Current challenges and opportunities with CTs in oncology - a regulatory point of view

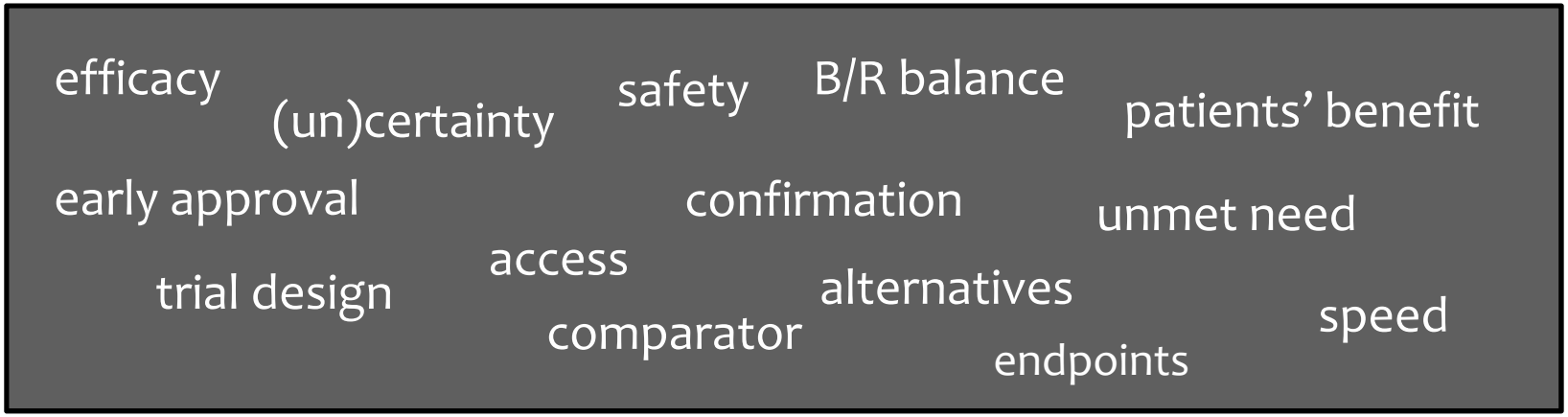
Blanca García-Ochoa (SAWP, AEMPS)

The views expressed are the personal views of the presenter and may not be understood or quoted as being made on behalf of or reflecting the position of EMA or its committees or working parties.
I have no conflicts of interest.

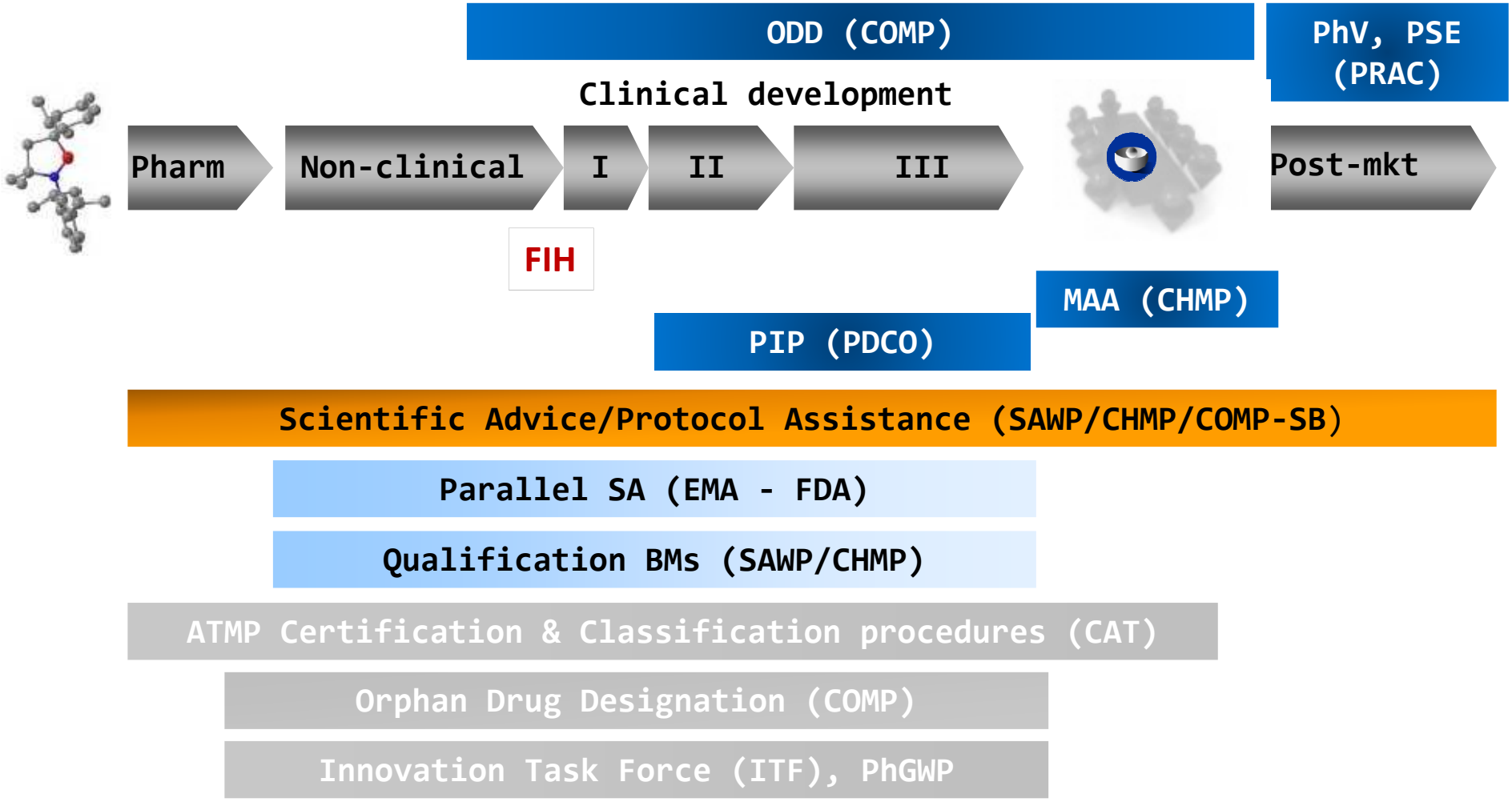
Innovation in Oncology Clinical Trial Design. 12-13 June 2017 – Frankfurt, Germany

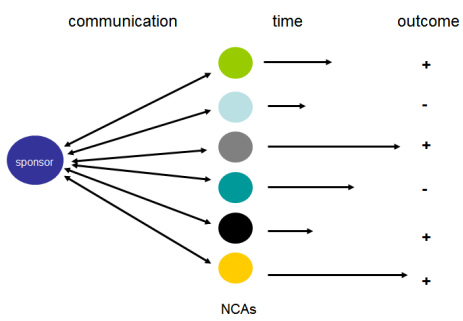
CTs in oncology

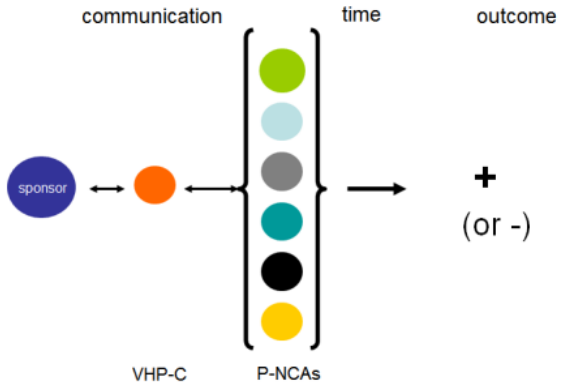
- Evolving field – exciting new data
- Different perspectives / views
  - Academia / investigators
  - Industry
  - Patients
  - Regulatory agencies
  - HTAs & payers



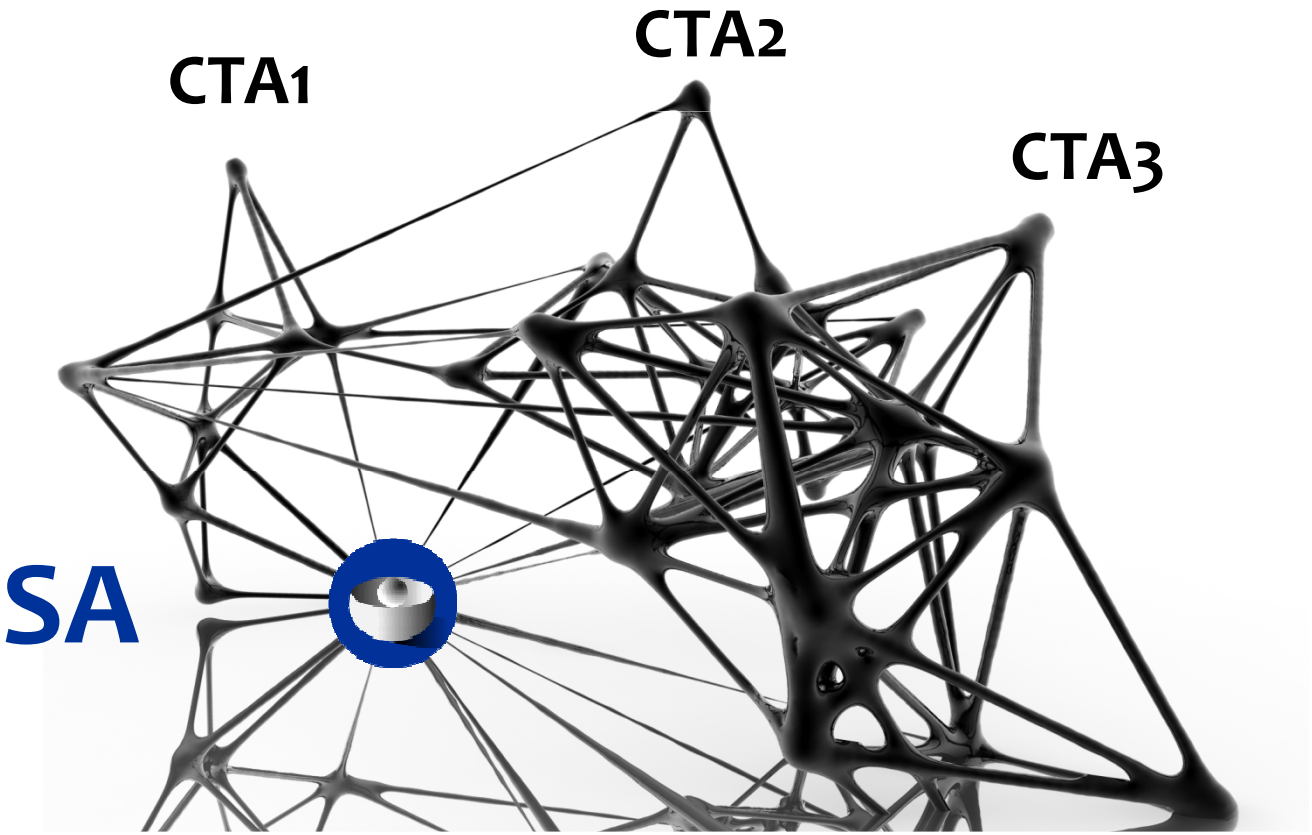
dialogue with EU regulators




communication
time
outcome
sponsor
+
-
+
-
+
+
NCAs


communication
time
outcome
sponsor
+
(or -)
VHP-C
P-NCAs

VHP


CTA1
CTA2
CTA3
SA

EMA scientific advice

EMA scientific advice & qualification

SAWP: multidisciplinary expert group (n>50)

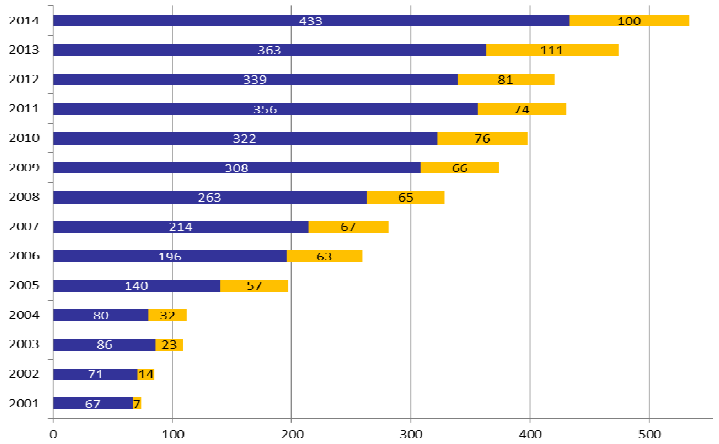
focus **phase 3 RCTs** - also exploratory, SATs

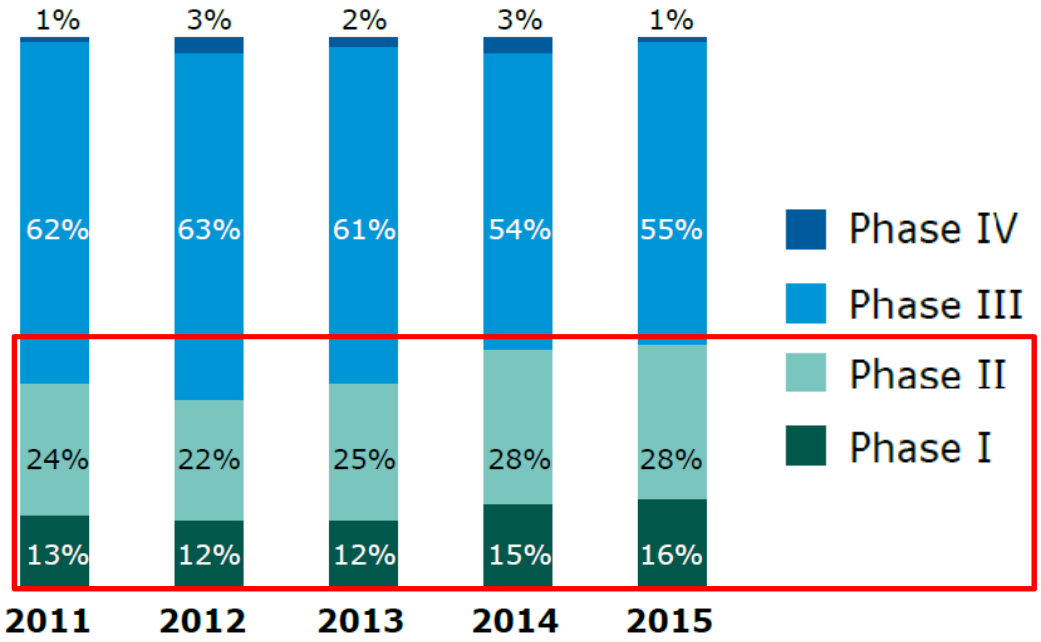
- **population** – all therapeutic areas
- **comparator**, blinding
- **endpoints**, **SAP**
- **safety**

product-specific
'case by case'

(post-authorisation safety & efficacy studies, pragmatic trials, registries, meta-analyses)

Qualification: platforms, master protocols…





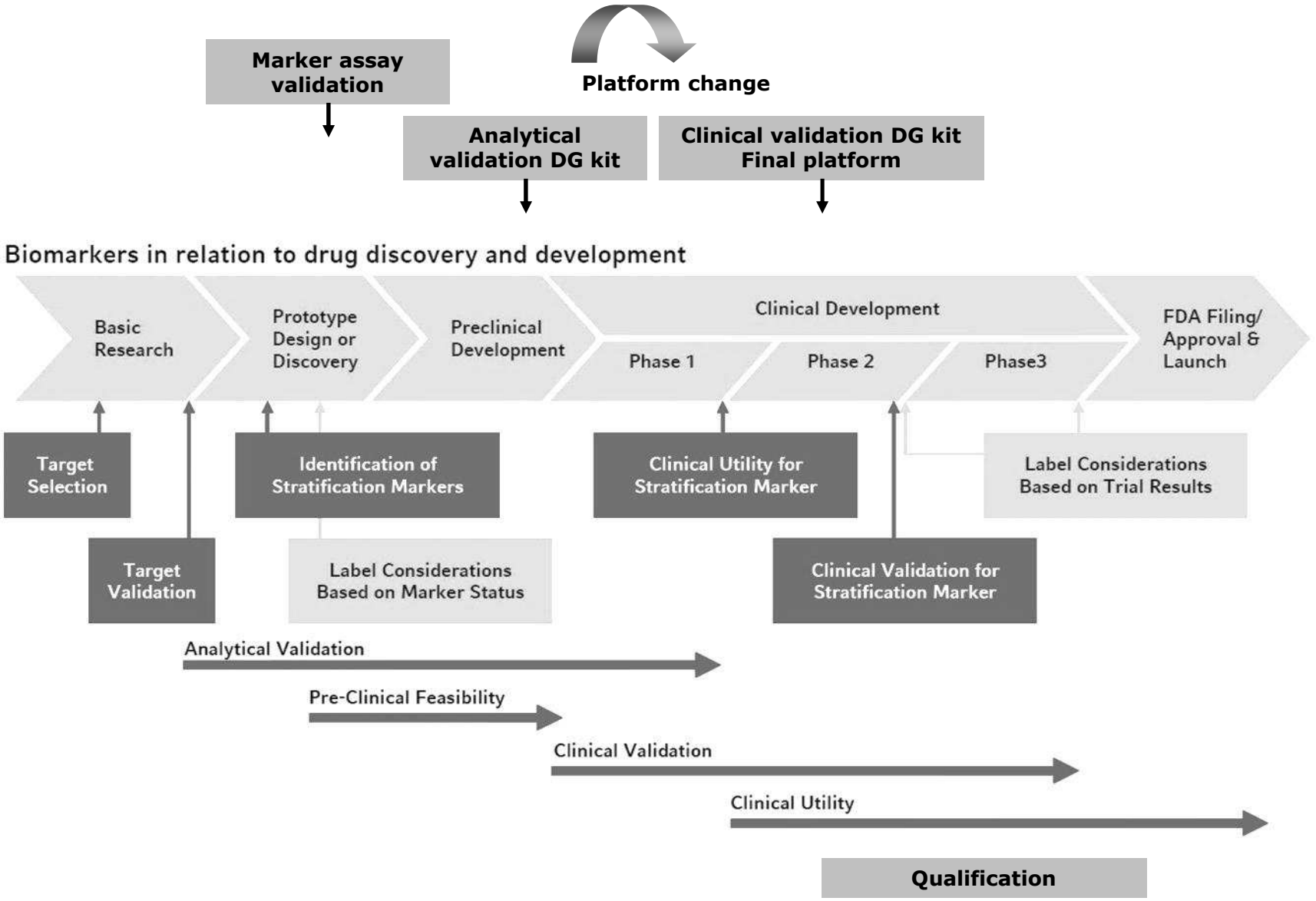
SA	422
PA	123
QO	3
QA	11
HTA SA	20
HTA PA	3

qualification scope BMs

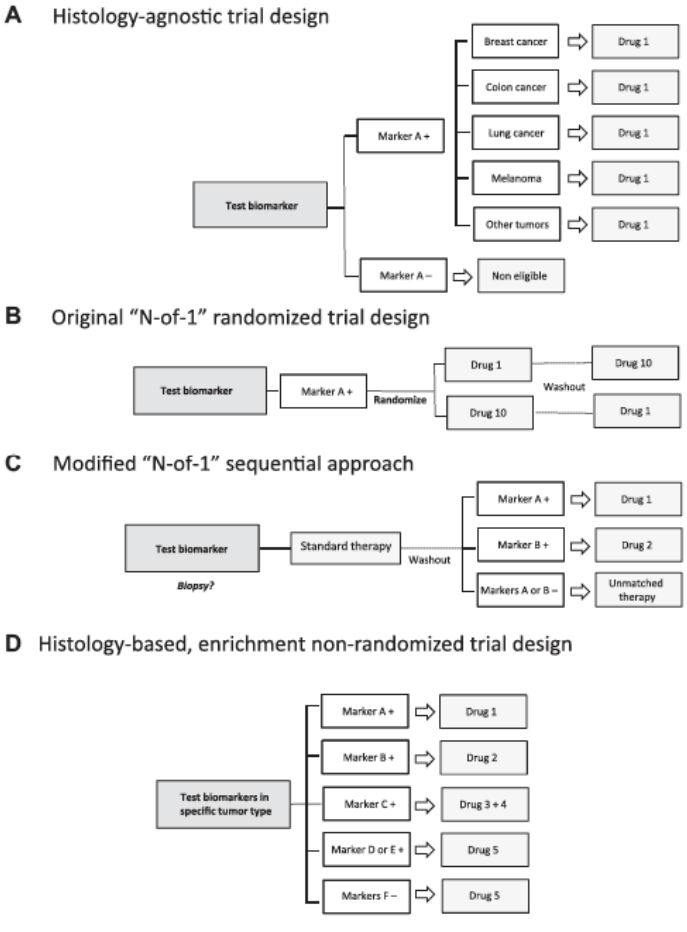
preclinical	preclinical	drug use
▪ pharmacological screening ▪ mechanism of action ▪ predict activity/safety ▪ PK/PD modelling ▪ toxicogenomics	▪ verify mechanism ▪ dose-response ▪ proof of concept ▪ input CT design ▪ **population** ▪ **surrogate endpoint**	▪ optimise population ▪ guide treatment regimen

- PhGen **predictive/prognostic BMs** to enrich/select population
- **surrogate E endpoints** (MRD, imaging to monitor disease progression)
- imaging and biochemical parameters to **diagnose early** disease stages
- **patient reported outcomes (PRO)** questionnaires

e.g. drug/DG co-development



novel CT designs…

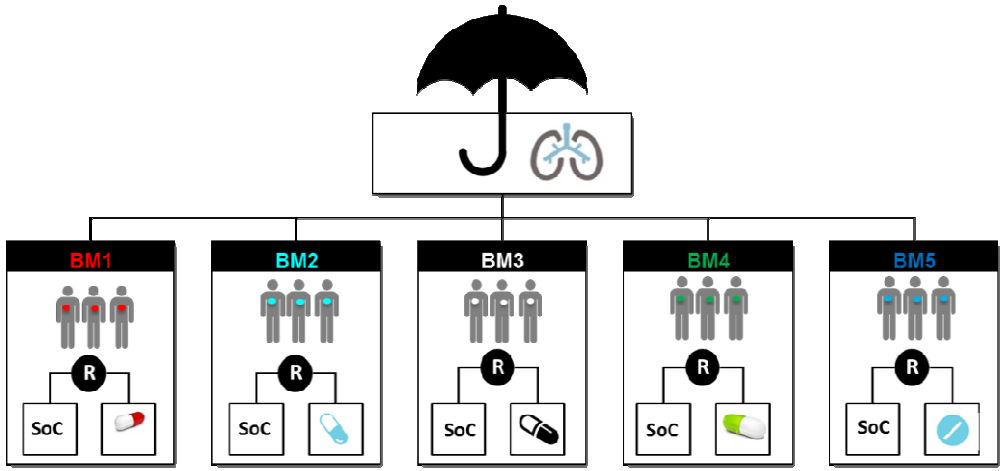


Dienstman, Mol Oncology 2015

BM-stratified trials

basket

umbrella



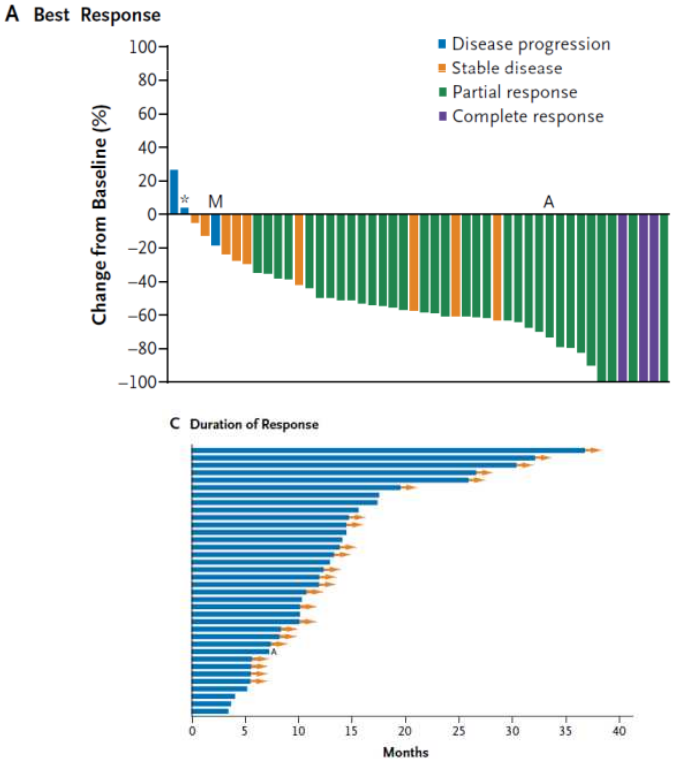
single-arm BM+

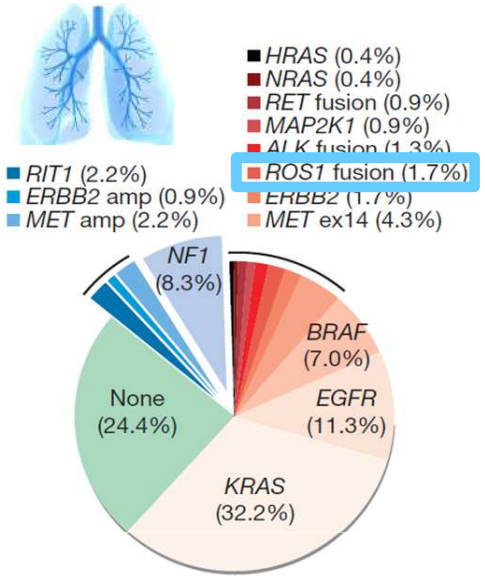
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.





rare molecular subgroups - SATs

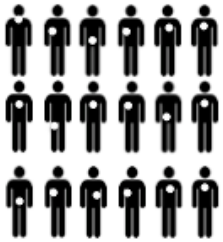
<< n pts screen - innovative CT design, analysis & approval

registries mol. annotation

- external controls BM+ prognostic? SoC response?
- post-approval RWD

non-RCT evidence?

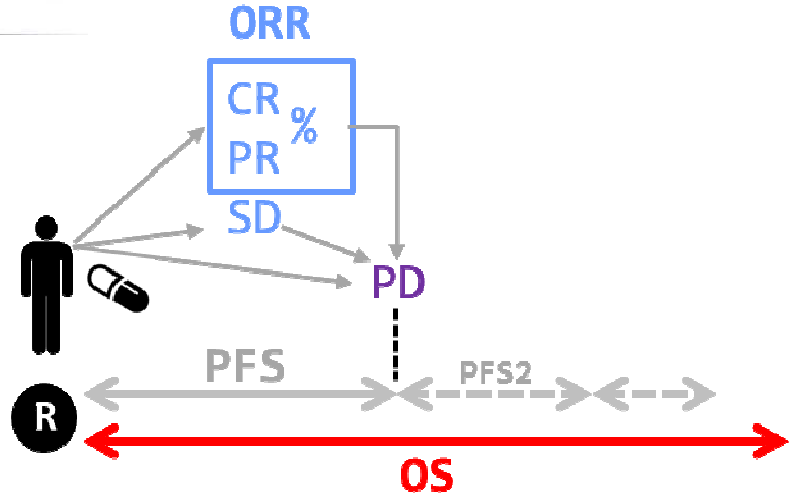
unmet need
- **population** well-defined
- **prognosis** (mol. subset?)
- therapeutic **alternatives**



ext. controls
- data sharing
- registries Dx+

sparse evidence

efficacy
- *compelling* **E thresholds** valid **endpoints** ORR, DoR (or novel clinically meaningful **alternatives**?)



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non-RCT evidence?

RCT feasibility?

- **rare** incidence/prevalence

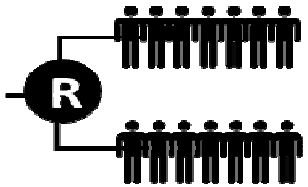
- BM+ mol screening uptake?

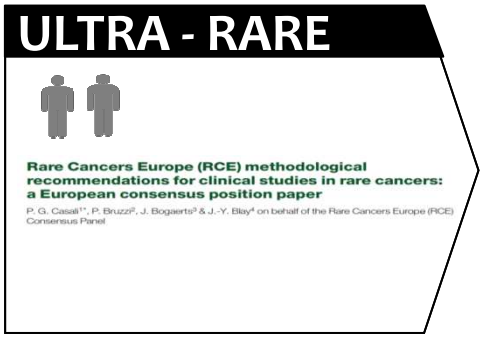
- clinical **equipoise**

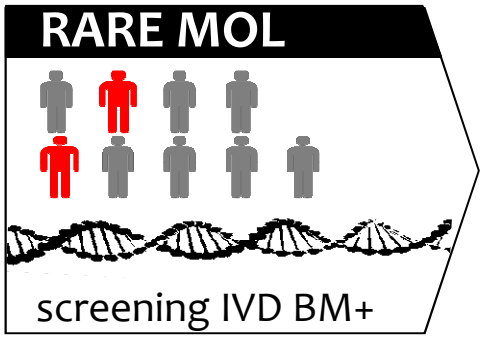
confirmatory

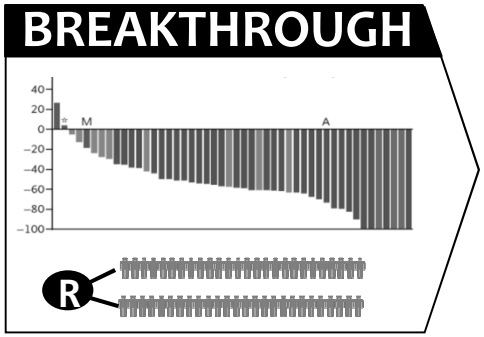
window of opportunity; timing - early approval;

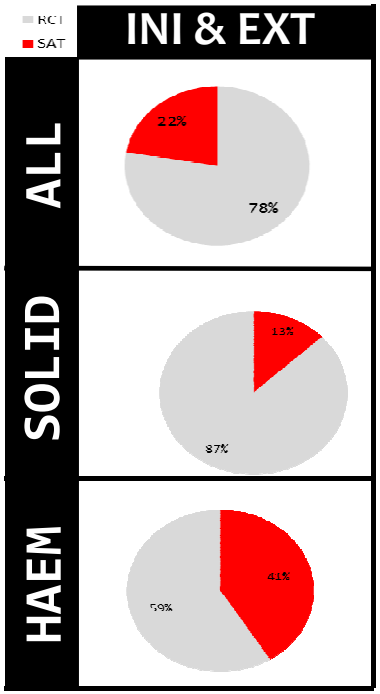
Alternatives registries, **RWD**











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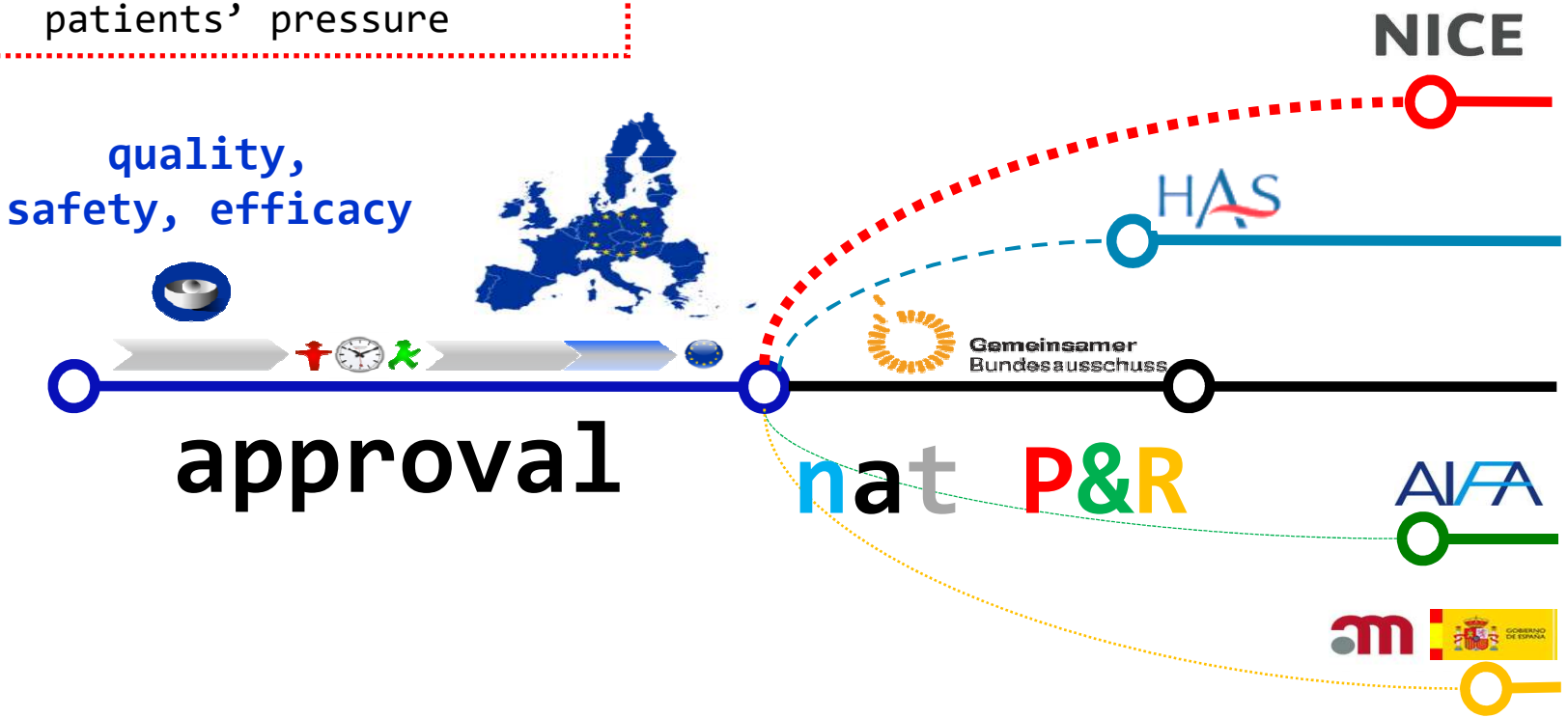
non-RCT evidence? A further issue…

HTA, P&R > uncertainty

data sources fill gaps?

model OS gain?

- value?
- high price (small pops)
- budget impact: *off label*
- patients' pressure



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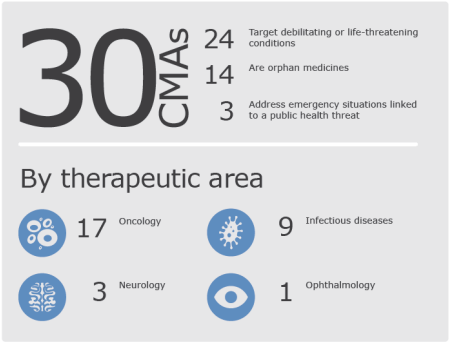
early access instruments EU

conditional marketing authorisations (~ 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.

approvals (basket)

Phase II, Open-Label Study Evaluating the Activity of Imatinib in Treating Life-Threatening Malignancies Known to Be Associated with Imatinib-Sensitive Tyrosine Kinases

Michael C. Heinrich,[1] Heikki Joensuu,[2] George D. Demetri,[3] Christopher L. Corless,[1] Jane Apperley,[5] Jonathan A. Fletcher,[4] Denis Soulieres,[6] Stephan Dirnhofer,[7] Amy Harlow,[1] Aji a Town,[1] Arin McKinley,[1] Shane G. Supple,[10] John Seymour,[11] Lilla Di Scala,[8] Allan van Oosterom,[12] Richard Herrmann,[9] Zariana Nikolova,[8] and Grant McArthur[11] for the Imatinib Target Exploration Consortium Study B2225

Clin Can Res 2008

Abstract

Purpose: To evaluate the activity of imatinib in treating advanced, life-threatening malignancies expressing one or more imatinib-sensitive tyrosine kinases.

Experimental Design: This was a phase II, open-label, single arm study. Patients ≥15 years old with malignancies showing histologic or molecular evidence of expression/activation of imatinib-sensitive tyrosine kinases were enrolled. Patients were treated with 400 or 800 mg/d imatinib for hematologic malignancy and solid tumors, respectively. Treatment was continued until disease progression or unacceptable toxicity. The primary objective was to identify evidence of imatinib activity with tumor response as the primary end point.

Results: One hundred eighty-six patients with 40 different malignancies were enrolled (78.5% solid tumors, 21.5% hematologic malignancies). Confirmed response occurred in 8.9% of solid tumor patients (4 complete, 9 partial) and 27.5% of hematologic malignancy patients (8 complete, 3 partial). Notable activity of imatinib was observed in only five tumor types (aggressive fibromatosis, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, myeloproliferative disorders, and systemic mastocytosis). A total of 106 tumors were screened for activating mutations: five *KIT* mutations and no platelet-derived growth factor receptor mutations were found. One patient with systemic mastocytosis and a partial response to therapy had a novel imatinib-sensitive *KIT* mutation (D816T). There was no clear relationship between expression or activation of wild-type imatinib-sensitive tyrosine kinases and clinical response.

Conclusion: Clinical benefit was largely confined to diseases with known genomic mechanisms of activation of imatinib target kinases. Our results indicate an important role for molecular characterization of tumors to identify patients likely to benefit from imatinib treatment.

Table 1. Response to imatinib by indication (analysis population, *N* = 186)

Main indication	CR, *n* (%)	PR, *n* (%)	SD, *n* (%)	PD, *n* (%)	Unknown, *n* (%)	Median TTP (95% CI), mo	Putative target
Solid tumors: sarcoma							
Synovial sarcoma (*n* = 16)	0	1 (6.3)	3 (18.8)	11 (68.8)	1 (6.3)	1.1 (1.0-4.1)	KIT
Dermatofibrosarcoma protuberans (*n* = 12)	4 (33.3)	6 (50.0)	0	1 (8.3)	1 (8.3)	23.9 (7.7-∞)	PDGFRB
Leiomyosarcoma (*n* = 11)	0	0	1 (9.1)	8 (72.7)	2 (18.2)	1.1 (1.0-2.9)	KIT
Liposarcoma (*n* = 11)	0	0	5 (45.5)	6 (54.5)	0	2.5 (2.1-12.5)	KIT
Chondrosarcoma (*n* = 7)	0	0	1 (14.3)	5 (71.4)	1 (14.3)	[0.03*-4.6*]	KIT
Ewing's sarcoma (*n* = 4)	0	0	0	3 (75.0)	1 (25.0)	[1.0-2.6]	KIT/PDGFR
Angiosarcoma (*n* = 2)	0	0	0	2 (100)	0	[0.7-0.8]	KIT/PDGFR
Rhabdomyosarcoma (*n* = 2)	0	0	0	2 (100)	0	[0.3-0.4]*	PDGFR
Aggressive fibromatosis (*n* = 20)	0	2 (10.0)	8 (40.0)	7 (35.0)	3 (15.0)	9.1 (2.9-17.0)	PDGFRA
Chordoma (*n* = 5)	0	0	4 (80.0)	0	1 (20.0)	[2.7-33.0*]	PDGFRB
Desmoplastic small round cell tumor (*n* = 5)	0	0	0	5 (100)	0	[0.5-1.4]	KIT, PDGFR
Neurofibrosarcoma (*n* = 3)	0	0	2 (66.7)	0	1 (33.3)	[0.03*-16.4]	PDGFR
Malignant schwannoma (*n* = 2)	0	0	0	1 (50.0)	1 (50.0)	[0.9*-1.0]*	PDGFR
Osteosarcoma (*n* = 2)	0	0	0	2 (100)	0	[1.0-2.8]*	PDGFR
Solid tumors: nonsarcoma							
Adenoid cystic carcinoma (*n* = 12)	0	0	6 (50.0)	5 (41.7)	1 (8.3)	5.7 (1.0-11.7)	KIT
Mesothelioma (*n* = 6)	0	0	0	3 (50.0)	3 (50.0)	[0.03*-2.3]	PDGFRB
Malignant melanoma (*n* = 5)	0	0	0	4 (80.0)	1 (20.0)	[0.2-2.8]	KIT
Intraocular melanoma (*n* = 3)	0	0	0	3 (100)	0	[1.0-2.8]	KIT
Breast carcinoma (*n* = 2)	0	0	0	1 (50.0)	1 (50.0)	[0.03*-0.6]*	KIT/PDGFR
Hematologic malignancies							
Hypereosinophilic syndrome (*n* = 14)	5 (35.7)	1 (7.1)	1 (7.1)	6 (42.9)	1 (7.1)	8.4 (2.33-∞)	PDGFRA/KIT
Multiple myeloma (*n* = 6)	0	0	0	6 (100)	0	[1.0-3.0]	KIT
Myelofibrosis (*n* = 8)	0	0	5 (62.5)	1 (12.5)	2 (25)	[0.03*-25.2*]	PDGFRB
Myeloproliferative disorders (*n* = 7)	3 (42.9)	1 (14.3)	0	2 (28.6)	1 (14.3)	[0.03*-26.7*]	PDGFRB
Systemic mastocytosis (*n* = 5)	0	1 (20.0)	1 (20.0)	0	3 (60.0)	[0.03*-22.3*]	KIT/PDGFRA

APPROVED

NSCLC ROS1/crizotinib

histology/site-agnostic?

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Listen to the FDA D.I.S.C.O. podcast about this approval

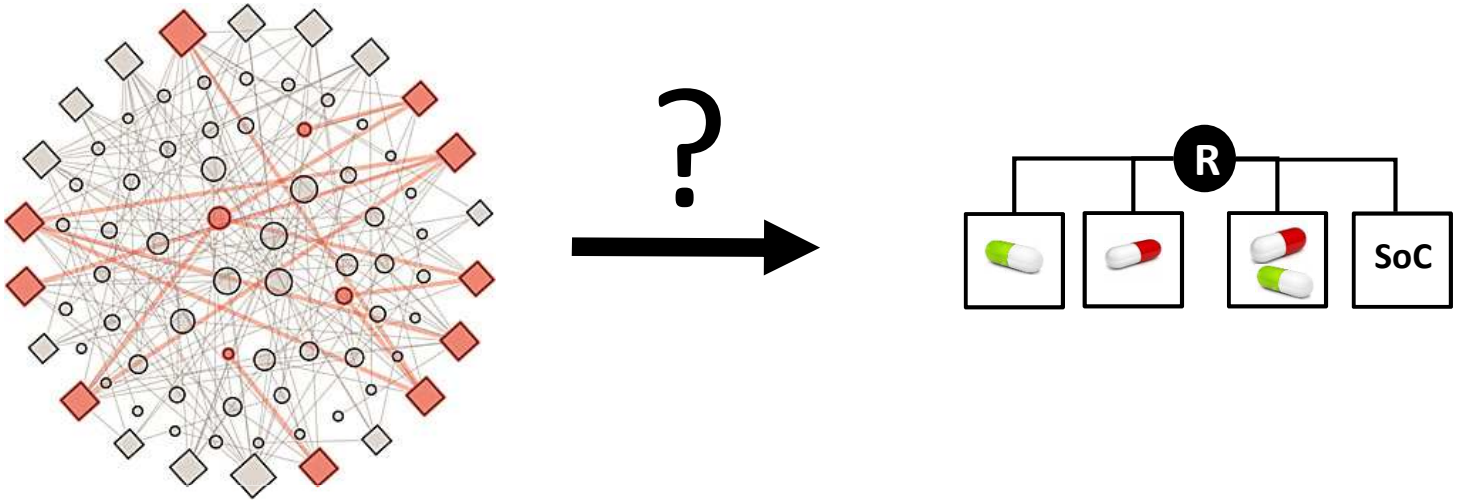
On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

basket

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator-initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi-center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		**149**			

CRC = colorectal cancer

combinations



- Combinations of immunotherapeutics or immunotherapeutics with SOC – including chemo/targeted therapies → increase the benefit over the monocomponents
- **CT methodology** and **regulatory issues**, e.g. need to demonstrate contribution of each component within the same trial (?), dose-finding, PK/PD interactions
- Better efficacy, worse safety? → **prioritisation**, understanding MoAs

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 A = *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

EMA-erging tools

- **R&D:** PRIME (~breakthrough), early dialogue, EMA-HTA joint advice

PRIority **ME**dicines

- **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

- **access:** adaptive pathways pilot (HTA), revisit AA/CMA

conclusions

- **Need to adapt**
- One of the identified major (regulatory) challenges → ***"certainty vs. speed"***
- **Ongoing and under development tools:**
  - **breakthroughs, early access** (EMA PRIME, EC STAMP), conditional authorisation 'refocus' & accelerated review
  - **multi-stakeholder dialogue** EMA, HTAs, developers, patients joint scientific advice pre-marketing on development plans
- **And to go beyond…**

Thanks!

bgarciao@aemps.es