Fast to market *vs* robustness of data

Conditional marketing authorisation (CMA)

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Disclaimer

- My personal opinions – not those of NoMA or EMA

- I was a regulator for 10 years and then took a 10 year break
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- Back part-time at NoMA/CHMP since 2021

Marketing authorisations (MA) in the EU

Standard MA

- one renewal after 5y

Conditional MA

- BR positive, but data not comprehensive at the time of MA
- subject to annual renewal

MA under exceptional circumstances

- comprehensive data not considered possible

Conditional marketing authorisation (CMA)

Scope

- for seriously debilitating or life-threatening diseases;
- or to be used in emergency situations;
- or orphan medicinal products.

Criteria

- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.

Post approval commitments/Specific obligations (SOB)

- Once a CMA has been granted, the MAH must fulfil **specific obligations** within defined timelines.
- SOB: Completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive.
- CMA can be converted into a **standard marketing authorisation** once the MAH fulfils the obligations imposed and the complete data confirm that the medicine's benefits continue to outweigh its risks.
- If new data show that the medicine’s benefits no longer outweigh its risks, or if the MAH does not comply with imposed obligations, the MA can be suspended or revoked.

CMA

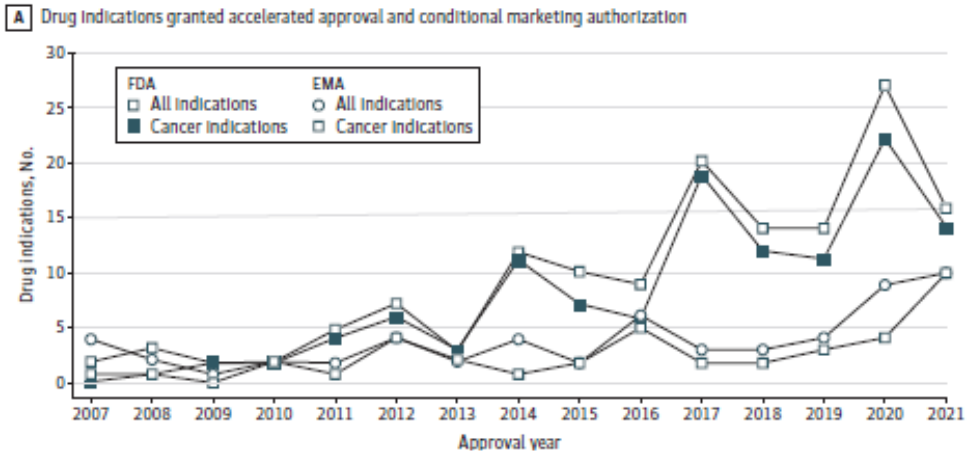
Pragmatic tool for fast approval

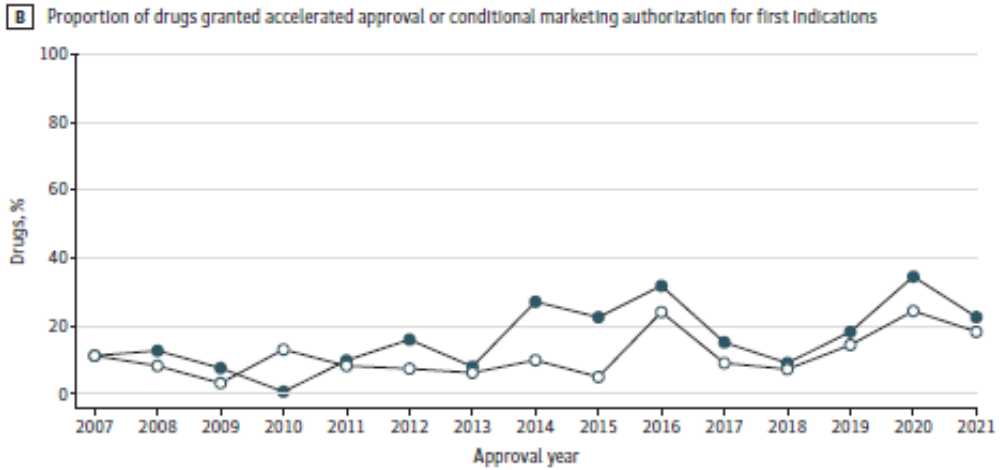
- Comprehensive data to come
  - Additional (comparative) trial(s) – most often RCT(s)
  - Preferably ongoing
  - Relevant population
    - Cancer: often in an earlier line of treatment

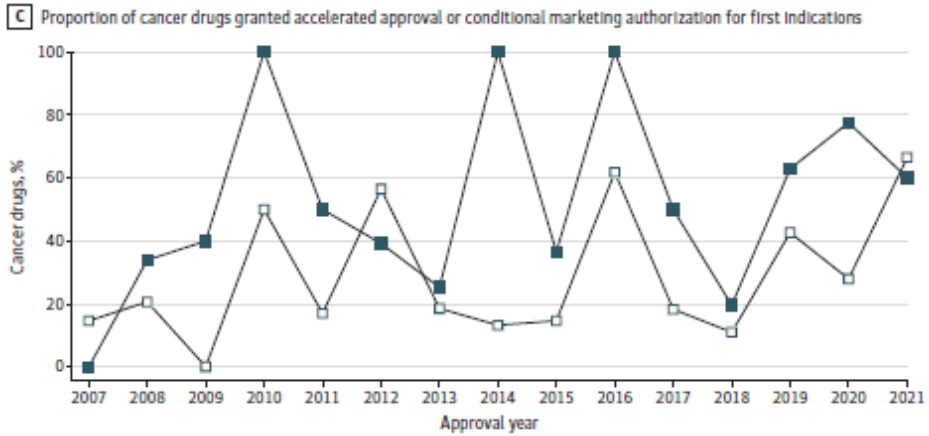
- Important
  - The intention is not to lower the bar for approval
  - BR must be considered positive (even if data are limited)

- Most products are converted to full MA once SOBs are fulfilled
  - May take time
  - What if efficacy is not confirmed when SOB studies are finalised? Non-renewal?

Trends in CMA 2007-2021







Vokinger et al (2022) JAMA Health Forum

Outcome of initial evaluation – cancer (2023)

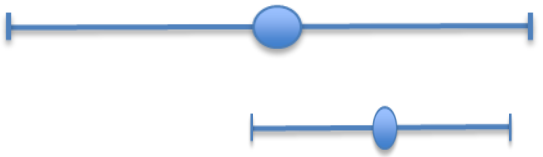
PRODUCT NAME	New active substance	PRIME	Orphan	Accelerated assessment	Conditional approval	Exceptional circumstances
Columvi	●		●		●	
Elrexfio	●	●				
Finlee			●			
Inaqovi	●					
Jaypirca	●				●	
Krazati	●				●	
Lytgobi	●				●	
Omjjara	●		●			
Orserdu	●					
Pedmarqsi						
Spexotras			●			
Talvey	●	●	●	●	●	
Tepkinly	●		●		●	
Tevimbra	●		●			
Tibsovo	●		●			
Vanflyta	●					

6 of 13 NAS CMA

Cancer indications

CMA often based on ORR from single arm trial (SAT)

- Documentation of **activity** – ORR threshold?
- Patient numbers often low – uncertainty



- External comparator – challenges/bias

SOB

Clinical efficacy endpoints from RCT

- Overall survival (OS)
- Progression free survival (PFS)

RWE?

Examples of challenging procedures

- **Blenrep (belantamab mafodotin)**
  - in multiple myeloma (≥4 prior therapies)
- CMA August 2020 – no comparative data
  - ORR=0.32 (95%CI 22, 44)
  - Median duration of response 11 months
- SOB: RCT with pomalidomide+dexamethasone as comparator (DREAMM-3)
  - PFS HR=1.03 (95%CI 0.72, 1.47)
  - OS HR=1.14 (95%CI 0.77, 1.68)
- Safety: Keratopathy very common (already known)
- CMA not renewed (2023)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 March 2024
EMA/108999/2024
EMEA/H/C/004935

Public statement

Blenrep (belantamab mafodotin)
Non-renewal of the conditional marketing authorisation in the European Union

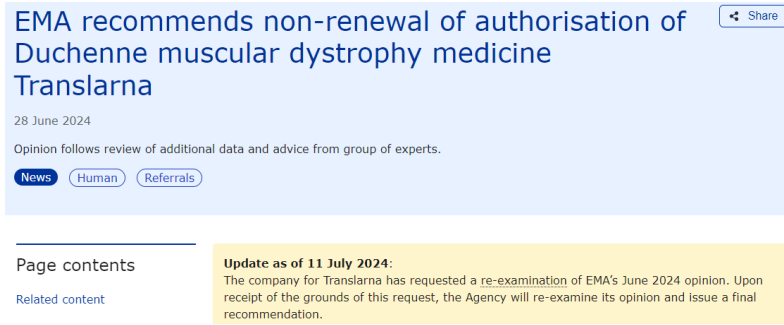
On 23 February 2024, the European Commission issued a decision to not renew the conditional marketing authorisation for Blenrep (belantamab mafodotin) in the European Union (EU). The marketing authorisation holder for the medicine was GlaxoSmithKline (Ireland) Limited.

Examples of challenging procedures

- **Ocaliva (obeticholic acid)** - primary biliary cholangitis
- Orphan designation 2010
- CMA 2016
  - one 3 arm RCT obeticholic acid *vs* placebo, n=217
  - response based on biomarkers /surrogate endpoints
    - proportions 47% Ocaliva 10 mg and 10% placebo
- SOB
  - double blind, placebo controlled RCT with clinical endpoints
  - main study composite endpoint (death, liver transplant or liver failure) – no sign of efficacy; HR close to 1
- CHMP recommended revocation (June 2024)

Examples of challenging procedures

- **Translarna (ataluren)** – Duchenne muscular dystrophy
- CMA 2014
- 2016: SOB/comparative study assessed - still uncertainties
  New RCT requested (in patients with progressive decline in walking ability)
- Result: No stat.sign. difference between Translarna and placebo on 6 min walk test
- Analysis of patient registry data comparing health outcomes with Translarna with those of patients who had not received Translarna seem to show benefit
  Methodological weaknesses
- Two RCTs considered more robust than registry data – no beneficial effect demonstrated
- MAH has asked for re-examination of the negative CHMP opinion


EMA recommends non-renewal of authorisation of Duchenne muscular dystrophy medicine Translarna

Share

28 June 2024

Opinion follows review of additional data and advice from group of experts.

News Human Referrals

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Update as of 11 July 2024:
The company for Translarna has requested a re-examination of EMA's June 2024 opinion. Upon receipt of the grounds of this request, the Agency will re-examine its opinion and issue a final recommendation.

Therapeutic value (CMA)

- 2007-2021 n=58 first indications EU (40 cancer)
- Therapeutic value rating n=56
  - based on health technology assessment in Germany, France, Canada
- 21 of 56 (38%) had high therapeutic value
- 12 of 29 (31%) of cancer drugs

Vokinger et al (2022) JAMA Health Forum

Is fast access always good?

- for patients
- for society