ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

NEWS

In the literature: July 2022

TARGETING HER2-AXL HETERODIMERIZATION TO OVERCOME RESISTANCE TO HER2 BLOCKADE IN BREAST CANCER

HER2 is a transmembrane receptor belonging to human epidermal growth factor receptor (EGFR) family, and its overexpression has been found in ∼20% of breast cancer. The gene amplification and thus the protein's overexpression define a more aggressive tumor phenotype characterized by early metastasis and poor prognosis.[1] At the same time, HER2 is a well-established therapeutic target and HER-2-amplified tumors benefit from HER2 blockade both in adjuvant—neoadjuvant and in the metastatic setting. Unfortunately, a subset of patients develop resistance to the initially active drugs.[1]

AXL is a member of the TAM (TYRO3, AXL, MER) receptor tyrosine kinase family. In the last decade, AXL signaling has been associated with tumor progression, immune suppression, angiogenesis and epithelial-to-mesenchymal transition (EMT) in solid tumors.[2] In many tumors, AXL is a biomarker of poor prognosis as its expression has been associated with a mechanism of primary as well of acquired cancer cell resistance to anti-EGFR drugs in RAS WT metastatic colorectal cancer (mCRC) patients.[3] Little was known on its role in mediating resistance to HER2 blockade in breast tumors. In this respect, Adam-Artigues and colleagues published on Science Advances a relevant work on the role of AXL in determining resistance to anti-HER2 therapy.[4] The authors first demonstrated that acquired trastuzumab-resistant HER2-positive breast cancer cells have significantly higher AXL expression than sensitive cells. In the resistant clones, AXL mediates the EMT and its genetic or therapeutic inhibition is sufficient to reduce migration and invasion capacity, EMT marker expression and acquired trastuzumab resistance. Interestingly, the authors further demonstrate that AXL activation arises through heterodimerization with HER2 followed by the trigger of PI3K and mitogen activated protein kinases cascades in a ligand-independent manner. Moreover, in patient-derived xenograft model with acquired resistance to trastuzumab, concomitant HER2 (trastuzumab) and AXL (TP-0903) inhibition results in complete tumor regression. Finally, the study on the dataset from the PAMELA trial (neoadjuvant dual HER2 blockade) reveals the increase of AXL expression in residual disease during treatment corroborating the previous demonstration of its role in anti-HER2 resistance. Taken together, this study highlights the role of AXL overexpression as a new mechanism of resistance to anti-HER2 therapy. Its concomitant inhibition with anti-HER2 drugs could represent a novel therapeutic approach in HER2-positive breast cancers.

TEMOZOLOMIDE TREATMENT ALTERS MISMATCH REPAIR AND BOOSTS MUTATIONAL BURDEN IN TUMOR AND BLOOD OF COLORECTAL CANCER PATIENTS

CRC is one of the most common and lethal cancers and it is responsible for about 9% of cancer-related deaths worldwide. Beyond molecular classification and oncogene driver alterations, those tumors can be classified as mismatch repair proficient (pMMR) or deficient (dMMR). pMMR mCRCs account for 95% of all the cases and these tumors are known to be unresponsive to immunotherapy.[5] In a relevant article recently published in *Cancer Discovery*, Crisafulli et al.[6] show the translational analyses of a phase II trial suggesting how the use of an alkylating agent, temozolomide (TMZ), in MMR CRC might trigger a hypermutant status in MGMT-hypermethylated patients leading to increased sensitivity to checkpoint inhibitors.

The authors demonstrated, using a syngeneic CRC mouse model, that TMZ treatment led to the emergence of immunogenic dMMR cells. On the other hand, the tumor biopsies from patients diagnosed with mCRC who relapsed to TMZ revealed MMR mutations as a potential resistance mechanism. In both patients and mice models, MMR inactivation was related to increased tumor mutational burden (TMB) and predicted neoantigens.[7] According to this background, they promoted a 'proof-of-concept' two-step phase II trial (ARETHUSA). In this trial, mCRC patients received a first-step treatment with TMZ. This drug was selected for its direct antitumor effect but also as an immunological trigger. In the second step, at the time of progression, pembrolizumab was administered in those patients whose TMB was $\geq$ 20 mut/Mb.

In this article, the authors showed the results of the translational analyses carried out across tumor samples and liquid biopsies of the first 21 patients enrolled. This study confirmed that the use of TMZ affects the genome of MGMT-negative RAS-mutated mCRC. Firstly, the authors demonstrated that the TMZ changes occurred according to the exposure level. Moreover, it was also possible to observe that those patients who presented with an increase in TMB had tumors carrying the characteristic TMZ signature. The authors also underlined the huge complexity of tumor heterogeneity, showing that TMZ differentially affects distinct regions of the same lesion. Therefore, to overcome the limitation of the tissue analyses, they measured TMB in circulating tumor DNA (ctDNA) and found it largely comparable to the subclonal TMB calculated by whole exome sequencing data obtained by tissue biopsy. Both the analyses in tissue and through ctDNA were complementary, and singularly neither TMB (from tissue) nor bTMB (from blood) analyses could correctly stratify the

patients. The authors also underline that the TMZ mutational signature is heralded by the presence in plasma and tissue of the p.T1219I variant of the MMR gene *MSH6*. Additional mutations in *MSH6* were also found exclusively in both tissue and plasma after TMZ treatment, suggesting the potential role of MSH6 p.T1219I variant as a potential marker for TMZ molecular efficacy in CRC.

In conclusion, TMZ is related to increased mutational and neoantigen burdens and therefore could drive immune modulation. However, there is an urgent need for a better definition of mechanisms linking DNA damage and immune surveillance. For this reason, further validations are warranted.

CIRCULATING TUMOR DNA MAY GUIDE ADJUVANT TREATMENT DECISIONS IN STAGE II COLON CANCER

ctDNA has been established in several studies as a very strong prognostic factor in localized colon cancer, indicating the presence of minimal residual disease and announcing an eventually clinical detectable relapse in the coming months after its detection.[8,9] In a very important paper recently published in the *New England Journal of Medicine*, Tie et al. reported for the first time that ctDNA may guide our clinical decisions to administer or not adjuvant chemotherapy in patients with stage II colon cancer.[10] Patients were assigned after a 2 : 1 randomization to a ctDNA-guided strategy versus a conventional approach, based only upon the recognition of established pathological factors. Patients assigned to the ctDNA-guided approach got significantly less frequently adjuvant chemotherapy than those assessed by the conventional strategy (15% versus 28%). The risk of receiving adjuvant chemotherapy for patients presenting pathologically defined high-risk features was more than double, compared with those in which that decision was ctDNA guided. Using ctDNA may lead us to avoid overtreatment in a significant number of patients that are already cured by radical surgery without the addition of adjuvant chemotherapy.

The next question analyzed by this trial is on the efficacy of adjuvant chemotherapy, proving that the ctDNA-guided strategy was noninferior relative to standard management. Recurrence-free survival at 2 years was 93.5% for the ctDNA-guided cohort versus 92.4% in the standard management group. Moreover, 3-year recurrence-free survival was 86.4% for ctDNA-positive patients who got adjuvant chemotherapy and 95.2% for ctDNA-negative patients who never received adjuvant treatment. Some questions still remain unanswered, such as the value of clearance or persistence of ctDNA after adjuvant chemotherapy, indicating potential sensitivity or resistance to chemotherapy and even a potential individualization of treatment of some ctDNA-positive patients, according to some specific molecular findings. ctDNA analysis is becoming a useful and potent tool to avoid adjuvant chemotherapy in stage II patients with negative results, without risking relapses, relative to a more conventional approach based only upon clinical and pathological features.[11] Studies assessing ctDNA in stage III colon cancer are also underway and we expect them to bring further light for a more personalized approach to better guide our adjuvant treatment decisions.

V. Gambardella[1,2†], E. Martinelli[3†], N. Tarazona[1,2†] & A. Cervantes[1,2*†]

[1]*Department of Medical Oncology, Hospital Clínico Universitario, INCLIVA Biomedical Research Institute, University of Valencia, Valencia;*
[2]*CIBERONC, Instituto de Salud Carlos III, Madrid, Spain;*
[3]*Medical Oncology, Department of Precision Medicine, Università Della Campania 'L. Vanvitelli', Naples, Italy*
(*E-mail: andres.cervantes@uv.es).
[†]All authors contributed equally to this article.

Available online 9 August 2022

https://doi.org/10.1016/j.esmoop.2022.100556

FUNDING

This work was supported by grants from the Instituto de Salud Carlos III [grant number PI21/00689] to AC and NT. VG and NT were supported by Juan Rodés contracts [grant numbers JR 21/0042, JR20/0005] from the Carlos III Health Institute.

DISCLOSURE

AC declares institutional research funding from Genentech, Merck Serono, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astellas, Takeda and Fibrogen; and advisory board or speaker fees from Amgen, Merck Serono, Roche, Bayer, Servier and Pierre Fabre in the last 5 years. All other authors have declared no conflicts of interest.

REFERENCES

1. Loibl S, Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389:2415-2429.
2. Graham DK, DeRyckere D, Davies KD, Earp HS. The TAM family: phosphatidylserine sensing receptor tyrosine kinases gone awry in cancer. *Nat Rev Cancer*. 2014;14:769-785.
3. Cardone C, Blauensteiner B, Moreno-Viedma V, et al. AXL is a predictor of poor survival and of resistance to anti-EGFR therapy in RAS wild-type metastatic colorectal cancer. *Eur J Cancer*. 2020;138:1-10.
4. Adam-Artigues A, Arenas EJ, Martínez-Sabadell A, et al. Targeting HER2-AXL heterodimerization to overcome resistance to HER2 blockade in breast cancer. *Scie Adv*. 2022;8:eabk2746.
5. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectalcancer. *Nature*. 2012;487(7407):330-337.
6. Crisafulli G, Sartore-Bianchi A, Lazzari L, et al. Temozolomide treatment alters mismatch repair and boosts mutational burden in tumor and blood of colorectal cancer patients. *Cancer Discov*. 2022;12(7):1656-1675.
7. Germano G, Lamba S, Rospo G, et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. *Nature*. 2017;552:116-120.
8. Henriksen TV, Tarazona N, Frydendahl A, et al. Circulating tumor DNA in stage III colorectal cancer beyond minimal residual disease

detection, toward assessment of adjuvant therapy efficacy and clinical behavior of recurrences. *Clin Cancer Res*. 2022;28:507-517.
9. Tarazona N, Gimeno-Valiente F, Gambardella V, et al. Targeted next generation sequencing of circulating-tumor DNA for tracking minimal residual disease in localized colon cancer. *Ann Oncol*. 2019;30:1804-1812.
10. Tie J, Cohen JD, Lahouel K, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. *N Eng J Med*. 2022;386:2261-2272.
11. Montagut C, Vidal J. Liquid biopsy for precision adjuvant chemotherapy in colon cancer. *N Eng J Med*. 2022;386:2330-2331.