Farmaci orfani e innovazioni farmacologiche

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Workshop «Malattie rare e pediatria: innovazione terapeutica e misure nazionali ed europee di attrazione degli investimenti»

Rare diseases

- Between 5,000 and 8,000 distinct rare diseases exist, affecting between 6% and 8% of the population in total
  - They affect between 27 million and 36 million people in the EU
  - Most people suffer from diseases with an incidence lower than 1 in 100,000 people
- 80% of rare diseases have identified genetic origins, and affect between 3% and 4% of newborns
  - Other rare diseases are due to degenerative and proliferative causes

Orphan designation

Some 60% of designated orphan medicines are intended for pediatric use

Orphan medicinal products must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating

The prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development

No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition

Exclusive for EU

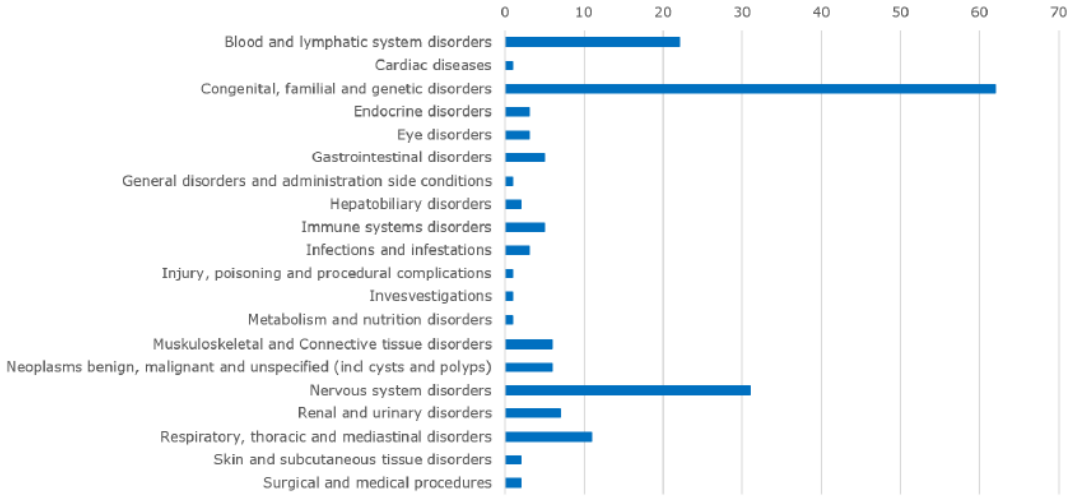
Orphan medicinal products EMA in 2021

Orphan medicinal product activities

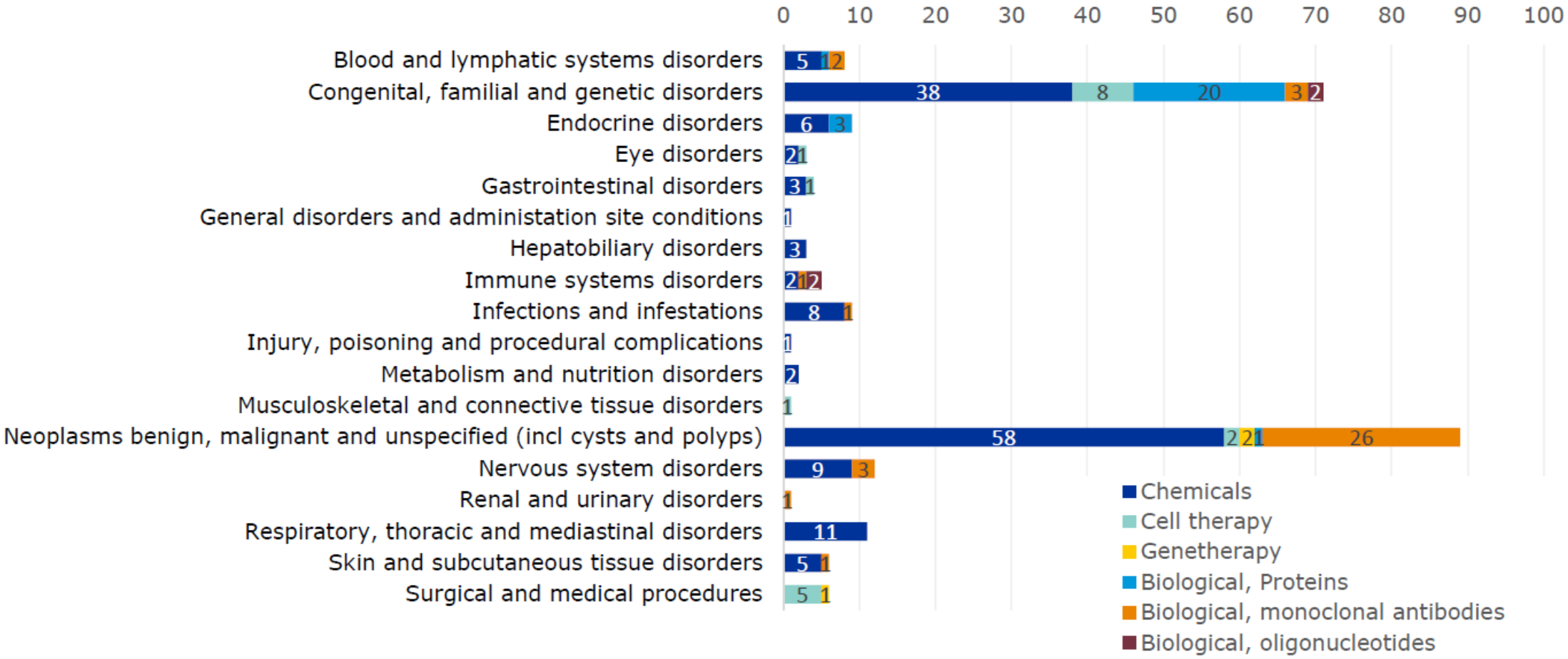
- The number of submitted applications for orphan medicines designation **(251)** stayed that same as for 2020
- Commission decisions on designation **were 170**
- **17 new marketing authorizations** for orphan medicinal products were granted by the European Commission

Annual report on the use of the special contribution for orphan medicinal products EMA/770190/2021

Committee for Orphan Medicinal Products (COMP) adopted positive opinions: 175



EMA marketing authorizations (including extensions of indication)



Orphan Medicinal Product Designation - Overview 2000-2021 © European Medicines Agency, 2022

2021 marketing authorizations

Sogroya® (somapacitan)	Novo Nordisk A/S	Growth hormone deficiency	31/03/2021
Enspryng® (satralizumab)	Roche Registration GmbH	Neuromyelitis Optica Spectrum disorders (NMOSD)	24/06/2021
Bylvay® (odevixibat)	Albireo	+6 months with progressive familial intrahepatic cholestasis (PFIC)	16/07/2021
Skysona® (elivaldogene autotemcel)	bluebird bio (Netherlands) B.V.	Under 18 years of age with early cerebral adrenoleukodystrophy (CALD)	16/07/2021
Imcivree® (setmelanotide)	Rhythm Pharmaceuticals Limited	+6 years who have pro-opiomelanocortin (POMC) deficiency or leptin receptor (LEPR) deficiency	16/07/2021
Voxzogo® (vosoritide)	BioMarin International Limited	Achondroplasia in patients aged +2 years	26/08/2021

2022 marketing authorizations

Voraxaze® (glucarpidase)	SERB SAS	Adults and children (aged 28 days and older) with delayed methotrexate elimination or at risk of methotrexate toxicity	11/01/2022
Lonapegsomatropin Ascendis Pharma® (lonapegsomatropin)	Ascendis Pharma Endocrinology Division A/S	Children who do not produce enough growth hormone (GHD)	11/01/2022
Oxbryta® (voxelotor)	Global Blood Therapeutics Netherlands B. V.	Haemolytic anaemia, and +12 years old sickle cell disease	14/02/2022
Ngenla® (somatrogon)	Pfizer Europe MA EEIG	Children and adolescents with growth hormone deficiency	14/02/2022

EURORDIS
RARE DISEASES EUROPE

AIFA

- AIFA was the first European regulatory agency to include the promotion of independent scientific research within its institutional objectives, also encouraging the development of orphan drugs through funding of non-profit clinical trials.
- AIFA orphan medicines lists on December 31, 2021: 81 drugs

AGENZIA ITALIANA DEL FARMACO

Pediatric and orphan medicines

- Improve the health of children:
  - Increase high quality, ethical research into medicines for children
  - Increase availability of authorized medicines for children
  - Increase information on medicines
- Achieve the above:
  - Without unnecessary studies in children
  - Without delaying authorization for adults

Incentives for Pediatric medicines

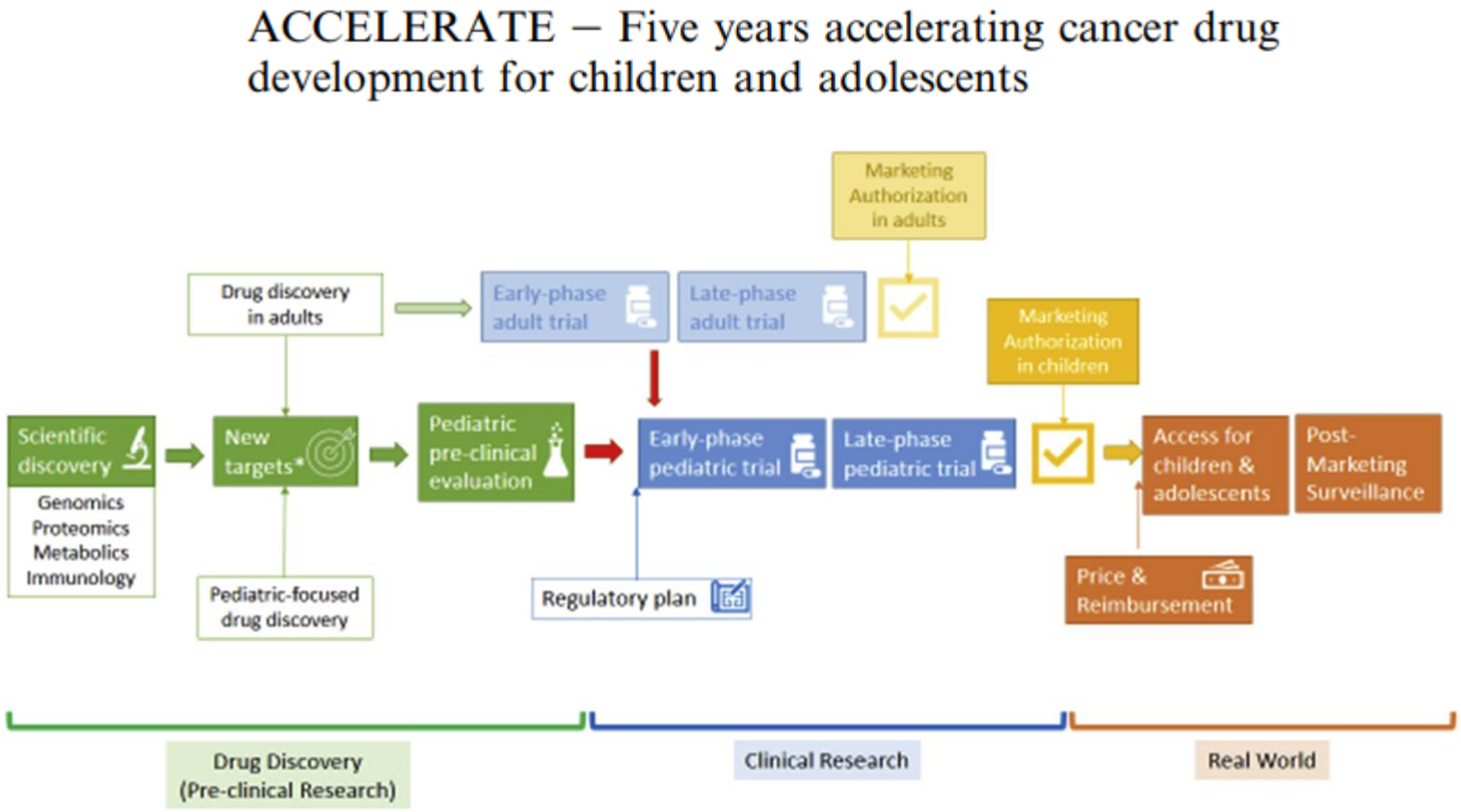
- Reward is given to completed pediatric investigation plans
  - if development is compliant with agreed PIP (compliance statement in marketing authorizations)
  - if results of studies (positive or negative) included in Summary of Product Characteristics + patient's leaflet
  - if product is authorized in all marketing stages (except for PUMA)
- Non-orphan products: 6-month extension of SPC (patent protection)
- Orphan medicinal products: + 2 additional years of market exclusivity
- Paediatric-use marketing authorization (PUMA): 8 + 2 years of data + market protection

Challenges in Pediatric Oncology Drug Development

Topic	2015	2021
Drug development	Driven by the adult condition (not by science, mechanism of action or unmet need)	**Change to a mechanism of action approach** RACE Act in US, change of Class Waiver List in Europe
Multi-stakeholder collaboration	Lack of true understanding and communication between the stakeholders (Industry, Academia, Regulators, Patient Advocates)	**Increase in multi-stakeholder interaction, especially within ACCELERATE Paediatric Strategy Forums**
Molecularly targeted therapies	Very few assessed in paediatrics and integrated into front-line therapy - BCR-ABL	Increasing inclusion in front-line therapy - ALK, BRAF, TRK inhibitors
Immunotherapy	New and effective therapies approved for adult cancers, none for children	**Blinatumomab, dinutuximab, dinutuximab beta, CAR T-Cells approved for paediatric malignancies**
Early-phase trials	In Europe early phase trials delivered by ITCC increased: from one in 2007 to 12 in 2013	In Europe, 26 open studies in ITCC One multi-arm (now 15 arms) combination phase I/II platform trial (ESMART)
Number of PIPs	The expected increase after change in EU regulation not materialised 17 PIPs in 2007–2013	124 PIPS in oncology after 2013 141 PIPS in oncology 2007–2021
Approved anti-cancer agents with at least on paediatric indication	9	**19**
PIP strategy	Multiple PIPs in very rare paediatric populations	Focused and sequential strategy for development of novel agents has been developed
Access of AYAs to adult trials	PIPs for conditions in adolescents were not possible to complete (rarity in the population) Adolescents were denied access to adult clinical trials investigating innovative drugs when suffering from the same malignancy, such as metastatic melanoma	Increasing the inclusion of adolescents in adult trials and age inclusive marketing authorization using of extrapolation
Methodology innovation	Lack of innovative trial designs	**Increasing the use of platform trial designs – ESMART, Pedal/EUPAL, GloBNHL, Paediatric MATCH**
Incentives	No incentives to develop drugs against specific paediatric targets	No incentives to develop drugs against specific paediatric targets

European Journal of Cancer. Volume 166 Pages 145-164 (May 2022)

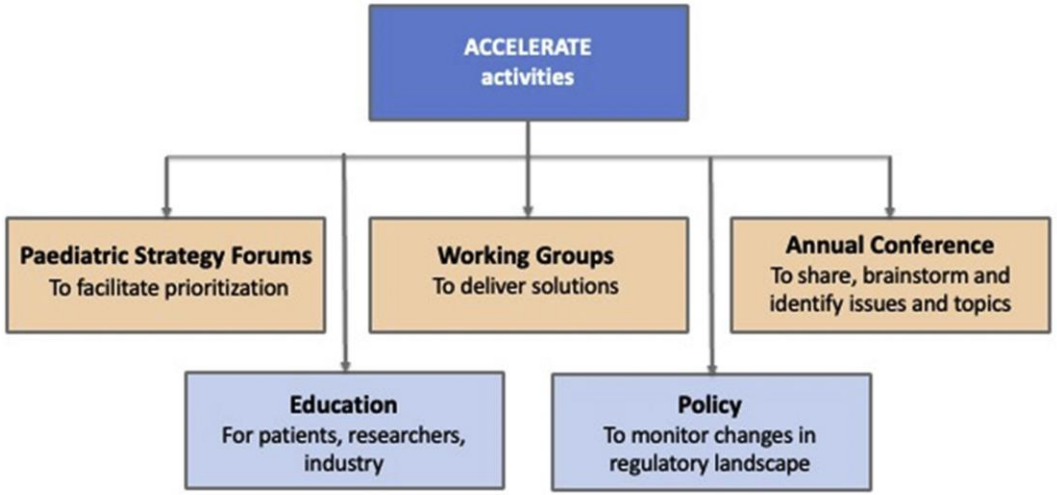
Drug development for children's malignancies



European Journal of Cancer. Volume 166 Pages 145-164 (May 2022)

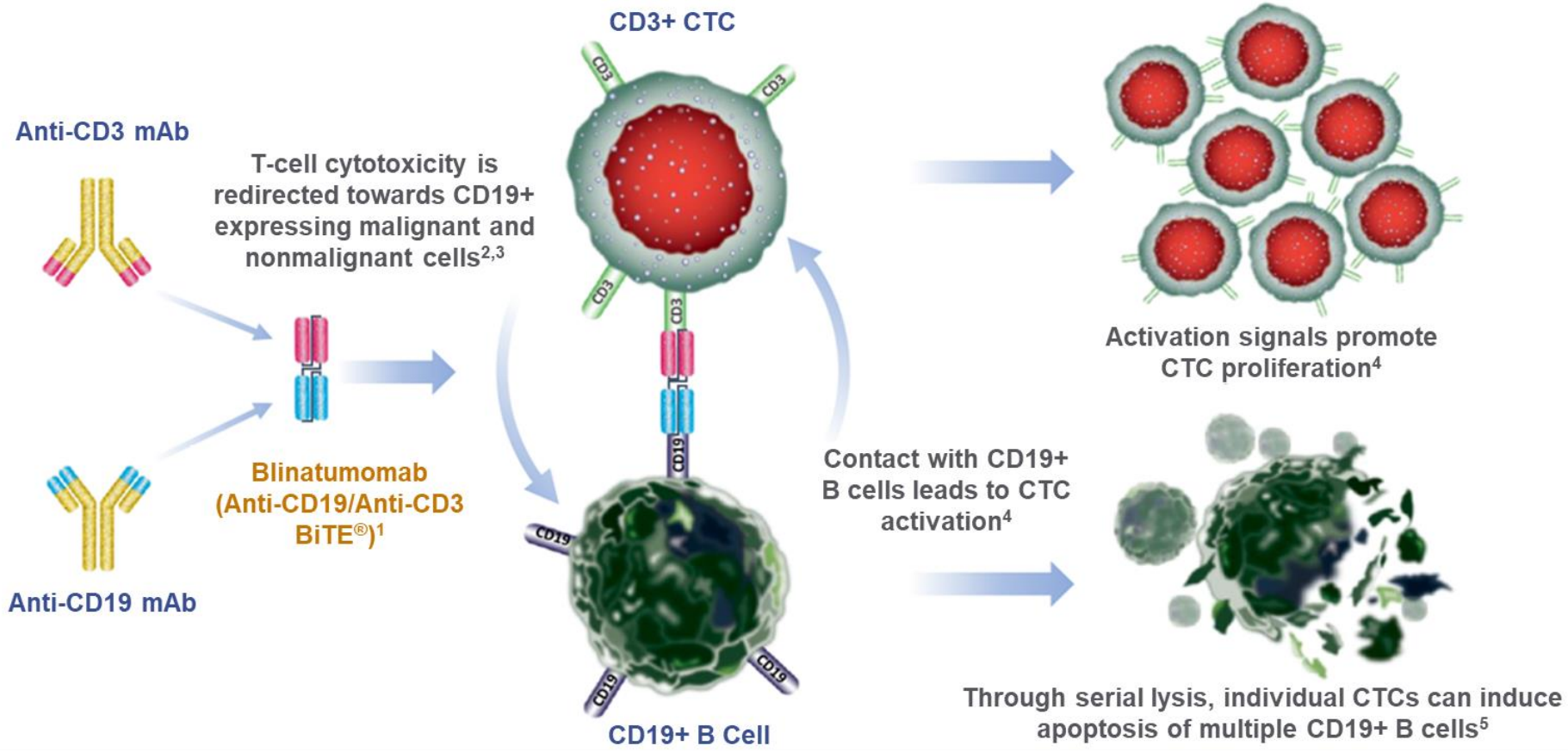
ACCELERATE

International multi-stakeholder organization created to advance the timely investigation of new anti-cancer drugs



European Journal of Cancer. Volume 166 Pages 145-164 (May 2022)

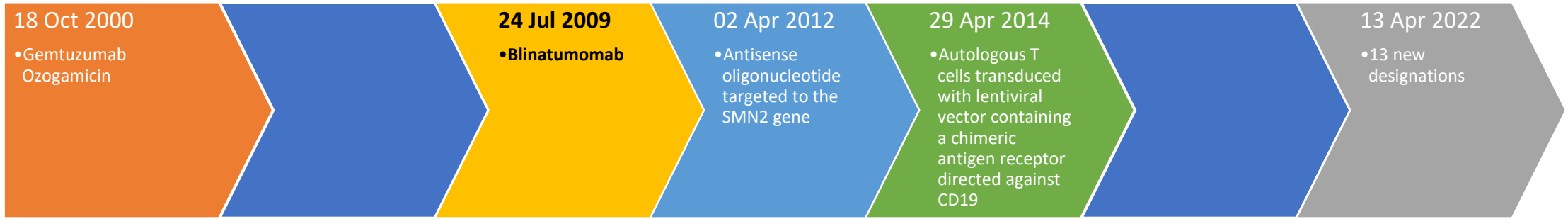
Blinatumomab (CD19 BiTE® molecule)



BiTE®, bispecific T cell engager; CD, cluster of differentiation; CTC, cytotoxic T cell; mAb, monoclonal antibody

1. Baeuerle PA, et al. Cancer Res. 2009;69:4941-4944. **2.** Bargou R, et al. Science. 2008;321:974-977. **3.**Topp MS, et al. Lancet Oncol. 2015;16:57-66. **4.** Klinger M, et al. Blood. 2012;119:6226-6233. **5.**Hoffmann P, et al. Int J Cancer. 2005;115:98-104.

Community Register of orphan medicinal products



On 24 July 2009, orphan designation (EU/3/09/650) was granted by the European Commission to Micromet AG, Germany, for blinatumomab for the treatment of acute lymphoblastic leukaemia

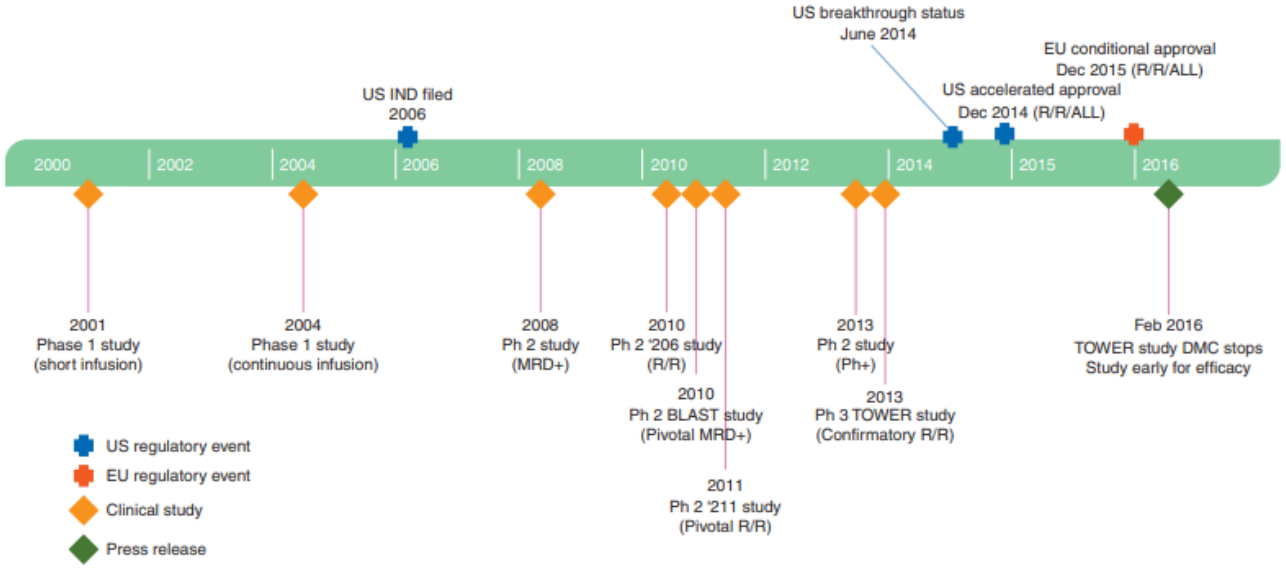
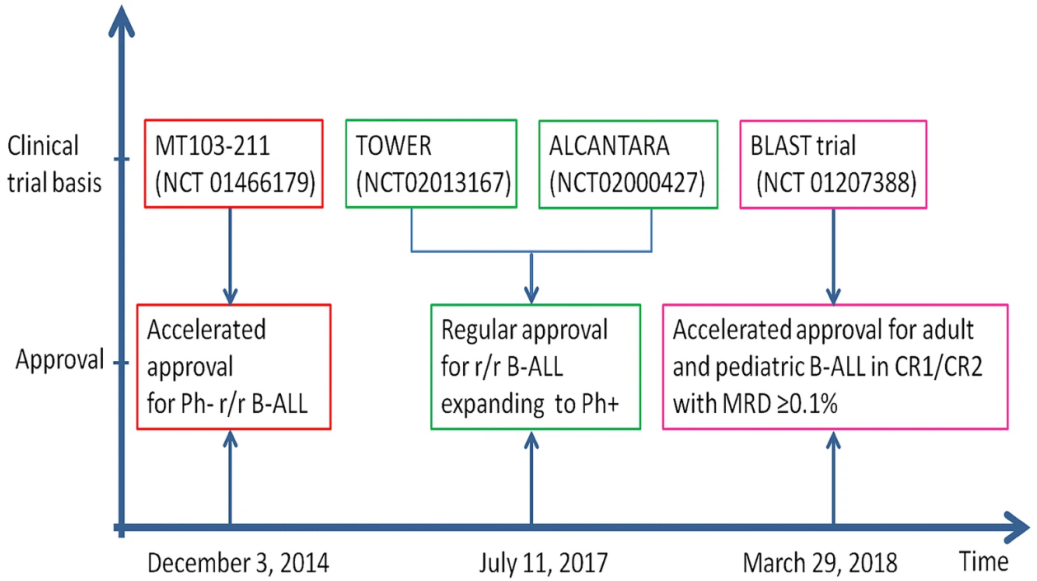


Figure 1. Blinatumomab adult acute lymphoblastic leukemia development timeline.

Annals of Oncology 2017 282009-2012DOI: (10.1093/annonc/mdx150)

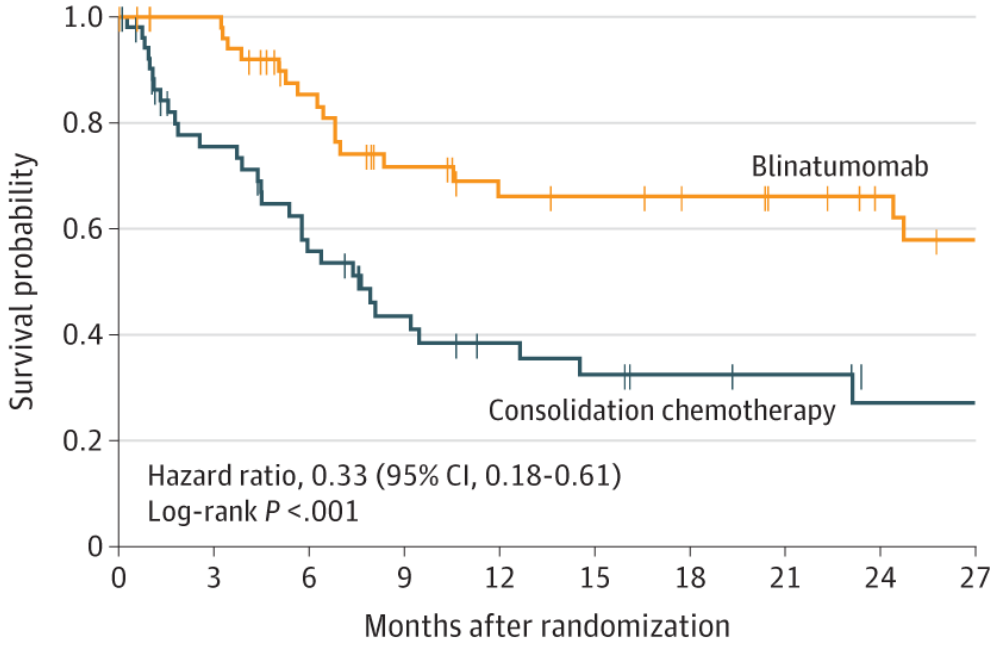
Experimental Hematology & Oncology 2019



The approval timeline of blinatumomab by US FDA. *r/r* refractory/relapsed

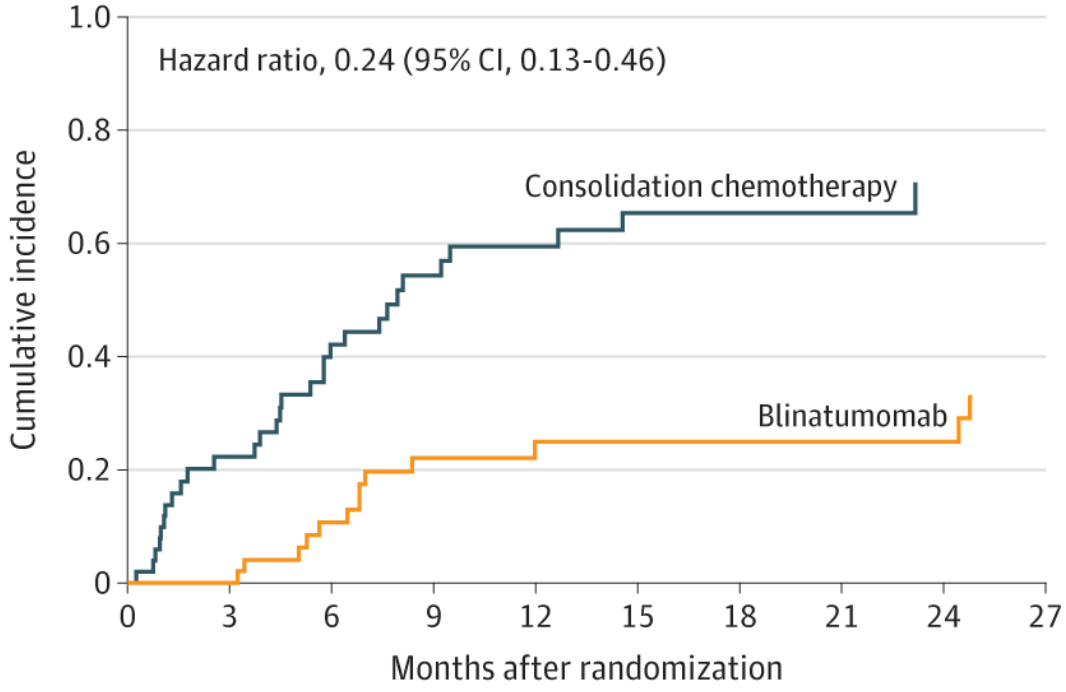
Study 20120215: survival and relapse

Event-free survival (primary endpoint)



No. at risk										
Blinatumomab	54	50	38	29	24	23	21	19	16	13
Chemotherapy	54	35	25	17	13	11	9	8	5	5

Cumulative incidence of relapse

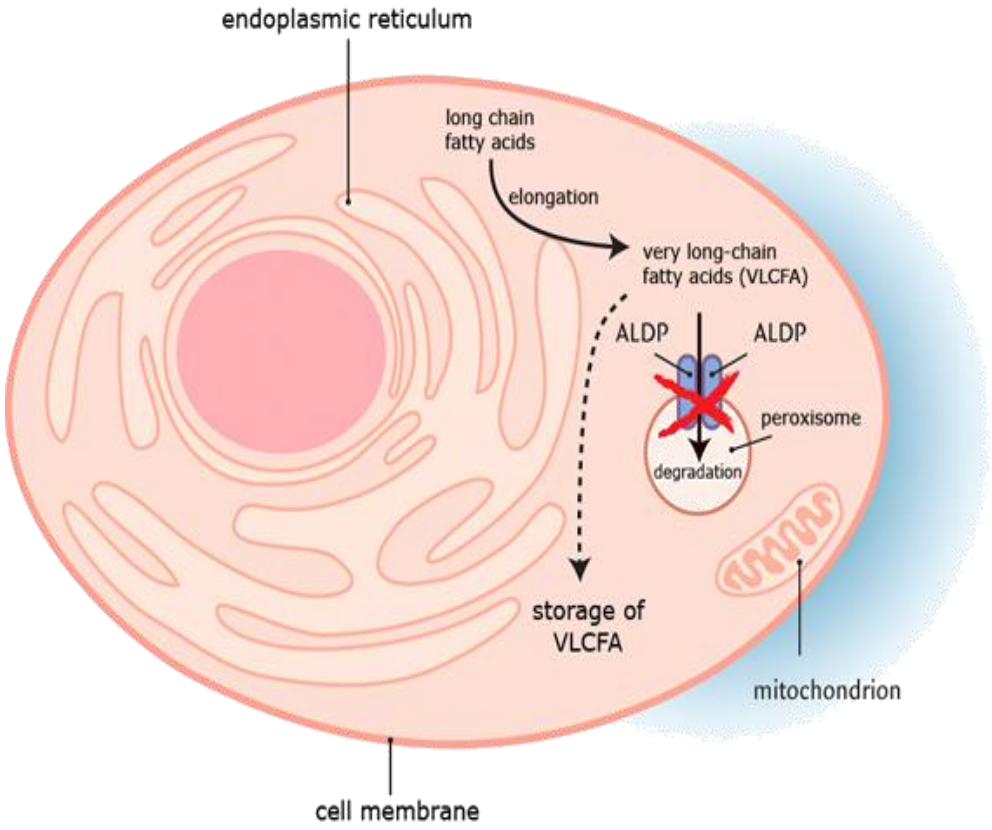


No. at risk										
Blinatumomab	54	51	39	30	25	24	22	20	17	14
Chemotherapy	54	36	26	18	14	12	10	9	6	6

Locatelli F, et al. JAMA 2021;325:843–54.

The dosing and administration of blinatumomab in this study may differ from that which is approved in your country. Please refer to your local Prescribing Information.

Adrenoleukodystrophy (ALD)



- X-linked metabolic disease
- Mutations in *ABCD1* gene lead to impaired expression of the peroxisomal ALDP needed to transport VLCFA into the peroxisome for degradation[1]
- VLCFA accumulate in adrenal and nervous system tissues, without correlation with phenotype[1]
- The estimated incidence of ALD is ~1:20,000 to 1:30,000 males[2]
- There are four forms of ALD that range in severity[2]

Asymptomatic	**Adrenal insufficiency**	**Adrenomyelo-neuropathy (AMN)**	**Cerebral ALD (CALD)**

- **~40% of boys with ALD will develop cerebral ALD (CALD)[3]**

1. Moser HW. *Brain* 1997;120:1485; 2. Wiesinger C et al. *Appl Clin Genet.* 2015;8:109–21; 3. Engelen M. et al. *Orphanet J Rare Dis* 2012;7:51. Image from http://www.x-ald.nl/biochemistry-genetics/vlcfa/

ALD, adrenoleukodystrophy; ALDP, adrenoleukodystrophy protein; VLCFA, very long chain fatty acid

Elivaldogene autotemcel (eli-cel; Lenti-D) consists of autologous CD34+ cells transduced with the Lenti-D lentiviral vector encoding the ABCD1 cDNA

HSC collection
Mobilization (G-CSF +/- plerixafor)[a] & apheresis

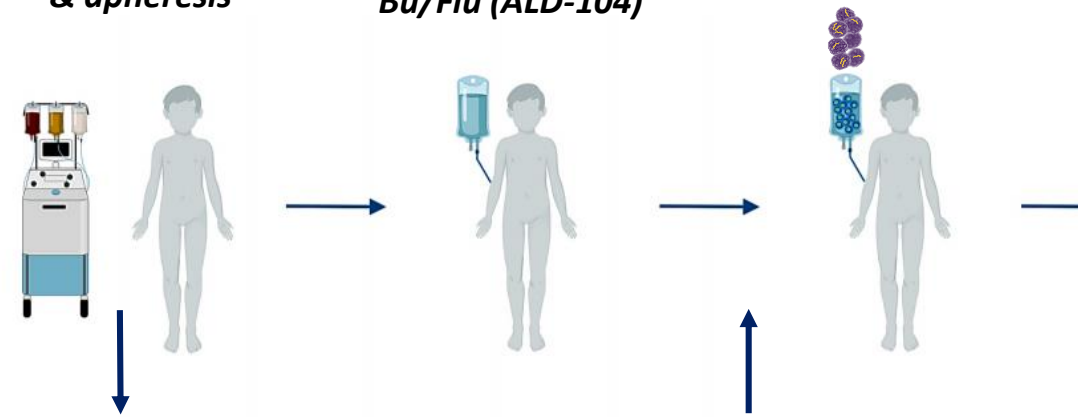
Myeloablative conditioning
Bu/Cy (ALD-102) or Bu/Flu (ALD-104)

eli-cel infusion

Transduced HSCs and progenitors engraft and differentiate into cerebral microglia expressing ALDP

2-year follow-up

Long-term follow-up study (LTF-304) 15-year total follow-up

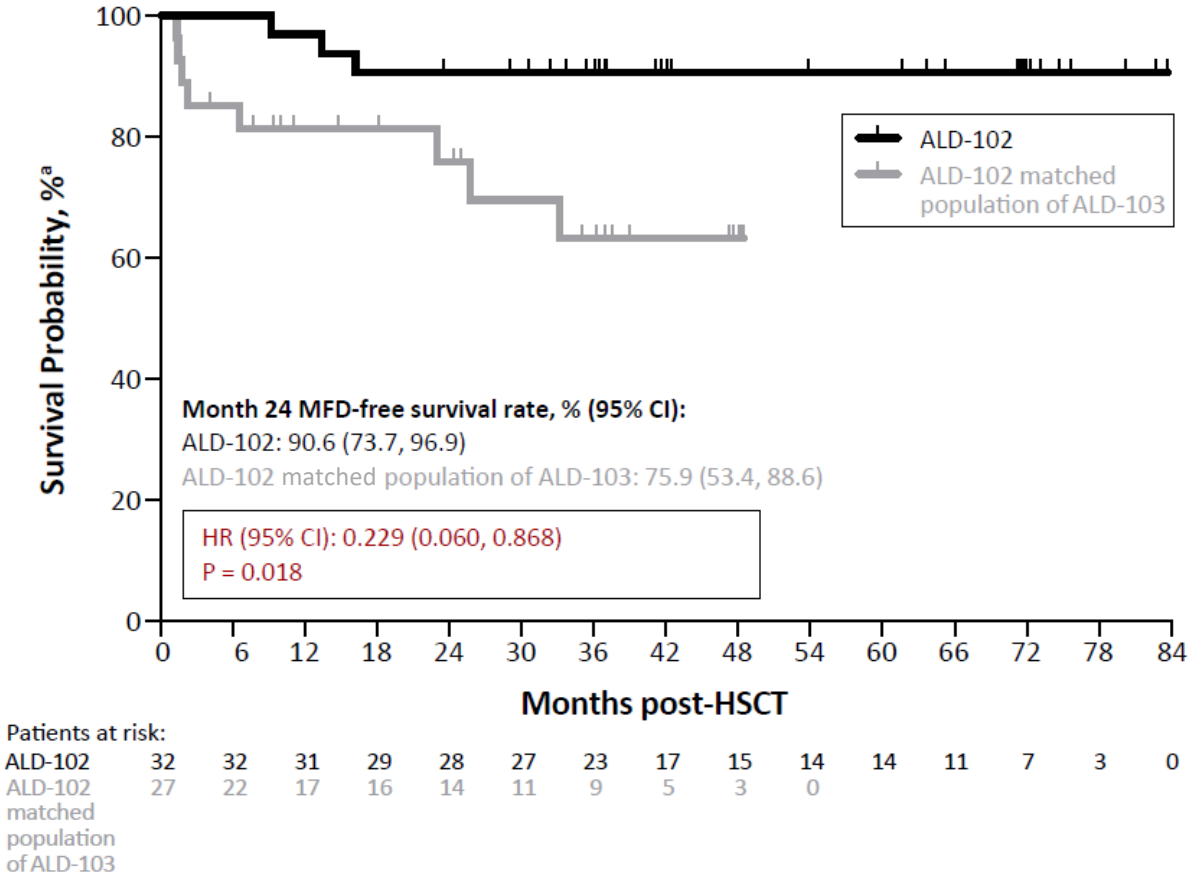


[a] Plerixafor is required in ALD-104.

ALDP, adrenoleukodystrophy protein; Bu, busulfan; Cy, cyclophosphamide; Flu, fludarabine; G-CSF, granulocyte colony-stimulating factor; HLA, human leukocyte antigen; HSC, hematopoietic stem cell.

91% of Patients in ALD-102 and 76% of Patients in ALD-103 met the Primary Efficacy Endpoint of MFD-Free Survival at Month 24

Kaplan-Meier analysis of MFD-free survival for the first transplant period over time for ALD-102 and ALD-102 matched population of ALD-103



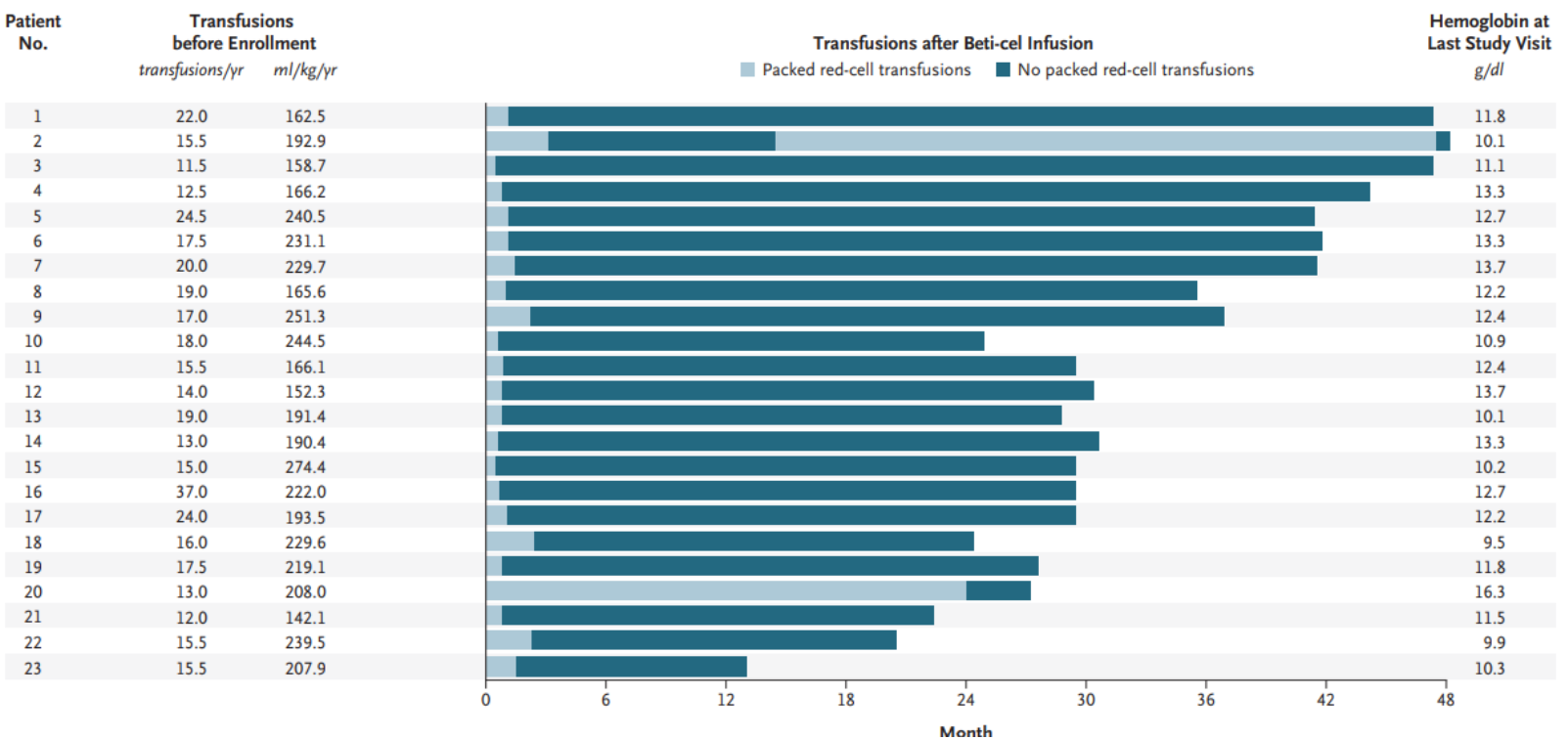
- ALD-102 – 3 patients failed the MFD-free survival endpoint: 1 patient died; 2 patients withdrawn to undergo allo-HSCT
- ALD-103 (matched cohort) – 8 patients failed the MFD-free survival endpoint: 3 patients died; 5 patients underwent a second allo-HSCT

- Due to limited follow-up duration for the ALD-104 study, the efficacy data are from ALD-102 (as of March 2021) only. Only safety data from ALD-104 are presented.
- One case of MDS was observed in a patient from ALD-102 at ~7.5 years, resulting in an event rate that is uncharacterized after that timepoint and does not feature in the Kaplan-Meier plot

Data as of: **26 March 2021 (ALD-102)**
26 March 2021 (LTF-304)

[a]The ALD-102 matched population consists of 27 patients in ALD-103 who have the same baseline disease-related characteristics that would make them eligible for eli-cel study ALD-102 (or ALD-104), i.e., NFS ≤1, Loes score ≥0.5 to ≤9, and positive GdE status (GdE[+]). Of 27 patients in the ALD-102 matched population of ALD-103, 10(37%) had matched sibling donors and 17 (63%) had alternative donors. ALD, adrenoleukodystrophy; allo-HSCT, allogeneic hematopoetic stem cell transplantation; CI, confidence interval; GdE, gadolinium enhancement; MFD, major functional disability; NFS, neurologic function score.

Patient No.	Transfusions before Enrollment (transfusions/yr)	Transfusions before Enrollment (ml/kg/yr)	Hemoglobin at Last Study Visit (g/dl)
1	22.0	162.5	11.8
2	15.5	192.9	10.1
3	11.5	158.7	11.1
4	12.5	166.2	13.3
5	24.5	240.5	12.7
6	17.5	231.1	13.3
7	20.0	229.7	13.7
8	19.0	165.6	12.2
9	17.0	251.3	12.4
10	18.0	244.5	10.9
11	15.5	166.1	12.4
12	14.0	152.3	13.7
13	19.0	191.4	10.1
14	13.0	190.4	13.3
15	15.0	274.4	10.2
16	37.0	222.0	12.7
17	24.0	193.5	12.2
18	16.0	229.6	9.5
19	17.5	219.1	11.8
20	13.0	208.0	16.3
21	12.0	142.1	11.5
22	15.5	239.5	9.9
23	15.5	207.9	10.3



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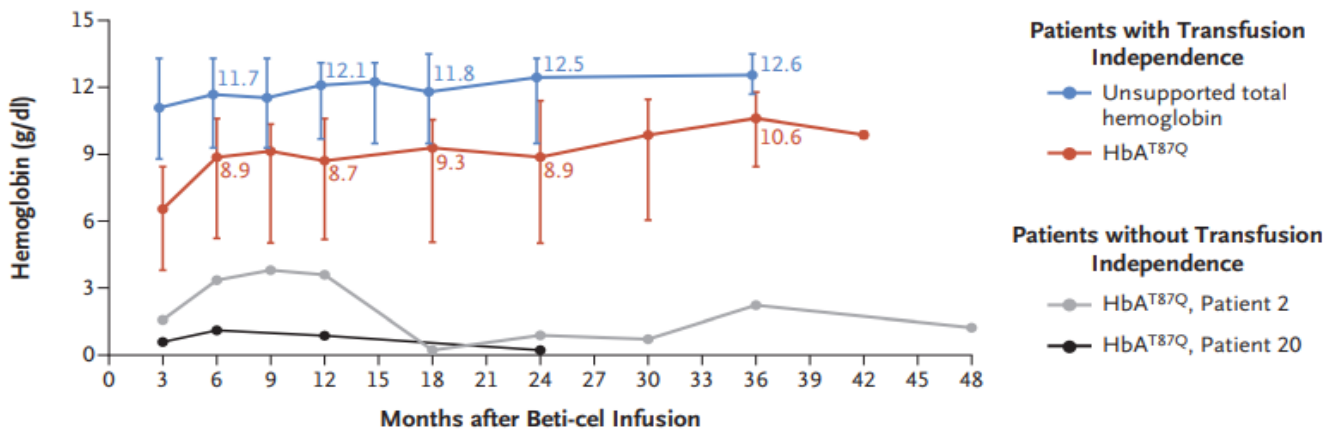

Patients with Transfusion Independence											
Unsupported total hemoglobin	12	20	20	19	18	17	NR	8	NR	NR	
HbA^T87Q	20	18	20	20	19	18	11	7	2	NR	
Patients without Transfusion Independence											
HbA^T87Q	2	2	1	2	1	2	1	1	NR	1	

Transfusion Status and Hemoglobin Levels in Patients Who Had Transfusion Independence.

F Locatelli et al. N Engl J Med 2021.

Official statement of bluebird bio concerning the decision to discontinue their operations in Europe.
The statement reflects only the Company position.

On Aug 9th, bluebird bio announced that they will be winding down their operations in Europe.

The company did not take this decision, or its impact on patients, lightly. The decision to cease operations in Europe came after two years of discussions with European authorities in which they did not agree to a reimbursement level greater than what it costs bluebird to provide its therapies to patients. Bluebird is a small company without revenue or profit and could not afford to continue in Europe.

The company is actively exploring ways to continue access for patients, including seeking a partner to assume the products in Europe.

Future directions

Increase the number of potentially beneficial innovative drugs being evaluated in children in a timely fashion to address unmet needs of patients
Improve access for children and adolescents to innovative new drugs
Improve the selection and prioritization of innovative drugs being evaluated for children and adolescents cancer
ACCELERATE evaluation and introduction of innovative drugs into front-line therapy
Increasing early global HTA and payers' involvement, engaging all stakeholders, aligning processes and specific pathways to assess new therapies
Document the long-term adverse effects of innovative anti-cancer drugs through a harmonized and sustainable data registry to collect long-term side-effects of new therapies
Strengthen and reinforce true multi-stakeholder collaboration and further define the role of patient advocates in drug development
Through a well-defined educational approach, ensure these strategies and lessons learnt are understood and appreciated by all pediatricians involved in clinical trial design