:
5.1. Both:
5.1.1. Patient has received one line of previous treatment with platinum-based chemotherapy; and
5.1.2. Documentation confirming that the patient has been informed and acknowledges that the funded treatment period of olaparib will not be continued beyond 2 years if the patient experiences a complete response to treatment and there is no radiological evidence of disease at 2 years; or
5.2. Patient has received at least two lines of previous treatment with platinum-based chemotherapy.

Note: *Note "high-grade serous" includes tumours with high-grade serous features or a high-grade serous component. A line of chemotherapy treatment is considered to comprise a known standard therapeutic chemotherapy regimen and supportive treatments.

5.4. In making this high priority recommendation for olaparib, the Subcommittee noted that:

- Patients with ovarian cancers in New Zealand have a particularly high health need due to disease severity and the lack of effective, curative treatment options; and
- There is mature evidence of a significant clinical benefit in terms of progression-free survival from treatment with olaparib in the first line maintenance setting for BRCAm disease, and considered that an overall survival benefit would be expected in this setting; and
- There is a well-defined BRCAm population who would receive the greatest benefit from treatment with olaparib; and
- Olaparib treatment was well tolerated by SOLO-1 clinical trial participants; and
- Funded first-line maintenance treatment with olaparib would have a maximum duration of two years for most patients; and
- If funded for use as either first-line or second-line maintenance, a similar number of patients would receive olaparib overall.

Discussion

Health need in ovarian cancers

5.5. The Subcommittee noted that in August 2020, PTAC reviewed the supplier application for widened access of olaparib (Lynparza) as first-line maintenance treatment of newly diagnosed, advanced (stage III or IV) high-grade serous or endometroid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination thereof), with a BRCA1 or BRCA2 mutation (or both), who have had a complete or partial response after one line of platinum-based chemotherapy and had recommended that access to olaparib be widened for first-line maintenance treatment of high-grade ovarian cancers with a mutation in breast cancer susceptibility gene 1 or 2 (BRCAm) with a medium priority, subject to Special Authority criteria.

5.5.1. In August 2020, PTAC highlighted specific areas where it was particularly interested in CaTSoP's advice including: whether there is a class effect among polyadenosine 5'-diphosphoribose polymerase (PARP) inhibitors for BRCAm ovarian cancers; whether a similar benefit from olaparib would also be expected in patients with homologous recombination deficiency (HRD); the potential benefit of olaparib treatment in patients with somatic BRCAm ovarian cancers; the appropriate duration of funded treatment; the proportion of patients with other gynaecological cancers (serous fallopian tube or peritoneal carcinomas) who may be within the target population for olaparib; and appropriate Special Authority criteria for widened access that would allow for one funded course - per-patient-lifetime access to olaparib.

5.6. The Subcommittee noted that patients with ovarian cancers in New Zealand have poor survival rates and was made aware of evidence that only about 22% of patients who received chemotherapy or neoadjuvant chemotherapy remained alive at five years (Yeoh et al. Aust N Z J Obstet Gynaecol. 2019;59:861-66). The Subcommittee noted the lack of curative treatments for ovarian cancers and considered that these patients have a high health need.

5.7. The Subcommittee considered that, in practice, patients with fallopian tube or primary peritoneal cancers are not distinguished from patients with ovarian cancers and therefore estimates of incidence should pool these cancer registrations; and of these patients, approximately 80% would have high-grade serous histology.

5.8. The Subcommittee noted that while the pathological impact of BRCA 1 and BRCA 2 mutations is well known, there is sparse New Zealand data to inform the rate of germline BRCA 1 and BRCA 2 mutations within Māori and Pacific patient populations with ovarian cancers, and no data regarding the rates of HRD in these ethnic groups.

5.9. The Subcommittee was made aware of New Zealand data that suggests that overall BRCA mutation incidence can vary from 16% up to 20% and noted that this included data for patients of relevant ethnicities (Fraser et al. N Z Med J. 2019;132:26-35). Based on this evidence, the Subcommittee considered that the supplier's estimate that about 24 patients per year would be eligible for the proposed first-line maintenance treatment with olaparib was reasonable.

5.10. The Subcommittee considered there to be a need for at least one PARP inhibitor to be funded in New Zealand for germline BRCAm ovarian cancers.

PARP inhibitors and potential class effect in ovarian cancers

5.11. The Subcommittee noted that four randomised, phase III clinical trials investigating first-line treatment with a PARP inhibitor for the treatment of high-grade serous ovarian cancers have been published:

5.11.1. The SOLO-1 trial of olaparib maintenance (Moore et al. N Engl J Med. 2018;379:2495-2505); and

5.11.2. The VELIA trial of veliparib with chemotherapy (Coleman et al. N Engl J Med. 2019;381:2403-15); and

5.11.3. The PRIMA trial of niraparib maintenance (González-Martín et al. N Engl J Med. 2019;381:2391-402); and

5.11.4. The PAOLA-1 trial of olaparib and bevacizumab maintenance, which was not reviewed or discussed as the underlying treatment with bevacizumab in both study arms was not applicable to the New Zealand setting where bevacizumab is not funded for this indication.

5.12. The Subcommittee noted that the SOLO-1 patient population were essentially a BRCAm cohort, whereas VELIA and PRIMA included patients with non-BRCA homolgous recombination deficiency (HRD); the Subcommittee considered that the patient groups were otherwise similar in the SOLO-1, VELIA and PRIMA trials. However, the duration of PARP inhibitor treatment varied between trials (treatment until disease progression, or up to two years if no evidence of disease [ie complete response], or ongoing for patients with a partial response in SOLO-1; treatment up to two years in VELIA, and treatment until progression or up to three years in PRIMA).

5.13. The Subcommittee noted that SOLO-1 was a randomised (2:1), phase III, double-blind trial investigating olaparib 300 mg twice daily compared with placebo in 391 patients with newly diagnosed advanced (FIGO stage III or IV) high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer with mutation in BRCA1, BRCA2 or both (99% of which were germline mutations) and who had obtained either a complete response (82%) or partial response (18%) after six cycles of platinum-based chemotherapy and surgery (Moore et al. 2018).

5.13.1. The Subcommittee noted that SOLO-1 included a mix of BRCA1 and BRCA2 germline mutations, however, only two SOLO-1 participants had somatic BRCAm.

5.13.2 Members considered that SOLO-1 participants were comparable to New Zealand patients with advanced ovarian cancers in representation of histologic disease subtypes (predominantly high-grade serous, with a small proportion of endometrioid cancers) and prior chemotherapy including the number of prior treatment cycles.

5.13.3. The Subcommittee noted that 13 patients randomised to olaparib received a partial response and continued treatment after two years, as permitted by protocol.

5.13.4. The Subcommittee noted that the SOLO-1 primary endpoint was progression free survival (PFS) and secondary endpoints included quality of life, overall survival, freedom from second progression (PFS2) and time to subsequent treatment. The Subcommittee acknowledged PTAC's review of the SOLO-1

results after median follow-up of 41 months reported by Moore et al. and, in particular, noted the statistically significant difference in PFS (HR 0.3, 955 CI: 0.23 to 0.41, P<0.001) with a PFS benefit observed across all patient subgroups.

5.14. The Subcommittee was made aware of updated SOLO-1 results (data cut-off of 5 March 2020) that were presented at the European Society for Medical Oncology (ESMO) 2020 conference, reporting median PFS of 56.0 months with olaparib vs 13.8 months with placebo (HR 0.33, 95% CI: 0.25 to 0.43) Banerjee et al. ESMO Open. 2020;5:e001110. doi: 10.1136/esmoopen-2020-001110). The Subcommittee noted that more than 10% of patients from both study arms remained in follow-up at five years (>20% of patients from the olaparib arm), and that most patients had stopped olaparib treatment at two years. Members considered that the data suggested ongoing benefit from treatment with olaparib that continued even after olaparib treatment was stopped. Members considered this was promising, and unusual in the context of ovarian cancer treatments.

5.14.1. The Subcommittee noted that, although the median times for PFS2 and the time to subsequent treatment were reported as not reached with olaparib in the ESMO 2020 update, it appeared the medians were greater with olaparib compared to placebo in both the overall population and in patients who had a complete response to prior treatment at baseline.

5.14.2. Members considered that the difference in PFS at five years and the delay in time to subsequent therapy was clinically significant and meaningful for this patient group who benefit from avoiding further chemotherapy. Members considered that, while all patients appeared to benefit, those who received the most benefit were those who had a complete response at baseline.

5.14.3. The Subcommittee noted that even with longer SOLO-1 follow up, the incidence of myelodysplastic syndrome and acute myeloid leukaemia remained less than 1.5%. The Subcommittee noted that common adverse events with olaparib were nausea and fatigue which improved over time, and that 12% of olaparib patients compared with 3% of placebo patients discontinued due to adverse events.

5.15. The Subcommittee noted that international jurisdictions have approved the use of olaparib in this indication based on the SOLO-1 trial data. Members considered that olaparib is well tolerated based on local clinical experience in the currently funded setting.

5.16. The Subcommittee considered that it would be clinically appropriate, based on the evidence, to limit duration of treatment to two years in those patients who had a complete response to treatment with olaparib by that time.

5.17. Members considered that the available evidence does not indicate an optimal duration of treatment for patients who have a partial response to olaparib after two years of treatment, and considered it would be difficult to estimate how long partial responders would continue to benefit if olaparib were funded in the first line maintenance setting. The Subcommittee considered that the number of trial participants to whom this applied was small and would be less than 5% of the total eligible patient population based on SOLO-1 data. For patients with a partial response after two years of treatment, the Subcommittee considered that, in the absence of evidence to support or dispute ongoing treatment, it would be appropriate to continue treatment until disease progression, at the discretion of the treating clinician.

5.18. The Subcommittee noted that VELIA is a randomised (1:1:1), multicentre, double-blind, placebo-controlled, phase III, three-arm trial investigating veliparib in combination with chemotherapy in 1,140 patients with previously untreated stage III or IV high-grade serous or epithelial ovarian, fallopian tube or primary peritoneal cancer (Coleman et al. N Engl J Med. 2019;381:2403-15). The Subcommittee noted that other studies of combination treatment with PARP inhibitors often reduce the chemotherapy dosing to avoid increased myelosuppression when used in combination with chemotherapy; in VELIA, the veliparib dosing differed. The three VELIA treatment arms were:

- Chemotherapy (carboplatin (area under the curve [AUC] of 6 mg per millilitre per minute, every 3 weeks) and paclitaxel (175 mg per m^2, every 3 weeks, or 80 mg m^2, administered weekly) + placebo then placebo maintenance (control); and
- Chemotherapy + oral veliparib 150 mg twice daily then placebo maintenance (veliparib combination only); and
- Chemotherapy + oral veliparib 150 mg twice daily then veliparib 300 mg increasing to 400 mg twice daily maintenance (veliparib throughout).

5.18.1. The Subcommittee noted that VELIA defined HRD as tumours that were BRCA-mutated or had HRD according to the Myriad Genetics myChoice assay initially with a threshold of 33; during the study, this was revised to 42. Members considered it was unclear from the results what impact this threshold change may have had.

5.18.2. The Subcommittee noted that median PFS in the BRCAm cohort was 34.7 months with veliparib vs 22.0 months control (HR 0.44, 95% CI: 0.28 to 0.68, P<0.001); median PFS in the HRD cohort was 31.9 months with veliparib vs 20.5 months control (HR 0.57, 95% CI: 0.43 to 0.76, P<0.001); and median PFS in the intention-to-treat population was 23.5 months with veliparib vs 17.3 months control (HR 0.68, 95% CI: 0.56 to 0.83, P<0.001).

5.18.3. The Subcommittee noted that PFS according to BRCAm and HRD status was similar between all three treatment arms, with PFS ranging from 27-31% for patients with BRCAm across the three arms vs 69-73% for patients with no BRCAm; and 63% for patients with HRD across all three arms vs 37% for patients with no HRD.

5.18.4. The Subcommittee noted that 19.0% of patients who received veliparib and 6.0% of placebo patients discontinued treatment due to adverse events; members considered that this discontinuation rate was higher than for olaparib in SOLO-1 and may have been influenced by the combination chemotherapy treatment.

5.19. The Subcommittee noted that PRIMA is a randomised (2:1), multicentre, double-blind, placebo-controlled, phase III trial investigating oral niraparib 300 mg once daily (amended to 200 mg OD for patients with baseline body weight <77 kg) or placebo once daily for 28-day cycles in 733 patients with newly diagnosed advanced (FIGO stage III or IV) high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer who responded to prior platinum-based chemotherapy (González-Martín et al. 2019).

5.20. The Subcommittee noted that PHARMAC received a funding application for niraparib as first- or second-line maintenance treatment for ovarian cancer in January 2021 and that a fulsome review of the evidence for niraparib for ovarian cancer would occur as part of the assessment of that application. At this time, based on the publication by González-Martín et al.:

5.20.1. The Subcommittee considered the PRIMA population was similar to that of SOLO-1, however, differences included shorter follow-up (median 13.8 months) and earlier publication in PRIMA compared with SOLO-1, and a three-year duration of placebo treatment compared with two years in SOLO-1 and VELIA.

5.20.2. The Subcommittee noted that PRIMA defined HRD as the presence of a BRCA deleterious mutation and/or a score of at least 42 on the Myriad Genetics myChoice test (the same assay used in VELIA). The Subcommittee noted that 373 (50.9%) of PRIMA participants had HRD of which 233 were BRCAm, and that the trial reported outcomes for the HRD subgroup, rather than just for BRCAm, and for the intention-to-treat population.

5.20.3. The Subcommittee noted that median PFS in the HRD cohort was 21.9 months with niraparib vs 10.4 months with placebo (HR 0.43, 95% CI: 0.31 to 0.59, P<0.001) and median PFS in the overall population was 13.8 months with niraparib vs 8.2 months placebo (HR 0.62, 95% CI: 0.50 to 0.76, P<0.001). The Subcommittee considered that this suggests that the patients with ovarian cancer who received the greatest magnitude of benefit from niraparib were those with BRCAm disease, followed by non-BRCA HRD, followed by those without HRD.

5.20.4. The Subcommittee noted that 12% of patients who received niraparib discontinued treatment due to adverse events and considered this discontinuation rate was similar to olaparib.

5.21. The Subcommittee considered that differences in the length of follow up and proportion of patients with BRCAm disease that would make cross-trial comparison challenging; however, the SOLO-1, VELIA and PRIMA trials were well conducted, good quality randomised controlled trials providing evidence that is applicable to patients with ovarian cancers in New Zealand.

Class effect

5.22. Acknowledging the absence of head-to-head trials of these PARP inhibitors, the Subcommittee considered that the evidence of a PFS benefit for patients with BRCAm disease in the SOLO-1, VELIA and PRIMA trials suggests there may be a class effect among these agents in terms of efficacy for BRCAm ovarian cancers. The Subcommittee noted there is a clear signal that patients with BRCAm disease receive the greatest magnitude of benefit from these agents. The Subcommittee considered that there may be inter-individual variability in how different PARP inhibitors are tolerated. Members considered that that olaparib is particularly well tolerated. The Subcommittee noted that rucaparib was another agent in this class that was being used in BRCAm ovarian cancers in other jurisdictions.

5.23. Members considered that the deciding factor would generally be the safety profile, rather than efficacy, in a clinical situation where multiple PARP inhibitors may be available as options for treatment of ovarian cancers and noted that niraparib is associated with a greater degree of myelosuppression than olaparib or veliparib, although they have not been compared head-to-head in a clinical trial. Members considered that, in making a recommendation for funding it would be important to

have at least one PARP inhibitor funded for the first-line maintenance treatment of BRCAm ovarian cancers.

5.24. Members considered that second-line maintenance data indicates that olaparib has an overall survival benefit in BRCAm ovarian cancers, although no updated evidence for overall survival outcomes was available for SOLO-1 at this time. Members considered that evidence of a survival benefit from olaparib as first-line maintenance in SOLO-1 would likely be forthcoming as an overall survival benefit was seen with second-line olaparib maintenance in the SOLO-2 trial, which represents a setting where an overall survival benefit would be more unlikely to occur. Members considered it was unclear whether first-line or second-line olaparib maintenance offered a higher chance of cure for ovarian cancers.

Germline BRCA testing

5.25. The Subcommittee noted that germline BRCA testing is routinely offered to inform subsequent treatment decisions for patients with ovarian cancers who are less than 70 years of age (a threshold no longer used by many other countries), however, only about 70% of eligible patients seek referral to genetics services for consultation and testing with declines primarily due to this being discussed at recurrence; a time of greater stress.

5.26. Members considered that it takes an average of 146 days from the date of referral to genetics services to the provision of results and that access to BRCA testing and turnaround time varies around the country but can take up to six months for urgent testing to be performed. Members noted that in some DHBs these tests are conducted through the medical oncology service, which results in a substantially abbreviated processing time. Members considered there is work underway to streamline germline BRCA testing in New Zealand but accessing timely results remains difficult.

5.27. In considering access to germline BRCA testing, the Subcommittee considered whether it would be practical to commence first-line olaparib treatment within 8 weeks of the last dose of the immediately preceding platinum-based chemotherapy regimen. Members considered this would be achievable based on the length of the chemotherapy regimen and that BRCAm testing would occur prior to commencing this treatment. Members considered an urgent test may be required and that this could have flow-on effects for testing capacity.

Somatic BRCAm

5.28. The Subcommittee noted evidence regarding olaparib treatment in patients with ovarian cancers with somatic BRCAm, suggesting a similar benefit to those with germline BRCAm (Mohyuddin et al. BMC Cancer. 2020;20:507; George et al. Oncotarget. 2017;8:43598-9).

5.29. The Committee was made aware of evidence from NOVA; a randomised (2:1), double-blind, phase 3 trial investigating niraparib (300 mg) or placebo once daily in 553 patients with platinum-sensitive, recurrent ovarian cancers who were categorised according to the presence or absence of a germline BRCA mutation (gBRCA cohort and non-gBRCA cohort) and the type of non-gBRCA mutation (Mirza et al. N Engl J Med. 2016;375:2154-64). The Committee noted that median PFS in the gBRCA cohort was 21.0 months with niraparib (HR, 0.27; 95% CI: 0.17 to 0.41; P<0.001) and that there was a PFS benefit in patients with HRD-positive tumours and somatic BRCAm (HR, 0.27; 95% CI: 0.08 to 0.90; P=0.02).

5.30. Members noted that somatic BRCA testing is not routinely available nor is it funded in New Zealand, however, this capability may be developed in future at select centres. Members noted that a cost-share arrangement exists between patients and AstraZeneca which can enable suitable patients who privately fund this to have somatic BRCA testing performed at Peter MacCallum Cancer Centre in Melbourne, Australia. Members noted that the challenges with somatic BRCAm testing are experienced internationally, with some centres moving toward somatic BRCAm testing at diagnosis to avoid experiencing access issues subsequently.

5.31. The Subcommittee noted that the evidence for first-line PARP inhibitor treatment of patients somatic BRCAm was based on small patient numbers (0.5% [2/391] of intention-to-treat patients in SOLO-1 had somatic BRCAm) making it difficult to assess any difference in the magnitude of this benefit compared to patients with germline BRCAm and supported the clinical rationale for this treatment. However, the Subcommittee considered that the lack of a funded care pathway for somatic testing would present a barrier to equitable access to treatment with olaparib, and therefore could not recommend olaparib be funded for patients with somatic BRCAm at this time.

HRD testing

5.32. The Subcommittee noted that SOLO-1 did not test or report HRD status and considered that while PRIMA and VELIA used the same HRD assay, there remained uncertainty in the understanding of HRD. In particular, it was noted that the variation in the thresholds and assays used to define an HRD population in clinical trials investigating first-line or second-line use of PARP inhibitors for ovarian cancers are varied. The Subcommittee considered that while the understanding of HRD would continue to develop through clinical trials, including clarity on the significance of detected variations and treatment outcomes for these, the evidence reviewed suggested a benefit from treatment with PARP inhibitors in patients with HRD but of a lesser magnitude than the benefit received by patients with BRCAm.

5.33. Members considered that the varied HRD assays and thresholds used to define clinical trial and validation study populations may not be directly applicable to the New Zealand population, noting that Māori and Pacific patients are not represented in the evidence informing these HRD definitions.

5.34. The Subcommittee noted that HRD testing is only available in New Zealand via private funding arrangements and considered that implementation and standardisation of this testing in New Zealand would be a challenging, long-term process. Members considered that the cost of testing is currently about $4,000 (Foundation medicine assay) or $5,000 (Myriad assay), noting that the latter is approved by the US FDA as a companion diagnostic for olaparib in advanced ovarian cancer. Members considered that, if a treatment were to be funded for HRD- positive disease, early engagement with pathology services would be crucial given the potential variation in assays, access barriers and turnaround times.

Olaparib in ovarian cancers

5.35. The Subcommittee considered that the available evidence supported once-per-patient-lifetime access to olaparib for patients with germline BRCAm ovarian cancers, either as a first-line maintenance therapy or as second-line maintenance, noting a clear PFS benefit in each setting. The Subcommittee considered that, based on the available evidence at this time, it was unclear whether first-line or second-line olaparib maintenance offered a higher chance of cure.

5.36. The Subcommittee considered that use of olaparib in the first line would likely impact the same pool of patients as the currently funded second-line maintenance usage (ie 80% of all patients diagnosed with ovarian cancers; those with high-grade serous disease), therefore the number of potentially eligible patients would be as estimated (24 patients in year one, increasing to 52 patients by year five).

5.37. The Subcommittee noted that standard of care monitoring for patients with ovarian cancers following either first- or second-line treatment consists of three- to four-monthly clinic visits with blood tests; for patients receiving a PARP inhibitor this would increase to monthly clinic visits for the first 6 months, then clinic visits two- to three-monthly, all accompanied by blood tests.

5.38. The Subcommittee considered that the funding criteria for olaparib should not specify a maximum treatment duration for patients who have a partial response to olaparib after two years, as there is insufficient evidence to inform an appropriate duration of treatment and noted that very few patients remained on treatment at five years in SOLO-1.

5.39. The Subcommittee considered that Special Authority criteria for olaparib should not facilitate access to olaparib for (non-BRCA) HRD-positive ovarian cancers or for patients with ovarian cancers who have somatic BRCAm, primarily due to the poor evidence and understanding of HRD and due to the high potential for inequitable access to testing for somatic BRCAm.
