Medicina di Precisione in oncologia: dalla sperimentazione alla clinica

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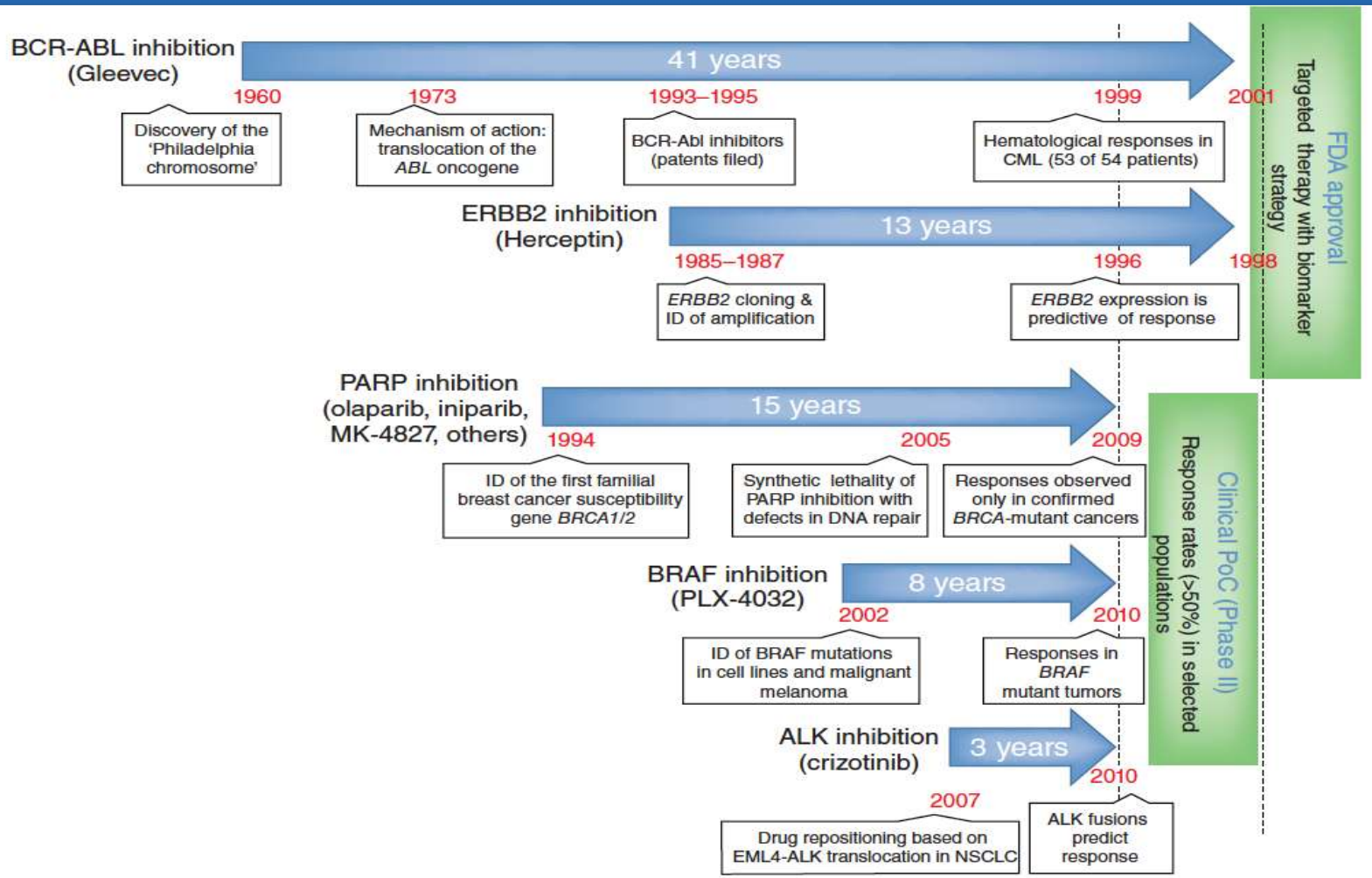
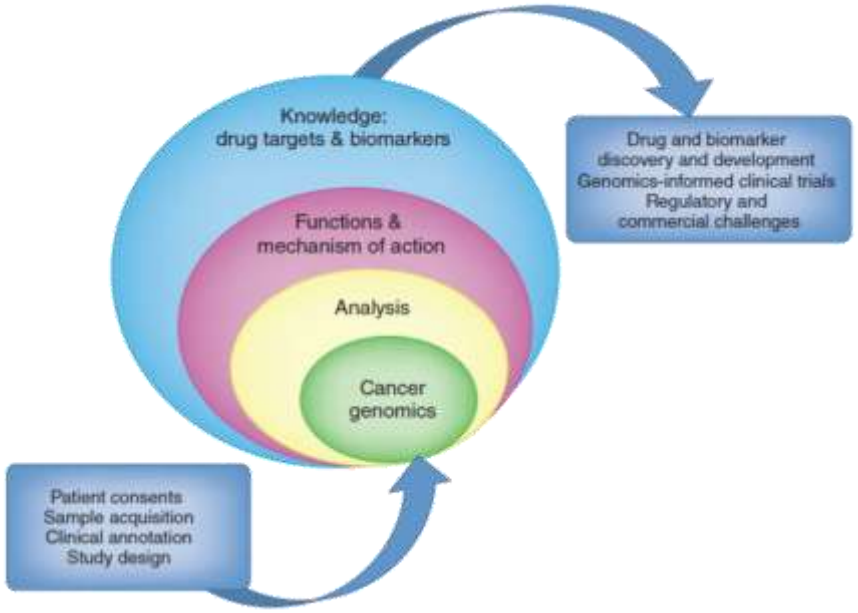
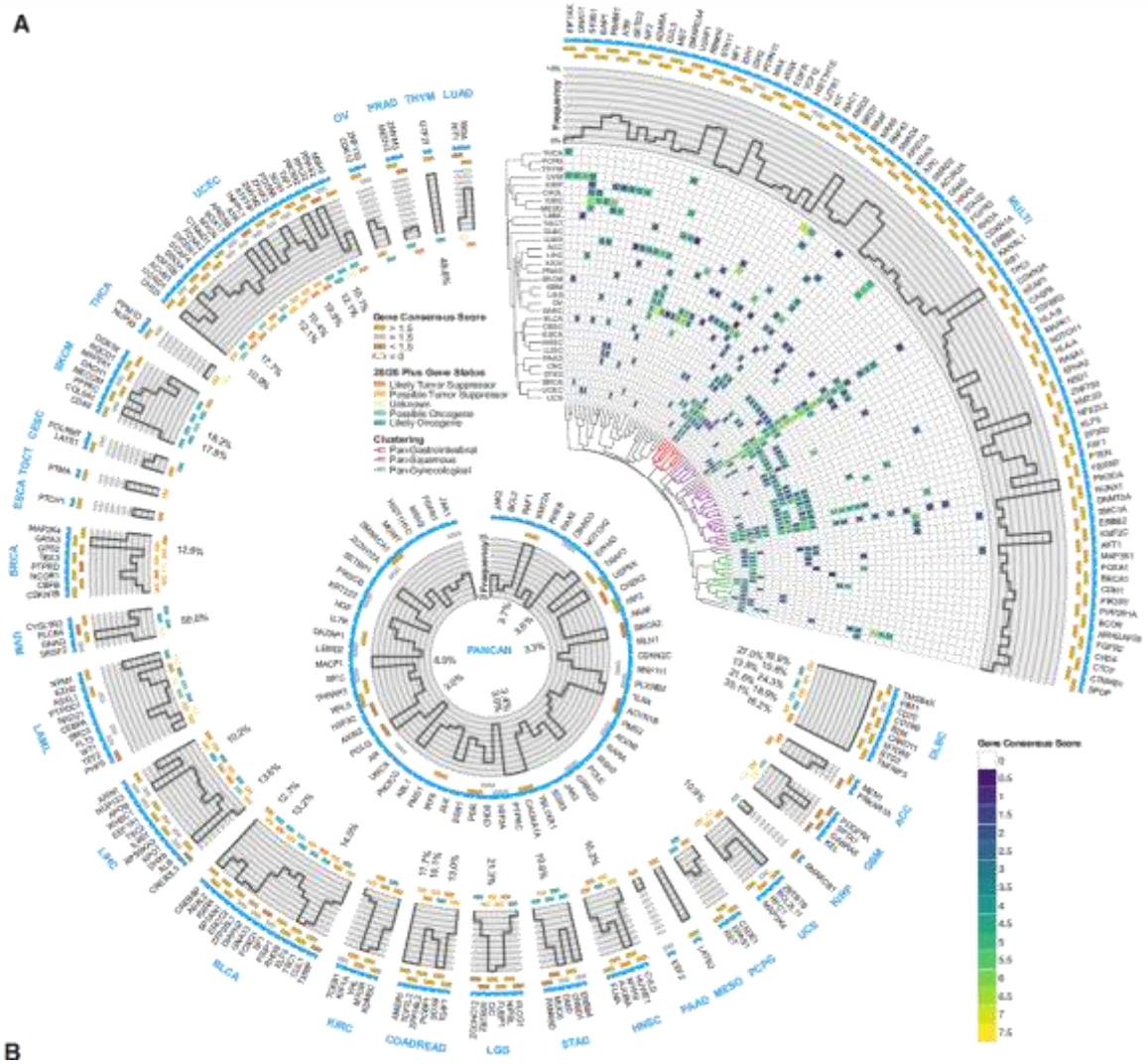


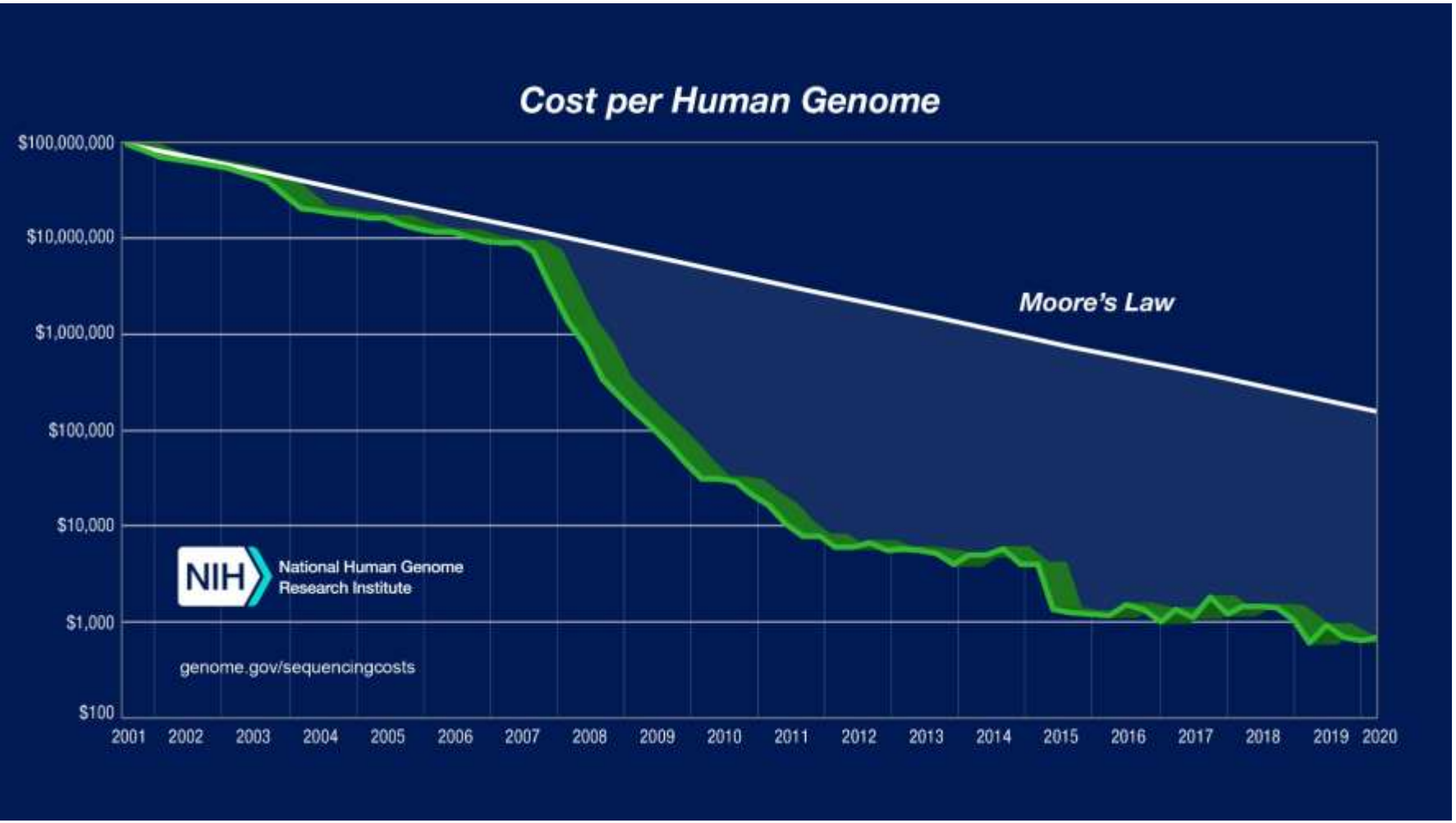


Cancer genomics: from discovery science to personalized medicine Chin L. et al. Nature Med 2011 Mar;17(3):297-303



Regarding the associations
of driver genes with different cancer types,
many genes (142 out of 258) are associated
with a single cancer, whereas
87 genes have driver roles in two or more
cancer types

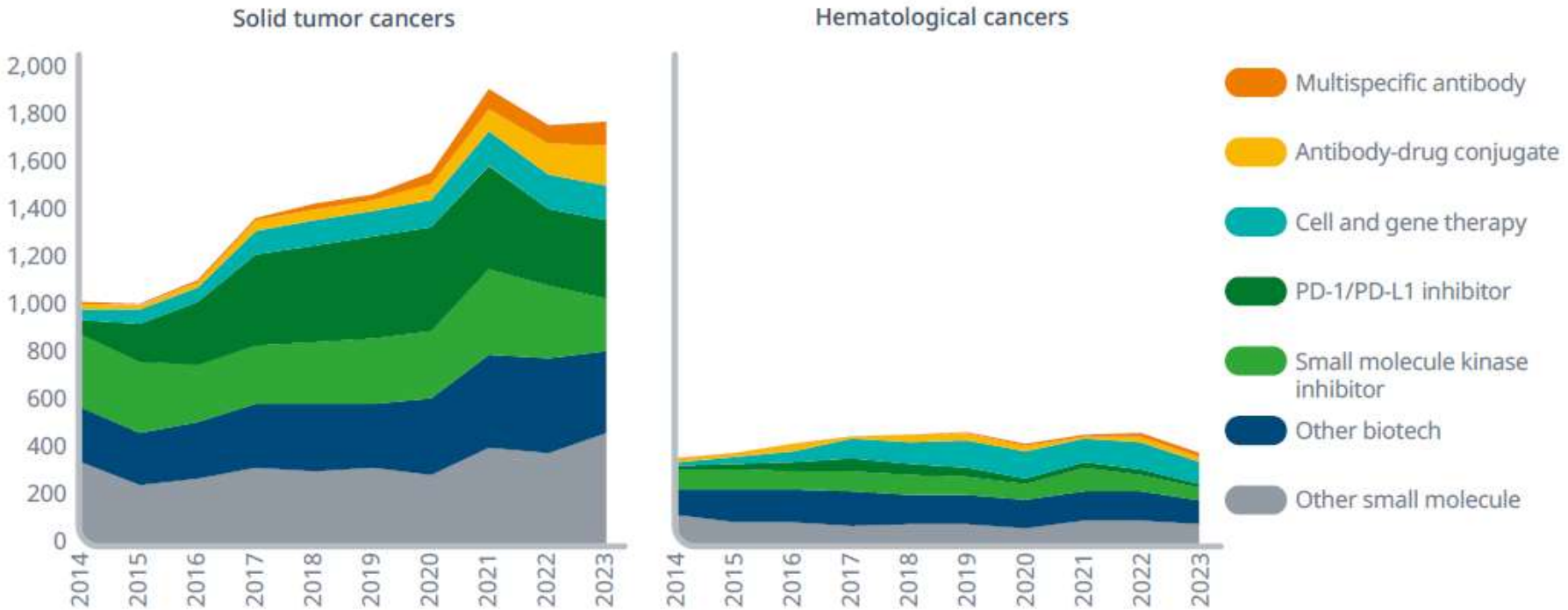
Bailey et al. Cell 173, 371–385, 2018



https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost

Novel oncology mechanisms, especially cell and gene therapies, ADCs, and multispecific antibodies have risen to 25% of trial starts

Exhibit 8: Oncology clinical trial starts Phase I to III by primary tested drug type, 2014–2023



Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

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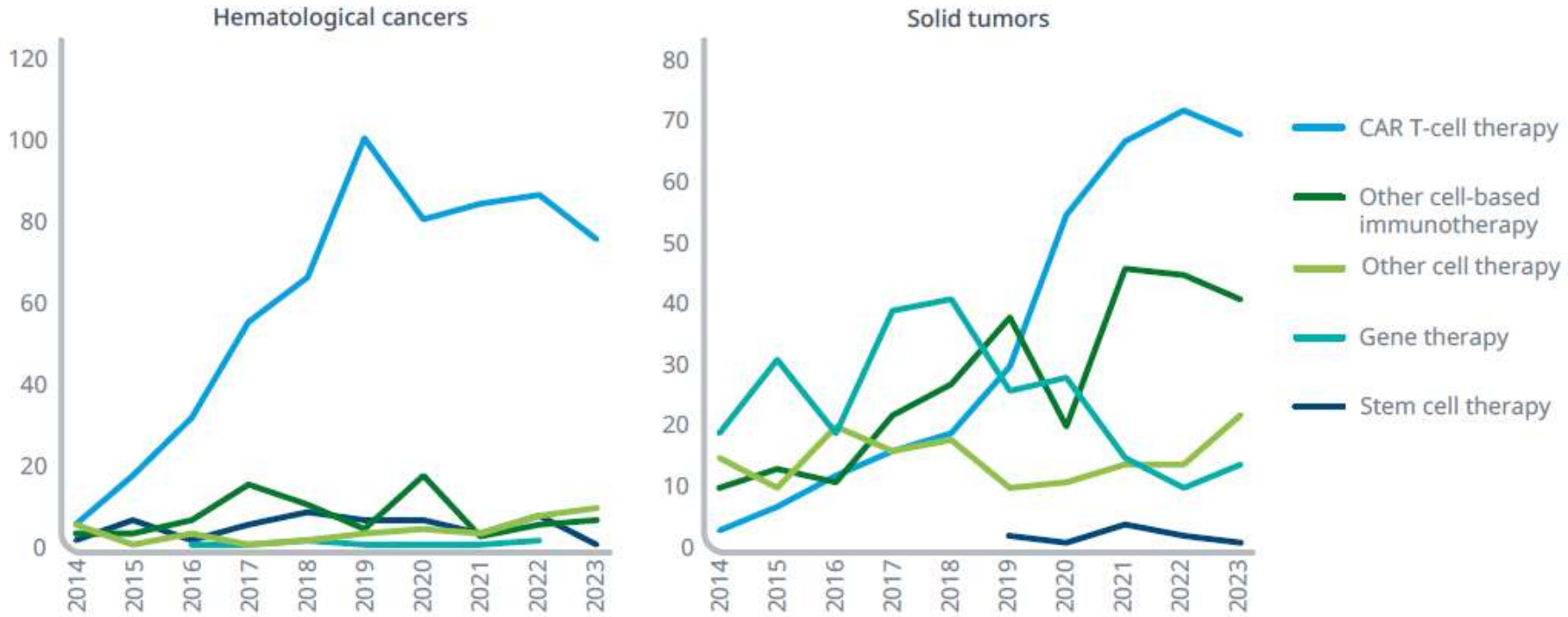
Oncology cell and gene therapy trials are focused on CAR T, particularly in hematological cancers

Exhibit 10: Oncology cell and gene therapy trials Phase I to Phase III by mechanism, 2014–2023



Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Apr 2024.

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Authorization procedure for clinical trials (Part I - Centralized)

Sponsor submits the application

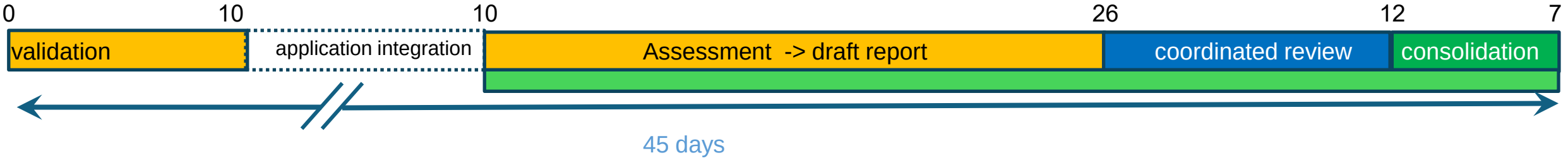
Reporting Member State validates the application (falls within the scope of application and has a complete dossier)

Sponsor submits any additional documents and responds to objections

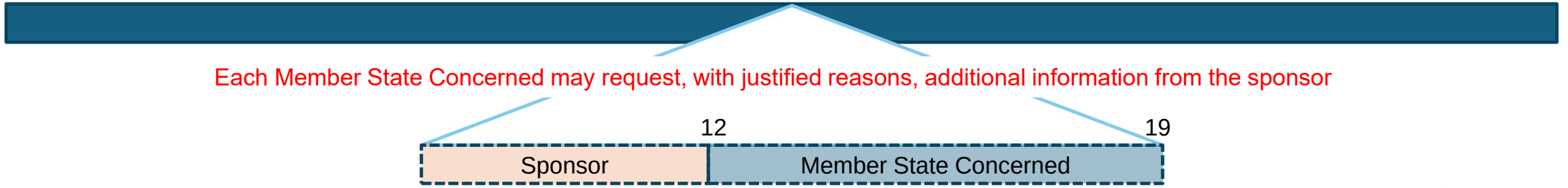
Reporting Member State submits the initial report for evaluation by the concerned States

Member States Concerned participate in the coordinated review of the report (from the Reporting State)

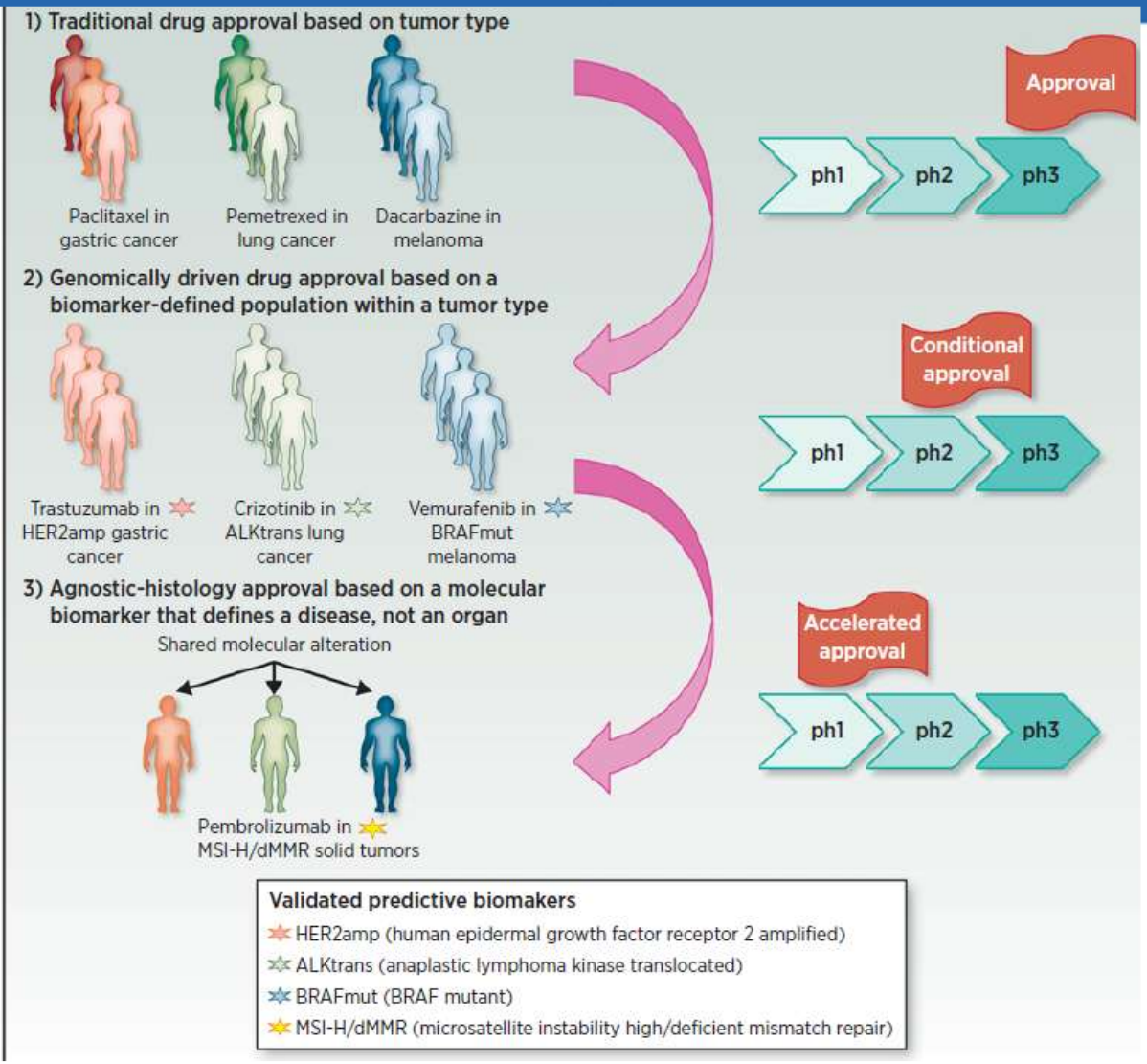
Reporting Member State submits the final report to the Sponsor (through the portal)



Authorization procedure for clinical trials (Part II - National)



Modelli non tradizionali di sperimentazione clinica



Agnostic-Histology Approval of New Drugs in Oncology: Are We Already There?
Hierro et al. Clin Cancer Res; 25(11), 2019

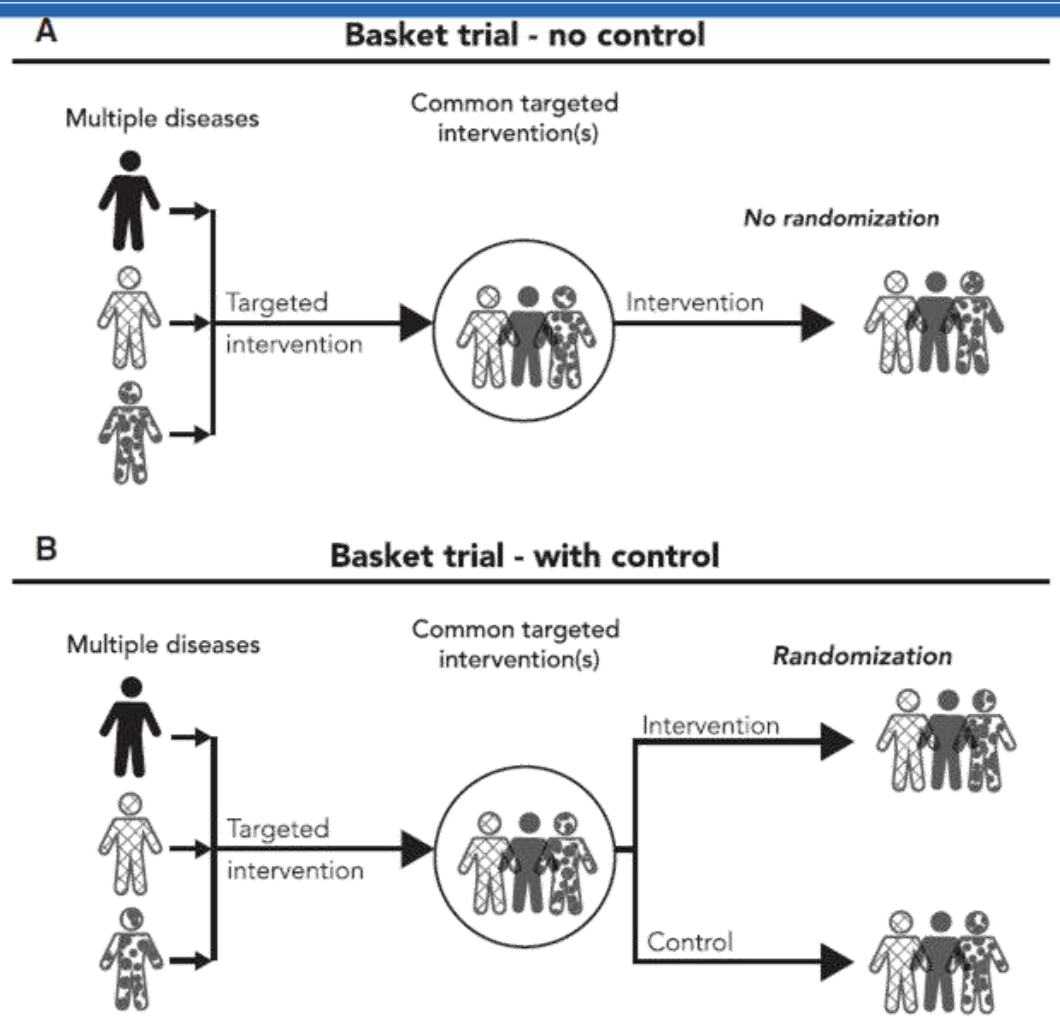


FIGURE 1. Illustrative Examples of a Basket Trial. (A) A single-arm basket trial with a single targeted intervention without a control group is illustrated. (B) A 2-arm randomized basket trial is shown.

Histology-agnostic indication?

CA: A Cancer Journal for Clinicians 70: 125-137, 2020

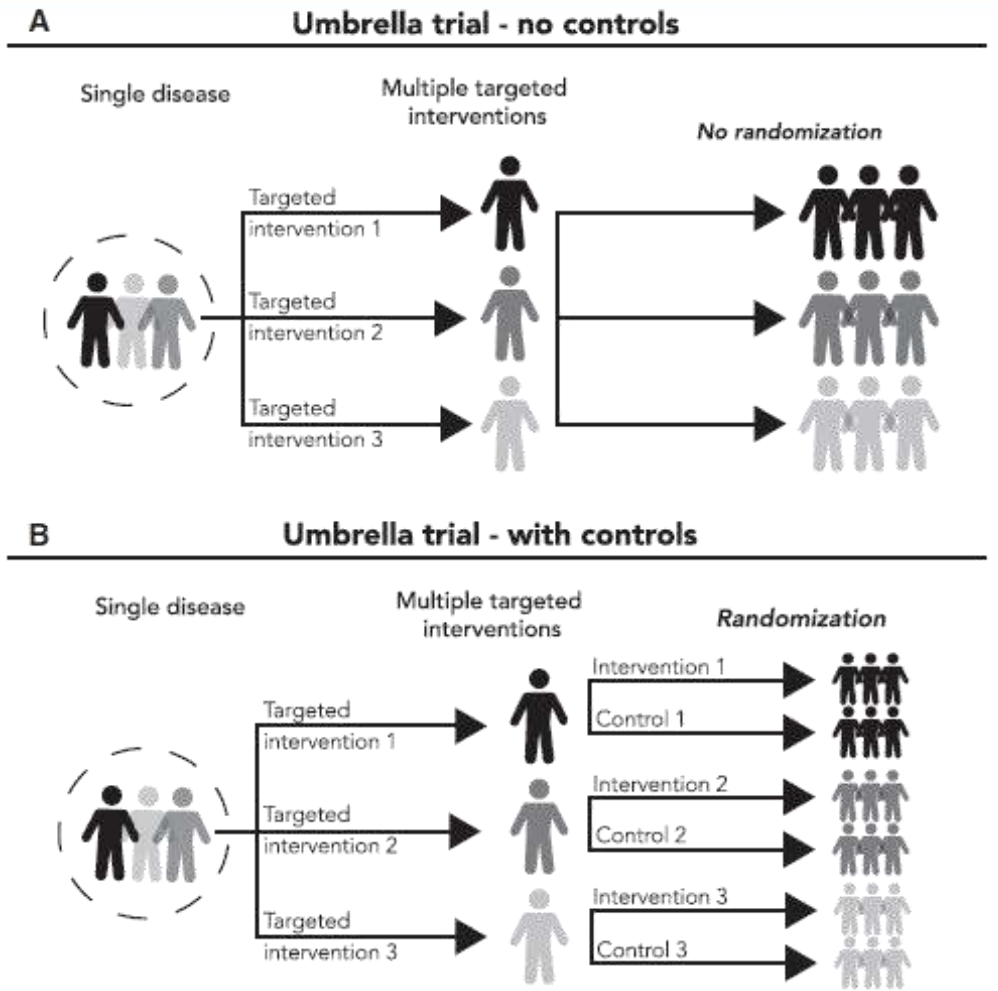
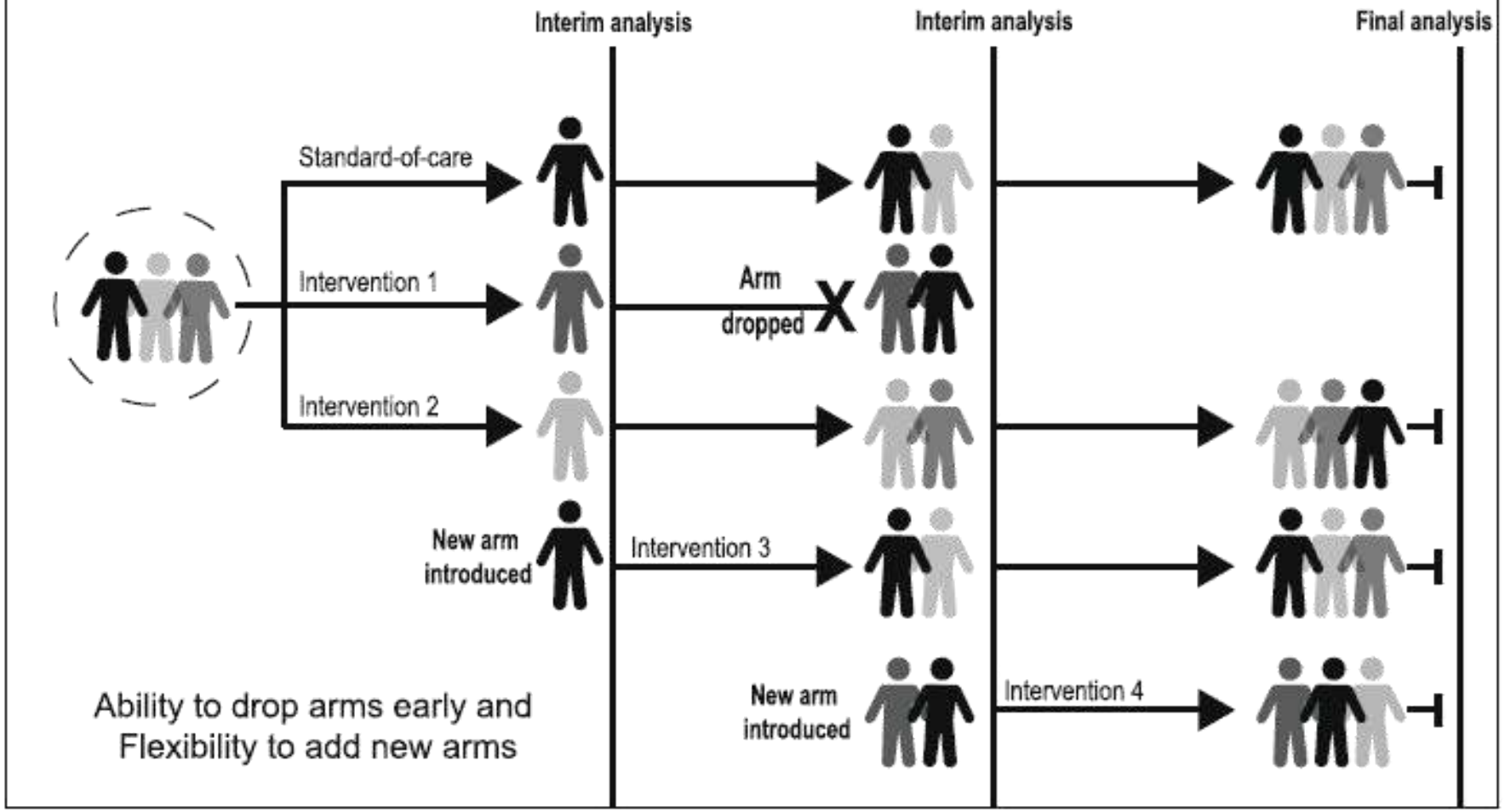


FIGURE 2. Illustrative Examples of an Umbrella Trial. (A) A nonrandomized umbrella trial with 3 targeted interventions is illustrated. (B) A randomized umbrella trial that includes 3 subgroups, each with a targeted intervention and a control group.

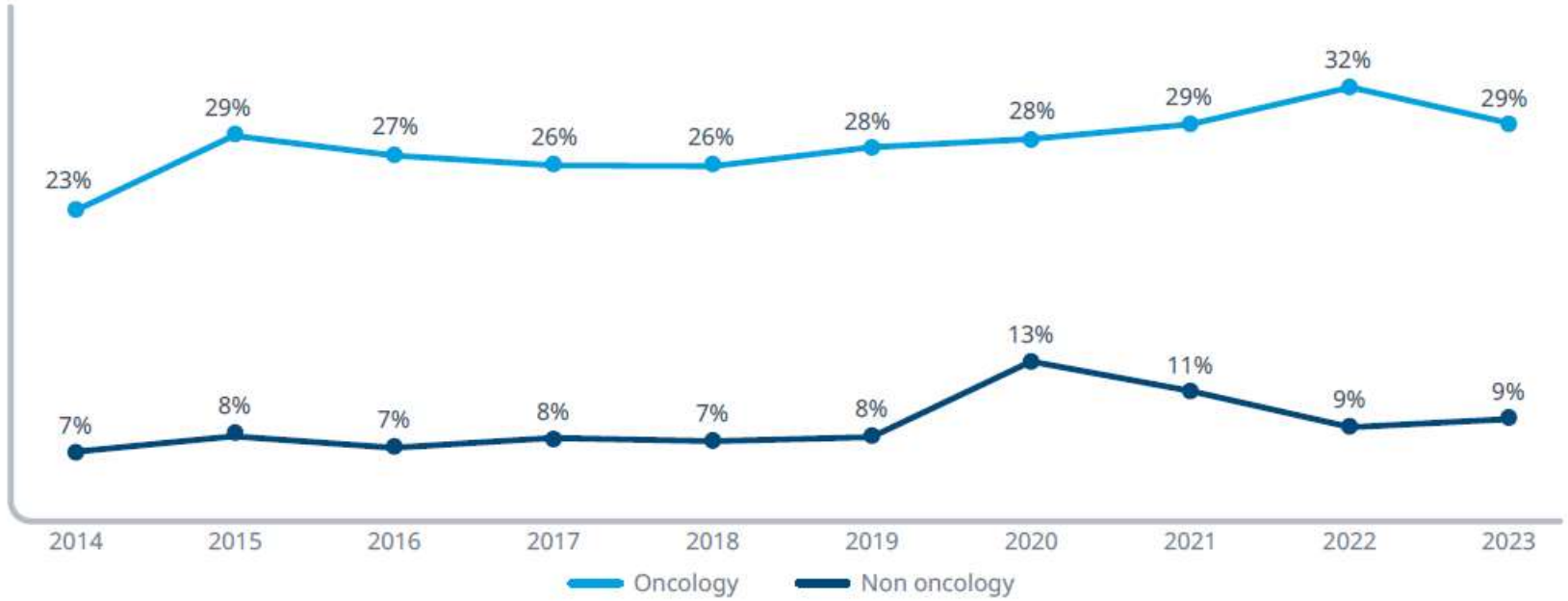
Platform trial



Park et al. Trials (2019) 20:572

Oncology trials more frequently use novel trial designs than trials for other diseases

Exhibit 25: Percent of industry-sponsored trials with novel trial design by start date, 2014–2023



The number of oncology trials utilizing novel trial designs has more than doubled since 2014, with 667 trials in 2023, while use in other therapy areas has grown more slowly and 253 non-oncology trials started in 2023 utilizing novel trial designs.

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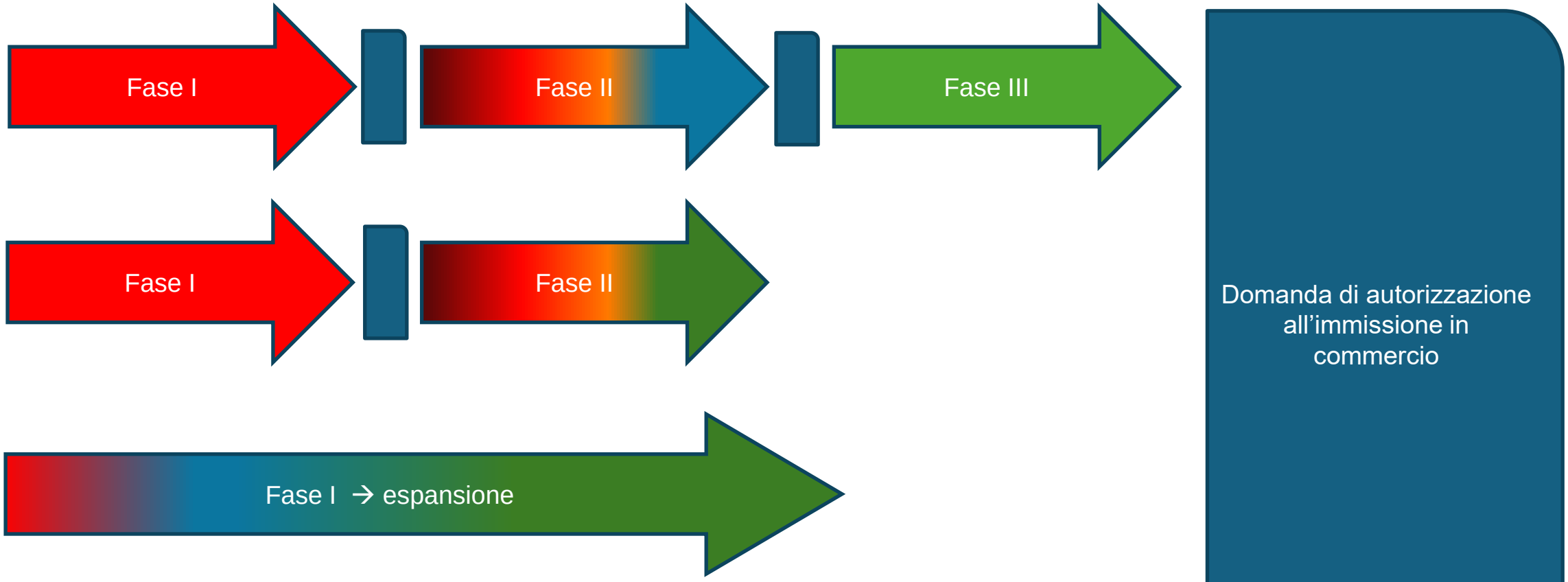
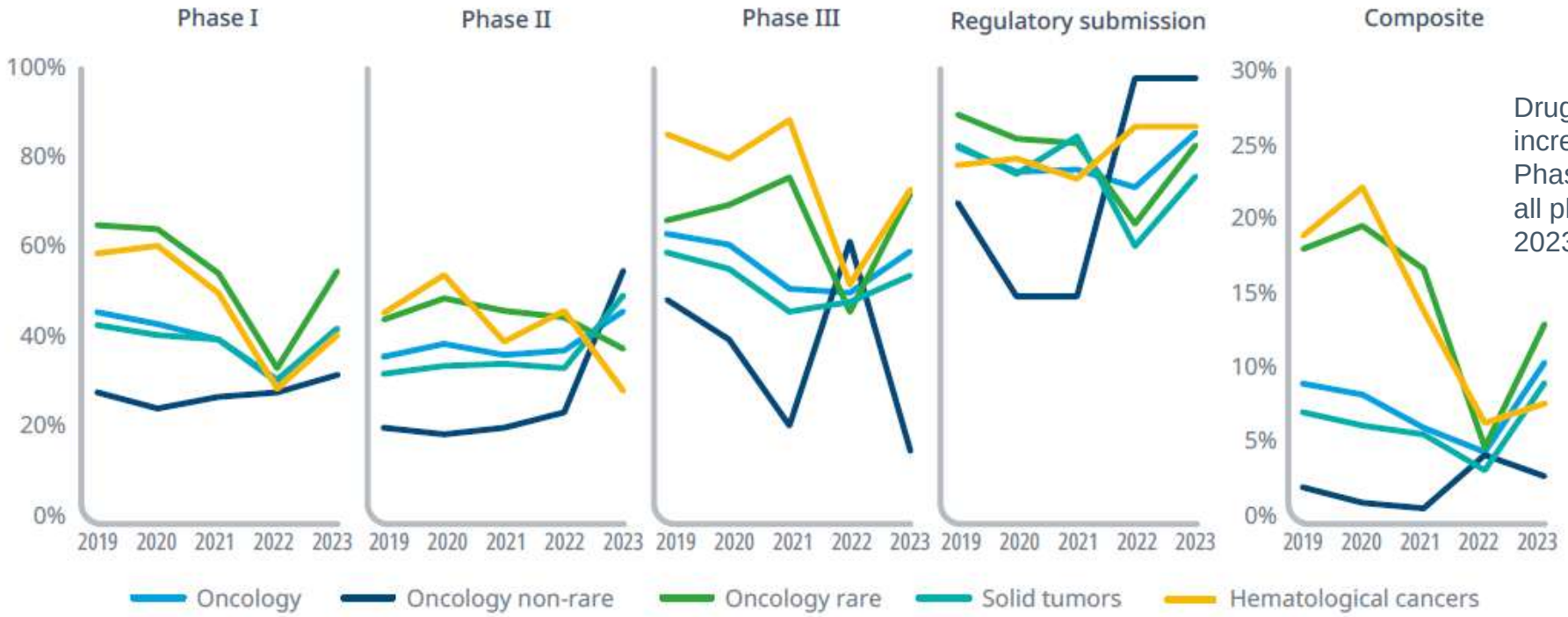

Fase I
Fase II
Fase III
Fase I
Fase II
Fase I → espansione
Domanda di autorizzazione all'immissione in commercio

The composite success rate in oncology rose in 2023 driven primarily by increases in rare oncology and solid tumor success rates

Exhibit 18: R&D phase and composite success rates by therapy area, 2019–2023



Drugs being investigated for rare cancers saw a sharp increase in success in 2023 across all phases except Phase II, resulting in a composite success rate across all phases that jumped from 5% in 2022 to 13% in 2023.

Source: IQVIA Pipeline Intelligence, Dec 2023; IQVIA Institute, Apr 2024.

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Exhibit 30: Oncology novel active substances (NASs) launched in 2023 in the United States

*ATTRIBUTES KEY: 1 = Oral, 2 = Biologic, 3 = Next-gen biotherapeutic, 4 = Orphan, 5 = First-in-class, 6 = Expedited review, 7 = U.S. Patent to launch ≤5 years, 8 = EBP originated, 9 = EBP launched.

TYPE	INDICATION	MOLECULE	BRAND	ATTRIBUTES* 1	2	3	4	5	6	7	8	9
Hematological cancers	Acute myeloid leukemia (AML)	quizartinib	Vanflyta	●			●		●			
	Hematologic malignancies planned for umbilical cord blood transplantation	omidubicel	Omisirge		●	●	●	●	●		●	●
	Myelofibrosis with anemia	momelotinib	Ojjaara	●			●				●	
	Relapsed or refractory diffuse large B-cell lymphoma	epcoritamab	Epkinly		●				●	●	●	●
	Relapsed or refractory follicular lymphoma	mosunetuzumab	Lunsumio		●		●	●	●			
	Relapsed or refractory large B-cell lymphomas	glofitamab	Columvi		●				●			
	Relapsed or refractory mantle cell lymphoma (MCL)	pirtobrutinib	Jaypirca	●			●		●		●	
	Relapsed or refractory multiple myeloma	elranatamab	Elrexfio		●		●		●			
		talquetamab	Talvey		●		●	●	●		●	
Solid Tumors	Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC)	nadofaragene firadenovec	Adstiladrin		●	●		●	●			
	Desmoid tumors	nirogacestat	Ogsiveo	●			●	●	●			●
	ER+, HER2-, ESR1-mutated breast cancer	elacestrant	Orserdu	●					●			●
	HR+, HER2- breast cancer with one or more PIK3CA/AKT1/PTEN-alterations	capivasertib	Truqap	●				●	●		●	
	Intrahepatic cholangiocarcinoma with FGFR2 fusions or rearrangements	futibatinib	Lytgobi	●			●		●		●	●
	Merkel cell carcinoma	retifanlimab	Zynyz		●		●		●		●	●
	Prostate cancer	flotufolastat F 18	Posluma							●	●	●
	Refractory metastatic colorectal cancer	fruquintinib	Fruzaqla	●					●		●	
	ROS1-positive non-small cell lung cancer	repotrectinib	Augtyro	●			●		●		●	
Totals				9	8	2	11	6	16	2	11	7

There were 18 new cancer medicines launched in the U.S. in 2023, with 11 that were orphan designated

Source: IQVIA Institute, Apr 2024.

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Azienda

Presentazione della domanda di autorizzazione all'immissione in commercio

EMA

Approvazione
Approvazione condizionata
Approvazione in circostanze eccezionali

Valutazione e concessione AIC (CHMP, CE)

Azienda

Presentazione della domanda di classificazione, rimborsabilità e prezzo

Decisione sulla rimborsabilità

AIFA

Commissione Consultiva Scientifico-Economica (CSE)

Valutazione del ruolo del farmaco nella terapia della patologia in indicazione (ammissibilità al rimborso, regimi di fornitura, eventuali restrizioni dell'indicazione approvata a livello europeo …)

Negoziazione del prezzo e delle condizioni di pagamento

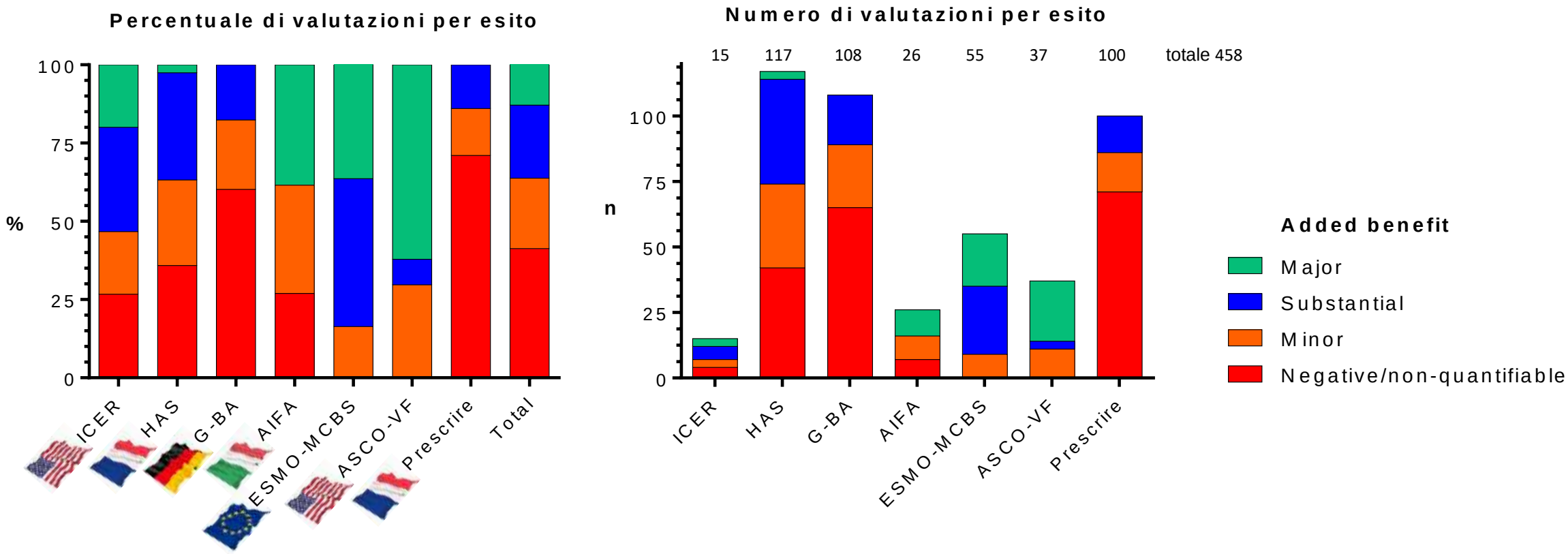
Consiglio di Amministrazione AIFA

Pubblicazione in Gazzetta Ufficiale

PRIME – Benefits and Enhanced Support

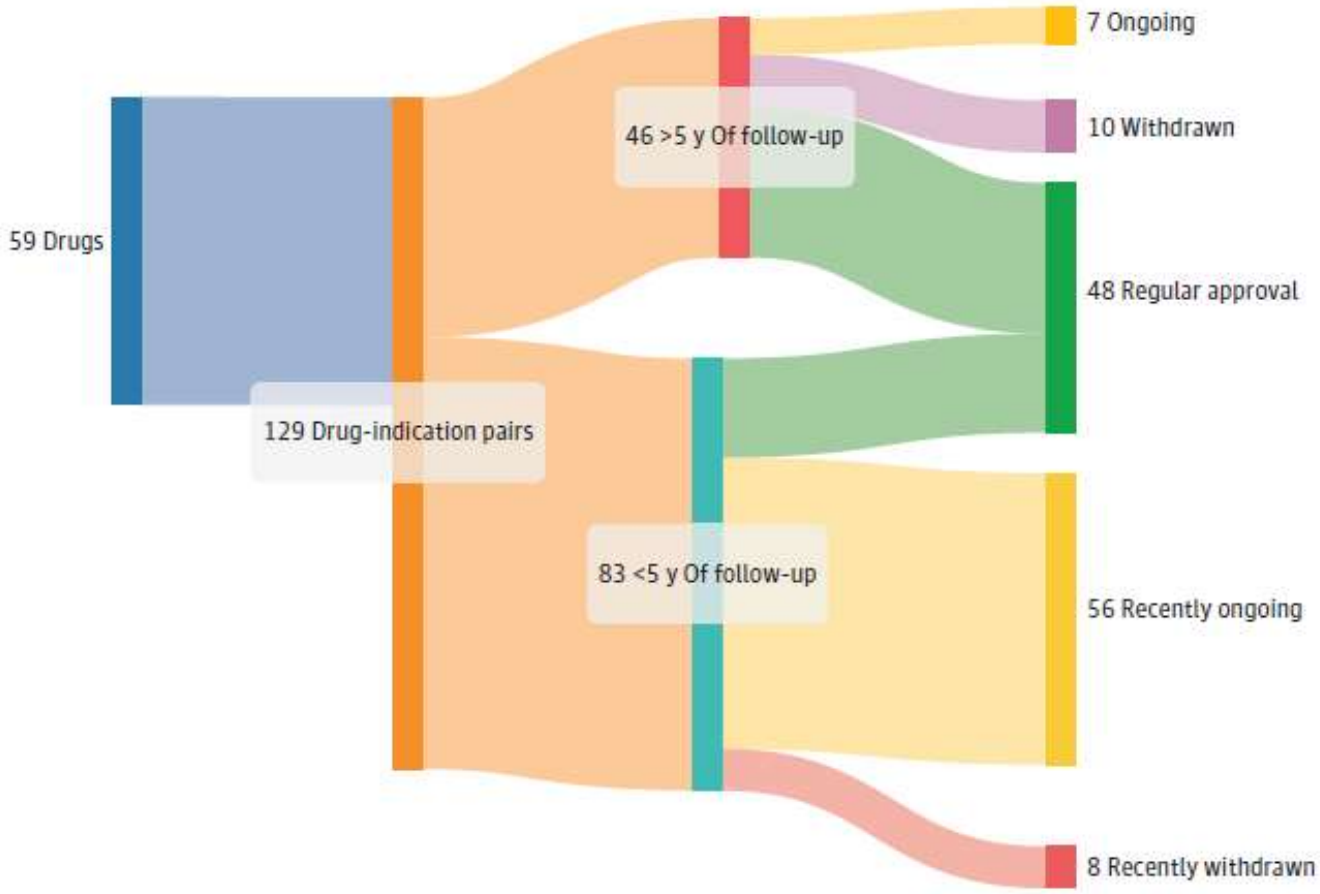
Benefit	Stage	Details
Appointment of PRIME Scientific Coordinator	**Immediately** after PRIME eligibility is granted	Dedicated EMA contact point to coordinate all support provided through PRIME
Early appointment of CHMP or CAT rapporteur	**One month** after PRIME eligibility is granted	Discussion on technical and scientific preparatory aspects of the marketing authorisation application
Kick-off meeting with rapporteur and multidisciplinary group of experts from EMA / European medicines regulatory network	**Three-four** months after PRIME eligibility is granted	Guidance on overall development plan, future scientific advice and regulatory strategy
Iterative scientific advice on overall development plans and key issues **NEW in 2023** Supported by Regulatory Roadmap and development tracker)	At any stage, and at major development milestones	Opportunity to involve other stakeholders such as health technology assessment (HTA) bodies, patients and the US Food and Drug Administration (FDA)
Expedited follow-up scientific advice (under certain criteria) with shortened timelines **NEW in 2023**	At any stage	Increased flexibility in providing scientific advice and a shortened timeline for related procedures
Submission readiness meeting **NEW in 2023**	Approximately one year ahead of marketing authorisation application	Discussion on development status and dossier maturity, application type (e.g. conditional marketing authorisation application), post-marketing evidence-generation and potential regulatory challenges
Confirmation of potential accelerated assessment	At time of marketing authorisation application	Increased certainty of assessment timelines

if the CHMP decides the product is of major interest for public health and therapeutic innovation 210 gg -> 150



Dati da: Brinkhuis F, et al. Added benefit and revenues of oncology drugs approved by the European Medicines Agency between 1995 and 2020: retrospective cohort study. BMJ. 2024;384:e077391

Figure 1. Oncology Drugs Granted Accelerated Approval From 2013 to 2023, and Regulatory Outcomes



Oncology drugs granted accelerated approval and regulatory outcome, based on follow-up time.

Liu ITTet al. Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval. JAMA. 2024 May 7;331(17):1471-1479.

Rimborso SSN	Secondo l'indicazione approvata (*on label*)	Al di fuori dell'indicazione approvata (*off label*)	
Sì	Classificazione in classe di rimborso (A, H)	Inserimento nella lista dei farmaci previsti dalla legge 648/96	CSE
		Ammissione, su base individuale, al fondo 5% (Legge 326/2003, Art. 48)	AIFA
No	Classe C , C/osp		CSE
	Classe Cnn		Legge Balduzzi (CSE)

Pagatore	Secondo l'indicazione approvata (*on label*)	Al di fuori dell'indicazione approvata (*off label*)
Regione	Acquisto da parte dell'azienda sanitaria di farmaci non ammessi alla rimborsabilità	Acquisto da parte dell'azienda sanitaria di farmaci non autorizzati per l'indicazione
Azienda farmaceutica		"Uso compassionevole" (farmaci in sperimentazione clinica): cessione gratuita da parte delle aziende farmaceutiche (D.M. 7 settembre 2017)
Promotore		Inserimento in studi clinici
Cittadino	Spesa privata (Classe C, Cnn)	Spesa privata (prescrizione sotto la responsabilità del medico)

Elementi critici per la valutazione delle ATMP, farmaci per malattie rare e terapie di precisione

- Studi clinici condotti su popolazioni limitate
- Frequente mancanza di un gruppo di controllo
- Incertezza sulla storia naturale spesso basata su dati storici che comprendono trattamenti evoluti nel tempo
- Utilizzo di endpoint surrogati di validità incerta
- Follow up brevi per la valutazione di endpoint robusti

Elementi che condizionano la negoziazione

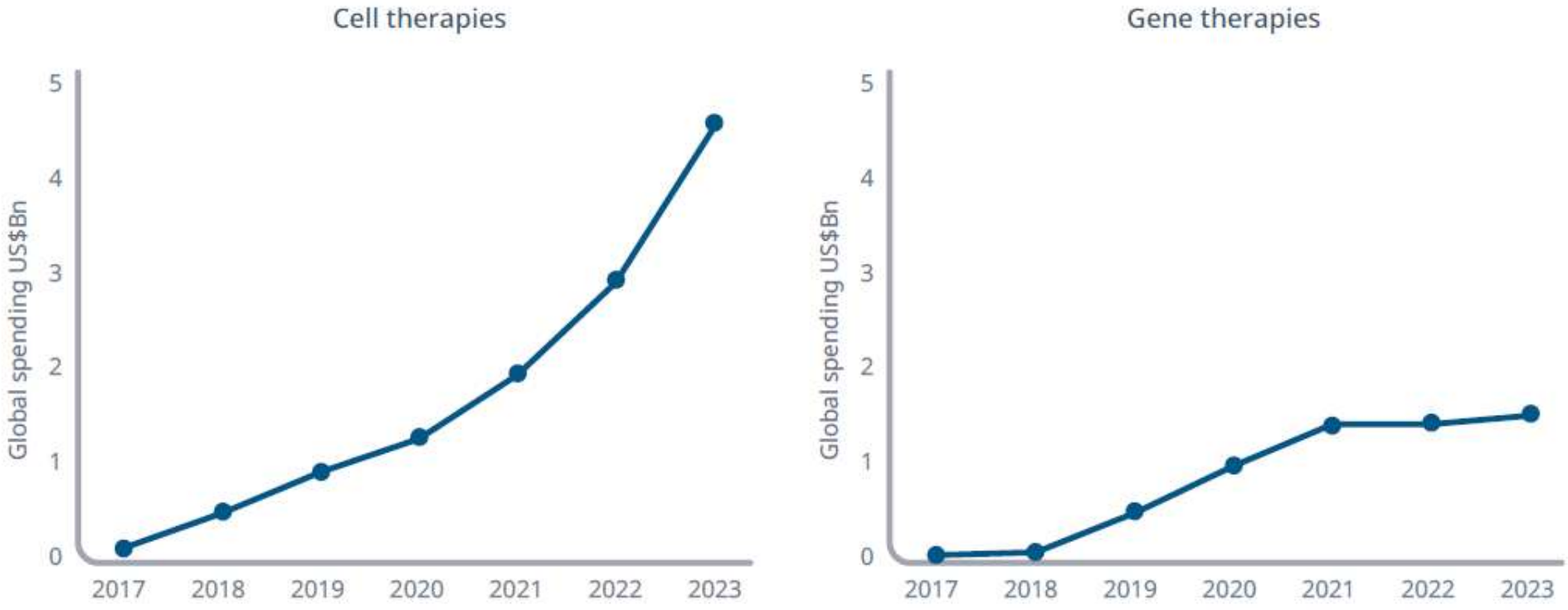
- Prezzo di partenza definito dalle aziende più sulla base dei risultati economici che intendono raggiungere (valore finanziario) che dei benefici apportati alla terapia
- Ridotti margini di negoziazione delle filiali italiane nell'ambito della strategia globale
- Difficoltà a comprendere a pieno reali benefici aggiuntivi
- Volontà di dare al più presto opzioni terapeutiche quando le terapie correnti sono poco efficaci contro il costo elevato a fronte di evidenze preliminari
- Equità dell'impiego di risorse ingenti in un ambito di limitazione della spesa per trattare piccoli numeri di pazienti (problema fortunatamente non attuale)

Meccanismi che tengano conto delle incertezze
- durata dei contratti (impegni per la rinegoziazione)
- flessibilità nella definizione del prezzo sulla base delle evidenze accumulate
- condizionalità

Controllo della spesa

- Sconti (fissi o progressivi sulla base del fatturato)
- Tetti di spesa per prodotto
- Managed Entry Agreements
  - Finanziari
    - Cost-sharing (mediante payback o nota di credito)
    - Tetti di spesa (per paziente)
  - Basati sui risultati
    - Pagamento per risultato (il prezzo viene pagato ma l'azienda rimborsa quanto pagato per i pazienti che non rispondono)
      - Condivisione del rischio (rimborso parziale)
      - Rimborso totale
    - Pagamento al risultato (il prezzo viene suddiviso in rate che vengono pagate al raggiungimento/mantenimento di un determinato risultato, applicato per farmaci somministrati una sola volta da cui ci si attendono risultati durevoli)

Andamento della spesa per ATMP (globale)



Source: Company Financials; IQVIA Institute, Dec 2023.
Notes: Spending estimates based on company reported sales.

Source: IQVIA Institute for Human Data Science. Strengthening Pathways for Cell and Gene Therapies: Current State and Future Scenarios. March 2024. Available from www.iqviainstitute.org

Grazie per l'attenzione

Multi-specific antibodies	The emergence of bi-specific (and eventually tri-, quad-) antibodies bring enhanced targeting and improved efficacy to a variety of solid and hematological malignancies. Novel biomarker targets are being discovered and then being joined to more well-established immune system targets on T-cells to enable more effective engagement of the immune system to fight tumors
Non-coding RNAs	The role of non-coding RNAs as potential targets and as diagnostic markers is linked to their cellular function described as passing on the memory of 'self' and 'non-self' to subsequent generations of cells. The body's inability to identify cancers as exogenous threats is one of the key mechanisms by which cancers evade the immune system
mRNA cancer vaccines	Cancer vaccines are unlike traditional vaccines and act more like immune system amplifiers rather than as a prevention of disease. Immunotherapies, CAR T-cell therapies and other modalities coupled with readily engineered mRNA vaccines promise to boost the efficacy of the standalone treatments. The most recent example being a combination RNA-based individualized neoantigen therapy (mRNA-4157) with a PD-1 blockade (pembrolizumab) in adjuvant treatment of high-risk resected melanoma is showing positive results at three years in a phase 2b study (KEYNOTE-942)
Antibody-drug conjugates (ADCs)	There have been 15 antibody-drug conjugates launched globally, and 857 trials started in the past decade, representing the fastest growing area in oncology trials. Dozens of targets, binding mechanisms and conjugates (chemotherapy payloads) are being researched, and many show significant promise with high specificity and tolerability. ADCs have shown promise in solid tumors and hematological cancers and often result in sustained response and lack of resistance, enabling them to be used for multiple lines of therapy with additional therapies added on to prolong patient response
Radioligands	Representing the modern iteration of traditional systemic radiotherapy, novel targeting using ligands brings therapeutic radiation precisely to tumors with greater specificity and less toxicity. There are nearly 100 trials ongoing with a focus in prostate and neuroendocrine tumors where ligand affinity has been best demonstrated to date
Cell and gene therapies	Cell and gene therapies are moving beyond CAR T-cell therapies with CD19 or BCMA targets, and shifting to other targets as well as approaches that amplify or redirect the body's processes to anticancer approaches. These include the 2023 approvals of nadofaragene firadenovec for bladder cancer that encourages interferon alfa-2b production and omidubicel, which reduces immunocompromised periods for hematological cancer patients by boosting their own neutrophil production
Next wave of IO targets beyond PD-1/PD-L1	Emerging immune checkpoints such as LAG-3 and TIM-3 have shown positive results in melanoma and others, paving the way for immunotherapy beyond PD-1/PD-L1. Combinations of existing PD-1/PD-L1s and TKIs, CTLA-4, IgA/PD-1, TIL, cell therapies, cancer vaccines, and novel biomarkers like Claudin18.2, Claudin6, CEACAMS, offer better targeting, less resistance, and greater efficacy across a range of tumors. Tissue-agnostic drug approvals To date there have been five tissue agnostic approvals, the first was pembrolizumab in 2014. Research has found that tumors with some specific mutations correlate with drug response across tumors, and as more biomarkers with these attributes are found, treatment can shift from tumor-specific to mutational biomarker-driven. Biomarkers central to this area include microsatellite instability (MSI), high tumor mutation burden (TMB), NTRK1-3, RET inhibitors, BRAF V600E and more in ongoing research. Most drugs are also studied in confirmatory trials in specific tumor populations, and many other medicines are being studied in combination with these 'backbone' therapies.

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