FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

June 20, 2018

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package will not include issues relevant to any final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

The issues under consideration are- Topic 1: Target List, Topic 2: FDARA Implementation, and Topic 3: Mechanisms to Assure Efficiency and to Enhance Global Coordination Through International Collaboration.

The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Memorandum

Date: June 5, 2018

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Gregory Reaman, MD
Associate Director, Office of Hematology and Oncology Products, CDER, and
Associate Director for Pediatric Oncology, Acting, Oncology Center of Excellence, FDA

Subject: FDA Background Package for June 20, 2018 Meeting

Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC. The Subcommittee will hear about the review and discussion of a list of molecular targets for which evidence and/or biologic rationale exist to determine their potential relevance to the growth or progression of one or more pediatric cancers and a list of those targets deemed unlikely to be associated with the growth or progression of pediatric tumors. These lists are expected to fulfill the statutory obligation of the Food and Drug Administration Reauthorization Act (FDARA) and provide some guidance to industry in planning for initial Pediatric Study Plan submissions for new drug and/or biologic products in development for cancer in accordance with the amended provisions of the Pediatric Research Equity Act. The Subcommittee will review and discuss considerations other than scientific relevance that FDA will include in decision making with respect to the need and timing of pediatric evaluation of specific new drug and biologic products. The Subcommittee will discuss possible criteria and mechanisms for the prioritization by sponsors and the clinical investigator community of select targeted new agents for pediatric evaluation especially in the setting of multiple same in class agents. Preliminary discussion will focus on approaches to coordination of and collaboration in pediatric clinical investigations of new agents that might be pursued to efficiently accommodate international regulatory requirements and global pediatric product development. The open public hearing sessions are- Topic 1: Target List, Topic 2: FDARA Implementation, and Topic 3: Mechanisms to Assure Efficiency and to Enhance Global Coordination Through International Collaboration.

We believe that this focused discussion will utilize the expertise of the Pediatric Oncology Subcommittee in guiding the Agency's decisions related to the potential relevance of new drugs and biologics that require early pediatric evaluation to assure timely development of and access to safe and effective new therapies for children with cancer. As well, the expertise of the subcommittee is expected to inform the FDA and its development of a guidance on the implementation of the FDARA 2017 pediatric provisions.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 20, 2018.

REFERENCE:

1. **Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)**: Title V – Pediatric Drugs and Devices (pages 47-58).

   FDASIA legislation is available at: http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

2. **FDA Reauthorization Act of 2017 (FDARA):** Title V-Pediatric Drugs and Devices (Section 501-505)

   FDARA legislation is available at: https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf

Pediatric Oncology Subcommittee of the
Oncologic Drugs Advisory Committee (ODAC)
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Relevant Molecular Targets in Pediatric Cancers: Applicability to Pediatric Therapeutic Investigations Required Under FDARA 2017

Pediatric cancer drug development typically leverages adult cancer drug discovery but has lagged far behind development of cancer drugs for adults. To date, the Pediatric Research Equity Act (PREA) has not been an effective mechanism to support the development of drugs for pediatric cancers because the requirement for conduct of pediatric studies is linked to the indication sought in adults and most adult cancers occur rarely, if ever, in children (e.g., cancers of the lung, prostate and breast). Therefore, sponsors obtain waivers for conducting assessments of these drugs in pediatric patients because studies would be infeasible or highly impracticable. Additionally, drugs developed for those rare cancer indications which may occur in both adult and pediatric populations which are frequently granted orphan designation are exempt from the requirements of PREA.

While there has been limited obligation to study investigational cancer therapies in children, incentives exist to promote the development of oncology products for pediatric cancer when these agents are in development or already approved for adult use. The Best Pharmaceuticals for Children Act (BPCA) is a voluntary mechanism which provides incentives in the form of 6 months of exclusivity for marketing to sponsors upon the completion and submission of pediatric studies that meet the terms of a written request from FDA (FD&C Act Sec. 505A, 21USC 355a, FDA Amendments Act (FDAAA) Public Law 110-85). BPCA has been the sole legislative mechanism available to evaluate those oncology products of interest for their potential role in the treatment of malignancies in children and adolescents.

The 2017 enactment of Title V of the Food and Drug Administration Reauthorization Act (FDARA) (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52), which amends the requirement for pediatric assessment of new drugs under the Pediatric Research Equity Act (PREA) based on molecular mechanism of action rather than clinical indication, may dramatically change the landscape for pediatric cancer drug development. FDARA has now created a mechanism to expedite the evaluation of novel medicines with the potential to address the unmet need in the pediatric population.

Molecularly targeted agents have advanced the concept of Precision Medicine in oncology. As malignancies occurring in children and adolescents can harbor molecular abnormalities similar to those found in adult cancers, these agents may be relevant to the treatment of pediatric patients with cancer. Although large scale sequencing efforts, such as TARGET, the Pediatric Cancer Genome Project, and the International Cancer Genome Consortium's Pedbrain Tumor and MMML-seq projects provide evidence that the genetic and epigenetic repertoires of driver gene aberrations often differ between adult and pediatric cancers, a growing body of evidence suggests that genetic and other molecular biological vulnerabilities of certain adult cancers may also occur in pediatric cancers, thereby providing opportunities for the use of targeted therapies in select pediatric tumors; up to 50% of pediatric cancers harbor a potentially druggable event. Timely investigation of the antitumor activity of potentially useful targeted drugs and biologics

under development in adults, and of their toxicities relative to the unique growth and developmental considerations of pediatric patients, is warranted for pediatric populations with cancer.

Title V of FDARA has amended PREA to support early evaluation of such drugs by requiring pediatric investigation of appropriate new drugs intended for adults with cancer. The investigations that FDA may require by statute are referred to as **molecularly targeted pediatric** cancer investigations. These investigations may include clinical studies designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling [FDARA Title V Sec 504 (a)(3)(A), FD&C Act Sec. 505B (a)(3)(A), 21 USC 355c(a)(3)(A)]. Importantly, Title V of FDARA also specifies that the requirement for early pediatric investigations of drugs directed at molecular targets considered substantially relevant to the growth or progression of a pediatric cancer be applied, even when the adult indication has received an orphan designation, or when the adult cancer indication does not occur or is biologically different in the pediatric population.

The statute also directs the FDA, in collaboration with the National Cancer Institute (NCI), to establish, publish, and regularly update a list of molecular targets considered, on the basis of data the Agency determines to be adequate, to be substantially relevant to the growth or progression of pediatric cancers, and that may trigger the requirement for pediatric investigations [21 USC 355c (m)(1)(A)]. Molecular targets that are considered "not relevant" to the growth or progression of pediatric cancers will be placed on a second list [21 USC 355c (m)(1)(B)]. The statute does not stipulate that a molecular target to which a specific drug is directed must appear on the relevant target list to require a clinical evaluation of the drug in the pediatric population. Furthermore, presence of a target on the relevant target list does not in itself constitute a requirement for a clinical study.

The FDA is mandated to convene a public meeting no later than 1 year after the date of the enactment of FDARA to solicit views of physicians, academic researchers (including pediatric oncologists and rare disease specialists), patient advocates, industry and other stakeholders for the establishment of the molecular targets lists [21 USC 355c (m)(2)(1)]. This meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) on June 20, 2018 is one such meeting.

A Friends of Cancer Research (FOCR)-sponsored multi-stakeholder public workshop held on February 20, 2018, discussed approaches for developing, updating and applying the molecular target list. This meeting included discussions of a framework to assess factors to define molecular targets as substantially relevant or not relevant to the growth or progression of one or more pediatric cancers; proposed processes and timelines for regularly updating the lists of molecular targets; and additional considerations for the application of the molecular target lists to decision-making regarding pediatric evaluation of specific drugs.

Although there may be differences in the way "molecular target" is defined, for the purposes of establishing a list of molecular targets considered to be substantially relevant to the growth or progression of pediatric cancer, a molecular target is defined **as a molecule in human cells that**

is intrinsically associated with a particular disease process, such as etiology, progression, or drug resistance. To be referred to as a target, there must be evidence that by engaging the target, either with a targeted small molecule, biologic product, or other treatment intervention, a desired therapeutic effect is produced that results in the alteration of the disease process. In other words, a molecule would not be referred to as a molecular target if there is no evidence to inform the hypothesis that its modulation (i.e., inhibition or activation) alters the disease.

The proposed framework for assessing those factors that may guide the definition of molecular targets as substantially relevant or not relevant to the growth or progression of one or more pediatric cancers includes a classification system to facilitate an organized approach to determination of relevance. Targets may represent the result of specific gene abnormalities, are present in a critical biologically-related pathway of a gene abnormality or exhibit a synthetic lethal relationship to a gene abnormality (**gene abnormality-based targets***)*. Targets can be intrinsic to the cancer cell lineage or developmental stage (**cancer cell lineage-based targets**), or they may be identified in non-cancer cells, such as normal immune cells or supporting cells contributing to the tumor micro-environment (**non-cancer cell targets**). Targets may exist as essential elements of cancer cells as well as some non-cancer cells and are not caused by a specific genetic aberration, such as tubulin or heat-shock proteins (**other targets**).

Evidence of effectiveness for a drug or biologic directed at a molecular target in an adult cancer and identification of the target as substantially relevant for the growth or progression of a pediatric cancer provide a rationale for the agent's evaluation in the pediatric cancer population, regardless of similarity to the histologically-defined cancer found in the adult. Although not a requirement, it is beneficial for sponsors of such an agent to develop *in vitro* and/or *in vivo* data using pediatric non-clinical models to provide increased confidence in either establishing or refuting potential relevance.

Two specific elements of a framework were identified, one that outlines factors that may be useful when determining whether a target is substantially relevant in pediatric cancer and may trigger the requirement for pediatric investigations. The second outlines factors to consider when assessing the available data that may help determine there is insufficient evidence of relevance, and that the target is hence "not relevant". (See Tables 1 and 2)

The FDA, in collaboration with the NCI, is tasked with determining whether a molecular target is or is not considered substantially relevant to the growth or progression of pediatric cancer. FDA has the regulatory authority to determine whether adequate evidence is available to define a target as substantially relevant to require pediatric investigation of a drug directed at that target. Defining a specific evidence standard for determination of target relevance is not feasible for several reasons, including the different classes of targets, variability in evidence base that may exist among targets and between specific target classes, and the fact that emerging science evolves making pre-defined qualifications based on peer-reviewed publications or publicly available registry data difficult. Several factors may support a scientifically-based and data-driven decision-making approach. These factors are not meant to be either all-inclusive or prescriptive, as there may be additional factors for some specific targets and some factors may not be required for all targets within a class. Table 1 characterizes the factors used in the

determination of whether a molecular target is substantially relevant to the growth or progression of pediatric cancers. The framework is not meant to be interpreted as a checklist, and it is important to note that the totality of evidence available may be considered when guiding discussions to determine target relevance. Additionally, the presence of a single factor or a combination of factors may not be sufficient to define relevance.

Table 1: Framework of factors and characteristics that may guide the determination of whether molecular targets are *substantially relevant* in the growth or progression of pediatric cancer

Factors		Considerations
Presence of target		The target has been identified in at least one case of a pediatric cancer
	Target class: Gene abnormality	The gene abnormality has been identified in at least one case of a pediatric cancer
	Target class: Cancer cell lineage	The target is intrinsically and differentially expressed in the cancer of interest compared to normal site-specific tissues.
Function/Mechanism		The biological function of the target is relevant to the etiology and growth of the childhood cancer
	Target class: Gene abnormality	Modulation of the affected gene product or of a critical downstream pathway or correction/deletion of the affected gene defect adversely affects cancer cells
		The presence of the gene abnormality creates a synthetic lethal relationship with another cellular pathway
	Target class: Cancer cell lineage	The target is associated to cancer cell development, growth and survival
Non-clinical evidence		Non-clinical evidence supports relevance of target in one or more pediatric cancers
	In vitro activity	Target modulation shows *in vitro* selectivity for cancer cell lines containing/expressing the molecular target (pediatric or adult cell lines if target is known to be shared by multiple cancer types regardless of patient population) compared to the sensitivity of cell lines not containing/expressing the target
	In vivo activity[1]	Target modulation shows *in vivo* activity manifested as tumor stabilization or regression in models of pediatric cancers with the molecular target of interest (or adult cancer models containing/expressing the target)
	Lack of *in vitro* or *in vivo* activity	For targets for which target modulation does not show *in vivo* or *in vitro* activity, support for relevance may be found in evidence for supra-additive or synergistic activity when target modulation is used in biologically rational combinations
Adult clinical experience		Target modulation by investigational agents known to affect the target, shows clinical activity in specific cancers in adults
Predictive biomarkers		Biomarkers that predict responses to target modulation may be useful in the selection of appropriate pediatric study populations
Location		For immunotherapy targets, the target is expressed on the cell surface (excepting immunotherapies that target intracellular antigens that are displayed as peptides by MHC proteins on the cell surface)
Agent under development		There is an agent in development or proceeding to development that addresses the specific target

[1]The *in vivo* activity should be observed at drug exposures that are relevant to the clinical setting if there is clinical experience with the agent. Prolonged stable disease may be relevant, particularly for agents that induce their anticancer effect through mechanisms other than cancer cell apoptosis.

Because of the potential importance of non-clinical evaluation in contributing to the evidence base for relevance of a molecular target, every effort should be made to ensure sponsors expedite early non-clinical investigation, which could be in collaboration with academic research teams with pediatric expertise in non-clinical testing. The creation of these collaborations and/or partnerships, ideally international in scope, should be explored further as they will be crucial for early testing of non-clinical models, such as patient-derived xenograft models.

Biomarkers that are identified as predictive for the activity of adult cancer targeted agents should also be evaluated for prevalence of expression and potential utility across pediatric cancers. Sponsors are strongly encouraged to test samples from pediatric cancers to determine prevalence, especially when an assay to identify a biomarker is developed in conjunction with the investigational agent and may not be available for use on patient samples by investigators.

There may be evidence available that demonstrates a molecular target is not relevant in pediatric cancers that would prevent it from being added to the substantially relevant molecular target list. The factors listed in Table 2 highlight considerations that may guide the determination of whether a molecular target is not relevant to the growth or progression of pediatric cancer. Again, it is solely the FDA's responsibility to determine what evidence is necessary to determine whether a molecular target is considered not relevant in pediatric cancer, and thus this document does not attempt to define what "adequate evidence" refers to in this context.

Table 2: Framework of factors and characteristics to consider that may guide the determination of whether molecular targets are *not relevant* to the growth or progression of pediatric cancer[1]

Factors	Considerations
Biologically implausible	Molecular targets for which available evidence supports no role for the targets in pediatric cancers (e.g. endocrine/autocrine sex steroid hormonal pathways that are known to be drivers of specific adult cancer types but are very rarely to never observed in pediatric cancers)
Non-clinical evidence	Evidence of lack of activity of an agent in development against a specific target in non-clinical systems could be a component of the evidence base used to determine that a specific molecular target may not be relevant to the growth or progression of a pediatric cancer.
Adult clinical evidence	Evidence of lack of clinical activity of an agent in development against a specific target could be a component of the evidence base used to determine that a specific molecular target may not be relevant to the growth or progression of a pediatric cancer.

[1]There may be agents that are relevant to the growth or progression of disease but that would not be considered for development because of their association with developmental processes such that their inhibition would raise concerns about irreversibly deleterious developmental effects and subsequent growth-related toxicities.

Molecular targets which lack sufficient evidence to make a determination of "substantially relevant" or "not relevant" will not be included in either list. Decisions regarding relevance of these targets to the growth or progression of pediatric cancers will be made when there is an adequate evidence base to make such a determination. Sponsors and investigators are strongly encouraged to investigate the potential relevance of new and currently unlisted targets as expeditiously as possible, especially when there are early non-clinical or clinical signals of activity.

To ensure molecular targets lists are updated in a timely fashion using the most relevant evidence available in light of the rapid pace of scientific advances, three distinct suggestions emerged:

- The first suggestion includes a semi-annual public workshops at which all stakeholders could discuss potential changes to the molecular targets lists. The FDA is responsible for

convening and presiding over these workshops , which may occur following a national or international scientific meeting. These meetings will seek input from individual stakeholders on advances in relevant scientific evidence that may impact the inclusion of one or more molecular targets on the current published lists, including potential relevance of unlisted targets. Decisions related to the lists will also reflect input from the Pediatric Subcommittee of ODAC.

- The second mechanism is a transparent nomination process open to sponsors and academic investigators to occur during or prior to meetings of the Pediatric Subcommittee of the ODAC. The details of such a transparent electronic nomination process, coordinated by the FDA's Oncology Center of Excellence will be determined.

- The third proposed mechanism is for clinical investigators or sponsors to request a meeting with the Pediatric Oncology Program of the FDA's Oncology Center of Excellence to discuss new scientific data related to a new or existing molecular target which may warrant a change in that target's status as relevant or non-relevant.

Information from these sources could then be assessed by the FDA, with possible input from the Pediatric Subcommittee of the ODAC, to determine whether there is sufficient new evidence to support changing the relevance status of the target of interest.

Additional factors that may require consideration when seeking to utilize the list of molecular targets for decisions regarding pediatric evaluation include analysis of clinical benefit and risk, the availability of pediatric formulations, and the adequacy of patient populations when planning clinical trials. These factors may vary with each targeted product under consideration for pediatric study and will be assessed and subject to multi-stakeholder discussion.

The preliminary list of relevant and non-relevant targets (attached) has been constructed in collaboration with the NCI and with input from recognized, international, multi-disciplinary experts in translational and clinical research in pediatric cancer from academia and the pharmaceutical industry and reviewed publicly on April 20, 2018. The FDA welcomes discussion of the proposed lists and input on the additional considerations and factors to guide pediatric clinical investigations with the expectation of expediting the development of safe and effective therapies for children with cancer.

First Session

Topic 1: Target List

Issues Relating to the Development of the Target List

1. Title V of the FDA Reauthorization Act (FDARA) 2017 assigns FDA to establish, publish and regularly update a list of molecular targets considered on the basis of data the FDA determines to be adequate to be substantially relevant to the growth or progression of pediatric cancers. New drug products directed at these targets may trigger the requirement for pediatric investigations [21 USC 355c(m)(1)(A)]. As well, a list of targets considered "not relevant" [21 USC 355c(m)91)(B)] has been developed. Comment on the process utilized to construct the list, the classification of molecular targets, the factors utilized to designate a target as relevant or non-relevant and indicate your concurrence with the lists as currently presented.

2. Please comment on the process proposed for formally updating the lists at semi-annual public workshops , the methods for nominating potential future candidate targets, and the required transparency in multi-stakeholder discussions to determine relevance. Comment on additional measures to assure timely discussion of emerging science and its clinical translation which has the potential to expedite drug development to improve the care and outcome of children with cancer.

Second Session

Topic 2: FDARA Implementation

Issues Relating to FDARA Implementation

1. Please comment on the proposed additional considerations for which the FDA might engage with industry, clinical investigators, and advocates when making decisions regarding the requirement for pediatric studies of new drug and biologic products based on molecular mechanism of action and their timing.

Third Session

Topic 3: Mechanisms to Assure Efficiency and to Enhance Global Coordination Through International Collaboration

Issues Relating to the Mechanisms to Assure Efficiency and to Enhance Global Coordination Through International Collaboration

1. Please discuss transparent mechanisms for industry, advocates, and the academic investigator community to communicate and provide input to the FDA for purposes of eliminating unnecessary duplication of clinical trials in rare pediatric cancer populations of same in class agents.

2. Please comment on process development aimed at enhancing international collaboration between clinical trial networks to facilitate global cancer drug development for children in light of currently non-aligned regulatory requirements.

Please see next page.

Target Symbol	Gene Abnormality	Citation(1)	Link(1)	Citation(2)	Link(2)	Citation(3)	Link(3)
ABL1/2	ABL1/2 gene fusions (BCR-ABL1, etc.)	Greuber, E. K., Smith-Pearson, P., Wang, J., & Pendergast, A. M. (2013). Role of ABL family kinases in cancer From leukaemia to solid tumours. Nature Reviews Cancer, 13(8), 559-571. doi 10.1038/nrc3563	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC3935732/				
ACVR1	ACVR1	Taylor, K. R., Vinci, M., Bullock, A. N., & Jones, C. (2014). ACVR1 mutations in DIPG lessons learned from FOP. Cancer Research, 74(17), 4565–4570. http //doi.org/10.1158/0008-5472.CAN-14-1298	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4154859/				
ALK	ALK and ALK gene fusions	Holla, V. R., Elamin, Y. Y., Bailey, A. M., Johnson, A. M., Litzenburger, B. C., Khotskaya, Y. B., … Simon, G. R. (2017). ALK a tyrosine kinase target for cancer therapy. Cold Spring Harbor Molecular Case Studies, 3(1), a001115. http //doi.org/10.1101/mcs.a001115	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC5171696/				
ASCL1	ASCL1 gene	Kasim, M., Benko, E., Winkelmann, A., Mrowka, R., Staudacher, J. J., Persson, P. B., . . . Fähling, M. (2014). Shutdown of Achaete-scute Homolog-1 Expression by Heterogeneous Nuclear Ribonucleoprotein (hnRNP)-A2/B1 in Hypoxia. Journal of Biological Chemistry, 289(39), 26973-26988. doi 10.1074/jbc.m114.579391	http //www.jbc.org/content/289/39/26973.full				
BRAF	BRAF	Kieran, M. W. (2014). Targeting BRAF in Pediatric Brain Tumors. American Society of Clinical Oncology Educational Book, 34. doi 10.14694/edbook_am.2014.34.e436	https //meetinglibrary.asco.org/record/89039/edbook#fulltext	Dahiya S, Emnett RJ, Haydon DH, et al. BRAF-V600E mutation in pediatric and adult glioblastoma. Neuro Oncol. 2014;16 318-319.	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC3895374/		
CDK12	EWSR1-FLI1	Iniguez, A. B., Stolte, B., Wang, E. J., Conway, A. S., Alexe, G., Dharia, N. V., . . . Stegmaier, K. (2018). EWS/FLI Confers Tumor Cell Synthetic Lethality to CDK12 Inhibition in Ewing Sarcoma. Cancer Cell, 33(2). doi 10.1016/j.ccell.2017.12.009	https //www.ncbi.nlm.nih.gov/pubmed/29358035				
CSF1R	CSF1R gene fusions	Rovida, E., & Sbarba, P. D. (2015). Colony-Stimulating Factor-1 Receptor in the Polarization of Macrophages A Target for Turning Bad to Good Ones? Journal of Clinical & Cellular Immunology, 06(06). doi 10.4172/2155-9899.1000379	https //www.omicsonline.org/open-access/colonystimulating-factor1-receptor-in-the-polarization-of-macrophagesa-target-for-turning-bad-to-good-ones-2155-9899-1000379.pdf	Butowski, N., Colman, H., Groot, J. F., Omuro, A. M., Nayak, L., Wen, P. Y., . . . Prados, M. (2015). Orally administered colony stimulating factor 1 receptor inhibitor PLX3397 in recurrent glioblastoma An Ivy Foundation Early Phase Clinical Trials Consortium phase II study. Neuro-Oncology, 18(4), 557-564. doi 10.1093/neuonc/nov245	https //academic.oup.com/neuro-oncology/article/18/4/557/2509330		
CTNNB1 (β-catenin)	CTNNB1	Shukla, N., Ameur, N., Yilmaz, I., Nafa, K., Lau, C., Marchetti, A., . . . Ladanyi, M. (2011). Oncogene Mutation Profiling of Pediatric Solid Tumors Reveals Significant Subsets of Embryonal Rhabdomyosarcoma and Neuroblastoma with Mutated Genes in Growth Signaling Pathways. Clinical Cancer Research, 18(3), 748-757. doi 10.1158/1078-0432.ccr-11-2056	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC3271129/				
DDX3X	DDX3X	Epling, L. B., Grace, C. R., Lowe, B. R., Partridge, J. F., & Enemark, E. J. (2015). Cancer-associated mutants of RNA helicase DDX3X are defective in RNA-stimulated ATP hydrolysis. Journal of Molecular Biology, 427(9), 1779–1796. http //doi.org/10.1016/j.jmb.2015.02.015	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4402148/				
DOT1L	MLL gene fusions	Wong, M., Tee, A., Milazzo, G., Bell, J., Hüttelmaier, S., Polly, P., . . . Liu, T. (2017). Abstract LB-080 The histone methyltransferase DOT1L promotes neuroblastoma by regulating gene transcription. Cancer Research, 77(13 Supplement). doi 10.1158/1538-7445.am2017-lb-080	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4633909/				
EGFR	EGFR	Lee, J. A., Ko, Y., Kim, D. H., Lim, J. S., Kong, C.-B., Cho, W. H., … Koh, J.-S. (2012). Epidermal Growth Factor Receptor Is It a Feasible Target for the Treatment of Osteosarcoma? Cancer Research and Treatment Official Journal of Korean Cancer Association, 44(3), 202–209. http //doi.org/10.4143/crt.2012.44.3.202	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC3467424/				
ERK	BRAF, MAP2K1	Tp, T. A. (2015). Targeted Therapy for MAPK Alterations in Pediatric Gliomas. Brain Disorders & Therapy, S2. doi 10.4172/2168-975x.s2-005	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4627711/	Knight, T., & Irving, J. A. (2014). Ras/Raf/MEK/ERK Pathway Activation in Childhood Acute Lymphoblastic Leukemia and Its Therapeutic Targeting. Frontiers in Oncology, 4. doi 10.3389/fonc.2014.00160	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4067595/		
EWSR1-FLI1	EWSR1-FLI1	Gamberi, G., Cocchi, S., Benini, S., Magagnoli, G., Morandi, L., Kreshak, J., . . . Alberghini, M. (2011). Molecular Diagnosis in Ewing Family Tumors. The Journal of Molecular Diagnostics, 13(3), 313-324. doi 10.1016/j.jmoldx.2011.01.004	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC3077725/				
EZH2	SMARCB1, SMARCA4	D Angelo, V., Iannotta, A., Ramaglia, M., Lombardi, A., Zarone, M. R., Desiderio, V., . . . Caraglia, M. (2015). EZH2 is increased in paediatric T-cell acute lymphoblastic leukemia and is a suitable molecular target in combination treatment approaches. Journal of Experimental & Clinical Cancer Research, 34(1). doi 10.1186/s13046-015-0191-0	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4535295/	Chang, C., & Hung, M. (2011). The role of EZH2 in tumour progression. British Journal of Cancer, 106(2), 243-247. doi 10.1038/bjc.2011.551	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4132442/		
FGFR	FGFR and FGFR gene fusions	Venneti, S., & Huse, J. T. (2015). The Evolving Molecular Genetics of Low-grade Glioma. Advances In Anatomic Pathology, 22(2), 94-101. doi 10.1097/pap.0000000000000049	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4667550/	Porta, R., Borea, R., Coelho, A., Khan, S., Araújo, A., Reclusa, P., . . . Rolfo, C. (2017). FGFR a promising druggable target in cancer Molecular biology and new drugs. Critical Reviews in Oncology/Hematology, 113, 256-267. doi 10.1016/j.critrevonc.2017.02.018	http //www.croh-online.com/article/S1040-8428(17)30085-9/fulltext	Linzey, J. R., Marini, B., Mcfadden, K., Lorenzana, A., Mody, R., Robertson, P. L., & Koschmann, C. (2017). Identification and targeting of an FGFR fusion in a pediatric thalamic “central oligodendroglioma”. Npj Precision Oncology, 1(1). doi 10.1038/s41698-017-0036-8	https //www.nature.com/articles/s41698-017-0036-8
FLT3	FLK2, STK1, CD135	Grafone, T., Palmisano, M., Nicci, C., & Storti, S. (2012). An overview on the role of FLT3-tyrosine kinase receptor in acute myeloid leukemia Biology and treatment. Oncology Reviews, 6(1), 8. doi 10.4081/oncol.2012.e8	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4419636/	Levis, M. (2013). FLT3 mutations in acute myeloid leukemia what is the best approach in 2013? Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program, 2013, 220–226. http //doi.org/10.1182/asheducation-2013.1.220	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC4714709/		
Gamma secretase	NOTCH1 and FBXW7	Kolb, E. A., Gorlick, R., Keir, S. T., Maris, J. M., Lock, R., Carol, H., . . . Smith, M. A. (2011). Initial testing (stage 1) by the pediatric preclinical testing program of RO4929097, a γ-secretase inhibitor targeting notch signaling. Pediatric Blood & Cancer, 58(5), 815-818. doi 10.1002/pbc.23290	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC3276746/				

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ATR	Weber, A. M., & Ryan, A. J. (2015). ATM and ATR as therapeutic targets in cancer. Pharmacology & Therapeutics, 149, 124-138. doi 10.1016/j.pharmthera.2014.12.001	https //www.ncbi.nlm.nih.gov/pmc/articles/PMC5066844/ [Erratum of the research article]https //www.sciencedirect.com/s		
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AR	Sun, J., Wang, D., Guo, L., Fang, S., Wang, Y., & Xing, R. (2017). Androgen Receptor Regulates the Growth of Neuroblastoma Cells in vitro and in vivo. Frontiers in Neuroscience, 11, 116. http://doi.org/10.3389/fnins.2017.00116	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5339338/			
ESR1	Lovén, J., Zinin, N., Wahlström, T., Müller, I., Brodin, P., Fredlund, E., … Henriksson, M. (2010). MYCN-regulated microRNAs repress estrogen receptor-α (ESR1) expression and neuronal differentiation in human neuroblastoma. Proceedings of the National Academy of Sciences of the United States of America, 107(4), 1553–1558. http://doi.org/10.1073/pnas.0913517107	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2824410/			
ESR2	Ashton, K., Proietto, A., Otton, G., Symonds, I., Mcevoy, M., Attia, J., . . . Scott, R. (2009). Estrogen receptor polymorphisms and the risk of endometrial cancer. BJOG: An International Journal of Obstetrics & Gynaecology, 116(8), 1053-1061. doi:10.1111/j.1471-0528.2009.02185.x	https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/j.1471-0528.2009.02185.x			
GnRHR	Cheng, C. K., Chow, B. K., & Leung, P. C. (2003). An Activator Protein 1-Like Motif Mediates 17β-Estradiol Repression of Gonadotropin-Releasing Hormone Receptor Promoter via an Estrogen Receptor α-Dependent Mechanism in Ovarian and Breast Cancer Cells. Molecular Endocrinology, 17(12), 2613-2629. doi:10.1210/me.2003-0217	https://academic.oup.com/mend/article-pdf/17/12/2613/10716982/mend2613.pdf			
PSA	Matera, L. (2010). The choice of the antigen in the dendritic cell-based vaccine therapy for prostate cancer. Cancer Treatment Reviews, 36(2), 131-141. doi:10.1016/j.ctrv.2009.11.002	https://www.ncbi.nlm.nih.gov/pubmed/19954892	Cho H. Cockle P. Binder J. Resini W. White P. & Jooss K. Vaccine based immunotherapy regimen (VBIR) for the treatment of prostate cancer. Cancer Res. 76 (14 Supplement) LB-093-LB-093 (2016)		https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html
PSCA	Matera, L. (2010). The choice of the antigen in the dendritic cell-based vaccine therapy for prostate cancer. Cancer Treatment Reviews, 36(2), 131-141. doi:10.1016/j.ctrv.2009.11.002	https://www.ncbi.nlm.nih.gov/pubmed/19954892	Cho H. Cockle P. Binder J. Resini W. White P. & Jooss K. Vaccine based immunotherapy regimen (VBIR) for the treatment of prostate cancer. Cancer Res. 76 (14 Supplement) LB-093-LB-093 (2016)		https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html
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