ESMO Open Cancer Horizons

In the literature: June 2019

Angela Lamarca,[1] Valentina Gambardella,[2] Juan-Miguel Cejalvo,[2] Tania Fleitas-Kanonnikoff,[2] Andrés Cervantes[2]

To cite: Lamarca A, Gambardella V, Cejalvo J-M, *et al*. In the literature: June 2019 *ESMO Open* 2019;**4**:e000547. doi:10.1136/esmoopen-2019-000547

[1]Department of Medical Oncology, Division of Cancer Sciences, University of Manchester, Manchester, UK
[2]Department of Medical Oncology, Biomedical Research Institute INCLIVA, CiberOnc, University of Valencia, Valencia, Spain

Correspondence to
Professor Andrés Cervantes, Dept. Medical Oncology, Biomedical Research institute INCLIVA, University of Valencia, Valencia 46010, Spain; andres.cervantes@uv.es

ADJUVANT CAPECITABINE: A NEW STANDARD OF CARE IN BILIARY TRACT CANCER

Biliary tract cancer (BTC) includes cholangiocarcinoma and gallbladder cancer. BTCs are known to have a poor prognosis, with a 5-year overall survival below 20%.[1] Unfortunately, majority of patients are diagnosed with advanced stage, being palliative chemotherapy with cisplatin and gemcitabine the current standard of care.[2] Poor prognosis is due to the fact that only 20% of patients are diagnosed in early stages[3] and the high risk of relapse following curative surgery. Unfortunately, the lack of randomised studies has made the role of adjuvant treatment in BTC following surgery an unresolved matter for many years.[4 5] Adjuvant therapy (either in the form of chemotherapy or chemoradiotherapy) was supported by a meta-analysis published in 2012, which showed that tumours with lymph node metastases and microscopic invasion of resection margins were the ones benefiting the most.[5] However, this meta-analysis consisted of retrospective studies that employed different chemotherapy schedules; thus, adjuvant strategies were not widely adopted and practice varied significantly between countries worldwide.

Fruit of a huge effort and investment from the BTC scientific community, three phase III randomised trials were recently reported.[6–8] All these three prospective studies randomised patients with resected BTC to chemotherapy or observation alone. The chemotherapy arm consisted of gemcitabine in the bile duct cancer adjuvant trial (BCAT), which included patients diagnosed with extrahepatic cholangiocarcinoma only,[6] gemcitabine and oxaliplatin (GemOx) in the PRODIGE-12 (Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected BTC) study[7] and capecitabine in the resected biliary tract cancer (BILCAP) study.[8] BCAT and PRODIGE-12 randomised 225 and 186 patients, respectively. Unfortunately, none of these studies showed a significant benefit from adjuvant therapy (BCAT: primary endpoint was overall survival (OS) (HR 1.01 (95% CI 0.70 to 1.45); p value 0.964); PRODIGE-12: primary endpoint was relapse-free survival (RFS) (HR 1.28 (95% CI 0.62 to 1.25); p value 0.48)) and therefore did not change practice.

In contrast, the BILCAP (capecitabine compared with observation in resected biliary tract cancer) study suggested a benefit from adjuvant chemotherapy[8] that has been recently adopted by international guidelines which recommend adjuvant capecitabine for a period of 6 months following curative resection of BTC as the current standard of care.[9] In addition, these guidelines do also suggest consideration of chemoradiotherapy strategies in patients with extrahepatic cholangiocarcinoma and gallbladder cancer with R1 resection due to higher risk of recurrence despite this recommendation being based on a single arm phase II study.[9] Despite changing practice, the BILCAP study has generated lots of controversy due to the fact that it did not meet its primary endpoint. The BILCAP study randomised a total of 447 patients with resected cholangiocarcinoma and gallbladder cancer to 6 months of adjuvant capecitabine or observation alone. Patients were eligible if macroscopic complete resection had been achieved (R0 or R1) and if performance status at time of randomisation was of less than 2. Primary endpoint was OS in the intention-to-treat (ITT) population; in addition, there was a prespecified sensitivity analysis in the ITT population to assess OS adjusted to prognostic factors such as nodal status, grade of disease and gender. Secondary endpoints included OS analysis in the per-protocol population (excluding patients who had been randomised despite not being eligible and also patients who failed to complete at least one cycle of capecitabine; total of 210 patients in the capecitabine arm and 220 in the observation arm), RFS, toxicity, health economics and quality of life.

Median OS was 51.1 months and 36.4 months in the capecitabine and observation arms, respectively. The study did not meet the primary endpoint since it did not reach statistical significance in the ITT population (HR 0.81; 95% CI 0.63 to 1.04; p value 0.097). In

contrast, when analysis was adjusted to prognostic factors as prespecified in the clinical trials protocol and statistical plan, the study did reach statistical significance (HR 0.71 (95% CI 0.55 to 0.92); p value 0.010). The study was also significant for OS in the per protocol population (HR 0.75 (95% CI 0.58 to 0.97); p value 0.028). In addition, there was also benefit in terms of RFS with a median of 24.4 months and 17.5 months in the capecitabine and observation arms, respectively (p value 0.033) with a tolerable toxicity profile. It is worth noting that 55% of the patients started on capecitabine completed the full eight cycles of adjuvant therapy and that 46% required at least one dose reduction. Interestingly, the study did not show a benefit in RFS after the 24 months from randomisation what added to the limited benefit in reduction of the absolute recurrence rate (60% vs 65% in the capecitabine and observation arms, respectively) has raised the possibility 'that capecitabine only defers recurrence'.[10] Despite the limitations and based on the benefit in OS mentioned above, the study has been classified as 'statistically negative but clinically meaningful' by experts in the field.[10] The fact that international guidelines have adopted capecitabine as the new standard of care is reflection of such clinical significance despite a statistically not significant primary endpoint and highlights the importance of looking beyond the primary endpoint when interpreting clinical trial results especially in rare diseases when power of studies is limited by the difficulties in recruitment.

BILCAP has changed practice in 2019 but outcome of patients with BTC are still to be improved. Ongoing studies will evaluate the role of combination chemotherapy such as cisplatin and gemcitabine (CisGem) (ACTICCA-1 trial; NCT02170090; www.clinicaltrials.gov) in the adjuvant setting and their results are awaited.

TARGETING WRN HELICASE INDUCES SYNTHETIC LETHALITY IN MICROSATELLITE UNSTABLE CANCERS

Defects in DNA mismatch repair promote a hypermutable state with frequent insertion and deletion mutations that occur in nucleotide repeat regions, known as microsatellites. Microsatellite instability (MSI) can be caused by germline mutations in the mismatch repair (MMR) genes *MSH2*, *MSH6*, *PMS2* or *MLH1*, as occurred in the Lynch syndrome, or can arise from somatic MMR inactivation, such as *MLH1* hypermethylation.[11] This alteration is extensively related to the development of cancers, and, although MSI has been associated with notable benefit from the use of checkpoint inhibitors,[12] a significant proportion of tumours do not respond to immunotherapy.

The concept of synthetic lethality indicates an interaction between two genetic events leading to cell death. DNA repair processes represent attractive synthetic lethal targets, as widely demonstrated by the use of PARP inhibitors in *BRCA*-mutated tumours. In an inspirational paper published by Chan *et al*,[13] they demonstrate that the inhibition of WRN helicase in MSI cancers induces synthetic lethality.

Two wide cancer cell biobanks were analysed to study diverse MSI models. They found that the RecQ DNA helicase WRN was essential for survival of MSI models in vitro and in vivo. In particular, the viability of WRN knockdown was significantly reduced. WRN inhibition also induced a decrease of the S phase of cell cycle causing a downregulation of genes associated with G2/M checkpoint progression and E2F target signatures and upregulated signatures of apoptosis. The hypothesis that MSI is a predictive biomarker for WRN dependency was validated. The MSI–WRN relationship compared favourably to other strong biomarkers for vulnerabilities, such as the relationships between activating *KRAS* and *BRAF* mutations and *KRAS* and *BRAF* dependencies, respectively. In elegant experiments, depletion of WRN-induced double-stranded DNA breaks and promoted apoptosis and cell cycle arrest selectively in MSI models. Moreover, no increased dependence on WRN in cell lines with hypermutations related to mutations in polymerase epsilon (POLE) 21 were found, suggesting that hypermutability alone cannot account for WRN dependency.

According to these results, WRN induces a synthetic lethal vulnerability and represents a promising drug target for MSI cancers. Further studies will be needed to further explore the intersecting roles of MMR deficiency and genomic lesions in MSI with WRN dependence. More broadly, the findings of this work highlight the power of large-scale cancer profiling efforts to identify cancer vulnerabilities and therapeutic biomarkers, illustrating how a cancer dependency map can accelerate the development of precision therapy for patients with cancer.

PARP INHIBITOR EFFICACY DEPENDS ON CD8+ T CELL RECRUITMENT VIA INTRATUMOURAL STING PATHWAY ACTIVATION IN BRCA-DEFICIENT MODELS OF TRIPLE-NEGATIVE BREAST CANCER

Despite extensive research looking for new biomarkers, chemotherapy remains the primary systemic treatment for patients with triple-negative breast cancer (TNBC) and clinical outcomes for patients diagnosed with advanced disease are still poor. Among breast cancer, TNBC is the subtype with the greatest number of tumour-infiltrating lymphocytes (TIL). In fact, tumour immune infiltrate has been associated with an improved survival. Moreover, TNBC has a significant number of genetic alterations, such as *BRCA* mutations. BRCA-mutant tumours are deficient in homologous recombination (HR) repair pathways.[14 15] Consequently, PARP inhibitors did show efficacy in this subset of TNBC, but despite the clinical benefit seen with PARP inhibitors, both de novo and acquired resistance to treatment are frequent events.

Pantelidou *et al* published in a recent issue of *Cancer Discovery* an interesting paper based on the hypothesis that PARP inhibition might activate stimulator of interferon genes (STING)-dependent signalling in *BRCA*-associated

TNBC, leading to an antitumour immune response.[16] For this purpose, a genetically engineered mouse model with *BRCA1* and *TP53*-deficient mice was used. Individual tumours from this model were transplanted to immunocompetent and immunodeficient mice.

Some remarkable observations were derived from this work. The authors reported that olaparib-treated tumours regressed in immunocompetent mice. Tumours from immunocompetent mice showed that olaparib significantly increased both innate and adaptive immune responses. Those findings could not be reproduced in BRCA-proficient TNBC models. This suggested that an intact immune system is required for an optimal response. The authors also provided evidence that this antitumour immune response was achieved through the activation of the cyclic GMP-AMP synthase/STING pathway in both tumour and dendritic cells (DCs). These results were indicative of tumour cell-mediated paracrine activation of the pathway in DCs that stimulates antigen presentation and consequently CD8+ T cell infiltration and activation. Using clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 technology, they showed that tumour cell activation of the STING pathway and subsequent production of proinflammatory cytokines in response to PARP inhibition was necessary for recruitment and activation of cytotoxic CD8+ T cells and consequent antitumour efficacy. This work finally demonstrates a cross-talk between PARP inhibition and immune microenvironment via STING pathway activation in BRCA-deficient TNBC.

These findings suggest that PARP inhibitors can enhance the antitumour immune response in TNBC. Notably, these results provide a mechanistic rationale for combining PARP inhibition with novel therapies, such as immunotherapy. In patients with BRCA-deficient TNBC, PARP inhibitor-mediated DNA damage may, through STING pathway activation, convert immunologically cold tumours into hot ones and sensitise those tumours to immune checkpoint blockade.

Contributors All authors contributed equally.

Funding AL receives funding from The Christie Charity. This paper was supported by grants from the Instituto de Salud Carlos III (PI15/02180 and PI18/01909 to AC; PI18/01508 to TF). VG was supported by the ESMO 2014 fellowship program, and by Rio Hortega contract CM18/00241 from the Carlos III Health Institute. JMC was supported by a SEOM-Rio Hortega 2019 Contract. TF is supported by Joan Rodes contract 17/00026 from the Carlos III Health Institute.

Competing interests AL received travel and educational support from Ipsen, Pfizer, Bayer, AAA, Sirtex, Novartis, Mylan and Delcath; speaker honoraria from Merck, Pfizer and Ipsen; advisory honoraria from EISAI and Nutricia; she is also a member of the Knowledge Network and NETConnect Initiatives funded by Ipsen. AC declares institutional research funding from Genentech, Merck Serono, BMS, MSD, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astellas and Fibrogen and advisory board or speaker fees from Merck Serono, Roche, Bayer, Servier and Pierre Fabrein the last five years. All remaining authors have declared no conflict of interest.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1. DeOliveira ML, Cunningham SC, Cameron JL, *et al*. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245:755–62.
2. Valle J, Wasan H, Palmer DH, *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273–81.
3. Valle JW, Borbath I, Khan SA, *et al*. Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2016;27(suppl_5):v28–37.
4. Zhu AX, Knox JJ. Adjuvant therapy for intrahepatic cholangiocarcinoma: the debate continues. *Oncologist* 2012;17:1504–7.
5. Horgan AM, Amir E, Walter T, *et al*. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *JCO* 2012;30:1934–40.
6. Ebata T, Hirano S, Konishi M, *et al*. Randomized clinical trial of adjuvant gemcitabine chemotherapy *versus* observation in resected bile duct cancer. *Br J Surg* 2018;105:192–202.
7. Edeline J, Benabdelghani M, Bertaut A, *et al*. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER Gi): a randomized phase III study. *JCO* 2019;37:658–67.
8. Primrose JN, Fox RP, Palmer DH, *et al*. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *The Lancet Oncology* 2019;20:663–73.
9. Shroff RT, Kennedy EB, Bachini M, *et al*. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. *JCO* 2019;37:1015–27.
10. Malka D, Edeline J. Adjuvant capecitabine in biliary tract cancer: a standard option? *The Lancet Oncology* 2019;20:606–8.
11. Kim T-M, Laird PW, Park PJ. The landscape of microsatellite instability in colorectal and endometrial cancer genomes. *Cell* 2013;155:858–68.
12. DT L, Durham JN, Smith KN, *et al*. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017;357:409–13.
13. Chan EM, Shibue T, McFarland JM, *et al*. WRN helicase is a synthetic lethal target in microsatellite unstable cancers. *Nature* 2019;568:551–6.
14. Robson M, Im S-A, Senkus E, *et al*. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. *N Engl J Med* 2017;377:523–33.
15. Schmid P, Adams S, Rugo HS, *et al*. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med* 2018;379:2108–21.
16. Pantelidou C, Sonzogni O, De Oliveria Taveira M, *et al*. PARP inhibitor efficacy depends on CD8 $^{+}$ T-cell recruitment via intratumoral STING pathway activation in BRCA-deficient models of triple-negative breast cancer. *Cancer Discov* 2019.