

This article has been published in Lancet Oncology:

The Lancet Oncology, Vol. 16, No. 9, e425–e426

Visit Lancet Oncology website: www.thelancet.com/oncology

Visit the ITCC website: www.ITCC-consortium.org

Will the revised class waiver list make it?

Gilles Vassal*, Patricia Blanc, Chris Copland, Andrew Pearson

Institut Gustave Roussy, Villejuif, France (GV)

European Consortium for Innovative Therapies for Children with Cancer, Villejuif, France (GV, AP)

Imagine for Margo, Paris, France (PB)

Centre for English Language Teaching, University of York, UK (CC)

Institute for Cancer Research, London, UK (AP)

* Corresponding author: gilles.vassal@gustaveroussy.fr at Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France

The 2007 European Paediatric Medicine Regulation requires a paediatric investigation plan (PIP) for drugs being developed for adults before marketing authorization is given, unless a waiver is granted by the Paediatric Committee (PDCO) at the European Medicine Agency (EMA). Waivers can be given because the medicine is likely to be ineffective, unsafe, not have a significant therapeutic benefit over existing treatments, or intended to treat an illness that only occurs in adults. PDCO published a list of class waivers in 2008 (revised in 2009 and 2010) that provide exemption from the obligation to submit a PIP or specific waiver request. 42 class waivers were for medicines for the treatment of illnesses (25 malignant) that do not occur in children.

We, as paediatric oncologists and parents, pointed out that medicines were unjustifiably waived according to this list.¹ For example, crizotinib is authorised for the treatment of ALK positive lung cancer and was given a class waiver because lung cancer does not occur in children. However, ALK is a driver of paediatric malignancies (eg, anaplastic large cell lymphoma, neuroblastoma, and inflammatory myofibroblastic tumours) and crizotinib showed tumour responses in an academic

paediatric phase I trial.² We called for the implementation of PIPs on the basis of the mechanism of action of drugs and revocation of the class waiver list.³

In July, 2015, the EMA published a revised class waiver list, to come into effect in 2018.⁴⁵ Eight class waivers were revoked because the diseases can occur in children, including two for cancer (liver or intrahepatic bile duct carcinoma and kidney or renal pelvis carcinoma) and 15 were revised.

PDCO should be congratulated for its extensive work, which provides detailed information about medicines that are likely to be ineffective in children with cancer. However, we wonder whether this revised class waiver list will increase the availability of potentially effective drugs.

For example, the class waiver can be applied for any medicine developed in adults for lung carcinoma (panel). With the revised list, only taxoids, thymidylate synthase inhibitors, pyrimidine-containing medicines, and platinum compounds will be class waived. For other drugs, a pharmaceutical company will need to submit a PIP or a request for a waiver. PDCO will now have the opportunity to review more medicines for children. However, if the company decides to request a waiver because the illness does not exist in children even though the drug's mechanism of action is relevant for paediatric malignancies, PDCO cannot force the company to assess a drug in children. The revised class waiver list will not prevent a repetition of the crizotinib story and the development of many oncology drugs for children will still be dependent on the willingness of a pharmaceutical company to voluntarily provide a PIP, as has occurred with the BRAF inhibitor dabrafenib.

In conclusion, although this important initiative by PDCO is progress, we are concerned that it might not substantially reduce the number of relevant medicines unjustifiably class waived. As we have emphasised before, the real change will come from considering the mechanism of action of a medicine, and setting up an efficient prioritisation process involving all stakeholders, industry, regulatory, parents and paediatric oncologists, and more efficient obligations and incentives.⁶⁷

Panel: Class waivers for medicines for the treatment of lung cancer

- In the current class waiver list: treatment of lung carcinoma (small cell and non-small cell lung carcinoma)
- In the revised class waiver list: the class of first-generation taxoid and thymidylate synthase inhibitor and pyrimidine-analogue-containing and pyrimidine-analogue-containing and first-generation and second-generation platinum-containing medicinal products for the treatment of lung malignancies

References

- ¹ Vassal G, Geoerger B, Morland B. Is the European pediatric medicine regulation working for children and adolescents with cancer? *Clin Cancer Res.* 2013; **19**:1315-25.
- ² Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol.* 2013;**14**:472-80
- ³ Vassal G, Blanc P, Pearson A. Need for change in implementation of paediatric regulation. *Lancet Oncol.* 2013; **14**:1156-7.
- ⁴ European Medicines Agency. European Medicines Agency decision (CW/0001/2015) of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190385.pdf (accessed August 5, 2015)
- ⁵ Burki TK. EMA paediatric medicine waivers. *Lancet Oncol* 2015; **16**: e429
- ⁶ Vassal G, Zwaan CM, Ashley D, et al. New drugs for children and adolescents with cancer: the need for novel development pathways. *Lancet Oncol.* 2013; **14**:e117-24.
- ⁷ Vassal G, Rousseau R, Blanc P, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *Eur J Cancer* 2015; **51**: 218-24.