a subgroup analysis of a phase 3 study in 64 patients with *EGFR* mutations showed improved progression-free survival and overall survival in those given bevacizumab and atezolizumab in combination with paclitaxel and carboplatin compared those treated with only paclitaxel and carboplatin.[9] These results needs to be confirmed by future randomised studies.

Bevacizumab improves the overall survival of patients with stage IV NSCLC who are treated with paclitaxel and carboplatin.[10] Although bevacizumab and chemotherapy are widely used in many cancers, the exact mechanism by which bevacizumab increases the anti-cancer effect of chemotherapy is unclear. This paucity of knowledge increases the difficulty of identifying biomarkers to select patients for bevacizumab treatment. The benefit of bevacizumab might extend to combination with osimertinib, which is currently being investigated in several trials (NCT02803203, NCT02971501, and NCT03133546).

In the NEJ026 study, *EGFR* activating mutations and Thr790Met cell-free DNA were detected in the patient's plasma,[8] and the results were provided to the researchers during the trial. This study also selected a large cohort of patients without de novo *EGFR* Th790Met mutations using sensitive detection methods. It will be interesting to assess the dynamic changes in cell-free DNA during treatment and the development of resistance in this cohort of patients.

The number of possible combinations and treatment sequences of EGFR TKIs, chemotherapy, bevacizumab, or anti-PD-1 and PD-L1 inhibitors complicate recommendations for first-line and second-line treatment in patients with NSCLC and *EGFR* mutations. At present, no biomarkers exist to enable the selection of the optimum treatment order for patients. Future studies might provide more evidence about treatment strategies.

James Chih-Hsin Yang
Department of Oncology, National Taiwan University Hospital and Graduate Institute of Oncology, National Taiwan University, Taipei 100, Taiwan
chihyang@ntu.edu.tw

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Fighting against the challenge of treating patients with late-line ovarian cancer: are we there yet?

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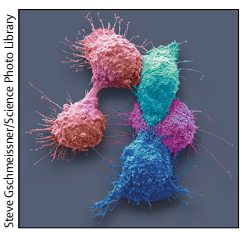
Treatment of subsequent relapses after the first recurrence of ovarian cancer remains challenging. Few studies have been designed in this patient setting, with varying inclusion and exclusion criteria and, as a result, outcomes remain poor and expectations are often unmet.

In *The Lancet Oncology*, Kathleen Moore and colleagues[1] present the results of the QUADRA study, which try to overcome these challenges. In this multicentre, single-arm, phase 2 trial, patients with relapsed high grade serous ovarian cancer, who had previously received three or four chemotherapy regimens were enrolled and treated with 300 mg once daily niraparib—one of the most investigated poly(ADP-ribose) polymerase (PARP) inhibitors in high grade serous ovarian cancer. Patients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had to have been platinum-sensitive at their frontline platinum-based therapy and should have been tested for tumor homologous recombination deficiency (HRD) and blood germline *BRCA* mutation, even though enrolment was done regardless of *BRCA* mutation status.

Among the 463 patients who initiated niraparib therapy, 222 (48%) were HRD positive, with 87 (19%) presenting with a germline or somatic *BRCA* mutation.[1] 38 (10%) of 387 response-evaluable patients and 38 (8%) of 456 patients in the modified intention-to-treat population achieved an overall response, with a median duration of response of 9·4 months (95% CI 6·6–18·3).[1] The toxicity profile was manageable, as expected.[2]

In terms of overall survival, Moore and colleagues[1] found a median overall survival of 17·2 months (95% CI 14·9–19·8) in the modified per-protocol population (all treated patients with measureable disease and at least two lines of previous treatment), regardless of *BRCA* status. This finding is very encouraging, as 58% of patients had received four or more lines of previous treatment and previous data found a median overall survival expectation of 10·6 months after the fourth line of chemotherapy.[3]

Nonetheless, other key findings of the study require some reflection. Moore and colleagues[1] showed a gradient of efficacy on the basis of platinum sensitivity in the *BRCA*-mutated population, similar to other PARP inhibitors.[4] Indeed, patients with *BRCA* mutation showing platinum-sensitivity at the most recent previous chemotherapy had a proportion of overall response of 39%, which decreased to 27% in platinum-resistant or refractory women. Interestingly, in the group of patients with HRD-negative or HRD-unknown status, the overall response rate dropped to 4%, even in those patients who were sensitive at the last line of platinum-based therapy. Once again, these results suggest that *BRCA* mutation status remains a driver of patient response to PARP inhibitors, even more so than platinum sensitivity.

However, since PARP inhibitors not only act by shrinking the tumour, but also by disrupting the tumour machinery, the duration of response rather than proportion of patients achieving an overall response seems a more accurate endpoint to evaluate activity.[5] Furthermore, disease stabilisation has recently emerged as a contributor to long-term benefit and overall survival[6,7] and could be considered as a measure of disease control and symptom-free survival.

Taking this alternative measure of activity into account, patients in the QUADRA study had a clinically meaningful duration of response.[1] Moreover, in a subgroup analysis, women with a clinical benefit for 24 weeks or more (according to Response Evaluation Criteria in Solid Tumors version 1.1) had a median overall survival of 28 months, regardless of *BRCA* mutation status and type of response (stable disease *vs* partial or complete response). This group of patients, who account for around 20–25% of the entire patient population, could achieve an extraordinary survival improvement with niraparib treatment in the late phase of disease, even in the absence of a reduction in tumour size. Unfortunately, this set of patients remains unidentifiable, and neither *BRCA* or HRD status nor platinum sensitivity have helped in their identification in this[1] and other trials.[2,8]

There remains a crucial need for more accurate biomarkers. We must remain committed to research and signature characterisation, both for patients who will unequivocally benefit the most and have to receive niraparib during their disease course, but also for those who are not showing a substantial clinical benefit and for whom overall survival remains disappointing. This latter group of patients should be involved in other well-designed clinical trials so that they can obtain similar improvements. However, in the present context, improving overall survival and disease control in this critical population with an oral drug that has a manageable toxicity profile, as has been achieved with niraparib in the QUADRA study, deserves to be considered a therapeutically successful achievement.

Claudia Marchetti, Anna Fagotti, Giovanni Scambia
Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome 00168, Italy (CM, AF, GS); and Catholic University of the Sacred Heart, Rome, Italy (AF, GS)
clamarchetti@libero.it

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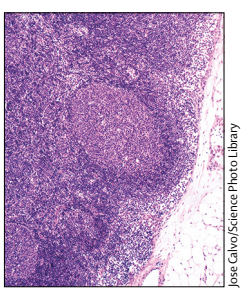
Improving R-CHOP in diffuse large B-cell lymphoma is still a challenge

Since the introduction of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) as the gold standard for the treatment of diffuse large B-cell lymphoma , clinical investigators have constantly tried to improve its effectiveness by adding new drugs and proposing combinations (ie, R-CHOP plus drug X).[1] This strategy is justified by the great biological heterogeneity of diffuse large B-cell lymphomas, suggesting that R-CHOP cannot be a universal treatment but can instead provide a rational basis for personalised therapy. As such, for the past decade molecular classification on the basis of the distinction between germinal centre B-cell-like and activated B-cell-like subtypes has largely dominated the debate and focused efforts in terms of targeted therapy and biomarker research.[2]

To show the potential of such a strategy, biologically relevant, reliable, reproducible biomarkers and a corresponding effective molecule that are likely to improve the efficacy of the R-CHOP regimen need to be identified.

The prospective multicentre phase 3 REMoDL-B trial, reported in *The Lancet Oncology* by Andrew Davies and colleagues,[3] shows that real-time characterisation of diffuse large B-cell lymphoma is feasible by use of molecular biology with RNA extracted from formalin-fixed paraffin-embedded (FFPE) samples and cDNA-mediated annealing, selection, extension, and ligation techniques.[3] Among the 1128 eligible patients in this trial, 918 (81%) were effectively classified according to their cell of origin (244 [27%] activated B cell, 475 [52%] germinal centre B cell, and 199 [22%] unclassified). Phenotyped patients were subsequently randomly assigned (1:1) after the first R-CHOP cycle to receive either R-CHOP or R-CHOP with bortezomib (RB-CHOP). The primary outcome analysis showed that the addition of bortezomib does not provide any benefit in terms of progression-free survival in the overall population (30-month progression-free survival 70·1% [95% CI 65·0–74·7] with R-CHOP *vs* 74·3% [69·3–78·7] with RB-CHOP; adjusted hazard ratio 0·84, 95% CI 0·64–1·11; p=0·23), with the same conclusion drawn in the secondary outcome analyses in the germinal centre B-cell, activated B-cell, and unclassified subgroups. These results support those of a randomised phase 2 trial by Leonard and colleagues.[4] However, Davis and colleagues point out a potential benefit of the combination for patients with double-hit lymphoma or dual-expressor lymphoma (ie, *MYC* and *BCL2*), although this benefit was not significant. The results show that despite overexpression of the nuclear factor (NF)-κB pathway and activating mutations of this pathway in activated B-cell diffuse large B-cell lymphoma, the addition of bortezomib—a proteasome and NF-κB pathway inhibitor—does not provide any benefit over R-CHOP.[3]

How can these ultimately disappointing results be explained? A relative under-representation of the activated B-cell subtype as compared with previous cohort studies in diffuse large B-cell lymphoma,[5] substantially older patients in the activated B-cell subgroup, and the use of bortezomib only from the second cycle onwards, with a relatively low dose, might all have affected the efficacy outcome of the addition of bortezomib. These results also suggest that the dichotomy of the germinal centre B-cell and activated B-cell subtypes of diffuse large B-cell lymphoma is probably too simplistic or reductive. A phase 3 randomised study (Phoenix)[6] that specifically targeted the activated B-cell subtype did not clearly show the value of adding ibrutinib (an inhibitor of Bruton's tyrosine kinase) to R-CHOP in this setting. However, the toxicity of this combination in patients aged 60 years and older is probably partly responsible for the negative conclusion since a benefit in overall survival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