Therapeutic benefit of orphan drugs in oncology: Evidence at the point of European marketing authorisation

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Background

- Rare diseases are inherited, life-threatening, or chronically debilitating diseases that affect less than 5 in 10,000 persons[1].
- In oncology, despite the low number of patients per indication, rare cancers represent 22% of the total burden of cancer within in the EU[2].
- Although there is a need for new and effective drugs to treat rare cancers, their small patient populations often make recruitment and retainment difficult.
- The European Medicines Agency (EMA) grants new medicines one of two types of approval: full approval or conditional marketing authorisation (CMA).
- CMA allows a more rapid patient access to new medicines[3] and is granted if all the following requirements are met: a positive benefit-risk balance, a likelihood that the applicant will be able to provide additional comprehensive data from ongoing or new studies, that unmet medical needs will be fulfilled, and that the benefit to public health of the product's immediate availability outweighs the risks due to need for further data[4].

Objective

- We analysed evidence on the therapeutic benefit of orphan oncology medicines approved in the past five years, at the point of marketing authorisation by the EMA.

Methods

- Orphan oncology medicines authorised between 2014–2018 were identified from the EMA website and information on marketing authorisation, CMA award and obligations, and post-authorisation updates were extracted from the European public assessment reports.
- Data on trial design, overall survival (OS), progression-free survival (PFS), event-free survival (EFS), overall response rate (ORR), complete response rate (CRR), serious adverse events (SAEs) and health-related quality of life (HRQoL) were extracted from reports.
- Trial design and primary endpoints were assessed and for those indications with comparative data, therapeutic benefit was evaluated. For the purpose of this review, a difference in SAEs between treatment arms was defined as a variance of ≥5%.

Results

Overview of products

- In the last five years, 23 products were approved in a total of 38 rare oncology indications. Nine drugs were granted CMA and 14 granted full approval (Table 1).
- The mean time between the initial indication approval and additional indication approvals was 654 days (range 224 to 1,155).
- Of those granted CMA, there was a requirement for future submission of additional clinical and safety data from ongoing phase 2 and 3 trials.
- To date, three drugs have fulfilled their CMA obligations and were granted a full approval marketing authorisation by the EMA (blinatumomab, daratumumab, ventoclax), one had their marketing authorisation revoked (olaratumab) and the remainder had their CMA renewed.

Study design of main clinical trials

- Evidence was based on RCTs in 47% and 67% of CMAs and full approvals, respectively (Figure 1A). Non-RCT trials included single-arm studies (with and without a historical comparison), dose-comparison studies, combination studies, and exposure to other drugs. In addition, were three potentially curative advanced therapies for rare blood cancers, which reported comparisons with historical controls.
- Two-thirds of full approval indications (67%) included a phase 3 RCT in their submission, compared to under a third (26%) of CMA indications (Figure 1B). One indication included a retrospective data collection from a compassionate use programme.
- The EMA noted the lack of RCT evidence. However, it was acknowledged that for some indications RCTs were not feasible due to a number of factors including: a lack of an appropriate comparator; ethical considerations preventing the use of placebo; or too few patients available in order to appropriately power a trial.

Primary endpoints of clinical trials

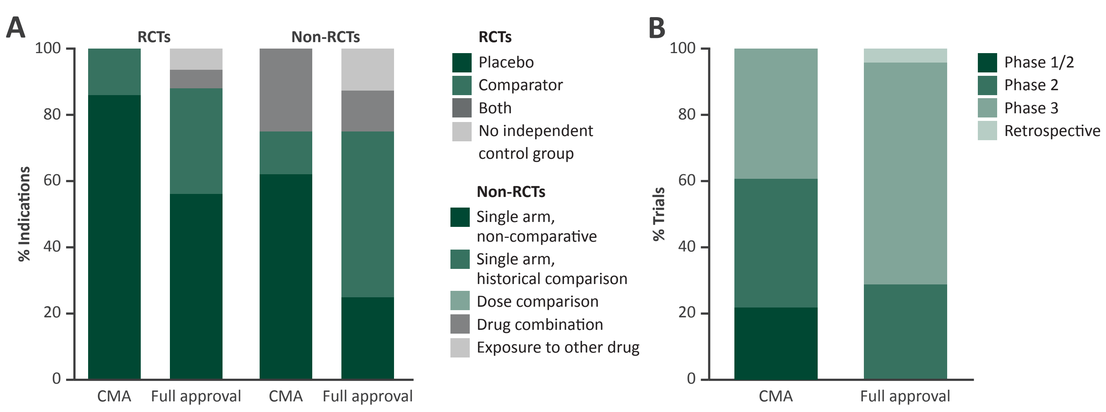
- Primary endpoints of the 38 indications included PFS, OS, EFS, ORR, and CRR.
- One indication included an RCT where both arms received the treatment with the drug of interest; this RCT was excluded from endpoint analysis for not having an independent control group.

Table 1: Rare oncology drugs receiving CMA (A) and full approval (B).

International nonproprietary name (brand name)	Marketing authorisation holder	Therapeutic area	Number of indications
(A) Conditional approval			
Avelumab (Bavencio)	Merck Europe B.V.	Neuroendocrine tumours	1
Blinatumomab (Blincyto)	Amgen Europe B.V.	Precursor cell lymphoblastic leukemia-lymphoma	3
Cabozantinib (Cometriq)	Ipsen Pharma	Thyroid neoplasms	1
Daratumumab (Darzalex)	Janssen-Cilag International N.V.	Multiple myeloma	3
Ixazomib (Ninlaro)	Takeda Pharma A/S	Multiple myeloma	1
Olaratumab (Lartruvo)	Eli Lilly Nederland B.V.	Soft tissue sarcoma	1
Ventoclax (Venclyxto)*	AbbVie Deutschland GmbH Co. KG	Leukaemia, lymphocytic, chronic, B-cell	2
Allogeneic T-cells (Zalmoxis)	MolMed SpA	Antineoplastic agents	1
Rucaparib (Rubraca)*	Clovis Oncology UK Limited	Ovarian neoplasms	2
(B) Full approval			
Carfilzomib (Kyprolis)	Amgen Europe B.V.	Multiple myeloma	2
Dinutuximab beta (Qarziba)	EUSA Pharma (Netherlands) B.V.	Neuroblastoma	1
Gemtuzumab ozogamicin (Mylotarg)	Pfizer Europe MA EEIG	Leukaemia, myeloid, acute	1
Ibrutinib (Imbruvica)	Janssen-Cilag International NV	Lymphoma, mantle-cell	5
Inotuzumab ozogamicin (Besponsa)	Pfizer Europe MA EEIG	Precursor cell lymphoblastic leukaemia-lymphoma	1
Lutetium (177Lu) oxodotreotide (Lutathera)	Advanced Accelerator Applications	Neuroendocrine tumours	1
Midostaurin (Rydapt)	Novartis Europharm Ltd	Leukaemia,myeloid, acute	2
Niraparib (Zejula)	TESARO Bio Netherlands B.V.	Fallopian tube neoplasms	1
Obinutuzumab (Gazyvaro)	Roche Registration GmbH	Leukaemia, lymphocytic, chronic, B-cell	3
Panobinostat (Farydak)	Novartis Europharm Limited	Multiple myeloma	1
Tisagenlecleucel (Kymriah)	Novartis Europharm Limited	Precursor B-cell lymphoblastic leaukemia-lymphoma	2
Axicabtagene ciloleucel (Yescarta)	Kite Pharma EU B.V.	Antineoplastic agents	1
Daunorubicin/cytarabine (Vyxeos)	Jazz Pharmaceuticals Ireland Limited	Leukaemia, myeloid, acute	1
Irinotecan hydrochloride trihydrate (Onivyde)	Les Laboratoires Servier	Pancreatic neoplasms	1

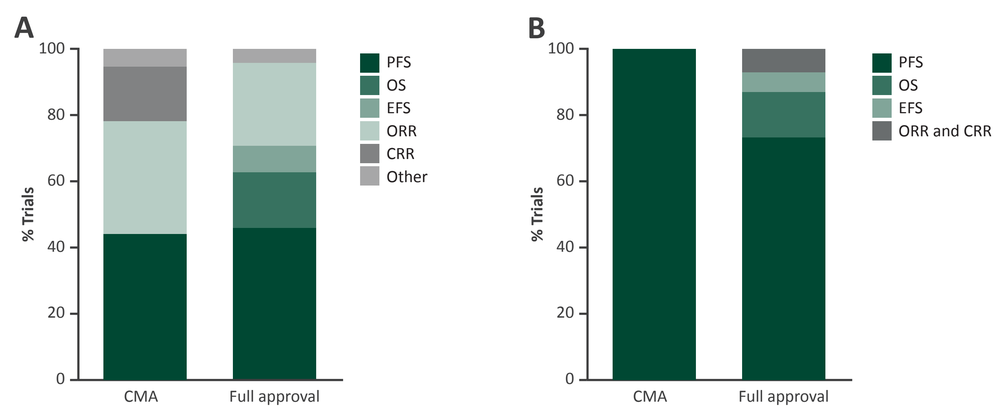
*Withdrawn from the register of orphan medicinal products

Figure 1: Clinical trial design (A) and phases (B) of CMA and full approval indications.



- PFS was the primary outcome reported in 44% and 46% of clinical trials for CMA and full approval indications, respectively (Figure 2A), and 100% and 73% of trials when considering only RCTs (Figure 2B).

Figure 2: Primary endpoints of (A) all trials and (B) RCT-only trials.



Progression-free survival

- PFS was reported as a primary or secondary endpoint in RCTs for 7 (100%) CMA and 13 (87%) full approval indications (Figure 3).
- A significant improvement in PFS in favour of the intervention was observed for 71% and 100% of these CMA and full approval indications, respectively (Figure 3).
- Median PFS gain ranged from 2.5 to 7.2 months for CMA indications and from 1.6 to 19.9 months for full approval indications.

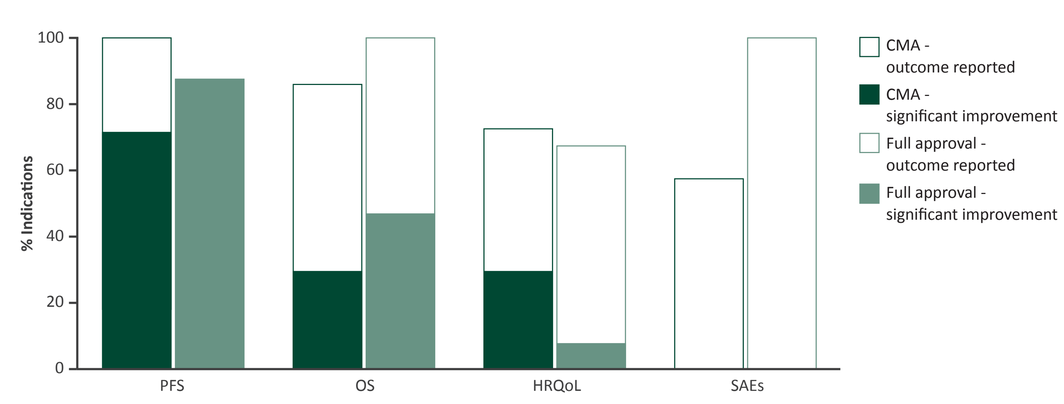
Overall survival

- OS was reported as a primary or secondary endpoint in RCTs for seven (100%) CMA and 15 (100%) full approval indications (Figure 3).
- A significant improvement in OS in favour of the intervention was observed for 33% and 47% of these CMA and full approval indications, respectively (Figure 3).
- Median OS gain ranged from 5.7 to 11.8 months for CMA indications and from 1.0 to 49.2 months for full approval indications.

Adverse events and health-related quality of life

- Over three-quarters of indications (77%) had more SAEs in the intervention arm than the comparator (67% for CMA, 87% for full approval). No indication had fewer SAEs in the intervention arm than the comparator.
- Data on HRQoL were available in 64% of RCTs, of which 18% demonstrated significant improvement with the intervention (Figure 3).

Figure 3: Summary of therapeutic benefit at the point of marketing authorisation for CMA and full approval indications reporting RCTs.



Conclusions

- In rare oncology, particularly in personalised treatments, demonstration of therapeutic benefit through RCTs is not always feasible.
- Most drugs evaluated in randomised settings demonstrated improvements in PFS and increases in SAEs. Evidence of OS gain was available in less than half of indications.
- Further efforts aimed at adaptive approaches to evidence generation are warranted, to ensure timely patient access and to stimulate innovation in medical practice.

References

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