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Perspectives on Precision Oncology

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Editorial and study commentary by Dr Angela George

Dr Angela George is the Consulting Editor for the Perspectives on Precision Oncology series. Born and trained in NZ, she is now Clinical Director of Genomics at The Royal Marsden Hospital (London, UK) specialising in the systemic treatment of gynaecological cancers.

Dr George has authored multiple peer-reviewed publications and book chapters and undertakes a variety of clinical and translational research projects, particularly in cancer genomics and targeted treatments.

In addition to her clinical responsibilities, Dr George is involved in multiple national and international groups, including the National Cancer Research Institute Gynaecological Cancers Group, the Precision Medicine Working Group for the European Society of Medical Oncology and the British Society of Genetic Medicine.

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Abbreviations used in this issue

AUC = area under the curve
CCND1 = cyclin D1
CI = confidence interval
ctDNA = circulating tumour DNA
DFS = disease-free survival
ESMO = European Society of Medical Oncology
HER-2 = human epidermal growth factor receptor 2
HR = hazard ratio
IV = intravenous
MET = hepatocyte growth factor receptor
MMR (MMRd/MMRp) = mismatch repair (deficient/proficient)
MSK-IMPACT = Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets
NGS = next-generation sequencing
ORR = objective response rate
OS = overall survival
PARP = poly (ADP-ribose) polymerase
pCR = pathological complete response
PD-L1 = programmed death-ligand 1
PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PFS = progression-free survival
T-DM1 = trastuzumab emtansine
TKI = tyrosine kinase inhibitor
VEGF = vascular endothelial growth factor

Refining patient populations for precision oncology

The rise of precision oncology has led to a massive increase in demand for clinical genetics services and input to molecular tumour boards. In part, this is a direct reflection of increasing understanding of the implications of specific mutations for the response to chemotherapy agents, and prognostic implications (such as *BRCA* mutations in those with breast and ovarian cancer). This is also driven by the now routine use of large somatic panels in patients with cancer, where testing may uncover a potentially inherited mutation in a cancer predisposition gene, either one related to the tumour or picked up incidentally.

The data from unselected series of metastatic cancers, such as MSK-IMPACT, which were used to inform the ESMO precision medicine guidelines,[1] suggest this will be the case for around 15% of patients. As we start to undertake more and more tumour testing through sequencing or surrogates such as immunohistochemistry, we have been able to identify patients who may benefit from different approaches to treatments, as well as those families with an inherited cancer risk. The integration of testing for *BRCA* mutations in those with ovarian, pancreatic, breast and prostate cancer is changing treatment at multiple levels for those found to have mutations, while adoption of routine MMR testing for colorectal and other Lynch-associated cancers has been driven by the availability of immunotherapy for these patients. The next step is to try to see how we can replicate these results for patients who do not fall into these categories, with combinations designed to mimic the molecular pathways that are activated or suppressed in these patients.

"Endometrial cancer rates are rising rapidly, driven partly by the increased prevalence of obesity"

Endometrial cancer has been one of the recent winners of a move to molecular profiling. For many years, studies for this tumour type have focused on surgical and radiotherapy techniques with little interest in systemic treatments. Yet endometrial cancer rates are rising rapidly, driven partly by the increased prevalence of obesity, which fuels many cases. We are increasingly seeing women with recurrent or advanced disease at presentation, and worrying rises in incidence in those who are premenopausal. However, interest in systemic treatment for endometrial cancer was rekindled with the benefit noted with immunotherapy in those with MMR deficient tumours. We had previously had preliminary results of the benefit of pembrolizumab in such patients, but the publication of KEYNOTE-158 provides efficacy and safety data for such patients.[2] This study reported an impressive ORR of 48% in those previously treated with platinum-based chemotherapy, which compares very favourably with the best of the chemotherapy regimens used in second-line treatment for relapsed disease. The median PFS of 13.1 months is also a significant improvement over chemotherapy options, which provide only a few months of PFS on average. Most importantly, pembrolizumab was generally very well tolerated, even in older patients in whom performance status may be borderline for chemotherapy. This will clearly become a new standard and has driven the desire to undertake universal MMR testing, so that the 30% of patients who may benefit from this approach are identified.

"For patients who are found to be MMRp on testing, there is some progress"

For patients who are found to be MMRp on testing, there is also some progress. As with many agents, there has been a desire to combine treatments in this setting to see if we can obtain similar results to those seen with single-agent checkpoint inhibitors in MMRd patients. This approach has already been trialled with PARP inhibitors in those without *BRCA* mutations or homologous recombination deficiency, with combinations of VEGF and PARP inhibitors investigated in a number of tumour types. Now we have lenvatinib, a TKI that targets a range of receptors including several VEGF receptors, numerous fibroblast growth factor receptors and *KIT*. Lenvatinib was combined with pembrolizumab in patients without MMR mutations in the phase 3 KEYNOTE-775 trial.[3] This study randomised predominantly MMRp endometrial cancer patients who had received prior chemotherapy for relapsed/advanced disease to receive either standard chemotherapy or the combination of pembrolizumab/lenvatinib. The results showed that the immunotherapy/TKI combination was associated with both statistically and clinically significant improvements in PFS and OS compared with chemotherapy. Approximately 50% of patients in both groups were aged >65 years (age was up to 82 years in the immunotherapy group and 86 years in the chemotherapy

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MoST vital research: new study examines how best to deliver genomic profiling across public settings

Access to genomic profiling can deliver remarkable treatment outcomes

Genomic profiling is a critical step towards personalised treatment, with the potential to radically alter the field of oncology. Unfortunately, cancer patients are usually left to pay for both genomic profiling and unfunded treatments themselves.

A new research initiative

The Cancer Molecular Screening and Therapeutics Programme (MoST) will offer cancer patients who have exhausted all publicly-funded options another chance at treatment via genomic profiling.

Patient recruitment across different tumour types has already begun, with a particular focus on rare cancers

There's no cost to the patients – whose participation will provide valuable insights in personalised cancer treatment, while offering them the priceless possibility of more time.

Based at Auckland City Hospital

MoST forms the first step in wider collaboration around oncology research with ADHB, the University of Auckland and genomic profiling company Foundation Medicine, part of multinational healthcare company Roche. Cristin Print, professor in molecular medicine and pathology at the University of Auckland, expresses excitement about the MoST trial:

> **"It's the fastest way to bring the benefits of genomic precision medicine to Auckland patients. By including ethically approved research at the centre of this trial, we learn more from every patient about the genetic re-wiring that drives tumours."**

By delivering precision cancer treatments to a diverse patient group representative of NZ's population, the trial aims to examine how best to deliver genomic profiling across public settings. It also emphasises equitable health outcomes for Māori and Pacific people, a core value of Auckland's Regional Cancer and Blood Service Te Puriri o Te Ora.

With the launch of MoST, personalised oncology services are one step closer to reality for everyday New Zealanders living with cancer.

In that sense, it's already a success.

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group). This is important to note given that patients with MMRd endometrial cancer secondary to Lynch syndrome enrolled in the single-agent immunotherapy studies were traditionally much younger than the MMRp patients. While it was not specifically powered for this, it is also very interesting to note that disease control rates in KEYNOTE-775 appeared equivalent for MMRp and MMRd patients. This suggests that the addition of lenvatinib was indeed improving outcomes for those with MMRp tumours.

The benefit of immunotherapy in triple-negative breast cancer has become a little less clear with the report of the NeoTRIP Michelangelo study in the *Annals of Oncology*.[4] This study assessed the addition of atezolizumab, a PD-L1 inhibitor, to standard neoadjuvant chemotherapy in patients with high-risk or locally advanced triple-negative breast cancer. The primary endpoint was pCR and, while PD-L1 expression was tested in all patients, its presence was not a requirement for inclusion in the study. There was no statistically significant difference in the pCR rate between the chemotherapy plus immunotherapy and chemotherapy alone groups, although there was benefit with the addition of atezolizumab in those with PD-L1 expression. These findings directly contrast the previous atezolizumab study in similar patients, where a benefit was seen irrespective of PD-L1 status.[5] Pembrolizumab has been licensed for use with neoadjuvant chemotherapy for the treatment of triple-negative breast cancer in patients with PD-L1-positive disease, but it looks as though the lack of patient selection for PD-L1 expression as an inclusion criteria in NeoTRIP may impact on a similar indication being granted, at least from this evidence.

"Molecular subtyping has improved outcomes for many tumour types, but may not always be better than standard of care"

Molecular subtyping has improved outcomes for many tumour types, but may not always be better than standard of care. There are many trials currently undertaking some form of genomic profiling (on tissue or ctDNA) and selecting targeted treatment based on the results. However, the BRE12-158 study of personalised treatment versus physicians choice in individuals with residual triple-negative breast cancer following neoadjuvant chemotherapy did not show benefit from a personalised approach.[6] This phase 2 study enrolled 193 women and undertook NGS to identify potential targets. After review at the tumour board, women with a target amenable to drug treatment were randomly assigned to personalised treatment or standard of care chemotherapy. Those without a treatable target were enrolled into the standard of care arm, in which almost all patients received capecitabine.

A wide range of targeted drugs was used, including pembrolizumab, olaparib, gemcitabine and agents targeting PIK3CA, MET, VEGF and CCND1. None of these were superior to standard of care chemotherapy, with a DFS of 56.6% in the personalised treatment arm compared with 62.4% in the standard of care arm.

"As well as improving treatment responses, precision oncology can also be utilised to minimise treatment toxicity"

As well as improving treatment responses, precision oncology can also be utilised to minimise treatment toxicity, either by avoiding exposure to drugs that will not be effective, or using targeted treatments as chemotherapy-sparing regimens. This approach has been looked at in several trials of HER2-positive breast cancer,[7,8] most recently with the KAITLIN study.[9] In this study, patients receiving adjuvant treatment were randomised to receive either T-DM1 and pertuzumab or taxane/trastuzumab/pertuzumab. The primary endpoint was invasive DFS, and this did not differ significantly between the two treatment groups. Of note, far more patients in the T-DM1 group discontinued treatment, primarily due to hepatotoxicity and thrombocytopaenia. This reinforces the findings of two other similar studies (KRISTINE[7] and MARIANNE[8]) and suggests that, at least for now, combination HER-2-directed treatment with chemotherapy remains the standard of care.

Finally, we have seen the recent publication of updated risks for those inheriting a pathogenic variant (mutation) in *BRCA1* or *BRCA2*.[10] This study, from the international CIMBA consortium, has data on over 7600 BRCA-positive families, mostly ascertained through family history clinics. This approach introduces some inherent bias when compared with families identified through mainstream testing, because the bar for testing through family history has traditionally selected more penetrant families, or those with female inheritance. This tends to mean more cases of breast and ovarian cancer, and higher estimates for cancer risk compared with those identified from mainstream approaches. The results of this study suggest that in addition to the established risks for carriers of breast, ovarian, pancreatic and prostate cancers, individuals may also be at risk for gastric cancer. It should be noted that gastric cancer has not been consistently noted in other such database studies, and that family history was self-reported, not confirmed with death certificates or histopathology reports. This could have led to significant classification issues. We are already aware that many self-reported cases of 'stomach cancer' in female carriers may well have been ovarian cancer or lobular breast cancer. In both sexes, this may also represent peritoneal dissemination from many other primaries rather than a specific gastric cancer. This requires further study and confirmation before any clear recommendations should be made regarding screening and interventions.

As we continue to progress in precision oncology, we need to ensure we are setting up studies or patient selection that will reflect this. Precision medicine does not benefit from an all-comers approach, unless there is a biological basis to support this. Otherwise, we will just continue to see conflicting results that take us no further forward.

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We hope that you find this editorial and these articles of academic or clinical interest and welcome any feedback.

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KEY PUBLICATION SUMMARIES

Pembrolizumab in patients with microsatellite instability–high advanced endometrial cancer

Authors: O'Malley DM et al.

Summary: Efficacy and safety outcomes were reported for ninety KEYNOTE-158 trial participants with microsatellite instability-high or MMRd endometrial cancer. At data cutoff (Oct 5, 2020), 20% of participants had completed 35 cycles of pembrolizumab and 58% had discontinued treatment. In those who had received ≥1 dose of pembrolizumab and had ≥26 weeks of follow-up (efficacy population; n=79; median time from first dose to data cutoff, 42.6 months), the ORR (primary endpoint) was 48%, median response duration was not reached, median PFS duration was 13.1 months, and median OS duration was not reached. Three-quarters (76%) of all treated participants experienced ≥1 treatment-related adverse event (12% grade 3–4; none fatal), and 28% experienced immune-mediated adverse events or infusion reactions (7% grade 3–4; none fatal).

Comment: The initial *N Engl J Med* paper of pembrolizumab in MMRd patients (Le DT et al. N Engl J Med 2015;372:2509–20) led to the first tumour agnostic US FDA licence for a drug. The KEYNOTE-158 study has now provided further evidence across a range of tumour types. The ORR of 48% in this group far exceeds rates for any of the existing second-line treatments for relapsed endometrial cancer, and highlights the need to routinely identify those with MMRd disease who would benefit from single-agent immunotherapy. Given that approximately 30% of patients with endometrial cancer will be MMRd, this is not an insignificant group of patients, particularly given that pembrolizumab is generally a well-tolerated treatment.

Reference: J Clin Oncol 2022;40:752–61
Abstract

Lenvatinib plus pembrolizumab for advanced endometrial cancer

Authors: Makker V et al., for the Study 309–KEYNOTE-775 Investigators

Summary: Patients with advanced endometrial cancer (697 MMRp, 130 MMRd) who had previously received ≥1 platinum-based chemotherapy regimen were randomised to receive oral lenvatinib 20 mg once daily plus IV pembrolizumab 200 mg every 3 weeks (n=411) or physician's choice chemotherapy (IV doxorubicin or paclitaxel; n=416) in this phase 3 trial. Compared with chemotherapy, lenvatinib plus pembrolizumab recipients had longer median PFS (7.2 vs. 3.8 months; HR for progression or death, 0.56 [95% CI 0.47, 0.66]) and OS (18.3 vs. 11.4 months; 0.62 [0.51, 0.75]), including in the MMRp population (6.6 vs. 3.8 months; HR for death, 0.60 [0.50, 0.72] and 17.4 vs. 12.0 months; 0.68 [0.56, 0.84], respectively). The grade ≥3 adverse event rates in the lenvatinib plus pembrolizumab and chemotherapy arms were 88.9% and 72.7%, respectively.

Comment: For patients with relapsed endometrial cancer that is not MMRd, the combination of pembrolizumab and lenvatinib offers a chemotherapy-sparing option that also significantly outperformed standard of care chemotherapy (in this case doxorubicin or weekly paclitaxel). However, the lenvatinib plus pembrolizumab combination is associated with more toxicity than single-agent immunotherapy, and most patients required dose reduction of lenvatinib. However, two-fold higher rates of complete and partial responses in the MMRp patients given lenvatinib plus pembrolizumab compared with chemotherapy, and a progressive disease rate that was half of that seen in the chemotherapy arm, this will be considered standard of care in advanced endometrial cancer patients with MMRp disease.

Reference: N Engl J Med 2022;386:437–48
Abstract

Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer

Authors: Gianni L et al.

Summary: The NeoTRIP Michelangelo study randomised patients with triple-negative breast cancer to receive neoadjuvant carboplatin (AUC2) and intravenous nab-paclitaxel 125 mg/m^2 on days 1 and 8, with (n=138) or without (n=142) intravenous atezolizumab 1200 mg on day 1; both regimens were given every 3 weeks for eight cycles prior to surgery followed by four cycles of an adjuvant anthracycline regimen. In an intent-to-treat analysis, there was no significant difference in the pCR rate between the atezolizumab-containing versus non-atezolizumab arm (48.6% vs. 44.4%; p=0.48). Atezolizumab recipients had a significantly higher incidence of serious adverse events and aminotransferase level abnormalities, but otherwise treatment-related adverse events were similar in the two groups.

Comment: In the study, the results differed between patients with and without PD-L1 expression on their tumours, irrespective of whether or not they received atezolizumab. It has previously been noted that those with PD-L1 expression also have much higher rates of tumour-infiltrating lymphocytes in their tumours, which may also be important in their response to neoadjuvant chemotherapy. Conflicting results regarding the benefit of using immunotherapy in patients with triple-negative breast cancer across several studies suggest that the most appropriate cohort of individuals may require further refinement.

Reference: Ann Oncol 2022;Feb 16 [Epub ahead of print]
Abstract

BRE12-158: a postneoadjuvant, randomized phase II trial of personalized therapy versus treatment of physician's choice for patients with residual triple-negative breast cancer

Authors: Schneider BP et al.

Summary: Following NGS, 193 patients with triple-negative breast cancer were randomised to receive four cycles of genomically-directed therapy or physician's choice of treatment; participants without a genetic target identified were enrolled in the physician's choice arm. There was no significant difference between the genomically-directed therapy versus physician's choice arm for the estimated 2-year DFS rate in the randomised population (primary endpoint; 56.6% vs. 62.4%), or for the secondary endpoints of distant DFS or OS rate in the entire and randomised populations. Over time, the uptake of capecitabine as physician's choice of treatment increased, and participants randomised later had fewer distant recurrences. ctDNA status persisted as a significant predictor of outcome, with some participants experiencing clearance on postneoadjuvant therapy.

Comment: Other studies such as PlasmaMATCH (Turner NC et al. Lancet Oncol 2020;21:1296–308) have clearly demonstrated a benefit from targeting mutations in patients with metastatic breast cancer, so why did this trial fail to show an advantage? It may be partly due to the range of treatments used, and the risk that in some cases they were targeting passenger mutations instead of drivers. We would expect some benefit of targeted treatment in individuals with *BRCA* or *PIK3CA* mutations, but the use of single-agent pembrolizumab for PD-L1-positive patients is not established, nor is the use of single-agent treatments such as crizotinib or bevacizumab. This trial would have benefitted from a more defined range of potentially targetable mutations, rather than a decision from a local molecular tumour board as to recommended treatments.

Reference: J Clin Oncol 2022;40:345–55
Abstract

Trastuzumab emtansine plus pertuzumab versus taxane plus trastuzumab plus pertuzumab after anthracycline for high-risk human epidermal growth factor receptor 2-positive early breast cancer

Authors: Krop IE et al.

Summary: In the phase 3 KAITLIN study, adults with excised HER2-positive early breast cancer were randomised to receive 3–4 cycles of anthracycline-based chemotherapy followed by 18 cycles of T-DM1 plus pertuzumab (n=928) or 3–4 taxane cycles plus trastuzumab plus pertuzumab (n=918); participants were allowed to receive adjuvant radiotherapy/endocrine therapy. After a median follow-up of ~57 months, there was no significant difference between the T-DM1-containing versus trastuzumab-containing arm with respect to invasive DFS in node-positive participants (stratified HR 0.97 [95% CI 0.71, 1.32]) or in the overall population (0.98 [0.72, 1.32]). For the respective T-DM1-containing and trastuzumab-containing arms, the proportions of participants who completed 18 cycles of treatment were 65.0% (driven by laboratory abnormalities due to T-DM1) and 88.4%, the grade ≥3 adverse event rates were 51.8% and 55.4%, and the serious adverse event rates were 21.4% and 23.3%. T-DM1 plus pertuzumab was associated with lower rates of clinically meaningful deterioration in global health status compared with trastuzumab plus pertuzumab (stratified HR 0.71 [95% CI 0.62, 0.80]).

Comment: T-DM1 already has a role in individuals with HER2-positive breast cancer who have disease resistant to the taxane/trastuzumab combination. Therefore, it is not surprising that this trial attempted to identify whether the combination of T-DM1 plus pertuzumab would be superior to the taxane/pertuzumab/trastuzumab combination, and potentially with fewer side effects. The study failed to meet its efficacy endpoint and fewer patients completed the trial arm treatment, reinforcing that taxane/pertuzumab/trastuzumab remains the appropriate first-line option in this setting, and T-DM1 should be reserved for those who become resistant.

Reference: J Clin Oncol 2022;40:438–48
Abstract

Cancer risks associated with *BRCA1* and *BRCA2* pathogenic variants

Authors: Li S et al.

Summary: Data from 3184 families with *BRCA1* pathogenic variants and 2157 families with *BRCA2* pathogenic variants were analysed to establish precise age-specific risk estimates for cancers (other than female breast and ovarian) that might be associated with pathogenic variants in these genes. *BRCA1* pathogenic variants were associated with elevated risks of male breast, pancreatic and stomach cancers (respective relative risks 4.30 [95% CI 1.09, 16.96], 2.36 [1.51, 3.68] and 2.17 [1.25, 3.77]), and *BRCA2* pathogenic variants were associated with increased risks of male breast, stomach, pancreatic and prostate cancers (44.0 [21.3, 90.9], 3.69 [2.40, 5.67], 3.34 [2.21, 5.06] and 2.22 [1.63, 3.03], respectively). There were also suggested associations between *BRCA1* pathogenic variants and increased risks of colorectal and gallbladder cancers, and the associations with stomach cancer were significantly higher for females than for males. For *BRCA1* carriers, the absolute risks up to age 80 years ranged from 0.4% for male breast cancer to ~2.5% for pancreatic cancer, and for *BRCA2* carriers they ranged from ~2.5% for pancreatic cancer to 27% for prostate cancer.

Comment: There are now large international consortia with combined databases of families with underlying gene alterations, including *BRCA1*/*BRCA2*. These allow updated risk assessments for those with mutations, and potential changes to management guidelines, as more robust information becomes available on individual cancer risk and age of risk. However, occasionally they throw up additional potential cancer risks not previously reported, which require further assessment. In this case there is the suggestion of an increased risk of stomach cancer, particularly for female carriers. Whilst it is possible this may be true, it must also be noted that all cases are self-reported by families and that there is a history of patients reporting 'stomach cancer' (meaning cancer somewhere in the abdominal cavity) to be translated by clinicians as gastric cancer. This suggestion therefore needs significantly more evidence in the form of histological confirmation of cases before we start undertaking gastroscopies on all *BRCA* carriers.

Reference: J Clin Oncol 2022;Jan 25 [Epub ahead of print]
Abstract