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EDUCATIONAL SERIES

Perspectives on Precision Oncology

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Issue 4 – 2021

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
ALT = alanine aminotransferase
AST = aspartate aminotransferase
ATR = ataxia telangiectasia and RAD3-related protein kinase
CI = confidence interval
CR = complete response
DCR = disease control rate
DDR = DNA damage repair
ER = estrogen receptor
HER-2 = human epidermal growth factor receptor 2
HR = hazard ratio
HRD = homologous recombination deficiency
HRR = homologous recombination repair
MMR = mismatch repair
ORR = objective response rate
OR = odds ratio
OS = overall survival
PARP = poly (ADP-ribose) polymerase
PCR = polymerase chain reaction
PD-1 = programmed death-protein 1
PFS = progression-free survival
PL-L1 = programmed death-ligand 1
PR = partial response
Q3W = every 3 weeks
RCT = randomised clinical trial
TMB = tumour mutational burden
TRAEs = treatment-related adverse events

Identifying patient sub-populations for treatment success

Another year is nearly over. It feels like only a few weeks ago that we (in the UK, anyway) were saying good riddance to 2020, and hoping for a COVID respite in 2021. We haven't yet seen that, as the Delta variant has wreaked havoc everywhere. At least things are starting to look up for NZ, with both enviable vaccination rates and a stabilising infection rate. As you prepare for a well-deserved summer break, we are taking the opportunity to wind up the year with a few final papers and a look forward to what we hope 2022 will bring.

Nothing is a more poignant reminder of the need to drown myself in sunblock than the recent flurry of melanoma papers across my desk. Whilst the treatment of metastatic melanoma has made huge gains in the last decade, it remains a disease that takes far too many lives in NZ. We at least have first-line options, but the need to find the best sequencing of these drugs, and the optimal regimens for difficult-to-treat sites such as the brain, remains. The addition of ipilimumab to PD-1 inhibitors has been a huge step forward over single-agent immunotherapy in patients with metastatic melanoma, but primary or secondary resistance is still a problem for a number of patients. We are now starting to see a range of studies with new combinations of PD-1/PD-L1 agents with other targeted drugs to try and overcome resistance.

"The addition of ipilimumab to PD-1 inhibitors has been a huge step forward over single-agent immunotherapy in patients with metastatic melanoma"

Firstly, we have a phase II study from South Korea assessing the addition of a DDR pathway inhibitor, ceralasertib, to durvalumab.[1] Patients entering this study had already failed, or relapsed following immunotherapy with a single-agent or combination treatment. Whilst this was only a small study of 30 patients (a sample size that could probably have been reached in a NZ oncology clinic in a week), it demonstrated an ORR of 31.0% and DCR of 63.3%, certainly worthy of further exploration. Most interestingly, a number of patients were still on study treatment with an ongoing response at data cut-off, including several who had demonstrated primary resistance to immunotherapy. The addition of ceralasertib, an oral inhibitor of ATR has been used previously in combination with PARP inhibitors to try to overcome resistance and is generally well-tolerated. This study is an exciting indicator of the possible benefit of targeting DDR in melanoma and deserves a larger study with more biomarker-related endpoints. It is a little disappointing that only ~50% of patients had available tumour samples of sufficient quality to perform the translational whole transcriptome sequencing because this suggested a clear clustering into four subgroups that predicted response or lack thereof. This raises further questions about the role of DDR in melanoma, and it would be good to see it validated in a larger cohort.

"This study is an exciting indicator of the possible benefit of targeting DDR in melanoma"

As well as new combinations, we also have the question about optimal use of existing treatments. BRAF inhibitors were the first drugs to show a positive trial outcome in melanoma, but these have been overtaken in the first line by immunotherapy. In the phase III KEYNOTE-006 study, investigator's choice of either ipilimumab or treatment with a BRAF ± MEK inhibitor was proposed for those progressing on pembrolizumab.[2] All of those receiving BRAF ± MEK inhibitors were known to have *BRAF* mutations (n=59), whilst another 17 patients with *BRAF* mutations were treated with ipilimumab. A superior response rate and duration of response were noted with combination treatment compared to monotherapy, along with a higher response rate in those who had not received prior BRAF monotherapy. The median OS across the three cohorts from randomisation was 21.5 months in those receiving ipilimumab, 13.8 months in those on BRAF monotherapy and 38.2 months in those treated with the BRAF/MEK combination. Whilst both are clearly good options, it does suggest the benefit of the combination in those with a *BRAF* mutation, in keeping with prior results in some other tumour types.

Finally, to wrap up the melanoma studies, we have the long-term outcome of those with brain metastases treated with ipilimumab and nivolumab in the CheckMate 204 study.[3] Brain metastases are a frequent site of disease in patients with melanoma and historically are one of the hardest sites from which to elicit

a good response. The presence of unstable brain metastases, or those that have not been actively treated, is also a frequent exclusion to trial admission. This means that patients with brain involvement participating in such trials are typically those with a prior response to other treatments, introducing some bias into the patient cohort. CheckMate 204 allowed both symptomatic and asymptomatic patients to be treated, with initial data showing that responses in those with asymptomatic brain metastases were equivalent to patients with extra-cranial disease. The patients were reported as two cohorts – Cohort A (asymptomatic brain metastases, n=101); and Cohort B (symptomatic brain involvement, n=18). It is clear that those with symptomatic brain metastases did far worse than asymptomatic patients (median PFS not reached by 39 months for Cohort A vs 1.2 months in Cohort B) by investigator assessment. However, within this dismal Cohort B figure there were 4/18 patients with durable intracranial/global responses, still on treatment at the time of the data lock. These patients need to be assessed further to identify indicators of response. It is important to note that two of the four were receiving corticosteroids at the start of treatment and two were not, suggesting that this does not preclude a response.

While immunotherapy revolutionised the treatment of melanoma, it still is yet to find a useful role in the treatment of patients with ovarian cancer. In NINJA, we have yet another negative study, in this case assessing nivolumab in those with platinum-resistant disease in a Japanese population.[4] As such, we see an over-representation of clear cell ovarian cancer by Western standards, with 21-22% of patients, and approximately 40% expressing PD-L1 receptor positivity. Despite this, we still see no benefit in the nivolumab group compared with the standard chemotherapy arms of gemcitabine or pegylated liposomal doxorubicin. It is disappointing that we don't have MMR testing results because there were a few patients who did benefit from the nivolumab, mainly in the clear cell cohort, and it would have been interesting to see if there was correlation between response and MMR status in that subgroup. This study adds to the previous immunotherapy studies in ovarian cancer, demonstrating that we have yet to come up with a well-tolerated regimen that has significant activity in ovarian cancer. The majority of the next wave of studies we are waiting to see report are those combining immunotherapy (PD-1 and PD-L1) with other novel agents to try and improve response rates. There is clearly much to do to find a wider audience for immunotherapy in this tumour type.

"While immunotherapy revolutionised the treatment of melanoma, it still is yet to find a useful role in the treatment of patients with ovarian cancer"

There is currently ongoing debate across a multitude of tumour types about the importance (or not) of repeat biopsies when there is disease relapse. Repeat biopsies are increasingly becoming a standard entry criteria for a number of studies, particularly in the earlier phases where appropriate translational work may define future treatment populations. With new drugs available for specific molecularly matched subpopulations, there are also potential new therapeutic reasons to consider biopsies. But what is less clear is whether all tumours will be likely to have an evolution of targetable mutations with later relapses. How many times is it necessary to recheck progesterone receptor/ER/HER-2 status in breast cancer with repeated relapses? Is it essential to recheck features such as MMR status with each relapse of colorectal or endometrial cancer? Such questions are frequently raised in a clinic setting as patients worry that potential therapeutic options are being missed. It is therefore interesting to see the work from Puccini and colleagues looking at the molecular differences between lymph nodes, colorectal primaries and distant metastases.[5] They found clear differences between the three in the same patients, including differing TMB and microsatellite status. Given that those with primary metastatic colorectal cancer may have metastatic disease only biopsied at diagnosis, should we be testing both? Or would the differences noted be sufficient to significantly impact on response? There isn't enough information from this study to determine this, but it is well known that we often see differential responses to treatment in different metastatic

sites due to clonal heterogeneity. This suggests it begins much earlier, and that we should perhaps at least compare metastatic disease to the primary tumour.

"With new drugs available for specific molecularly matched subpopulations, there are also potential new therapeutic reasons to consider biopsies"

The OlympiAD study of olaparib in the metastatic setting for *BRCA*-mutated breast cancer was reported a couple of years ago, demonstrating benefit with monotherapy compared to those treated with investigator's choice of chemotherapy.[6] Now, further translational work has been undertaken to assess homologous recombination status in these patients, to see if additional molecular testing would better define the patients who benefit most from PARP inhibition.[7] This follows on from work in the ovarian cancer setting which led to expansion of the potential treatment pool with niraparib and rucaparib. Patients in OlympiAD were all carriers of a pathogenic germline mutation, but were retrospectively assessed for the presence of tumour (t)*BRCA* mutations, loss of heterozygosity for BRCA1 and BRCA2, and had the Myriad myChoice® HRD test performed to assess impact on ORR and PFS. Sufficient tumour was available from just over half of the patients, with 41-47% of testing completed. There was an excellent correlation between (t)BRCA and germline (g)BRCA status, and loss of heterozygosity was reported for 94% of patients, confirming biallelic hits. Most were HRD positive but 16% were below the threshold on the Myriad test, more commonly those with ER-positive breast cancer. This did not impact on response to drug.

Conversely, the GeparSixto RCT of triple-negative breast cancer treated with one of three chemotherapy-based arms went back to assess HRD status in patients to look at response to treatment.[8] Tumour assessments were undertaken to assess tumour BRCA status, RAD51 score and Myriad myChoice® HRD score. A low RAD51 score correlated well with both the presence of a (t)*BRCA* mutation and a Myriad score consistent with HRD, suggesting that this could be used as a straightforward (and much cheaper) surrogate for HRD in breast tumours. This could be used to identify patients who would respond to carboplatin, and potentially PARP inhibitors, in the future. It would be interesting to see this validated in a prospective study.

"As the cost and turnaround times for sequencing continue to reduce, it becomes increasingly straightforward to undertake molecular profiling for more patients"

Moving forward into 2022, hopefully we will continue to see the incorporation of markers into the selection of optimal treatment for patients. As the cost and turnaround times for sequencing continue to reduce, it becomes increasingly straightforward to undertake molecular profiling for more patients, and identify the subgroups of patients who may have an inherently worse, or superior outcome, or those who require a different treatment approach.

I wish you all a safe and relaxing start to 2022, and look forward to further advances in precision oncology in the New Year.

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

Phase II study of ceralasertib (AZD6738) in combination with durvalumab in patients with advanced/metastatic melanoma who have failed prior anti-PD-1 therapy

Authors: Kim R et al.

Summary: Ceralasertib is an oral inhibitor of the ATR protein, and is crucial for DDR. The efficacy and safety of ceralasertib + durvalumab was investigated in this phase II trial involving 30 patients with metastatic melanoma who had failed anti-PD-1 therapy. The ORR and DCR were 31.0% and 63.3%, respectively, with responses evident in patients with acral, mucosal and cutaneous melanoma. The median duration of response, PFS and OS were 8.8 months (range 3.8–11.7 months), 7.1 months (95% CI 3.6–10.6 months) and 14.2 months (95% CI 9.3–19.1 months), respectively. Exploratory biomarker analysis indicated that tumours with an immune-enriched microenvironment or alterations in the DDR pathway were more likely to respond to treatment with ceralasertib + durvalumab. The majority of adverse events were haematologic, and these were manageable with dose reductions and/or interruptions.

Comment: The combination of a checkpoint inhibitor and an inhibitor of the DDR pathway has been assessed in a number of tumour types where the DDR pathway is commonly mutated, such as ovarian cancer. It has been demonstrated that the combination can increase immunogenicity and the TMB, therefore increasing the likelihood of response to a checkpoint-inhibitor containing regimen. In this case, ceralasertib was added therapy in a small number of patients who had failed first-line anti-PD-1 treatment, and the response rates were impressive. Of particular note were the biomarker exploratory endpoints, which suggested that those with detectable *DDR* mutations were more likely to respond, and it would be useful to see a larger study of the combination that selects patients who have this molecular marker. The ceralasertib + durvalumab combination could have significant application outside of metastatic melanoma, and should be investigated further.

Reference: Ann Oncol. 2021;Oct 25 [Epub ahead of print]
Abstract

Antitumor activity of ipilimumab or BRAF ± MEK inhibition after pembrolizumab treatment in patients with advanced melanoma: analysis from KEYNOTE-006

Authors: Long GV et al.

Summary: This study was a *post hoc* analysis of data from the phase III KEYNOTE-006 trial in patients with unresectable stage III/IV melanoma (n=555) treated with pembrolizumab 10 mg/kg Q3W or ipilimumab 3 mg/kg Q3W. It assessed outcomes in patients treated with ipilimumab or BRAF inhibitors with or without MEK inhibitors (BRAFi ± MEKi) after pembrolizumab. Over a median follow-up of 46.9 months, first therapy after pembrolizumab was ipilimumab in 103 (18.6%) patients and BRAFi ± MEKi in 59 (10.6%) patients (33 received BRAFi + MEKi and 26 received BRAFi alone). In ipilimumab recipients, the ORR with previous pembrolizumab was 17.5% (1 CR, 17 PR), and median OS was 21.5 months, but 79.6% of patients had discontinued pembrolizumab because of progressive disease. Subsequent ipilimumab recipients had an ORR of 15.5%; 8 CRs and 3 PRs were ongoing. In subsequent ipilimumab recipients who had PD as the best response to pembrolizumab, the ORR was 9.7%. Median OS from initiation of ipilimumab was 9.8 months. In BRAFi ± MEKi recipients, ORR with prior pembrolizumab was 13.5% (8 PR) and median OS was 17.9 months; 76.3% discontinued pembrolizumab because of PD. The ORR in subsequent BRAFi ± MEKi recipients was 30.5%, 4 CR and 3 PR were ongoing, and median OS was 12.9 months. In this group, the ORR for BRAFi ± MEKi-naive patients was 43.2% (3 CR and 3 PR were ongoing).

Comment: To maximise the benefit of having several treatment options for those with metastatic melanoma, it is important to look at the optimal sequencing of treatments. This study suggests that there is benefit from second-line ipilimumab in those treated with pembrolizumab alone, while in those with *BRAF* mutations, the optimal option is probably the combination of a BRAFi + MEKi. This seems to reduce the resistance that develops with those treated with a single-agent BRAFi regimen, and improves the overall response. The combination is well tolerated with little additional toxicity compared to a BRAFi alone, and the response rate of 43.2% in those naïve to such targeted agents is very promising. Further validation of the combination in these patients is of interest and will confirm the optimal use of these drugs in *BRAF*-mutated metastatic melanoma.

Reference: Ann Oncol. 2021;Oct 25 [Epub ahead of print]
Abstract

Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study

Authors: Tawbi HA et al.

Summary: This report provides final 3-year follow-up data from the multicentre, open-label, phase II CheckMate 204 study of nivolumab + ipilimumab in 165 patients with melanoma brain metastases. There was an investigator-assessed intracranial clinical benefit in 58/101 (57.4%; 95% CI 47.2–67.2) asymptomatic patients and 3/18 (16.7%; 95% CI 3.6–41.4) symptomatic patients. Investigator-assessed objective response was achieved in 54 (53.5%; 95% CI 43.3–63.5) asymptomatic patients and 3 (16.7%; 95% CI 3.6–41.4) symptomatic patients; 33 (33%) and 3 (17%) patients had an investigator-assessed intracranial CR. In asymptomatic patients, 36-month intracranial PFS was 54.1% (95% CI 42.7–64.1) and OS was 71.9% (95% CI 61.8–79.8); corresponding values in symptomatic patients were 18.9% (95% CI 4.6–40.5) and 36.6% (95% CI 14.0–59.8). The most common grade 3 or 4 TRAEs were increased ALT and AST (15% each) in asymptomatic patients; no grade 3 TRAEs occurred in >1 symptomatic patient. Serious TRAEs included colitis, diarrhoea, hypophysitis, and increased ALT (5% of each) in asymptomatic patients; no serious TRAE occurred in >1 symptomatic patients. There was one treatment-related death: myocarditis in an asymptomatic patient.

Comment: Brain metastases remain incredibly challenging to treat, and are a prognosis-defining site of disease. The current standard of care for such patients is a combination of nivolumab and ipilimumab, yet most patients with symptomatic brain metastases do not have a good response. In many cases, these patients have been excluded from studies due to their concurrent treatment with corticosteroids, which is generally thought to prevent a good response to immunotherapy. In the final analysis of CheckMate 204, it is notable that there were a small number of patients with symptomatic brain metastases who did have a much better response, with half of these patients treated with corticosteroids at the time of commencing treatment. This suggests that it may not be the steroid treatment that impacts on the likelihood of efficacy, and further assessment is required to identify patients more likely to have a durable response.

Reference: Lancet Oncol. 2021;22(12):1692-1704
Abstract

Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA)

Authors: Hamanishi J et al.

Summary: Nivolumab (n=157) was compared with gemcitabine or pegylated liposomal doxorubicin chemotherapy (n=159) in patients with platinum-resistant ovarian cancer in this multicentre, randomised, open-label, phase III study. Median OS was 10.1 months (95% CI 8.3–14.1) in patients treated with nivolumab and 12.1 months (95% CI, 9.3–15.3) in those receiving chemotherapy, with no significant between-group difference (HR 1.0; 95% CI 0.8–1.3). In contrast, median PFS was significantly shorter in the nivolumab versus chemotherapy group (2.0 months [95% CI 1.9–2.2] vs 3.8 months [95% CI 3.6–4.2]; HR 1.5; 95% CI 1.2–1.9; p = 0.002). There was no between-group difference in ORR (7.6% vs 13.2%; OR 0.6; 95% CI 0.2–1.3). Median duration of response was longer in the nivolumab group (18.7 vs 7.4 months) and the rate of TRAEs was lower with nivolumab compared with chemotherapy (61.5% vs 98.1%).

Comment: There remains no clear role for immunotherapy in ovarian cancer patients other than those with germline MMR mutations. However, this study is of interest because it has an over-representation of clear cell cancer patients, as is typical in the Japanese population. There had been previous work suggesting that clear cell cancer as a whole may benefit from immunotherapy more than other subtypes of ovarian cancer, and several studies recruiting ovarian cancer patients have had specific clear cell cohorts to assess this group. This study adds further evidence, suggesting that clear cell cancer as a whole does not specifically benefit. However, it is noteworthy that many of those with Lynch syndrome will develop either clear cell or endometrioid cancers, and this overlap may explain some of the earlier responses. The search for the right immunotherapy regimen for ovarian cancer patients goes on.

Reference: J Clin Oncol. 2021;39(33):3671-3681
Abstract

Molecular differences between lymph nodes and distant metastases compared with primaries in colorectal cancer patients

Authors: Puccini A et al.

Summary: This analysis used next-generation sequencing (MiSeq on 47 genes; NextSeq on 592 genes) and immunohistochemistry to characterise the molecular landscape and differences between lymph nodes, distant metastases and primary colorectal cancers. Data for 11,871 samples from 5,862 primary tumours, 5,605 distant metastases and 404 lymph node metastases were included. The most frequently mutated genes in lymph nodes were *TP53* (72%), *APC* (61%), *KRAS* (39%), *ARID1A* (20%) and *PIK3CA* (12%). Lymph nodes had a higher mean TMB based on somatic nonsynonymous missense mutations than did distant metastases (13 vs 9 mutations per megabase; p<0.0001). A high TMB (≥17 mutations per megabase) was more common in primary tumours and lymph nodes than in distant metastases (9.5% and 8.8% vs 4.2%, respectively; p<0.001). A high TMB was more common in lymph nodes than in distant metastases and primary tumours (p<0.0001), regardless of microsatellite instability status. Overall, lymph nodes had different rates of mutations in *APC, KRAS, PI3KCA, KDM6A*, and *BRIP1* compared with primary tumours (p<0.01), but also had a different molecular profile than distant metastases.

Comment: It has not been normal practice to rebiopsy when tumours first relapse unless there has been a long time since the primary tumour or the metastatic site is unusual, especially if there are concordant rises in tumour markers. This work suggests that there may be differences between primary site and metastases that would be important for choice of therapy or trial, especially if a targeted agent is being selected or if therapy is being chosen on the basis of TMB. It is common practice for molecularly matched studies to require a baseline biopsy for translational work, and this work demonstrates that, in some tumour types, it may be necessary to consider this with metastatic colorectal cancer where possible.

Reference: NPJ Precis Oncol. 2021;5(1):95
Abstract

Analysis of mutation status and homologous recombination deficiency in tumors of patients with germline *BRCA1* or *BRCA2* mutations and metastatic breast cancer: OlympiAD

Authors: Hodgson D et al.

Summary: Tissue samples from 161/302 patients with HER2-negative metastatic breast cancer who participated in the OlympiAD trial were evaluated in this prespecified exploratory analysis. The study evaluated whether tissue testing for *gBRCA1* and/or *BRCA2* mutations would facilitate the selection of patients for treatment with PARP inhibitors. A concordance of 99% was observed between *BRCA*1 and/or *BRCA*2 mutations in blood samples (g*BRCA*m) and tumour tissue (t*BRCA*m), while gene-specific loss of heterozygosity occurred in 118/125 patients (94%) (*BRCA1*m 96%; *BRCA2*m 92%). Two of three patients with *BRCA1*m without gene-specific loss of heterozygosity had a second mutation. Twenty-one of 129 patients (16%) had HRD-negativity (score <42), and this was more common with *BRCA2*m versus *BRCA1*m and/or for hormone receptor-positive versus triple-negative disease. The anti-tumour activity of olaparib was independent of HRD score.

Comment: In this analysis it is refreshing to note that there was no additional benefit to adding in HRD testing to standard BRCA testing in patients with metastatic breast cancer. Excellent concordance was noted between tumour and germline testing, providing the option for either testing approach in breast cancer patients in the future. The benefit of olaparib was seen regardless of HRD score, although it would be expected that the vast majority of those with a *BRCA* mutation would be deficient in homologous recombination, unless a reversion mutation had occurred. Still, it is always reassuring to note that more extensive testing with HRD scores did not define a patient population better than the widely available BRCA testing.

Reference: Ann Oncol. 2021;32(12):1582-1589
Abstract

Association of RAD51 with homologous recombination deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial

Authors: Llop-Guevara A et al.

Summary: This retrospective, blinded, biomarker analysis of data from the GeparSixto randomised clinical trial examined the use of an immunohistology-based RAD51 test compared with genetic/genomic tests in 133 triple-negative breast cancer patients with HRD. Functional HRD was identified in 81 (61%) tumours based on a predefined cut-off of <10% geminin-positive cells with ≥5 RAD51 or BRCA1 nuclear foci (RAD51-low). RAD51 testing showed that 93% (95% CI 76–99) of (t)*BRCA*-mutated tumours and 45% (95%CI 34–56) of non-t*BRCA*-mutant cases contained functional HRD. RAD51 identified genomic HRD in 86% of tumours, and 90% had genomic homologous recombination repair proficiency; concordance between RAD51 and genomic homologous recombination deficiency was 87% (95% CI 79–93). In RAD51-high tumours, the pathological CR was similar after neoadjuvant treatment with nonpegylated liposomal doxorubicin plus paclitaxel or carboplatin (31% vs 39%; OR 0.71; 95% CI 0.23–2.24). In RAD51-low tumours, the pathological CR was better when nonpegylated liposomal doxorubicin was combined with carboplatin versus paclitaxel (66% vs 33%; OR 3.96; 95% CI 1.56–10.05; p=0.004). Treatment with the carboplatin-containing combination was associated with similar DFS in RAD51-high (HR 0.40) and RAD51-low (HR 0.45) tumours.

Comment: The current commercially available tests for HRD are expensive and require significant amounts of DNA. This has dramatically limited the routine use of such tests for most tumours, and there is interest in identifying other surrogates that identify those likely to respond to PARP inhibitors, or to help define those more likely to respond to chemotherapy such as carboplatin. In this study, assessment of RAD51 performed well in identifying patients with functional HRD on the basis of a *BRCA* mutation or other *HRR* mutation. This makes it an attractive and cheap surrogate marker for HRD that could be performed as part of routine pathological assessment. Prospective validation of this approach in trials is required, but would be of great interest as a biomarker in breast cancer to predict response to platinum-based chemotherapy and PARP inhibition.

Reference: Ann Oncol. 2021;32(12):1590-1596
Abstract

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