New legislation to promote paediatric studies for new cancer medicines

Although few clinical trials or targeted therapies have historically been available for paediatric cancers, legislative efforts have sought to incentivise the study of new cancer medicines in children. Under the Research to Accelerate Cures and Equity for Children (RACE) Act, the US Food and Drug Administration (FDA) was, from August, 2020, authorised to require paediatric studies for new medicines indicated for adult cancers if the molecular targets are relevant to the growth or progression of a paediatric cancer. In June, 2022, the US House of Representatives passed legislation modifying the RACE Act to allow specific types of combination studies, with equivalent provisions included in the Senate version (the Give Kids a Chance Act of 2022).

To assess the effect of the RACE Act, we examined new cancer medicines submitted to and approved by the FDA before (January, 2012, to August, 2020) and after (August, 2020, to June, 2022) implementation of the legislation. Among 106 adult cancer medicines approved before the RACE Act, none were required to be studied in paediatric settings. However, since the law's implementation, paediatric studies were required for all five medicines with targets relevant for paediatric cancers (table). For example, the FDA required a study of infigratinib, which was approved for adult cholangiocarcinoma, in children aged 29 days or older with advanced or metastatic solid tumours harbouring *FGFR* alterations.

These observations indicate that the RACE Act is already influencing the number of paediatric studies for new cancer therapies.[1] We believe policy makers could build on this progress to maximise the benefits of these studies. Although legislation currently under consideration would allow some paediatric study requirements involving therapies considered the standard of care or those developed by the same manufacturer, the FDA should be granted additional flexibility to authorise studies involving multiple agents. For example, given the relatively small number of paediatric patients with cancer globally, the FDA could authorise a smaller number of studies assessing multiple recently approved therapies in series, instead of multiple simultaneous single-agent studies.[2]

Additionally, given the high rates of delay and non-completion of paediatric studies in general, the FDA could, when appropriate, require that sponsors begin enrolling patients in paediatric studies before or at the time of initial approval in adults.[3,4] The FDA could also direct sponsors to report progress on the completion of paediatric studies more frequently than currently required. Similar policies, already passed by the US House of Representatives for the accelerated approval pathway, could be extended to ensure timely completion of important paediatric studies.

	Approval date	FDA-approved indication	Paediatric study requirements
Loncastuximab tesirine	April 23, 2021	Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma	Assess the efficacy and safety of loncastuximab tesirine in paediatric patients aged 1 year or older with relapsed or refractory non-Hodgkin lymphoma
Infigratinib	May 28, 2021	Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement	Characterise the safety, pharmacokinetics, and anti-tumour activity of infigratinib for paediatric patients aged 29 days or older with advanced or metastatic solid tumours harbouring *FGFR2* alterations
Tisotumab vedotin	Sept 20, 2021	Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy	Investigate dose, tolerability, and preliminary evidence of activity of tisotumab vedotin in paediatric patients with cancers in which tissue factor is a relevant therapeutic target
Asciminib	Oct 29, 2021	Ph+ CML in chronic phase, previously treated with two or more tyrosine kinase inhibitors; and Ph+ CML in chronic phase with the Thr315Ile mutation	Assess safety, tolerability, pharmacokinetics, and pharmacodynamics of asciminib in paediatric patients with Ph+ CML chronic phase previously treated with one or more tyrosine kinase inhibitors, aged ≥1 to <18 years
Relatlimab and nivolumab	March 18, 2022	Unresectable or metastatic melanoma	Assess safety, pharmacokinetics, pharmacodynamics, and efficacy of relatlimab in combination with nivolumab in participants aged 0 to <30 years with relapsed or refractory Hodgkin lymphoma and an exploratory assessment in non-Hodgkin lymphoma

FDA=US Food and Drug Administration. DLBCL=diffuse large B-cell lymphoma. CML=chronic myeloid leukaemia. Ph+=Philadelphia chromosome-positive.

Table: **New cancer medicines approved by the FDA with paediatric study requirements**

We declare no competing interests. FTB was funded by the Burroughs Wellcome Fund for this work.

*Thomas J Hwang, Florence T Bourgeois
tjhwang@post.harvard.edu

Pediatric Therapeutics and Regulatory Science Initiative, Computational Health Informatics Program, Boston Children's Hospital, Boston, MA, USA (TJH, FTB); Cancer Innovation and Regulation Initiative, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Division of Urological Surgery, Brigham and Women's Hospital, Boston, MA 02115, USA (TJH); Department of Pediatrics, Harvard Medical School, Boston, MA, USA (FTB)

1 Hwang TJ, Orenstein L, DuBois SG, Janeway KA, Bourgeois FT. Pediatric trials for cancer therapies with targets potentially relevant to pediatric cancers. *J Natl Cancer Inst* 2020; **112:** 224–28.

2 Reaman G, Karres D, Ligas F, et al. Accelerating the global development of pediatric cancer drugs: a call to coordinate the submissions of pediatric investigation plans and pediatric study plans to the European Medicines Agency and US Food and Drug Administration. *J Clin Oncol* 2020; **38:** 4227–30.

3 Hwang TJ, Orenstein L, Kesselheim AS, Bourgeois FT. Completion rate and reporting of mandatory pediatric postmarketing studies under the US Pediatric Research Equity Act. *JAMA Pediatr* 2019; **173:** 68–74.

4 Hwang TJ, Tomasi PA, Bourgeois FT. Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: a cohort study. *PLoS Med* 2018; **15:** e1002520.