Evaluating the Impact of the RACE Act: An Interim Analysis

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Abstract Number: 1023

Background

Significant progress has been made in cancer care and treatment. However, these advancements have not easily translated to new treatment options and approvals for pediatric oncology patients. Over time, legislation has been enacted to help encourage and, in some instances, require pediatric studies for some cancer therapies. However, there have been limitations in increasing pediatric study due to exemptions built into these legislative acts. Most notable is the exemption of therapies with orphan designation. This has limited the ability to require pediatric studies for many oncology therapies, since 76% of NDAs and BLAs for oncology therapies received an orphan designation since 2013.

Recent Legislation Impacting Pediatric Oncology Drug Development

2002 BPCA
The Best Pharmaceuticals for Children Act (BPCA)

- **Voluntary:** Sponsors of NDAs only to conduct pediatric studies of a product under a written request (WR)
  - Sponsor may request the FDA issue a WR by submitting a proposed pediatric study request, or
  - FDA may issue a WR
- **Incentive:** Additional 6 months of exclusivity

2003 PREA
The Pediatric Research Equity Act (PREA)

- **Required:** Sponsors of NDA/BLA to submit assessments regarding appropriate formulations for each age group
- **Exempt:** Therapeutics with orphan designation
- **Waived:** Therapeutics with a non-pediatric-relevant indication (e.g., prostate cancer)

76.3% of original NDA and BLA oncology approvals received an orphan designation since 2013

2017 RACE Act
The Research to Accelerate Cures and Equity (RACE) Act

- **Required:** Sponsors of NDA/BLA to complete pediatric studies if:
  - The therapeutic is indicated for an adult cancer
  - Targets a molecular mechanism of action (MoA) relevant to pediatric cancer
  - Including orphan-designated indications
- **Waived:** If studies are impossible or highly impracticable due to prevalence

RACE Act Requirements Implemented August 18, 2020
- FDA publishes the Relevant Molecular Target (RMT) List, listing molecular targets that trigger a pediatric investigation

Objectives

- Evaluate the impact of the RACE Act on the number and types of pediatric studies required in the year after implementation, including the effect on orphan-designated products
- Analyze the effectiveness of the Relevant Molecular Target list to capture relevant mechanisms of action
- Identify additional opportunities to facilitate and encourage pediatric studies

Methods

Therapeutics

- All NDAs and BLAs for small molecule and biologic drug original applications
- Excluding non-treatment agents such as diagnostic and contrast agents and supportive care agents

Data Sources

Drugs@FDA, FDA's Approved Cellular and Gene Therapy Products	To determine applicable therapeutics to include
FDA Approval Letter	To determine the required pediatric assessments and orphan designation
FDA Label	To determine the indication and mechanism of action
RMT List	To cross-reference the agents' mechanism of action to determine applicability to pediatric cancer

Time Frame Analyzed

NDAs and BLAs included in this analysis were approved between Aug. 18, 2019 and Aug. 18, 2021. The date RACE was enacted (Aug. 18, 2020) was used to create two groups for the analysis:
- Pre-Implementation: Aug. 18, 2019- Aug 18, 2020
- Post-Implementation: Aug. 18, 2020- Aug. 18, 2021

Results

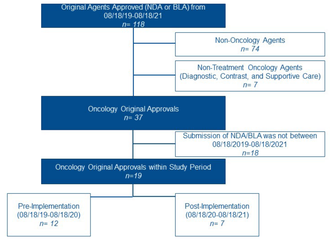


Figure 1: CONSORT diagram to show process for inclusion of drugs and biologics in the analysis.

Table 1: Drugs and Biologics One Year Pre- and Post-Implementation

RACE Implementation	Application Type	Therapeutic Agent	Indication	Mechanism of Action on RMT List	Pediatric Study Details
Pre-implementation	BLA	fam-trastuzumab deruxtecan-nxki	Adult Breast Cancer	Cell Lineage	Waived- Impossible/impracticable given cancer prevalence
	NDA	pemigatinib	Adult Cholangiocarcinoma	Gene Abnormality	Exempt- orphan
	NDA	mitomycin	Adult Urothelial Cancer	Others	Exempt- orphan
	NDA	selpercatinib	Adult NSCLC, Adult and **Pediatric** Thyroid Cancer	Gene Abnormality	Exempt- orphan
	BLA	belantamab mafodotin-blmf	Adult Multiple Myeloma	Not Listed	Exempt- orphan
	NDA	capmatinib	Adult NSCLC	Gene Abnormality	Exempt- orphan
	BLA	brexucabtagene autoleucel	Adult Mantle Cell Lymphoma	Cell Lineage	Exempt- orphan
	NDA	decitabine + cedazuridine	Adult Myelodysplastic Syndromes	Others	Exempt- orphan
	NDA	lurbinectedin	Adult SCLC	Others	Exempt- orphan
	BLA	pertuzumab, trastuzumab, and hyaluronidase-zzxf	Adult Breast Cancer	Cell Lineage	Waived- Impossible/impracticable given cancer prevalence
	NDA	tucatinib + trastuzumab + capecitabine	Adult Breast Cancer	Cell Lineage	Exempt- orphan
	BLA	tafasitamab-cxix + lenalidomide	Adult Large Cell Lymphoma	Cell Lineage	Exempt- orphan
Post-implementation	BLA	loncastuximab tesirine-lpyl	Adult B-Cell Lymphoma	Cell Lineage	Deferred required post-market study
	NDA	infigratinib	Adult Cholangiocarcinoma	Gene Abnormality	Deferred required post-market study
	BLA	amivantamab-vmjw	Adult NSCLC	Gene Abnormality	Waived- Impossible/impracticable due to cancer prevalence
	NDA	Sotorasib	Adult NSCLC	Not Listed	Waived- Impossible/impracticable due to mutation prevalence
	BLA	asparaginase erwinia chrysanthemi (recombinant)-rywn)	Adult and **Pediatric** ALL and LBL	Others	Deferred required post-market study
	NDA	belzutifan	Adult von Hippel-Lindau Associated Tumors	Not Listed	Waived- Impossible/impracticable due to mutation prevalence
	BLA	dostarlimab-gxly	Adult dMMR Solid Tumors	Tumor Microenvironment/ Immunotherapy	Waived- Impossible/impracticable due to prevalence

Orphan designated products are highlighted in blue and products with an initial approval for a pediatric indication are bolded. Abbreviations: NSCLC- non-small cell lung cancer, SCLC- small cell lung cancer, dMMR- mismatch repair deficient, ALL- acute lymphoblastic leukemia, LBL- lymphoblastic lymphoma.

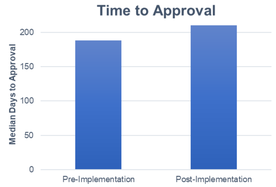
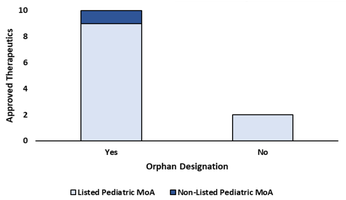


Figure 2: Median Time to Approval, in Days, for Drugs and Biologics Approved Pre- and Post-RACE implementation. The difference in median time to approval between pre- and post-implementation was not significant by unpaired t-test (p=0.84).

Results

Pre-Implementation

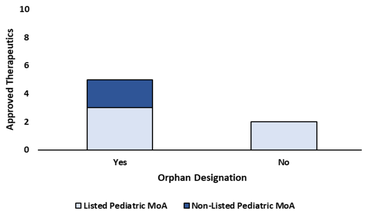


83.3% of approved applications in the year pre-implementation received an orphan designation

0 agents approved pre-implementation required pediatric study

Figure 3: Mechanisms of Action for Therapeutics Approved Pre-Implementation. Drugs and biologics approved the year prior to RACE implementation, categorized by orphan designation. The therapeutics are further stratified by if their mechanism of action (MoA) occurs on the Relevant Molecular Target List.

Post-Implementation



100% of required pediatric studies were for orphan-designated agents

42.9% of approved applications in the year post-implementation were required to conduct pediatric study

Figure 4: Mechanisms of Action for Therapeutics Approved Post-Implementation. Drugs and biologics approved the year after RACE implementation, categorized by orphan designation. The therapeutics are further stratified by if their mechanism of action (MoA) occurs on the Relevant Molecular Target List.

Table 2: Pediatric Study Requirements

Therapeutic Agent	Approved Indication	Pediatric Study Population	Study Completion	Final Report Submission
loncastuximab tesirine-lpyl	Adult relapsed or refractory large B-cell lymphoma	1-17 years relapsed or refractory non-Hodgkin lymphoma (waived in 0-12 months due to extremely rare incidence)	07/2027	07/2028
infigratinib	Adult unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusion/ rearrangement	29 days or older advanced solid tumors or recurrent/refractory low-grade gliomas harboring FGFR2 alterations (waived in cholangiocarcinoma due to extremely rare incidence)	03/2028	08/2028
asparaginase erwinia chrysanthemi (recombinant)-rywn)	Adult and pediatric patients 1 month or older acute lymphoblastic leukemia and lymphoblastic lymphoma	Pediatric patients with acute lymphoblastic leukemia or lymphoblastic lymphoma (dose finding for intravenous route)	06/2022	12/2022

Mechanism of Action

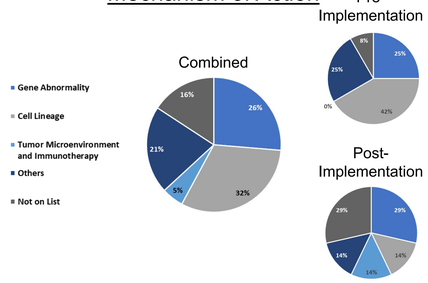


Figure 5: Approved Therapeutics' Mechanism of Action Categories. A depiction of the mechanisms of action of the approved therapeutics, based upon the Relevant Molecular Target List categories. The majority (84.2%) of approved therapeutics had a MoA included on the list.

Case Study

	Pre-Implementation	Post-Implementation
Drug:	Pemigatinib	Infigratinib
Approved:	April 2020	May 2021
Orphan Status:	Orphan Designation	Orphan Designation
Indication:	Cholangiocarcinoma with FGFR2 Alteration	Cholangiocarcinoma with FGFR2 Alteration
Pediatric Study Requirements:	Exempt due to Orphan Designation	Deferred Required Pediatric Study Subjects with advanced or metastatic solid tumors with FGFR2 alterations

Conclusions

- No approved therapeutics during the pre-implementation period required pediatric studies, mainly due to therapeutics receiving orphan designation
- Within the first year of implementation, almost half of approved therapeutics required pediatric study
- Closing the orphan designation loophole has shown to be effective in increasing pediatric study; However, future study on any resulting label expansions for pediatric indications will be needed to assess the full impact of the RACE Act
- The RMT list provides a foundation for evidence to support the requirement of study in pediatric cancers

Future Directions

- Longitudinal follow-up is necessary to confirm whether increased pediatric study translates to more labeling information to inform use in pediatric patient populations
- Many pediatric study requirements are still waived for therapeutics with a relevant MoA due to studies being deemed impossible or impracticable due to the prevalence of the mutation or cancer type
- Possible solutions to address clinical research for pediatric patient populations:
  - Encouraged use of master protocols and tissue agnostic trials
  - Extrapolating certain safety and efficacy data from adult clinical trials
  - Include at least adolescents in the pivotal registrational trial for relevant cancers

Sources

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Acknowledgements

This work was funded by Friends of Cancer Research.
The authors thank Eric Hua, Grace Collins, and Hillary Stires for their helpful contributions to the acquisition of the data and advice on study designs and analyses.