European Journal of Cancer 123 (2019) 25–27

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Revocation of the conditional marketing authorisation of a cancer medicine: The olaratumab experience

Ralf Herold [a,*], Jorge Camarero [a,b], Daniela Melchiorri [a,c], Zigmars Sebris [a], Harald Enzmann [a,d], Francesco Pignatti [a]

[a] European Medicines Agency, the Netherlands
[b] Agencia Espanola de Medicamentos y Productos Sanitarios, Spain
[c] University of Rome "La Sapienza", Italy
[d] Bundesinstitut für Arzneimittel und Medizinprodukte, Germany

Received 11 September 2019; accepted 12 September 2019

KEYWORDS
Sarcoma;
Clinical trials;
Drug development;
Regulation;
Marketing authorisation

Dear Editor,

This is to raise awareness on the revocation of the conditional marketing authorisation (CMA) for olaratumab (Lartruvo), after a trial of olaratumab with doxorubicin versus doxorubicin alone did not show superiority of the combination in terms of overall survival in patients with soft tissue sarcoma (STS).

The CMA is a framework in the European Union (EU) for timely access to medicines that address unmet needs and have demonstrated a positive benefit-risk balance with less comprehensive data than normally required, and where the expected benefits of immediate availability to patients outweigh the uncertainties until the positive balance of benefits and risks is confirmed by additional data. In just over 10 years, the CMA has been used for 23 anticancer medicines. For 14 of these anticancer medicines, benefit has already been confirmed; olaratumab is the first CMA that failed to confirm that the benefit-risk balance continued to be positive.

Olaratumab is a humanised antibody that inhibits a growth signalling pathway in sarcoma and stroma cells. In adult patients with a locally advanced, unresectable, or metastatic STS, a therapeutic-exploratory trial ('JGDG') showed increased progression-free and overall survival (OS) for the combination of olaratumab with doxorubicin, compared with doxorubicin alone. The median OS was 27 versus 15 months, with 50% versus 30% alive at 2 years, respectively, in the randomised

* *Corresponding author.*
E-mail addresses: ralf.herold@ema.europa.eu (R. Herold), jcamarero@aemps.es (J. Camarero), daniela.melchiorri@uniroma1.it (D. Melchiorri), zigmars.sebris@ema.europa.eu (Z. Sebris), harald.enzmann@bfarm.de (H. Enzmann), francesco.pignatti@ema.europa.eu (F. Pignatti).

https://doi.org/10.1016/j.ejca.2019.09.020

controlled part of the trial (133 patients). The unexpected increase was considered clinically important for a cancer with high unmet needs and limited treatment options.

The European Medicines Agency (EMA) scientific assessment concluded that the balance of benefits and risks was positive for olaratumab to treat STS, and also that the immediate authorisation of olaratumab would have benefits for patients. However, given the exploratory nature of the trial, it was considered that important uncertainties remained and required replication of the results.

When the CMA was granted (November 2016), a therapeutic-confirmatory trial (2015-000134-30, 'ANNOUNCE') was ongoing and was included as a specific obligation in the CMA, for the purpose of verifying the clinical benefit. The trial compared the same treatment regimens and was suitable to provide comprehensive data, given its advanced recruitment and robust design (double-blind, placebo-controlled, primary OS end-point, adequate patient number).

In January 2019, the marketing authorisation holder informed the EMA scientific Committee for Medicinal Products for Human Use (CHMP) that the trial failed to show a difference in efficacy of the regimens. With more than 2 years observation, data were mature enough to draw conclusions and showed that OS was not prolonged for the combination of olaratumab with doxorubicin, compared with doxorubicin alone, neither in the overall population nor the leiomyosarcoma subpopulation. Other efficacy end-points did not show favourable effects of the combination of olaratumab with doxorubicin over doxorubicin alone.

As a consequence, the CMA was revoked by the European Commission (July 2019), in line with the CHMP's assessment (April 2019, [7]) and communications that no new patients should receive Lartruvo and that treating physicians should consider available options for patients already on treatment. EU member states may in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product' [Article 117.3 in [1]]. The marketing authorisation holder announced working on options for continuing treatment of individual patients [2].

The CMA is a regulatory pathway that has been used across therapeutic areas for authorising medicines [3], including several to treat rare cancers, where the medicines will fulfil unmet medical needs when there are no authorised treatments, or will be a major therapeutic advantage. A CMA is valid for one year and can be renewed annually, until the comprehensive data set allows confirming that the benefit-risk balance is favourable. If this is the case, the marketing authorisation is no longer conditional. If not, the CMA framework enables taking appropriate regulatory action.

Anticancer medicines took in median 4 years for their clinical benefit to be confirmed and their marketing authorisation to be no longer conditional. This reflects the notable gains with the CMA pathway in terms of early access to patients and of less opportunity costs to society [4].

Communication is key for CMAs, and the conditional nature of the authorisation of Lartruvo is well explained in the product information. Also, health professional societies are proactively informed by the EMA about important changes of medicines, including this revocation. All stakeholders can readily find CMA products in the EMA website [5], with assessment reports detailing the strength of the evidence, the uncertainties, the clinical benefit related to end-points, and the additional data to be provided.

One of the principles shared across stakeholders is that public health is fostered through safe and timely access to medicines. The CMA framework provides the tools to ensure that the regulatory system can be trusted to follow this principle. At the outset, it was suspected that increasing CMA revocations would undermine trust in the regulatory system [6], yet this is the first case for the reason that a favourable benefit-risk balance was not confirmed. Since it is inevitable that the favourable benefit-risk balance for some CMAs cannot be confirmed, activities in the regulatory system focus on minimising this by stimulating the generation of extensive knowledge in biology, biomarkers, mechanisms of action, and explorative assessments to inform the benefit-risk assessment at the time of approval.

Although olaratumab did not meet the expectation for a confirmed survival benefit, we continue to see the value of every CMA medicine from the perspective of a patient for whom this is a new treatment option in a situation of unmet needs, despite the uncertainties. Clearly, communication and awareness about uncertainties is necessary to inform clinical decisions taken by patients and physicians.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or organisations with which the authors are affiliated.

Conflict of interest statement

None declared.

References

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32001L0083 (accessed August 23, 2019).

[2] Eli Lilly and Company. Lilly to establish an access program for patients as it prepares to withdraw Lartruvo from the global market. Eli Lilly Co; 2019. https://investor.lilly.com/news-releases/news-release-details/lilly-establish-access-program-patients-it-prepares-withdraw. [Accessed 29 May 2019].

[3] European Medicines Agency. Conditional marketing authorisation – report on ten years of experience at the European Medicines Agency. 2017. https://www.ema.europa.eu/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf. [Accessed 23 August 2019].

[4] Eichler H-G, Bloechl-Daum B, Brasseur D, Breckenridge A, Leufkens H, Raine J, et al. The risks of risk aversion in drug regulation. Nat Rev Drug Discov 2013;12:907–16. https://doi.org/10.1038/nrd4129.

[5] European Medicines Agency. European public assessment reports (EPAR) of medicinal products with a conditional marketing authorisation. https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/search_api_aggregation_ema_medicine_types/field_ema_med_condit_approval (accessed August 23, 2019).

[6] Eichler H-G, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008; 7:818–26. https://doi.org/10.1038/nrd2664.

[7] European Medicines Agency. Lartruvo Article 20 referral - CHMP assessment report; 2019 [Accessed 8 October 2019].