ASTERIX End Symposium (Zaandam. September 18-19 2017) *"New Methodology for Clinical Trials in Rare Diseases"*

Perspective on the minimum evidence to make regulatory decisions

(Session 7: *"How to justify different evidentiary standards for decision making in rare diseases?"*)

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Disclaimer

(In order to be open with the points of view)

The views expressed are personal of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the AEMPS, the EMA or any of their committees or working parties.

Regulatory decision, what for?

- **Conducting clinical trials?**
  - 1st in human?
  - In healthy volunteers?
  - In children?
  - "Pivotal"?
- **Price setting?**
- **Reimbursing by public institutions?**
- **Registration (approval) by Medicines Agencies?**
- **....**

Regulatory decision, what for?

Let us concentrate in registration understood as "approval" (registration) by medicines agencies, without taking into account socio economic arguments, and considering it as an all or none procedure (a situation increasingly under debate)

And where decisions are not always universally agreed:

Wonkblog

FDA committee votes against approval of controversial muscular dystrophy drug

By Carolyn Y. Johnson April 25, 2016

BIOTECH

Did the FDA set 'a dangerous precedent' with its latest drug approval?

By DAMIAN GARDE @damiangarde / SEPTEMBER 19, 2016

- While the drug is now accessible to patients, an additional clinical trial is still required by the FDA to demonstrate clinical benefit.
- Eteplirsen is still being evaluated by the EMA

REGULATION OF MEDICINES IS COMPLEX

In general, **medicines** are therapeutic, preventive or diagnostic tools of chemical, biological "recombinant" or "cell" type and of industrial origin, available on the market (with a price often artificially set) after having being authorised ("registered") by ad hoc official "agencies" **generally at the initiative of the industry** (sometimes incentivized/"rewarded") and on the basis of data (evidence) submitted and usually generated by it and not always easily available. They are normally prescribed and dispensed before being used by the **patient** ("consumer") who generally does not pay directly for them. In the EU, public institutions are the main reimbursing bodies

Many parts are involved (interests/ aims not always coincident)

For orphan drugs there is a "winner takes all" approach

There is room for many rules related to medicines …

"Regulation" for registration (some statements)

Medicines "Regulation" aims at protecting and promoting public health

Dangerous or ineffective (for their intended use) medicines should not be allowed into the market.

The needed evidence for useful drugs should be timely generated

Regulatory institutions are likely to perform their task better if they interact with those affected/ involved: society, health professionals, investigators, drug developers, patients…

But, in any case, the process should be **accountable and generally transparent**

And **should consider all the relevant available evidence** not just single pieces of it (however "pivotal" or "primary" they are declared).

Would the following drugs be approved?

- An antibacterial when six patients with resistant sepsis treated with it in an "exploratory" trial survive while other six, untreated, die?

  If, at least, the assessment is not accelerated there would be a lot of explaining to do

- An anticancer product for advanced unresponsive sarcoma that is given to 30 patients with 3 months life expectancy and after 3 years all of them are still alive?

  Again, if at least, the assessment is not accelerated there would be a lot of explaining to do

- A drug for heart failure showing a small favorable difference in a composite clinical endpoint in certain subgroups of patients, mainly due to the less "hard" component of the endpoint and after readjusting the initial definition of the subgroups?

  If it is approved, perhaps – some would say- for an "artificial" indication, a lot of explaining would be necessary

How much evidence is necessary for registration?

(letting aside "routine" situations for which specific detailed guidelines may directly apply)

Well, of course, it depends:

- **The urgency**: existence or anticipation of an unmet medical need (that can **plausibly** be met by the product)
- The likely/ possible **consequences of getting it wrong** (Could the product do more harm than good?)
- Whether there are solid **data that could reasonably be extrapolated** (e.g. from other age groups, other stages of the disease, other similar diseases, drugs with similar mechanism, ...)
  But **how much direct evidence is necessary for "validation"?**
- How much clinical evidence is it **feasible** to generate **on time**
- How much the **complementary evidence** (animal data, data on target engagement, proof of concept, dose- finding ....) can help
- .....

An element of judgement, requiring a case by case approach, is present in all the above points

Surrogate variables: The FDA and/or the CHMP have approved drugs that…:

- Lower VIH viral load without evidence of clinical improvement or on survival
- ……
- lower cholesterol levels without evidence on survival or coronary disease.
- Lower blood pressure without evidence on survival on CHF stroke, survival...
- Lower glycemia and glycosilated haemoglobin without evidence on complications of diabetes

Surrogate variables:
…But they have also approved…:

- Drugs for osteoporosis based on bone density without evidence on fracture reduction
- …….
- Antiarrythmic drugs that decrease ventricular extrasystoles without evidence on post-infarct mortality (before the CAST study).
- Positive inotropic drugs that increase cardiac output and improve CHF symptoms without evidence on survival (before study PROMISE)
- Drugs that lower body weight but increase blood pressure without evidence on cardiovascular outcomes (before sibutramine was suspended after 10 years on the market)

BIOMARKERS
(e.g. IMAGING)

The problem with biomarkers is when we are not sure that they mark what we think they are marking. And, who declares them valid? What for?

Clinical or economic endpoint?

- Days of hospitalisation
- Emergency room visits
- Healthcare resource utilisation

Could these be studied in a "regulatory" trial?

(Based on H-G Eichler DIA, March 2011)

On-going discussion on whether it could be of use combining the two approaches

And now the US FDA have approved their first gene therapy ...

Chimeric Antigen Receptor T Cells [Against CD19] for Sustained Remissions in Leukemia

Maude et al. N Engl J Med 2014;371:1507-17. Updated February 18, 2016

A total of **30 children and adults** received CTL019. **Complete remission was achieved in 27 patients (90%)**, including 2 patients with blinatumomab-refractory disease and 15 who had undergone stem-cell transplantation.

Is this due to treatment?

Well … at least it is very plausible

CTL019 cells proliferated in vivo and were detectable in the blood, bone marrow, and cerebrospinal fluid **of patients who had a response.**

Sustained remission was achieved with a 6-month event-free survival rate of 67% (95% confidence interval [CI], 51 to 88) and an overall survival rate of 78% (95% CI, 65 to 95). At 6 months, the probability that a patient would have persistence of CTL019 was 68% (95% CI, 50 to 92) and the probability that a patient would have relapse-free B-cell aplasia was 73% (95% CI, 57 to 94).

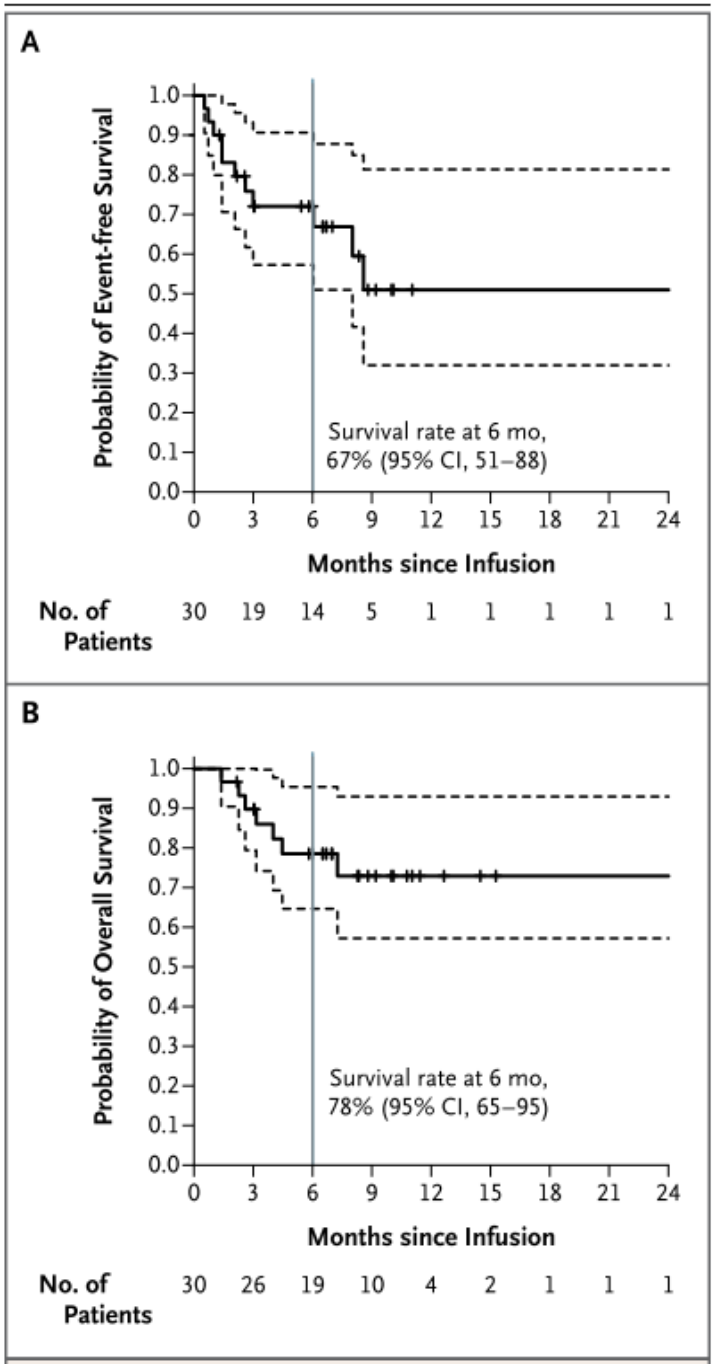


Figure 1. Probability of Event-free and Overall Survival at 6 Months.

Anti CD19 CAR T cells *historically* approved by the FDA shortly after the NEJM publication (1)

"The U.S. Food and Drug Administration issued a historic [Their own words] action today [**30 August 2017**] making the first gene therapy available in the United States …"

By **approving the autologous anti CD19 CAR T cells Kymriah (tisagenlecleucel)** for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Stating that **safety and efficacy of Kymriah were demonstrated in one multicenter clinical trial of 63 pediatric and young adult patients** [larger than in the earlier NEJM paper] with relapsed or refractory B-cell precursor ALL. The overall remission rate within three months of treatment was 83 percent.

Anti CD19 CAR T cells *historically* approved by the FDA shortly after the NEJM publication (2)

But the approval acknowledges uncertainties and requires precautions and further evidence generation

… Kymriah is being approved **with a risk evaluation and mitigation strategy (REMS)**, which includes **elements to assure safe use (ETASU)**…. The FDA is requiring that **hospitals** and their associated clinics that dispense Kymriah be **specially certified**…. required to have protocols in place to **ensure that Kymriah is only given to patients after verifying that tocilizumab** [Concurrently approved to treat CAR T-cell-induced severe or life-threatening CRS -cytokine release syndrome] is available for immediate administration.

…. Novartis is also required to **conduct a post-marketing observational study involving patients treated** with Kymriah.

Anti CD19 CAR T cells *historically* approved by the FDA shortly after the NEJM publication (3)

Making use of several “early access” type of procedures

“The FDA granted Kymriah **Priority Review** and **Breakthrough Therapy designations**. The … application was reviewed using a coordinated, cross-agency approach. The clinical review was coordinated by the FDA's Oncology Center of Excellence, while CBER conducted all other aspects of review and made the final product approval determination”

Three products based on anti CD19 CAR T cells have obtained the PRIME designation at the EMA.

- None of them has been approved yet.
- One is said to have stopped development
- Is it justified to extrapolate from a product to another in urgent situations?

Is this "relevant"? Given the accelerated review and approval, it was, obviously, considered relevant
Worth paying for?
Affordable?

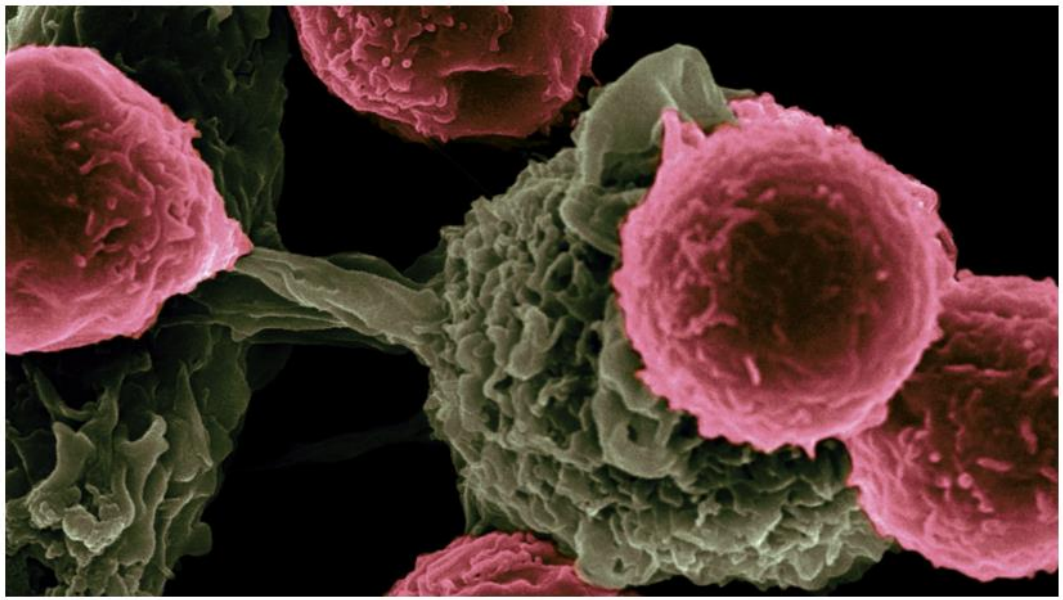
CAR-T cells

BIOTECH

STAT+

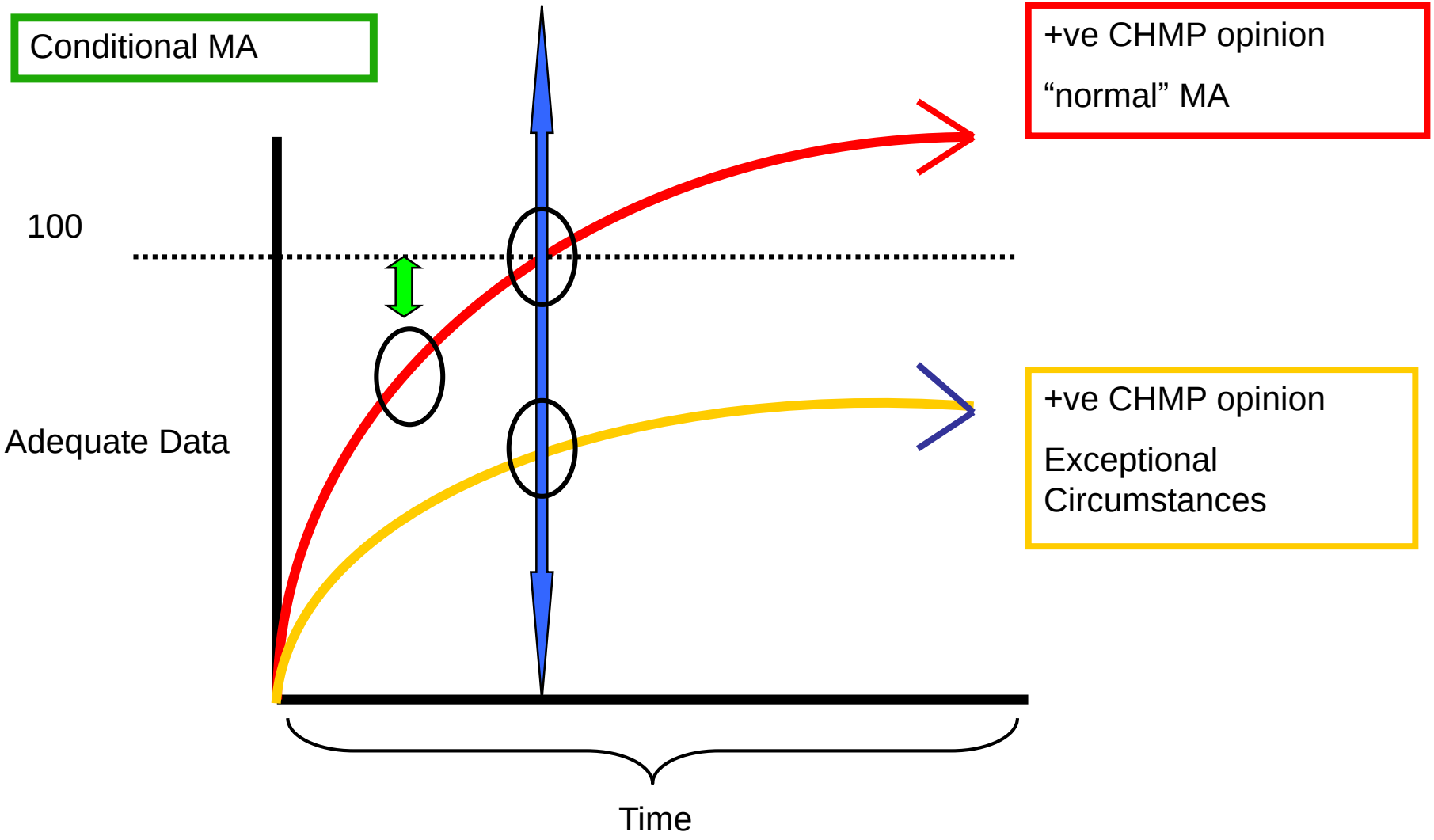
Pioneering cancer drug, just approved, to cost $475,000 — and analysts say it's a bargain

By DAMIAN GARDE @damiangarde / AUGUST 30, 2017



These are different - but very relevant- debates ….

Type of authorisation



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Early access instruments - EU

Other…Compassionate Use, Marketing Authorisation (MA) under exceptional circumstances, etc.

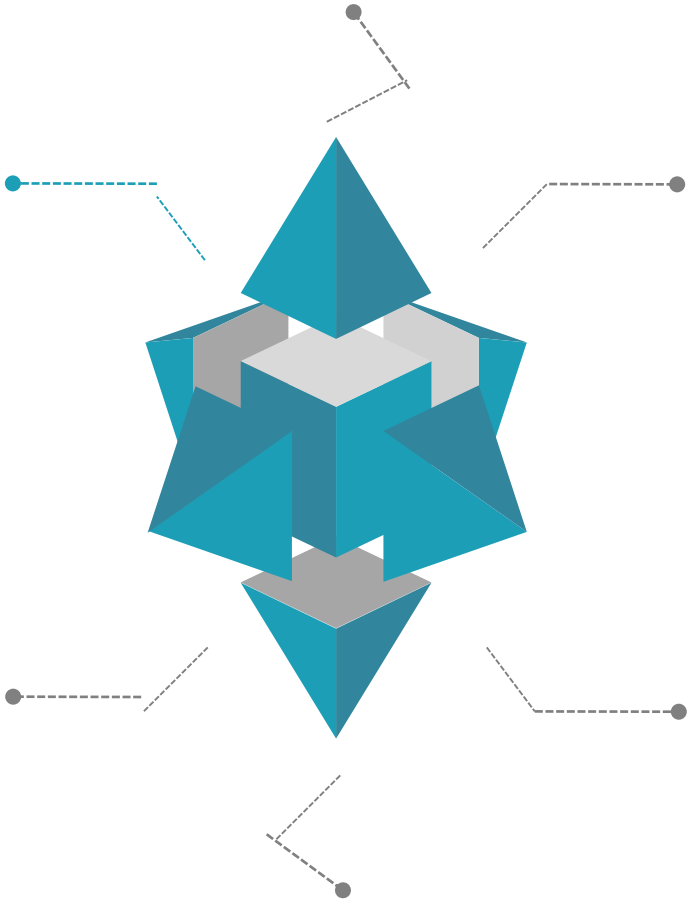
PRIME

Major public health interest, unmet medical need.

Dedicated and reinforced support.

Enable accelerated assessment.

Better use of existing regulatory & procedural tools.



Adaptive Pathways

Scientific concept of development and data generation.

Iterative development with use of real-life data.

Engagement with other healthcare-decision makers.

Accelerated Assessment

Major public health interest, unmet medical need.

Reduce assessment time to 150 days.

Conditional MA

Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.

Early approval of a medicine on the basis of less complete clinical data.

Parallel advice

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conditional marketing authorisation (~ US FDA accelerated approval)

The approval of a medicine that address **unmet medical needs** of patients on the basis of **less comprehensive data** than normally required. The available data must indicate that the medicine's **benefits outweigh its risks** and the applicant should be in a position to provide the **comprehensive clinical data** in the future.

exceptional circumstances

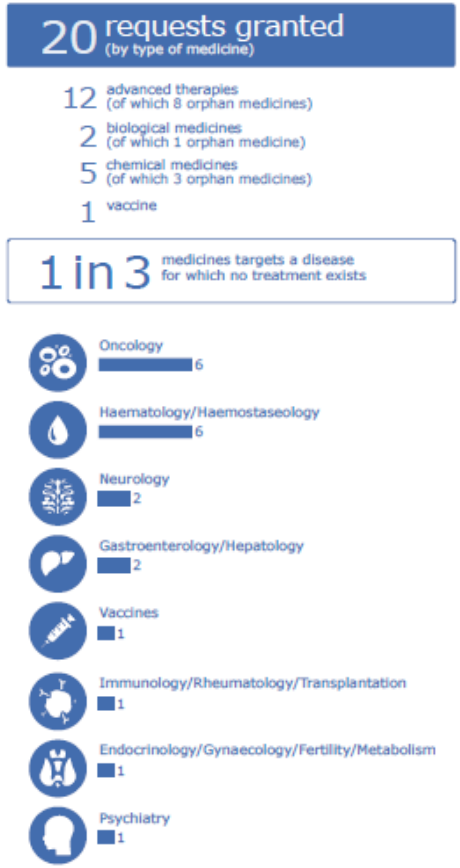
Comprehensive data **cannot be provided** (too rare, unethical, knowledge insufficient). Data package: initial + obligations < normal. Annual reassessment of the risk-benefit balance, focus safety, registries

accelerated assessment (~ US FDA priority review)

Rapid assessment of medicines in the centralised procedure that are of **major interest for public health**, especially ones that are **therapeutic innovations**. Accelerated assessment usually takes 150 evaluation days, rather than 210.

PRIME – PRIORITY MEDICINES

- **unmet medical need**
- potential to address this need and bring a **major therapeutic advantage** to patients – based on *"preliminary" data*
- **early and enhanced support** to:
  - ✓ optimise the development
  - ✓ speed up their evaluation – accelerated assessment
  - ✓ contribute to timely patients' access



Early access tools **are not mutually exclusive** →A product under the **PRIME** scheme could:

➢ follow an **accelerated assessment** at the time of MA;

➢receive an opinion from the CHMP on **compassionate use** while undergoing clinical trials;

➢be granted **conditional marketing authorisation** before comprehensive data are available.

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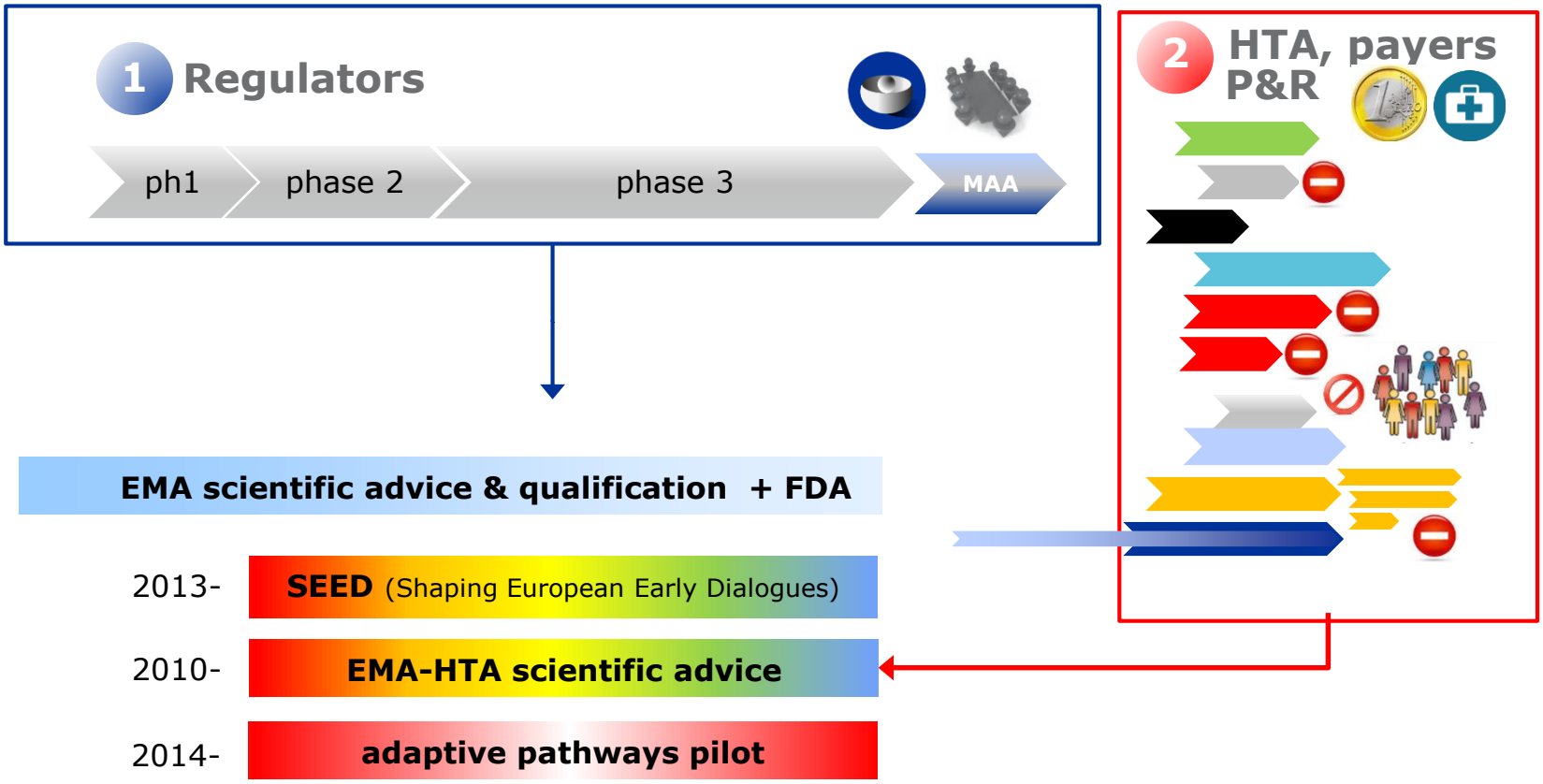
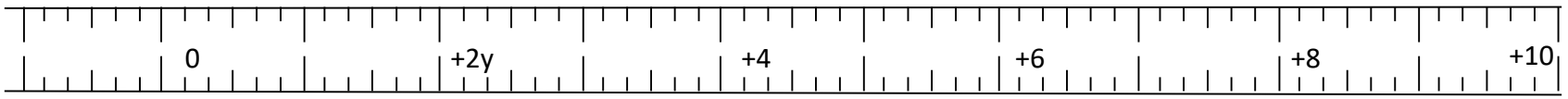
Multi-stakeholder dialogues

EMA-HTA to discuss/align evidence requirements **early** in development so drug **developers** can address information needs of both regulators and payers/HTAs





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earlier approval?

		FDA				EMA		Review time (days)		Difference in dates FDA–EMA (days)	
Drug	Indication	FT	BTD	PRev	AA	[b]CMA	[b]AccAs	FDA	[c]EMA	Rev. start	[d]Approval
Pomalidomide (Imnovid)	Multiple myeloma	●			●			304	344	71	178
T-DM1 (Kadcyla)	Breast HER2+	●		●			NO	182	365	26	266
Radium 223 Cl_2 (Xofigo)	CRPC	●		●			REV	154	232	49	172
Dabrafenib (Tafinlar)	Melanoma BRAFm	●						304	316	17	89
Trametinib (Mekinist)	Melanoma BRAFm	●					REV	299	422	208	397
Afatinib (Giotrif)	NSCLC EGFRm	●		●				240	309	−56	75
Obinutuzumab (Gazyvaro)	CLL CD20+		●	●			NO	193	365	30	264
Ibrutinib (Imbruvica)	MCL, CLL	●	●	●	●		NO	138	246	145	342
Ramucirumab (Cyramza)	Gastric	●		●				241	365	33	242
Ceritinib (Zykadia)	NSCLC ALK+		●	●	●	●		126	337	92	372
Belinostat (Beleodaq)	PTCL	●		●	●			207	n/a	n/a	n/a
Idelalisib (Zydelig)	CLL, FL	●	●[CLL]	●	●[FL]		REV	229/315[FL]	246	−16/70[FL]	57
Pembrolizumab (Keytruda)	Melanoma		●	●	●			189	330	118	321
Blinatumomab (Blincyto)	ALL Ph-		●	●	●			75	n/a	n/a	n/a
Olaparib (Lynparza)	Ovarian BRCA1/2m			●	●			319	393	−131	−3
Nivolumab (Opdivo)	Melanoma	●	●	●	●		●	145	239	56	182
	n/total (%)	69%	44%	81%	56%	7%	7%				
	Median (days)							200	333	49	210

FT, fast track; BTD, breakthrough designation; PRev, priority review; AA, accelerated approval; CMA, conditional marketing authorisation; AccAs, accelerated assessment: REV, initially accepted and later reverted to standard timetable; NO, request not accepted.

J. Martinalbo et al. Early market access of cancer drugs in the EU. *Ann Oncol* 27: 96–105, 2016

conditional approval = *early access*?

Drug	Indication	Pivotal clinical trial design (*N*) Primary efficacy results (95% CI)	EU CMA	Outcome HTA/P&R				Time from authorisation (m)			
				[a]EN&W	[b]DE	[c]FR	[d]IT	EN&W	DE	FR	IT
Sunitinib (Sutent)	GIST 2L mono	Phase 3 RCT versus BSC (312) PFS 6.25 versus 1.46 months—HR 0.33 (0.23–0.47)	July 06[S]	R	R	II	R	32	n/a	2	4
	RCC 2L mono	2 × phase 2 single-arm (106, 63) ORR 25.5% (17.5%–34.9%)	July 06[S]	R	R	III	R	37	n/a	2	4
Panitumumab (Vectibix)	CRC KRASwt 2L+ mono	Phase 3 RCT versus BSC (463) PFS 8 versus 7.3 months—HR 0.54 (0.443–0.663)	December 07[S]	NO	R	V	R	49	n/a	5	12
Lapatinib (Tyverb)	Breast HER2+ 2L comb. chemo	Phase 3 RCT add on to capecitabine (399) PFS 6.23 versus 4.26 months—HR 0.57 (0.43–0.77)	June 08[S]	Susp.	R	III	R	n/a	n/a	1	11
Ofatumumab (Arzerra)	CLL 3L mono	Phase 2 single-arm (154) ORR 58% (40%–74%)	April 10[S]	NO	R	V	R	6	n/a	6	13
Pazopanib (Votrient)	RCC 1L mono	Phase 3 RCT versus BSC (435) PFS 9.2 versus 4.2 months—HR 0.46 (0.34–0.62)	June 10[S]	R	R	NO	R	8	n/a	8	11
Everolimus (Votubia)	SEGA paediatric 1L mono	Phase 2 single-arm (28) volume 0.93 versus 1.74 cm^3 (0.4–1.2)	September 11	n/a	R	II	n/a	n/a	n/a	4	n/a
Vandetanib (Caprelsa)	Thyroid, MTC 1L mono	Phase 3 RCT versus BSC (331) PFS 30.5 versus 19.3 months—HR 0.46 (0.31–0.69)	February 12	n/a	3	IV	R	n/a	7	4	16
Pixantrone (Pixuvri)	DLBCL 2L mono	Phase 3 RCT versus BSC (140) CR 20 versus 5.7% (3.5–25.1); $P = 0.021$	May 12	R	5	n/a	NO	22	12	n/a	14[NO]
Crizotinib (Xalkori)	NSCLC ALK+ 2L mono	Phase 1 single-arm + phase 3 RCT versus chemo (125, 318) phase 1 ORR 60%, phase 3 PFS 7.7 versus 3 months—HR 0.49 (0.37–0.64)	October 12	NO	2/5[f]	III	R	10	6	17	29/5[e]
Brentuximab vedotin (Adcetris)	sALCL CD30+ 2L mono	Phase 2 single-arm (58) ORR 75%, CR 33%, DoR 6.7 months	October 12	n/a	4	III	R	n/a	7	4	20/0[e]
	Hodgkin CD30+ 3L mono	Phase 2 single-arm (102) ORR 86%, CR 59%, DoR 13.2 months	October 12	n/a	4	III	R	Exp 44	7	4	20/0[e]
Bosutinib (Bosulif)	CML Ph+ 2L+ mono	Phase 2 single-arm (four cohorts: 502) MCyR 2L 53.4% (47.2–59.5), 3L 27% (19–36)	March 13	NO	4	V	R	7	7	11	18
Vismodegib (Erivedge)	Basal cell, met. 1L mono	Phase 2 single-arm (two cohorts: 104) ORR 30.3% (15.6–48.2), 42.9% (30.5–56.0)	July 13	n/a	3/5[f]	IV	R	n/a	7	5	20
Cabozantinib (Cometriq)	Thyroid, MTC 1L mono	Phase 3 RCT versus BSC 2 : 1 (330) PFS 11.2 versus 4 months—HR 0.28 (0.19–0.4)	March 14	n/a	3	IV	n/a	n/a	10	8	n/a

perception of lower evidence standards by HTAs & payers?

J. Martinalbo et al. Early market access of cancer drugs in the EU. *Ann Oncol* 27: 96–105, 2016

Thank you