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"Signalling pathways in cancer" — a report from the European Society for Medical Oncology symposium

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ABSTRACT

On 4–5 March, 2016 the next symposium of the European Society for Medical Oncology (ESMO) about "Signalling pathways in cancer" was held in Sitges, Spain. The topics of the lectures were focused this year on mechanisms of action, resistance, new drugs, and the development of new therapies targeting human epidermal growth factor (HER) family receptors. During two days of symposium participants had an opportunity to familiarise themselves with the results of current research relevant to the main topic. This summary discusses selected topics presented during the symposium.

Key words: symposium, ESMO, EGFR, HER receptor, resistance, trastuzumab, pertuzumab

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Introduction

On 4–5 March, 2016 the next symposium of the European Society for Medical Oncology (ESMO) about "Signalling pathways in cancer" was held in Sitges, Spain, and its main topic concentrated on signalling pathway connected to HER/EGFR family receptors. This meeting was organised in collaboration with the European Association for Cancer Research (EACR) and the co-chairman was Professor Joseph Tabernero from Spain and Professor Clare Isacke from UK.

The meeting started with the presentation of mechanisms of action of different targeted therapies. The next topic included the role of circulating biomarkers, cancer DNA, and interactions between tumour microenvironment and stroma. Due to the speaker's absence the participants had no opportunity to listen to the lecture about mechanisms of immunological regulation in the microenvironment between tumour and host. Furthermore, the mechanisms of resistance to drugs targeting HER family receptors were discussed based on some therapies used in patients with colorectal cancer (CRC), lung cancer (LC), and breast cancer (BC). Additionally, professor Richard Marais presented previous experience regarding the resistance to drugs targeted other signalling pathways in patients with melanoma.

During the next day molecular features of breast cancer, colorectal cancer, lung cancer, and gastric cancer were discussed together with a detailed presentation of the role of anti-HER drugs in patients with those malignancies. During the closing session the speakers focused on new possibilities of development of precise medicine and some examples of its use in daily clinical practice.

The summary discusses the selected, main topics presented during the symposium.

Circulating biomarkers and circulating tumour DNA

Circulating tumour cells (CTCs) are released from the primary tumour and circulate in the bloodstream. It is believed that CTCs are important contributors in producing of distant metastases and possibility of their usefulness in clinical practice was already proven [1].

Cancer cells release their DNA fragments to the bloodstream, which are called circulating tumour DNA

(ctDNA) [1]. Usually ctDNA levels in blood increase with the tumour size. It is believed that ctDNA measurement could allow in the future the assessment of cancer disease stage and monitoring of treatment efficacy as well as disease progression [1].

Mechanisms of resistance

Lung cancer

The reasons of resistance against the drugs targeting epidermal growth factor receptor (EGFR) in patients with lung cancer includes the presence of T790M mutation of *EGFR* gene (50–60%), mutation of *HER2* gene (8–12%), amplification of *MET* (5–20%), or conversion into small cell lung cancer (SCLC) (< 5%) [1].

Professor Fortunato Ciardiello quoted during his lecture the results of Hata at al. study. Although the mechanisms of acquired resistance to EGFR inhibitors in patients with non-small cell lung cancer (NSCLC) were identified, there is still sparse information about evolution of resistant clones during therapy. Authors noted that acquired resistance due to *EGFR* T790M mutation could be a result of either the selection of previously existing *EGFR* T790M-positive clones or genetic evolution of previously *EGFR* T790M-negative cells [2]. Those cells had reduced apoptotic response to third generation EGFR inhibitors regardless of mechanism of induction. Treatment with navitoclax restored a sensitivity, which was already confirmed in the cells directly derived from patients with cancers resistant to EGFR inhibitors [2].

Two new clinical trials confirmed that mechanisms of acquired resistance to targeted therapy in NSCLC patients did not necessarily have to be connected with resistant subclones present from the beginning of the disease. Some cancers could show the potency to develop the mechanisms of resistance to targeted therapy after previous achieving response to the mentioned treatment [1–3].

During the next part of the lecture the registered indications to osimertinib treatment were discussed. In November 2015 the U.S. Food and Drug Administration (FDA) registered osimertinib for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with T790M mutation in *EGFR* gene [4, 5]. At the same time the FDA approved cobas® *EGFR* Mutation Test V2, adding T790M mutation to clinically important mutations, identified up to now by original cobas® *EGFR* Mutation Test (V1) [4]. In December, 2015 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion regarding conditional marketing authorisation of osimertinib in the above-mentioned indications [6].

Breast cancer

In the part dedicated to anti-HER2 therapy in patients with BC, a few possible mechanisms were presented, among them the development of cancer adaptation during treatment caused by increased expression of HER2 receptor [1]. Other mechanisms include structural changes of HER2 protein, alternative increasing of activity of other receptors with tyrosine kinase domain, like insulin-like growth factor receptor (IGFR), or changes within intracellular signalling pathways HER2-dependent, particularly involved in phosphatase and tensin homolog (PTEN) activity and PI3K/Akt pathway [7].

The potential possibility of reversing resistance to anti-HER2 therapy by activation of the immune system (e.g. combination of anti-HER2 and anti-PD1 drugs) was also presented [1].

Currently there is no known biomarker allowing prediction of the resistance to anti-HER2 therapy.

In summary, solutions were suggested, aimed at overcoming resistance to anti-HER2 therapy in patients with BC by administration of double HER2 blockade, inhibiting PI3K/mTOR pathway, immunomodulation, or blocking of oestrogen receptor in patients with tumour indicating its expression and overexpressing HER2 receptors [1].

Molecular features

Regarding BC, the participants were familiarised with already known data and additionally with the role of *PIK3CA* mutations. They are the most frequently observed in tumours indicating expression of oestrogen receptors and are associated with other factors of good prognosis [8]. *PIK3CA* mutations can coexist with *HER2* amplification and PTEN protein loss [8]. It is acknowledged that *PIK3CA* mutations are potentially a good prognostic factor, however, during trastuzumab-based therapy, the presence of *PIK3CA* mutations may be connected with worse tumour response as well as an uncertain influence on disease-free survival and overall survival [1, 8]. Recent results of clinical trials show that the presence of *PIK3CA* mutation does not guarantee a spectacular response to treatment with PI3K inhibitors [8]. Currently there are no data supporting the recommendation of routine *PIK3CA* genotyping [8].

There were four consensus molecular subtypes (CMSs) of CRC, distinguished based on the publication of Guinney et al.: CMS1 (microsatellite instability immune, 14%), hypermutated, microsatellite unstable and strong immune activation; CMS2 (canonical, 37%), epithelial, marked WNT and MYC signaling activa-

tion; CMS3 (metabolic, 13%), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal, 23%), prominent transforming growth factor–β activation, stromal invasion and angiogenesis [9]. It was highlighted during the symposium, that not only in CMS1 subtype (immuno-activated) immune system cells play some role [1]. In other subtypes immune system is acting in different way: immuno-ignorant in CMS2 and CMS3 subtypes and immuno-tolerant in CMS4 subtype [1].

Therapies targeting HER family receptors in selected malignancies

The results of the HERACLES trial were quoted several times during the symposium. Eligible patients include those with metastatic CRC with disease progression after use of derivatives of fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab, and with HER2 overexpression in tumour cells [10]. Patients received lapatinib in combination with trastuzumab weekly in standard doses. Response to the treatment was evaluated every eight weeks. The primary endpoint was objective response (OR) with use of Response Evaluation Criteria in Solid Tumours (RECIST) criteria, version 1.1 (v 1.1). The median age of the patients was 61 years. ORs were indicated in 6/18 patients (one complete response, four partial responses, one unconfirmed partial response; ORR = 33.3%, 95% CI 0.16–0.56) [10]. Additionally four patients achieved disease stabilisation lasting over four months. The treatment was well tolerated. Grade 2 diarrhoea, fatigue, and skin toxicities (grade 3 in one patient) were noted. The authors highlighted that the results of that study confirm the activity of combination treatment with lapatinib together with trastuzumab in patients with CRC who met the inclusion criteria [10].

One of the most highly anticipated lectures was the presentation by Dr. Javier Cortés about the current possibilities of anti-HER2 therapy and its development in BC patients. Due to spectacular results of the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) study, its results could not be missed during this year's symposium. CLEOPATRA is a multicentre, randomised, double-blinded, controlled phase III study, evaluating the efficacy and safety of systemic therapy with pertuzumab. Eligible patients were patients with, locally recurrent, unresectable, or metastatic HER2-positive breast cancer, previously untreated with chemotherapy or biological drugs due to metastatic disease [11]. The patients were randomised into groups receiving either placebo with trastuzumab and docetaxel or pertuzumab with trastuzumab and docetaxel. Patients were allowed to receive previously neoadjuvant or adjuvant chemotherapy with trastuzumab; however, it should be at least one year since cessation of the mentioned treatment. The primary endpoint of the study was progression-free survival (PFS), assessed by an independent review facility. Secondary endpoints included: overall survival (OS), PFS assessed by investigators, objective response rate (ORR), and safety. The independent review facility revealed significant prolongation of median PFS by 6.1 months (up to 18.5 months) in the pertuzumab-treated group (HR 0.62; 95% CI 0.51–0.75; $p < 0.001$) [11]. After an additional year of follow-up the median OS was 37.6 months in the control group, but it was not reached in the group treated with pertuzumab. Medians PFS assessed by the investigators were 12.4 months and 18.7 months in favour of the group receiving pertuzumab [12]. In final analysis, performed in 2015, medians OS were 56.5 months and 40.8 months in the groups receiving pertuzumab and placebo, respectively [13]. Thus, there was an increase in the OS median by 15.7 months in the group treated with pertuzumab [13].

Clinical trials with new compounds targeting HER2 in patients with BC were also presented (examples include margetuximab [monoclonal antibody against HER2] or MM-302) [14, 15]. MM-302 compound (HER2-targeted liposomal doxorubicin hydrochloride) is the drug targeting domain I of HER2 receptor [1, 14]. Taking into consideration its target point, which is different than trastuzumab and pertuzumab, it could be used in the future after disease progression in patients in whom those drugs were already administered, or it could be an alternative in combined treatment of double blockade of HER2 receptor. This matter demands further clinical trials [1].

Summary

In this annual ESMO symposium dedicated to the role of signalling pathways in cancers it was very important to present the current results of clinical trials with therapies targeting HER family receptors because the class of anti-HER drugs is being continuously developed. International sharing of experience, knowledge, and collaboration are essential factors contributing to the further development of anti-cancer drugs.

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