A RESEARCH REVIEW™ EDUCATIONAL SERIES

Perspectives on Precision Oncology

Making Education Easy

Issue 3 – 2021

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.

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.

Roche

Abbreviations used in this issue

BRCA = breast cancer gene
CAR T-cell = chimeric antigen receptor T-cell
CI = confidence interval
ctDNA = circulating tumour DNA
EGFR = epidermal growth factor receptor
HER = human epidermal growth factor receptor
HPV = human papillomavirus
HR = hazard ratio
HRD = homologous recombination deficiency
IDH1 = cytosolic isocitrate dehydrogenase 1
ITT = intention to treat
KRAS = Kirsten rat sarcoma virus
Mb = megabase
mCRC = metastatic colorectal cancer
MLH1 = MutL Homolog 1
MMR = mismatch repair
MMRd = mismatch repair deficiency
MRD = minimal residual disease
MSI = microsatellite instability
NSCLC = non-small-cell lung cancer
OS = overall survival
PARP = poly (ADP-ribose) polymerase
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
TMB = tumour mutational burden
TP53 = tumour protein p53

Advances in precision oncology for rare cancers at ESMO 2021

At ESMO this year, presentations continued the trend of molecular matching, reinforcing the need to subclassify tumour types by their characteristic genetic alterations. It was particularly exciting to see the increasing focus on rare cancers, with molecular subtyping, and successful trials in tumours such as cholangiocarcinoma and cervical cancer where we have had only limited success with chemotherapy. Similarly, there are now also trials in rare cancers that are more likely to succeed by selecting the subgroup of patients most likely to benefit from therapy, rather than the days of administering the same drug to all patients with a tumour type and hoping some will benefit.

In taking a different approach, we see benefits such as those reported with ivosidenib, a first-in-class oral small molecule that inhibits mutated *IDH1*.[1] These mutations are present in approximately 13% of intrahepatic and 1% of extrahepatic cholangiocarcinomas, and the results of a previous phase I trial in *IDH1*-mutated cholangiocarcinoma suggested efficacy. These data led to the ClarIDHy trial reported below. ClarIDHy is a placebo-controlled study that randomised patients with metastatic *IDH1*-mutated cholangiocarcinoma to treatment with ivosidenib or placebo (2:1), with crossover permitted for placebo-treated patients at disease progression. Even with a number of patients having crossed over, there was an OS advantage in the ivosidenib arm compared with placebo. Median OS in the ivosidenib group was 10.3 months for a disease where the median OS in chemotherapy-treated patients is around 6 months. This suggests a clinically meaningful benefit for these patients when treated with a well-tolerated oral tablet. Whilst this is not a solution for all cholangiocarcinoma, it does provide an option for the subgroup of patients with *IDH1* mutations and highlights the importance of molecular testing to identify those with mutations.

"There are now trials in rare cancers that are more likely to succeed because they include the subgroup of patients most likely to benefit from therapy"

Cervical cancer is another malignancy that is not usually included in plenary sessions at conferences like ESMO. Outcomes are generally dismal for patients with cervical cancer that recurs or does not fully respond to primary treatment. Although the use of HPV vaccines has thankfully seen a reduction in cervical cancer diagnoses in many countries, this continues to be a devastating illness for those who develop metastatic disease. There has been interest in using immunotherapy for the treatment of cervical cancer, and a number of recent studies have recruited those with metastatic disease to trial a variety of single-agent and combination immunotherapy regimens. The KEYNOTE-826 study was the first phase III trial to report on the addition of immunotherapy (in this case pembrolizumab) to standard of care treatment for recurrent or persistent cervical cancer.[2] The results showed a significant improvement in both PFS and OS in patients who had pembrolizumab added to their treatment regimen. Although the trial included testing for tumour expression of PD-L1 (with the proportion of PD-L1-positive cells classified as <1, 1–10 or >10), the majority of tumours were in the >10 category and only ~11% of pembrolizumab-treated tumours were in the <1 category. This made it difficult to draw conclusions about the association between treatment benefit and the proportion of PD-L1-positive cells present. It was suggested that most of the benefit of immunotherapy was likely to occur in those with >1% PD-L1-positive cells, but this requires further assessment. The addition of immunotherapy adds the risk of immunotoxicity, which has consistently been reported in about 10% of patients across gynaecological cancer trials. Therefore, it is important to identify patients who would not benefit from treatment so that unnecessary toxicity can be avoided.

The association between PD-L1 positivity and response to immunotherapy was also investigated in the IMpower010 trial, which examined the addition of immunotherapy (atezolizumab in this case) to standard adjuvant chemotherapy in patients with resected NSCLC.[3] This is another area that has seen little progress in nearly 20 years, despite the huge gains made in the treatment of those with advanced lung cancer over the last decade. Again, in this study, PD-L1 expression on tumour cells was determined and the benefits of atezolizumab therapy were seen in all patients. However, further scrutiny of the results suggests that the bulk of the benefit was in those with PD-L1 expression in >50% of cells. In this group, the HR for disease progression was half that seen in patients with PD-L1 expression in 1-49% of cells (0.43 vs 0.87 respectively). In the

population with PD-L1 on ≥1% of tumour cells the HR for disease progression was 0.66, but this also looks to be heavily influenced by those with PD-L1 expression >50%. This study showed a clinically and statistically meaningful improvement in OS in advanced NSCLC patients with >1% PD-L1 expression on tumour cells who were treated with atezolizumab following standard chemotherapy. The magnitude of benefit is such that this treatment approach will no doubt be widely adopted. However, this and the cervical cancer study again raise the issue of how we best identify patients who will get the greatest benefit from immunotherapy. To date, we have three widely used indicators of response (MMRd/MSI, PD-L1 expression, and TMB), but none of these are perfect.

The presence of MMRd/MSI is probably the most reliable indicator of likely response to immunotherapy, but its presence is limited to a small number of tumour types, predominantly the Lynch-associated cancers such as colorectal, gastric, endometrial and ovarian. Even so, within this group of patients there is a wide range of causes of MMRd, including the presence of a germline mutation in one of the four *MMR* genes, the presence of a somatic-only mutation, or the presence of an epigenetic change, such as MHL1 promoter hypermethylation. All will cause the MMRd phenotype, but there are significant differences in how the different underlying causes manifest in things such as TMB or the wider impact on tumour behaviour. It is unrealistic to expect that all will respond in the same way to immunotherapy and, in practice, this appears to be the case, with the most significant responses to single-agent immunotherapy occurring in patients whose tumours show germline mutations. Perhaps we should start to delineate between these groups in the same way we differentiate between germline BRCA, tumour BRCA and HRD in ovarian cancer when considering likely response to PARP inhibitors.

PD-L1 expression is the second of the options, and the most frequently used across a wide variety of tumour types. Performed by pathologists using one of several antibodies and scoring systems, PD-L1 expression is typically reported as the proportion of tumour cells expressing PD-L1 (0% or <1%, 1–49% or ≥50%). In most cases, immunotherapy is recommended for those with at least 1% PD-L1 expression, but the above studies raise the question of whether this is really the appropriate cutoff, or whether we should look more closely at the correlation between degree of expression and degree of response. It is easy to consider that any level of expression predicts some level of response but when the risk of severe immunotoxicity is considered, perhaps we should be more discriminatory.

The third way to assess likely response to immunotherapy is TMB. This was often measured using whole genome sequencing, or whole exome

sequencing, but is increasingly able to be reliably determined from large somatic panels. TMB is inherently high in several tumours (e.g., melanoma) but also in those with germline mutations in the *MMR* or the *POL* genes, where there is hypermutation and ultramutation, respectively. These patients are typically very sensitive to immunotherapy. By undertaking TMB analysis, we can also identify differences between the different causes of MMRd/MSI, showing highly variable levels of TMB between those with germline mutations versus epigenetic alterations. Many studies have used a cutoff of 10 mutations/Mb as a measure of high TMB for selecting patients suitable for immunotherapy but, again, this seems an arbitrary figure. We know that those who are particularly sensitive to immunotherapy will have a TMB that is over 10-fold higher than this, raising the possibility that the threshold is too low to accurately select patients who will truly benefit from immunotherapy.

Identifying patients at the greatest risk of immunotherapy-related immunotoxicity or those who will relapse after aggressive cellular therapies is also of great interest because although these treatments can bring great results, they also have potentially life-threatening risks. Assessment of MRD has been standard for leukaemia patients for some time, and we now have studies with ctDNA for MRD in several solid tumours that have been shown to predict those at higher risk of relapse after surgery or adjuvant chemotherapy. It has also been suggested that use of ctDNA in patients with large B-cell lymphoma treated with CAR T-cell therapy (axicabtagene ciloleucel) can identify those who will have a durable response (evidenced by no detectable ctDNA) compared with those who had ctDNA detectable after a week or at the 28-day mark.[4] Patients who continued to have a durable response had no ctDNA detected by 3 months after CAR T-cell therapy. Interestingly, those with a higher ctDNA concentration pre-treatment seemed to have higher rates of immunotoxicity, potentially allowing patients at higher risk of complications to be identified pre-treatment.

"The Holy Grail of precision medicine is to find treatments with a suitable tolerability profile that are active in a wide range of patients and target frequently mutated pathways across tumour types"

Moving to a different type of molecular testing, the value of molecular profiling in patients with advanced/metastatic lung cancer was demonstrated in the DESTINY-Lung01 study, which evaluated treatment with trastuzumab deruxtecan in a small subgroup of patients with HER2-mutated lung cancer.[5] HER2-mutated lung cancer is thankfully one of the rarer subtypes, but it is aggressive and associated with an inferior response to chemotherapy and immunotherapy in the advanced setting. There have been several other small studies looking at HER2-directed therapy in these patients but, to date, none have been approved in lung cancer. The results of the DESTINY-Lung01 study showed that there was benefit for patients refractory to standard treatment, although the exact mechanism of uptake of the conjugated drug payload is unclear and requires further investigation. Still, this study reported a much better duration of response than previously reported with HER2-directed treatment and provides a potential treatment option for these patients with very poor outcomes. Comparison against standard chemotherapy is now required.

The Holy Grail of precision medicine is to find treatments with a suitable tolerability profile that are active in a wide range of patients and target frequently mutated pathways across tumour types. Of these, *TP53* and *KRAS* are high on the list. Exciting treatment benefit with sotorasib has been seen in patients with lung cancer due to the specific G12C mutation in *KRAS*. Otherwise, however, KRAS remains a marker of aggressive, poorly responding tumours across a range of cancer types. The FOCUS4-C study showed the benefit of single-agent treatment with adavosertib, a WEE1 inhibitor, in colorectal cancer patients with *KRAS* and *TP53* mutations.[6] This approach had previously shown some exciting results in *TP53*-mutated cancers when combined with other treatments, but this study showed that adavosertib had single-agent activity in a hard-to-treat subgroup of colorectal cancer that tend to have particularly poor outcomes. It will be of great interest to see whether this benefit can be replicated in larger, phase III studies, given the potential wide-ranging tumour types that may benefit.

Finally, we come to the molecular typing of metastatic prostate cancer. Several years ago, primary prostate cancer was molecularly grouped into luminal A, luminal B and basal subtypes, replicating the breast characterisation that revolutionised breast cancer treatment. Two main groups of metastatic prostate cancer patients – the luminal B and basal subtypes – were included in a cohort study by Aggarwal et al.[7] The former are characterised by alterations in the androgen receptors, while the latter have a predominance of genes important in cell division and the cell cycle, such as *RB1* and *MYC*. It is notable that the luminal A subtype was essentially absent, because these tumours exhibit much more indolent behaviour than luminal B tumours and this may result in different treatment paradigms in the future. As with all such characterisations, there was a spectrum, with some of the basal tumours sharing some luminal markers and benefiting from androgen suppression, whilst those with the most basal-like features really only benefitting from chemotherapy. Going forward, if these data are verified in large prospective studies, we can start to accurately identify patients who require a more aggressive approach to primary treatment, potentially even validating an Oncotype-Dx-type approach for prostate cancer management.

"The increasing number of treatment options for rare tumours, or rare subtypes within common tumours, provides some hope for these patients"

In general, the increasing number of treatment options for rare tumours, or rare subtypes within common tumours, provides some hope for these patients, who have previously had more limited options than those with more common tumours and tumour types. However, this will only translate into better patient outcomes if we continue to undertake comprehensive profiling, including for the use of ctDNA monitoring, to identify the patient subgroups most likely to benefit from each treatment and continue to look out for indicators of problematic toxicity, such as the pulmonary complications and immunotoxicity that limit the use of some treatments.

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

Dr Angela George
angelageorge@researchreview.co.nz

REFERENCES:

1. Zhu AX et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation: The phase 3 randomized clinical ClarIDHy trial. JAMA Oncol. 2021 Sep 23;e213836 [Epub ahead of print]
2. Colombo N et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385(20):1856-1867
3. Felip E et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. Lancet. 2021;398(10308):1344-1357
4. Frank MJ et al. Monitoring of circulating tumor DNA improves early relapse detection after axicabtagene ciloleucel infusion in large B-cell lymphoma: Results of a prospective multi-institutional trial. J Clin Oncol. 2021;39(27):3034-3043
5. Li BT et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. N Engl J Med. 2021 Sep 18 [Epub ahead of print]
6. Seligmann JF et al. Inhibition of WEE1 is effective in *TP53*- and *RAS*-mutant metastatic colorectal cancer: a randomized trial (FOCUS4-C) comparing adavosertib (AZD1775) with active monitoring. J Clin Oncol. 2021 Sep 18;JCO2101435 [Epub ahead of print]
7. Aggarwal R et al. Prognosis associated with luminal and basal subtypes of metastatic prostate cancer. JAMA Oncol. 2021 Sep 23;e213987 [Epub ahead of print]

KEY PUBLICATION SUMMARIES

Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with *IDH1* mutation: the phase 3 randomized clinical ClarIDHy trial

Authors: Zhu AX et al.

Summary: This paper reports final OS results from the multinational, randomised, double-blind, placebo-controlled, phase III ClarIDHy trial. The study compared ivosidenib (n=126) with placebo (n=61) in patients with advanced intrahepatic cholangiocarcinoma with *IDH1* mutation. Median OS in patients treated with ivosidenib was 10.3 months (95% CI 7.8–12.4) compared with 7.5 months (95% CI 4.8-11.1) in those treated with placebo (HR 0.79; 95% CI 0.56–1.12; p=0.09). When the 43 patients who crossed over from placebo to ivosidenib were excluded, median OS in the placebo group reduced to 5.1 months (95% CI 3.8–7.6), decreasing the HR for survival in placebo versus ivosidenib recipients to 0.49 (95% CI 0.34–0.70; p<0.001). Ascites was the most common grade ≥3 treatment-emergent adverse event, reported by 9% of patients in the ivosidenib group and 7% of patients in the placebo group. Three patients reported serious treatment-emergent adverse events that were considered to be related to ivosidenib.

Comment: PFS data from this trial had previously been reported and generated great interest due to the extremely poor outcomes seen for the tumour type as a whole. Patients randomised to placebo were allowed to cross over to active treatment at the time of disease progression, an approach that has prevented detection of an OS advantage in many previous trials. After adjustment for crossovers, the results of this study showed that OS in the ivosidenib group was more than double that in those treated with placebo. Ivosidenib was incredibly well-tolerated, particularly in a pre-treated patient population for whom treatment with chemotherapy can be challenging and is often poorly tolerated. For the proportion of intrahepatic cholangiocarcinoma patients with an *IDH1* mutation, these data highlight a viable treatment option that is both well tolerated and significantly improves OS compared with standard chemotherapy.

Reference: JAMA Oncol. 2021 Sep 23;e213836 [Epub ahead of print]
Abstract

Pembrolizumab for persistent, recurrent, or metastatic cervical cancer

Authors: Colombo N et al.

Summary: The double-blind, placebo controlled, phase III KEYNOTE-826 trial investigated the benefit of adding pembrolizumab to chemotherapy with or without bevacizumab in 617 patients with persistent, recurrent or metastatic cervical cancer. Median PFS was significantly better in the pembrolizumab versus placebo group in the intention-to-treat population (10.4 vs 8.2 months; HR 0.65; 95% CI 0.53–0.79; p<0.001), in patients with a PD-L1 positivity score ≥1% (10.4 vs 8.2 months; HR 0.62; 95% CI 0.50–0.77; p<0.001), and in those with a PD-L1 positivity score ≥10 (10.4 vs 8.1 months; HR 0.58; 95% CI 0.44–0.77; p<0.001). Twenty-four month OS survival rates in these populations were 50.4% vs 40.4% (HR 0.67; 95% CI 0.54–0.84; p<0.001), 53.0% vs 41.7% (HR 0.64; 95% CI 0.50–0.81; p<0.001), and 54.4% vs 44.6% (HR 0.61; 95% CI 0.44–0.84; p=0.001). The most common grade 3-5 adverse events were anaemia and neutropenia, both of which were reported by slightly higher proportions of patients in the pembrolizumab versus placebo group.

Comment: Cervical cancer that relapses or persists after primary treatment has been remarkably challenging to treat. Several years ago the first positive trial outcome was reported, showing the benefit of adding bevacizumab to carboplatin/paclitaxel chemotherapy. This became the new standard of care, but the nature of cervical cancer and its usual sites of relapse/metastasis means that use of bevacizumab is not always safe or appropriate. There has been wide interest in immunotherapy for patients with cervical cancer, particularly those with HPV-mediated tumours. We have already seen great progress in the treatment of HPV-associated head and neck tumours with immunotherapy because the viral initiating event results in more genomically unstable tumours. KEYNOTE-826 added pembrolizumab or placebo to chemotherapy (with or without bevacizumab), and further categorised patients by the proportion of PD-L1 positive cells (<1, 1–10, >10). The benefit of immunotherapy was detectable by three months and persisted throughout follow-up. The benefit appeared to be primarily in patients with PD-L1 positivity of ≥1%, but the small proportion of patients with positivity of <1% (11.4%) makes this difficult to confirm. Nevertheless, the KEYNOTE-826 study provides evidence for the primary use of immunotherapy to improve outcomes in patients with persistent, recurrent or metastatic cervical cancer, and is viewed as a new standard of care for these difficult-to-treat patients with aggressive disease.

Reference: N Engl J Med. 2021 Sep 18; [Epub ahead of print]
Abstract

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Authors: Felip E et al.

Summary: The multinational, randomised, open-label, phase III IMpower010 study compared adjuvant treatment with atezolizumab (1200 mg every 21 days for 16 cycles or 1 year; n=507) with best supportive care (observation and regular scans; n=498) after adjuvant platinum-based chemotherapy in patients with early-stage NSCLC. Over a median follow-up of 32.2 months, the results of hierarchical testing showed that atezolizumab significantly improved disease-free survival compared with best supportive care in the population of patients with stage II-IIIA disease (HR 0.79; 0.64–0.96; p=0.020) and the subgroup of these patients who had tumours that expressed PD-L1 on ≥1% of tumour cells (HR 0.66; 95% CI 0.50–0.88; p=0.0039). However, the prespecified statistical significance boundary for the comparison of disease-free survival between the atezolizumab and standard care groups was not reached in the total ITT study population (HR 0.81; 95% CI 0.67–0.99; p=0.040). Atezolizumab-related grade 3/4 or 5 adverse events occurred in 11% and 1% of patients, respectively.

Comment: Despite the major gains made in advanced disease treatment, there has been little progress in the adjuvant treatment of resected lung cancer since 2004. Several phase III trials are currently assessing other approaches in specific subgroups of patients, but IMpower010 is the first study of adjuvant immunotherapy following standard of care chemotherapy to be published. The results showed additional benefit from immunotherapy after chemotherapy, with particular benefit in those with PD-L1 expression on ≥1% of tumour cells, and significantly greater benefit seen in patients with higher levels of PD-L1 expression. The OS data are not yet mature, but if these are consistent with the effects of atezolizumab in relapsed lung cancer or other tumour types such as melanoma, we may well have a new standard of care for the adjuvant treatment of PD-L1-expressing, resected stage II-IIIA lung cancer.

Reference: Lancet. 2021;398(10308):1344-1357
Abstract

Monitoring of circulating tumor DNA improves early relapse detection after axicabtagene ciloleucel infusion in large B-cell lymphoma: results of a prospective multi-institutional trial

Authors: Frank MJ et al.

Summary: This prospective multicentre study examined the prognostic value of pre- and post-treatment ctDNA for predicting patient outcomes in patients with relapsed or refractory large B-cell lymphoma treated with axicabtagene ciloleucel. A tumour clonotype was detected in 69/72 (96%) patients. Higher pre-treatment ctDNA concentrations were associated with progression after axicabtagene ciloleucel therapy and the development of cytokine release syndrome and/or immune effector cell-associated neurotoxicity syndrome. At 1 week after axicabtagene ciloleucel infusion, ctDNA was undetectable in 23/33 patients (70%) who had a durable response compared with 4/31 patients (13%) who had progressive disease (p<0.0001). After 28 days, patients with detectable versus undetectable ctDNA had a median PFS of 3 months versus not reached (p<0.0001) and an OS of 19 months versus not reached (p=0.0080). For patients who had a radiographic partial response or stable disease on day 28, relapse occurred in 1/10 with undetectable ctDNA compared with 15/17 with detectable ctDNA (p=0.0001). ctDNA was detected in 29/30 patients (94%) at or before radiographic relapse, and was undetectable at or before 3 months after axicabtagene ciloleucel infusion in all patients with a durable response.

Comment: Assessment for MRD is now standard for patients with many haematological malignancies, and is of increasing interest to allow identification of those with solid tumours and lymphoma who are at higher risk of relapse. In this study, not only did the identification of detectable ctDNA following CAR T-cell therapy predict those most likely to relapse, but it also predicted patients at a higher risk of experiencing immune-mediated toxicity. From a practical point of view, prior knowledge about which patients might be at increased risk of developing cytokine release syndrome or neurotoxicity is incredibly useful. It facilitates both pre-treatment patient counselling and post-treatment monitoring, and means that there is a low index of suspicion if any symptoms develop after treatment. This study also demonstrated clear differences in ctDNA detection between patients with a durable response and those who subsequently progressed, and suggests that the use of such monitoring may identify patients early who require further consolidation, with the possibility of improving the durability of response.

Reference: J Clin Oncol. 2021;39(27):3034-3043
Abstract

Trastuzumab deruxtecan in *HER2*-mutant non-small-cell lung cancer

Authors: Li BT et al.

Summary: Patients with *HER2*-mutant NSCLC refractory to standard treatment (n=91) were treated with trastuzumab deruxtecan (6.4 mg/kg) in the multinational, phase II DESTINY-Lung01 trial. Over a median follow-up of 13.1 months, centrally confirmed objective response occurred in 55% of patients (95% CI 44–65), median duration of response was 9.3 months (95% CI 5.7–14.7), median PFS was 8.2 months (95% CI 6.0–11.9), and median OS was 17.8 months (95% CI 13.8–22.1). Grade ≥3 drug-related adverse events occurred in 46% of patients, the most common of which was neutropenia (19%). Drug-related interstitial lung disease was observed in 26% of patients and resulted in two deaths. Responses occurred across all *HER2* mutation subtypes, and in patients with inactivating mutations resulting in no HER2 expression.

Comment: *HER2*-mutated lung cancer represents a small proportion of lung cancer, but (like *EGFR* mutations) is more common in younger, female, never-smokers. These patients tend to have worse responses to chemotherapy or immunotherapy than those with other lung cancer subtypes. The DESTINY-Lung01 trial assessed a trastuzumab-topoisomerase I inhibitor conjugate that is already in use in some countries for HER-2 positive breast and gastric cancer. Although patients were already refractory to standard treatment, high objective response rates were observed. This adds to existing data from small studies in these patients that showed objective response rates of 21% with trastuzumab/pertuzumab and 44% with the more familiar drug conjugate, trastuzumab emtansine (although with a much shorter duration of response of only 4 months with the latter). The prevalence of interstitial lung disease in patients treated with trastuzumab deruxtecan was of concern. Although this was mild in 75% of patients, two patients died as a result of this complication. A better understanding of the mechanism of this, and early identification of patients at risk, would be useful if treatment with trastuzumab deruxtecan is to succeed in larger patient populations.

Reference: N Engl J Med. 2021 Sep 18; [Epub ahead of print]
Abstract

Inhibition of WEE1 is effective in *TP53*- and *RAS*-mutant metastatic colorectal cancer: a randomized trial (FOCUS4-C) comparing adavosertib (AZD1775) with active monitoring

Authors: Seligmann JF et al.

Summary: Treatment of patients with *TP53*- and *RAS*-mutant mCRC using the WEE1 kinase inhibitor adavosertib was compared with active monitoring in this randomised phase II study (n=69). Median PFS was significantly improved in patients treated with adavosertib compared with active monitoring (3.61 vs 1.87 months; HR 0.35; 95% CI 0.18–0.68; p=0.0022), but median OS did not differ significantly between the two groups (14.0 vs 12.8 months; HR 0.92; 95% CI 0.44–1.94). In a prespecified subgroup analysis, the benefits associated with adavosertib treatment were greater in patients with left-sided (HR 0.24; 95% CI 0.11–0.51) versus right-sided tumours (HR 1.02; 95% CI 0.41–2.56; p=0.043). Grade 3 toxicities in adavosertib-treated patients included diarrhoea (9%), nausea (5%), and neutropenia (7%).

Comment: Targeting TP53 has long been the Holy Grail of targeted agents, given the frequency with which mutations are found in solid tumours. To date, many molecules have attempted to target TP53 but have failed to progress beyond phase I trials due to excessive toxicity, probably because of the multitude of cellular processes for which TP53 is vital. WEE1 inhibitors first started to show some promise several years ago, initially in combination with chemotherapy. In patients with ovarian cancer, treatment with a WEE1 inhibitor was found to resensitise *TP53*-mutated tumours to carboplatin, and did not have the toxicity noted in other drugs that impacted on the TP53 pathway. *KRAS* is another target of great interest, both as a frequently mutated pathway in common cancers such as lung and colorectal cancer, and one associated with particularly poor outcomes. This small phase II study showed very promising single-agent activity in patients with doubly-mutated colorectal cancer who would otherwise have fewer treatment options than *KRAS*-wildtype patients. A larger phase III study is awaited, both in colorectal cancer and other cancer types with these mutations.

Reference: J Clin Oncol. 2021 Sep 18;JCO2101435 [Epub ahead of print]
Abstract

Prognosis associated with luminal and basal subtypes of metastatic prostate cancer

Authors: Aggarwal R et al.

Summary: This retrospective, multicentre cohort study was conducted to identify the clinical and molecular correlates of luminal and basal subtypes of metastatic castration-resistant prostate cancer, and to determine differences in survival, particularly after androgen-signalling inhibitor (ASI) treatment. Overall, 288/634 patients (45%) had luminal tumours, and 346/634 (55%) had basal tumours. However, a high proportion (53/59; 90%) of small cell/neuroendocrine prostate cancer tumours were the basal subtype (p<0.001). Luminal tumours showed androgen receptor pathway gene overexpression, while basal tumours had higher rates of *RB1* loss (23% vs 4%; p<0.001), *FOXA1* alterations (36% vs 27%; p=0.03) and *MYC* alterations (73% vs 56%; p<0.001) than luminal tumours. In patients treated with an ASI, OS was significantly worse in those with basal versus luminal tumours. Treatment with an ASI significantly improved survival in patients with luminal tumours but not those with basal tumours. There was a significant interaction between tumour subtype and ASI treatment (HR 0.42; 95% CI 0.20–0.89; p=0.02).

Comment: This study of four cohorts of patients with biopsied metastatic prostate cancer adds further data on the molecular subtypes of prostate cancer and reinforces the similarities between prostate and breast tumours, with luminal A, luminal B and basal types. As with breast cancer, we see relatively indolent behaviour in patients with luminal A tumours, who were barely represented in this study of metastatic prostate cancer due to their very good outcomes. This leaves two major groups in metastatic prostate cancer – luminal (predominantly the luminal B patients from the early prostate cancer studies) and basal. Of these, patients with luminal tumours had a better outcome when treated with ASIs, while patients with the basal subtypes generally did not. Use of molecular profiling has been suggested to identify patients most suitable for ASI treatment in future; with patients having basal tumours likely to be better suited to an alternative treatment strategy, such as chemotherapy. This requires further assessment in larger prospective studies, but raises the possibility that such subtyping of prostate cancer in future trials may replicate the success seen in breast cancer.

Reference: JAMA Oncol. 2021 Sep 23;e213987 [Epub ahead of print]
Abstract

RACP MyCPD Program participants can claim one credit per hour (maximum of 60 credits per year) for reading and evaluating Research Reviews. **FOR MORE INFORMATION CLICK HERE**

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our **CPD PAGE**.

This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your **RNZCGP Dashboard**

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

RACP MyCPD Program participants can claim **one credit per hour** (maximum of 60 credits per year in Category One – Educational Activities) **for reading and evaluating Research Reviews.**

Please CLICK HERE to download CPD Information