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Editorial and study commentary by Dr Angela George

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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.

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Dr Angela George has been commissioned by Roche Products (New Zealand) Ltd, Auckland, to be the Consulting Editor of the Perspectives on Precision Oncology Educational Series. The editorial and expert comments have been written by Dr George in accordance with the requirements of the Association of the British Pharmaceutical Industry (ABPI) Code of Practice 2019. The views and opinions expressed are entirely those of Dr George. Roche reviews and approves the content for conformity with NZ regulatory and industry compliance requirements. Please consult the full Data Sheets for any medications mentioned in this article at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician.

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Abbreviations used in this issue
AML = acute myeloid leukaemia
ASCO = American Society of Clinical Oncology
BRAF = B-Raf proto-oncogene
BRCA1 = breast cancer gene 1
BRCA2 = breast cancer gene 2
CI = confidence interval
COVID-19 = coronavirus disease 2019
CR = complete response
DCR = disease control rate
DFS = disease-free survival
DOR = duration of response
EGF = epidermal growth factor
EGFR = epidermal growth factor receptor
HER2 = human epidermal growth factor receptor 2
HR = hazard ratio
HPV = human papillomavirus
IL = interleukin
KRAS = Kirsten rat sarcoma viral oncogene homolog
MMR = mismatch repair
NE = not evaluable
NRG1 = neuregulin 1
NSCLC = non-small-cell lung cancer
OR = odds ratio
ORR = objective response rate
OS = overall survival
PARP = Poly (ADP-ribose) polymerase
PD-1 = programmed death 1
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
PR = partial response

ASCO 2021 – Precision Oncology Advances and Equity

In the 12 months since the 2020 ASCO meeting was forced to go online due to the rapid escalation of the global COVID-19 pandemic, many clinical trials were suspended as research staff were redeployed into front-line work. Several studies have closed early, with funding reduced or withdrawn, and few have been published recently while full details of many are still awaited. Nevertheless, the virtual 2021 ASCO meeting still included presentation of some exciting studies. In addition, this year saw a new theme for ASCO: that of bringing equity to oncology care.

The ASCO conference has always been about highlighting the exciting new developments in technology and treatment that advance our specialty and improve outcomes, by small or large steps. However, as these innovations become more and more expensive, oncology is rapidly becoming characterised by a list of treatments and tests that are available to the few with deep enough pockets to fund them and denied to those without. For many countries, including NZ, the risk is that an increasing number of these potential treatments are not available in the public system. An assessment of cost-effectiveness has never been a part of routine ASCO presentations, but if they truly wish to get to a point of equity, it should certainly become a consideration moving forward.

For those interested in precision oncology, we were spoilt for choice with several presentations highlighting the ability to molecularly match specific subsets of patients to the treatments most likely to be successful. By recognising the molecular heterogeneity between patients, we continue to make real progress in improving management. Several recently published studies are highlighted in this issue.

"By recognising the molecular heterogeneity between oncology patients, we continue to make real progress in improving management"

Lung cancer continued its claim to be the poster child of precision oncology at ASCO. The first of two presentations with simultaneous journal publications concerned sotorasib, a small molecule that specifically targets KRAS in an irreversible manner.[1,2] *KRAS* mutations are present in 25-30% of non-squamous NSCLC tumours, making them the most common driver in lung cancer, and have been associated with a particularly poor outcome. This phase II study is a continuation of the phase I CodeBreaK 100 study and concentrated on those with the most common mutation, p.G12C, which is present in ~13% of lung adenocarcinomas. The results showed an objective response rate (ORR) of 37.1%, including four complete responses (3.2%) and 42 partial responses (33.9%). Disease control was achieved in 80.6% of patients with tumours shrinking or remaining stable. Median OS was 12.5 months, median DOR was 11.1 months, and median PFS was 6.8 months. Based on these findings, a phase III study comparing sotorasib to standard-of-care docetaxel chemotherapy has already begun.

The second of the simultaneously published lung studies focussed on one of the rarest lung cancer drivers, *NRG1* fusions.[3] These fusions are present at low levels in a wide range of cancers, including lung cancer, but their rarity means they are not routinely identified and little is known about the tumour features. Therefore, this international registry was initiated to identify the clinicopathologic features of *NRG1* fusion-positive tumours and assess their responses to specific systemic treatments. The study showed that these are a heterogenous group of tumours, making them difficult to identify for *NRG1* fusion testing on the basis of clinical phenotype, such as smoking status. In addition, these tumours

showed poor responses to immunotherapy and afatinib, with further work required to identify the optimal treatment(s).

The results from immunotherapy studies continue to dominate in many tumour types, including melanoma. Only a decade ago, metastatic melanoma was a diagnosis that was depressing in its lack of treatment options. Now, immunotherapy has revolutionised treatment in a way that was previously unthinkable. Yet there are still patients with immunotherapy-resistant disease (primary or acquired), those with treatment-limiting side effects, or those with *BRAF* mutations who progress on targeted treatment that need additional active treatment options. It is therefore hugely exciting to see the latest data presented on lifileucel, an autologous tumour-infiltrating lymphocyte product, in patients with melanoma.[4] These data were simultaneously published in the Journal of Clinical Oncology.[5] Patients from cohort 2 of a phase 2 clinical trial (C-144-01) showed an impressive ORR (36.4%) and stable disease, making lifileucel treatment of interest for a wide range of melanoma patients. Similar studies are being undertaken in several solid tumours, including HPV-driven tumours such as cervical cancer.

While immunotherapy was a huge advance in the treatment of solid tumours such as melanoma, lung cancer and renal cell cancer, it has struggled to find a role in other, more genomically stable, tumours. This is typified by use of immunotherapy in ovarian cancer, where previous studies in MMR-proficient tumours have had disappointing response rates of <10%. There was previously a suggestion that immunotherapy may be more effective in the first-line maintenance setting, particularly in those who have received neoadjuvant chemotherapy, which was thought to generate more neoantigens. Although we may imagine that such an approach would improve response rates, the IMagyn050 study has shown that we have yet to identify a real role for immunotherapy in ovarian cancer, at least in first-line treatment.[6] This study combined the PD-L1 inhibitor atezolizumab with standard carboplatin/paclitaxel in those with stage III/IV epithelial ovarian cancer and showed no benefit of immunotherapy over chemotherapy alone, even in those with PD-L1 expression.

There is better news in the adjuvant treatment setting for those with breast cancer harbouring a pathogenic variant in *BRCA1/BRCA2*, with the plenary presentation of data from the OlympiA study.[7] Previous trials of PARP-inhibitors in breast cancer have shown a role for olaparib and talazoparib in relapsed disease, but OlympiA is the first study to report benefit in the adjuvant setting for breast cancer. This follows on from similar positive findings in the adjuvant setting in ovarian cancer patients with *BRCA* mutations, as demonstrated in the SOLO1,[8,9] PRIMA,[10] PAOLA-1[11] and VELIA[12] studies. In OlympiA, patients with pathogenic variants were randomised to receive either olaparib or placebo after completing standard-of-care adjuvant treatments including surgery, chemotherapy, radiotherapy and/or concurrent endocrine therapy. At the pre-specified interim analysis, the risk of recurrent invasive disease was nearly halved in patients treated with olaparib versus placebo (HR 0.58). This brings us a step closer to optimising treatment in these patients and makes it increasingly important to identify patients with *BRCA1/2* mutations who may benefit from treatment.

Finally, we have a new publication from the International Mismatch Repair Consortium, that collects data from patients with Lynch syndrome in 32 countries across 6 continents.[13] This hugely valuable data set has provided important insights into variations in tumour risk by gene. The latest study reported variations in the risk of colorectal cancer based on gene, sex and continent. It is clear from many studies that there are a number of other factors that modify colorectal cancer risk in those with a high-risk gene, and studies such as these bring us closer to being able to provide carriers with more meaningful risk estimates. This then allows appropriate decisions around risk-reducing interventions and screening to be made.

"To see real gains in patient outcomes there needs to be a focus on the accessibility and affordability of new treatment options"

At the close of the second virtual ASCO programme, we can reflect on a number of promising studies in precision oncology, including those in disease types that have historically had few treatment options, such as bile duct, liver, bladder, and head and neck tumours. As full publications follow in the coming months, hopefully we will see real gains in outcomes possible, and the profession will continue to move forward. However, if we wish to translate these scientific advances into care that can be offered to all patients, and if ASCO is to truly move forward with equity of healthcare in oncology, we will have to pay more attention to accessibility and affordability. Otherwise, the excellent care we aim to provide to all patients will become an increasingly distant target.

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

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References in bold are summarised with additional expert commentary in our Key Publication Summaries section.

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KEY PUBLICATION SUMMARIES

Sotorasib for lung cancers with *KRAS* p.G12C mutation

Authors: Skoulidis F et al.

Summary: Patients with previously treated *KRAS* p.G12C-mutated advanced NSCLC (n = 126) were treated with sotorasib 960 mg once daily in this non-comparative, phase II trial (NCT03600883). After a median follow-up of 15.3 months, 46 patients (37.1%) had an objective response, including four complete and 42 partial responses. Median DOR was 11.1 months (95% CI 6.9-NE), and 100 patients (80.6%) had disease control. Median PFS was 6.8 months (95% CI 5.1-8.2), and median OS was 12.5 months (95% CI 10.0-NE). No new safety signals were detected. Treatment-related grade 3 and grade 4 adverse events occurred in 19.8% and 0.8% of patients, respectively.

Comment: The presence of a *KRAS* mutation in lung cancer is a poor prognostic indicator, with these patients generally having lower response rates and a shorter DOR compared with *KRAS* wildtype patients. As a group, they have been of particular interest in terms of trying to find further treatments to improve outcomes and increase survival. This study focused on a single mutation in *KRAS* that occurs in a large proportion of patients and is targeted by sotorasib. This phase II study demonstrated impressive rates of response and disease control in a pretreated cohort, suggesting that disease control can be achieved by targeting that mutation alone. A phase III trial in these patients is about to start and will be of great interest.

Reference: N Engl J Med. 2021;384(25):2371-2381
Abstract

Clinicopathologic features and response to therapy of *NRG1* fusion–driven lung cancers: The eNRGy1 Global Multicenter Registry

Authors: Drilon A et al.

Summary: The global eNRGy1 registry was established to characterise *NRG1* fusion-positive lung cancers in 22 centres across Europe, Asia, and the US. Based on data from 110 patients with *NRG1* fusion-positive lung cancer, the majority had never smoked (57%), had mucinous adenocarcinoma (57%), and had non-metastatic disease (71%). However, these patients were a heterogeneous group. *NRG1* fusions were identified using RNA-based testing in 74% of patients and DNA-based testing in the remaining 26%. *NRG1* fusions were mutually exclusive with other known oncogenic drivers in the majority of patients (94%), while a concurrent driver was identified in the remaining patients. The ORR after chemotherapy with platinum doublet and taxane-based regimens was poor (13% and 14%, respectively) and PFS was modest (5.8 and 4.0 months, respectively). Most tumours (96%) had low or no expression of PD-L1 and the median tumour mutational burden was low (0.9 mutations/megabase). Therefore, responses to chemoimmunotherapy (ORR 0%; PFS 3.3 months) and single-agent immunotherapy (ORR 20%; PFS 3.6 months) were poor. Patients treated with afatinib had an ORR of 25% and a median PFS of 2.8 months.

Comment: As molecular testing increases, the identification of patients with individually rare subtypes will increase. In lung cancer, surrogate markers for the likelihood of finding specific mutations (such as *EGFR* in non-smokers) have helped direct testing. It had been hoped that similar surrogates could be identified for some of the more rare molecular subtypes to help identify those most likely to benefit from this testing. The above study used an international database to try to assess clinicopathological features in patients with tumours showing *NRG1* mutations, and therefore identify the most beneficial treatments. However, the data showed universally poor responses to standard platinum-based chemotherapy, immunotherapy and combination immunochemotherapy. The *NRG1* fusion molecular subgroup requires further work to identify appropriate treatment, and currently this mutation appears to be a prognostic indicator only.

Reference: J Clin Oncol. 2021;Jun 2 [Epub ahead of print]
Abstract

Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma

Authors: Sarnaik AA et al.

Summary: This open-label, single-arm, multicentre phase II study investigated the efficacy and safety of an autologous, centrally manufactured tumour-infiltrating lymphocyte product, lifileucel. The trial included 66 patients with advanced melanoma who had progressed after treatment with checkpoint inhibitors and BRAF- +/- MEK-targeted agents. All were given a nonmyeloablative lymphodepletion regimen, followed by a single infusion of lifileucel then up to six doses of IL-2. The ORR was 36% (95% CI 25-49%), with two complete responses and 22 partial responses, and the DCR was 80% (95% CI 69-89%). Median DOR was not reached during a median follow-up of 18.7 months. Similar results were seen in the subgroup of patients who were refractory to anti-PD-1 or PD-L1 therapy, with an ORR of 41% (95% CI 26-57%) and a DCR of 81% (95% CI 66-91%). The safety profile was consistent with the known adverse events of non-myeloablative lymphodepletion and IL-2.

Comment: Metastatic melanoma is no longer the death sentence that it was only a few years ago but, at some point, the majority of patients will progress and be well enough to be considered for further treatment options. Therefore, the question has become what would be helpful for those who have failed BRAF-targeted treatments and checkpoint inhibitors? Tumour-infiltrating lymphocyte products have shown promise in a number of tumours, such as those associated with HPV, and now this study has shown an impressive ORR and a very impressive DCR. This provides an exciting possible future line of treatment for patients with advanced metastatic melanoma and, given that the median DOR was not reached in the 18 months of follow-up, suggests there may be some longer-term benefit with this approach.

Reference: J Clin Oncol. 2021;May 12 [Epub ahead of print]
Abstract

Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: Placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39)

Authors: Moore KN et al.

Summary: This multicentre, double-blind, randomised study (NCT03038100) investigated the addition of the anti-PD-L1 antibody, atezolizumab, or placebo to platinum-based chemotherapy plus bevacizumab in 1301 patients with newly diagnosed stage III or IV ovarian cancer. There was no significant difference in median PFS in the atezolizumab versus placebo groups, either in the intention-to-treat population (19.5 vs 18.4 months; HR 0.92; 95% CI 0.79-1.07), or in the subgroup of patients who were PD-L1-positive (20.8 vs 18.5 months; HR 0.80; 95% CI 0.65-0.99). Immature OS results also showed no significant difference between the atezolizumab and placebo groups. The most common grade 3-4 adverse events in both treatment groups were neutropenia, hypertension and anaemia, with no significant between-group differences.

Comment: Despite the suggestion that neoadjuvant chemotherapy may induce neoantigens that would result in a higher response rate to immunotherapy in ovarian cancer patients, this study has not borne that out. In addition to MMR deficiency, it was suggested that those with underlying *BRCA* mutations may have more genomically unstable cancers that would also respond well to immunotherapy but we still have not found good evidence to support this. In this study, atezolizumab added to standard-of-care first-line treatment with carboplatin/paclitaxel chemotherapy plus bevacizumab to see if it would improve PFS, but no benefit was seen, either in the intention-to-treat population or in those with PD-L1 positivity. The latter is particularly disappointing because PD-L1 positivity has been an indicator of response to immunotherapy in other tumour types. This study adds to the previous immunotherapy studies in ovarian cancer that have looked at relapsed disease and have again failed to demonstrate a clear benefit from immunotherapy in this setting.

Reference: J Clin Oncol. 2021;39(17):1842-1855

Abstract

Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer

Authors: Tutt ANJ et al.

Summary: The efficacy and safety of olaparib in patients with HER2-negative primary breast cancer with a germline *BRCA1* or *BRCA2* mutation were investigated in the phase III OlympiA trial (NCT02032823). Olaparib 300 mg/day or placebo were given for 52 weeks after definitive local treatment and neoadjuvant or adjuvant chemotherapy (n = 1836). In a prespecified interim analysis with a median follow-up of 2.5 years, the 3-year invasive DFS rate was significantly higher in patients treated with olaparib versus placebo (85.9% vs 77.1%; difference –8.8%, 95% CI 4.5-13.0%; $p < 0.001$). The 3-year distant DFS rate was also significantly higher in the olaparib group (87.5% vs 80.4%; difference –7.1%; 95% CI 3.0-11.1%; $p < 0.001$). The number of deaths in those treated with olaparib (59) was lower than that in the placebo group (86), but the difference was not statistically significant at an interim-analysis p-value of <0.01. Safety data were consistent with the known adverse event profile of olaparib.

Comment: The use of PARP inhibitors in breast cancer has lagged behind ovarian cancer since the false start of iniparib. This study built on the previous success of olaparib and talazoparib in advanced disease to assess the role of adjuvant olaparib in early *BRCA*-mutated breast cancer. It concentrated on patients with high-risk features, an important point given that many women with breast cancer will already have a good outcome. Therefore, consideration of the potential risk of myelodysplasia/AML needs to be balanced against the benefit. The study findings suggest that a higher proportion of patients with early breast cancer could be long-term survivors. It would be interesting to see if the longer-term risk of a second breast cancer is decreased in those treated with olaparib because there is interest in the potential use of PARP inhibitors as chemoprevention agents. However, additional information on long-term serious complications are required before this could be considered.

Reference: N Engl J Med. 2021;384(25):2394-2405

Abstract

Variation in the risk of colorectal cancer in families with Lynch syndrome: A retrospective cohort study

Authors: The International Mismatch Repair Consortium

Summary: This retrospective cohort study used data from the International Mismatch Repair Consortium to estimate variation in the penetrance of colorectal cancer between carriers of pathogenic variants in the same gene by sex and locality. Data from 5255 families including 79,809 individuals from 15 countries in North America, Europe and Australasia were analysed. The findings showed wide variation in the risk of colorectal cancer between Lynch syndrome carriers, especially those carrying the *MLH1* and *MSH2* variants. Thus, the observed family history of colorectal cancer was not fully accounted for by the pathogenic gene variant. Modifiers of colorectal cancer risk among carriers of the same gene variants included sex and continent of residence. Therefore, mean cumulative risk estimates might not apply to all carriers of pathogenic variants in *MMR* genes.

Comment: There are many potential modifiers of risk for those who carry an underlying gene alteration in one of the four *MMR* genes. We see widely varying risks of each of the common cancers amongst families, especially as we test more patients and identify mutations in those with fewer cancers in their family histories. To date, we ascribe the same level of cancer risk to all individuals with *MLH1* mutations, and do the same for those with any mutations in *MSH2*, *MSH6* and *PMS2*. It is clear though that some mutations and some individuals will have different risks, either higher or lower than the average, and such information is of great benefit when counselling individuals about their own personal risk, and to aid decision making about risk-reducing interventions. The benefit of a large number of prospective cohort databases having been set up is that we are starting to see much better risk estimates for patients and understanding of some of the major modifiers. In the above study, continent of origin and sex were shown to be modifiers of colorectal cancer risk.

Reference: Lancet Oncol. 2021;22(7):1014-1022

Abstract