context of unresectability. Metastatic spread is reported in around 10–15% of patients at diagnosis showing a poor prognosis. Among patients with metastatic disease, the heterogeneity of clinical behaviour not only depends on the histological subtype and grade, but also on the tumour burden. The oligometastatic subset, usually defined as patients with less than three nodules, is associated with significantly better survival.[8] Other variables such as depth and neurovascular tumour involvement have shown a prognostic role in univariate analysis; however, their independent prognostic role is more controversial and these factors were not included in a recent validated nomogram.[9]

This trial from the Children's Oncology Group constitutes a pertinent first step towards a rational perioperative use of chemotherapy and radiotherapy in children with NRSTS. Future studies should focus in more detail on different prognostic populations in resectable and unresectable localised NRSTS, as well as in the metastatic setting. Therefore, once this benchmark for the survival outcomes in these three different risk populations is established, a rational approach would be to select more homogeneous subsets of patients in which to test, by comparative designs, new therapeutic strategies that potentially will improve survival outcomes while preserving quality of life.

Javier Martin-Broto
Medical Oncology Department, University Hospital Virgen del Rocio, Seville, Spain; Institute of Biomedicine of Sevilla (IBIS, HUVR, CSIC, Universidad de Sevilla), 41013, Seville, Spain
jmartin@mustbesevilla.org

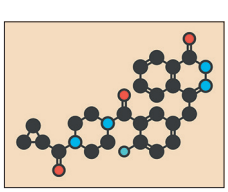
I report grants from Novartis and GSK; grants and personal fees from PharmaMar, Eisai, and Lilly; and personal fees from Bayer, outside the submitted work.

1 Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol* 2017; **18:** 719–31.
2 Pappo AS, Parham DM, Rao BN, Lobe TE. Soft tissue sarcomas in children. *Semin Surg Oncol* 1999; **16:** 121–43.
3 Ferrari A, Miceli R, Rey A, et al. Non-metastatic unresected paediatric non-rhabdomyosarcoma soft tissue sarcomas: results of a pooled analysis from United States and European groups. *Eur J Cancer* 2011; **47:** 724–31.
4 Ferrari A, De Salvo GL, Brennan B, et al. Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005). *Ann Oncol* 2015; **26:** 567–72.
5 Spunt SL, Million L, Chi Y-Y, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. *Lancet Oncol* 2019; published online Nov 27. https://doi.org/10.1016/S1470-2045(19)30672-2.
6 Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol* 2017; **18:** 812–22.
7 Pasquali S, Pizzamiglio S, Touati N, et al. The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial. *Eur J Cancer* 2019; **109:** 51–60.
8 Predina JD, Puc MM, Bergey MR, et al. Improved survival after pulmonary metastasectomy for soft tissue sarcoma. *J Thorac Oncol* 2011; **6:** 913–19.
9 Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. *Lancet Oncol* 2016; **17:** 671–80.

The tip of the iceberg: predicting PARP inhibitor efficacy in prostate cancer

In *The Lancet Oncology*, Joaquin Mateo and colleagues[1] report the results of the TOPARP-B trial, in which selected patients with metastatic castration-resistant prostate cancer and DNA damage response (DDR) gene aberrations were found to be responsive to the poly(ADP–ribose) polymerase (PARP) inhibitor, olaparib. Their study adds to the growing body of prospective studies evaluating different PARP inhibitors in patients with metastatic castration-resistant prostate tumours that harbour DNA repair defects. The recently reported phase 3 PROFOUND study showed an improved radiographic progression-free survival for patients with DDR gene aberrations treated with olaparib, compared with a control group treated with physician's choice of therapy.[2] These prospective studies are leading to a new era in which metastatic castration-resistant prostate cancer might have predictive, rather than prognostic, molecular markers to guide treatment decisions. Predictive assays are an important and innovative step in the treatment of metastatic prostate cancer. However, before we wholly embrace this approach, we should critically evaluate the outstanding issues, to improve precision in this changing treatment landscape.

TOPARP-B was a randomised, phase 2 study that compared 300 mg versus 400 mg twice daily oral olaparib through a pick-the-winner design. 711 patients previously treated with chemotherapy consented to prescreening, of whom 592 underwent targeted next-generation sequencing for DDR aberrations. Therefore, 119 (17%) patients in TOPARP-B could


Molekuul/Science Photo Library

Published **Online**
December 2, 2019
https://doi.org/10.1016/S1470-2045(19)30780-6

See **Articles** page 162

not be molecularly screened because of insufficient tissue or poor tissue quality. In the PROFOUND study, this proportion was reported to be even higher, at around 30%. Thus, the predictive testing for DDR mutations might not be achievable for 20–30% of patients, thereby preventing the use of a potential beneficial treatment because of inadequate tissue sampling and utility.

In TOPARP-B, the primary endpoint was confirmed response, defined as a composite of all patients presenting with a radiological response, a decrease in prostate-specific antigen (PSA) of 50% or more, or conversion of circulating tumour cell count (from ≥5 cells per 7·5 mL blood at baseline to <5 cells per 7·5 mL blood), or any combination of the three. This endpoint was in accordance with that used in the previous part of their study, TOPARP-A. However, this composite response cannot be directly compared with other studies that solely use PSA and radiographic responses.

The higher olaparib dose of 400 mg twice daily seemed to be more effective than the 300 mg dose and reached the predefined threshold for activity to confirm the putative biomarker data from TOPARP-A, whereas the 300 mg dose did not. However, the trial was not powered to formally compare the two doses, and toxicity also seemed to be increased in the 400 mg cohort. The correct dosing will need to be determined in a series of trials. Interestingly, long-lasting responses were noted in some patients in the 300 mg cohort and in patients of the 400 mg cohort who needed dose reductions.

How can we use this trial result to translate questions to the laboratory and improve the results of future trials? In TOPARP-B, some DDR gene aberrations seemed to be more responsive to olaparib than others, which seems to be recapitulated in other trials—eg, patients with *BRCA2* mutations are the most frequent and also seem to gain the greatest benefit,[3] but in TOPARP-B, the results for *BRCA1* and *BRCA2* are presented together. In addition, not all DDR-deficient tumours, including selected *BRCA1/2* mutated tumours, responded to PARP inhibition. This lack of response could be related to the need for specific germline versus somatic base pair mutations, or additional secondary gene hits within the monoallelic or biallelic DDR-inactivated tumours, to show maximum PARP inhibitor efficacy. The tumour microenvironment or immune response might also be heterogenous and differentially altered by PARP inhibition in patients.[4,5] Mutation-specific assays could be replaced by future assays that look for functional differences in DNA damage repair, such as genomic alterations in homologous recombination or DNA repair foci assays.[6,7] Functional assays could uncover additional patients who respond to PARP inhibition, and start to provide an explanation for the intriguing observation that radiographic progression-free survival is improved by PARP inhibition in patients with metastatic castration-resistant prostate cancer who lack DDR mutations.[8] Other reasons for differential response include inherent or acquired resistance mechanisms to PARP inhibition, including expression of multidrug-resistant genes and inhibition of the TP53-binding protein 1 and shieldin protein complexes that reactivate homologous recombination or alter intracellular drug concentrations.[9] To continue progress in this field, we need to examine in more detail the characteristics of patients who show a profound, durable response, to further tailor the approach to treatment.

When approved alongside a predictive assay, clinicians will have a new drug with a novel mechanism of action in their armamentarium to treat men with prostate cancer. But we still need to learn on the basis of biology how to make best use of it, ideally by finding the right drug combinations for each individual patient and maximising the opportunities for its use. In this regard, TOPARP-B also provides a rationale to study PARP inhibition in patients presenting with potentially aggressive, DDR-defective prostate cancers in hormone-naive settings.[10]

Silke Gillessen, Robert G Bristow
Oncology Institute of Southern Switzerland, Bellinzona, Switzerland (SG); Università della Svizzera italiana, Lugano, Switzerland (SG); Division of Cancer Sciences, University of Manchester, Manchester, UK (SG, RGB); and Translational Oncogenomics, Cancer Research UK Manchester Institute and Manchester Cancer Research Centre, Manchester, UK (RGB)
silke.gillessen@eoc.ch

SG reports being on advisory boards or independent data monitoring committees (compensated) for AAA International, Active Biotech, Astellas, Bayer, Bristol-Myers Squibb, Clovis, Curevac, Dendreon, Ferring, Innocrin, Janssen, MaxiVAX, Menarini Silicon Biosystems, Millennium, Orion, Roche, Sanofi, and Tolero; advisory boards (uncompensated) for Aranda, Astellas, Bayer, ESSA Pharmaceuticals, Nectar, ProteoMediX, and Sanofi; speakers bureaus (compensated) for Janssen and Novartis; and speakers bureaus (uncompensated) for Amgen, Astellas, Janssen, and Sanofi. She was also a co-inventor on a patent application (WO 2009138392 A1) for a method for

biomarker discovery. RGB reports being on advisory boards or independent data monitoring committees (compensated) for AstraZeneca, Onxeo, and Celgene; and an advisory board (uncompensated) for Cancer Research UK Therapeutic Discovery Laboratories. He also reports research grants from AstraZeneca and GenomeDx Biosciences.

1 Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2019; published online Dec 2. https://doi.org/10.1016/S1470-2045(19)30684-9.

2 Hussain M, Mateo J, Fizazi K, et al. PROfound: Phase 3 study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations. *Ann Oncol* 2019; **30** (suppl 5)**:** v851–934.

3 Nombela P, Lozano R, Aytes A, Mateo J, Olmos D, Castro E. *BRCA2* and other DDR genes in prostate cancer. *Cancers* 2019; **11:** 352.

4 Chabanon RM, Muirhead G, Krastev DB, et al. PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer. *J Clin Invest* 2019; **129:** 1211–28.

5 Bhandari V, Hoey C, Liu LY, et al. Molecular landmarks of tumor hypoxia across cancer types. *Nat Genet* 2019; **51:** 308–18.

6 Gulhan DC, Lee JJ, Melloni GEM, Cortés-Ciriano I, Park PJ. Detecting the mutational signature of homologous recombination deficiency in clinical samples. *Nat Genet* 2019; **51:** 912–19.

7 Meijer TG, Verkaik NS, Sieuwerts AM, et al. Functional ex vivo assay reveals homologous recombination deficiency in breast cancer beyond *BRCA* gene defects. *Clin Cancer Res* 2018; **24:** 6277–87.

8 Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2018; **19:** 975–86.

9 Gogola E, Rottenberg S, Jonkers J. Resistance to PARP inhibitors: lessons from preclinical models of *BRCA*-associated cancer. *Annu Rev Cancer Biol* 2019; **3:** 235–54.

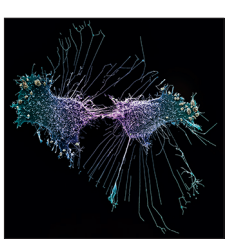
10 Taylor RA, Fraser M, Livingstone J, et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. *Nat Commun* 2017; **8:** 13671.

Is thermal ablation a new standard for cervical pre-cancer treatment in low-income and middle-income countries?

Cervical cancer in low-income and middle-income countries (LMICs) is a major health concern, largely due to persisting gaps in the access of women to screening and adequate treatment of pre-cancer.[1] In May, 2018, WHO launched a global call for action for the elimination of cervical cancer, with strategies including human papillomavirus (HPV) vaccination, and screening and treatment of women with pre-cancer or cancer.[2] The goal of the initiative is to achieve a screening coverage of 70% of the target population and adequately treat 90% of women with a positive screening test by 2030.[2]

For several decades now, cryotherapy has been recommended by WHO and remains the most widely used approach for cervical pre-cancer treatment in LMICs.[3] Using a screen-and-treat approach, women can be efficiently treated immediately after a positive screening test, thereby reducing clinic visits and the likelihood of loss to follow-up.[3] Additionally, the method is well accepted by women and providers, does not require anaesthesia, is safe, simple, cost-effective, and generally associated with only minor side-effects.[4] The disadvantage is that cryotherapy requires refrigerant gas, which makes the need for gas bottle transport, bottle supply, and refill a major challenge in LMICs.

Thermal ablation is based on locally heating (around 100°C) for 20–60 s, thereby destroying abnormal tissue by burning, and inducing a complete necrosis of pre-cancer and surrounding tissue. The best evidence for efficacy comes from high-income countries, essentially from the UK, with data supporting the fact that thermal ablation is an efficacious method.[4] Mindful of the differences in conditions and risk factors, results generated in high-income countries cannot simply be extrapolated to LMICs.[4] In *The Lancet Oncology*, Leeya Pinder and colleagues report results from the pilot phase of a randomised controlled trial,[5] in which 750 women who were eligible for ablative therapy received thermal ablation (n=250), cryotherapy (n=250), or large loop excision of the transformation zone (n=250). Most importantly, the authors assessed whether the performance of thermal ablation is similar to that of cryotherapy in terms of treatment success. The data suggest that thermal ablation and cryotherapy are similar in terms treatment success in women with pre-cancer (120 [60%] of 200 in the cryotherapy group and 123 [64%] of 192 in the thermal ablation group). However, the effects of a health intervention depend mainly on a reliable follow-up time and outcome assessment. The short-term follow-up (mean 6·6 months; range 4·8–19·6 months) in this study, as well as the small sample size, might mean underestimating the potential benefits of the treatment option and not detecting potential risks.



Anne Weston, Francis Crick Institute/Science Photo Library

Published **Online** November 13, 2019 https://doi.org/10.1016/S1470-2045(19)30732-6

See **Articles** page 175