「Undruggable targetに対する臨床開発」

2020's

2030's Rebuilding a hospital

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Undruggable target ?

- Undruggable target = 「創薬不可能」 または、「治療不可能な」標的

- 治療薬において、一般的な薬物標的はタンパク質の触媒部位

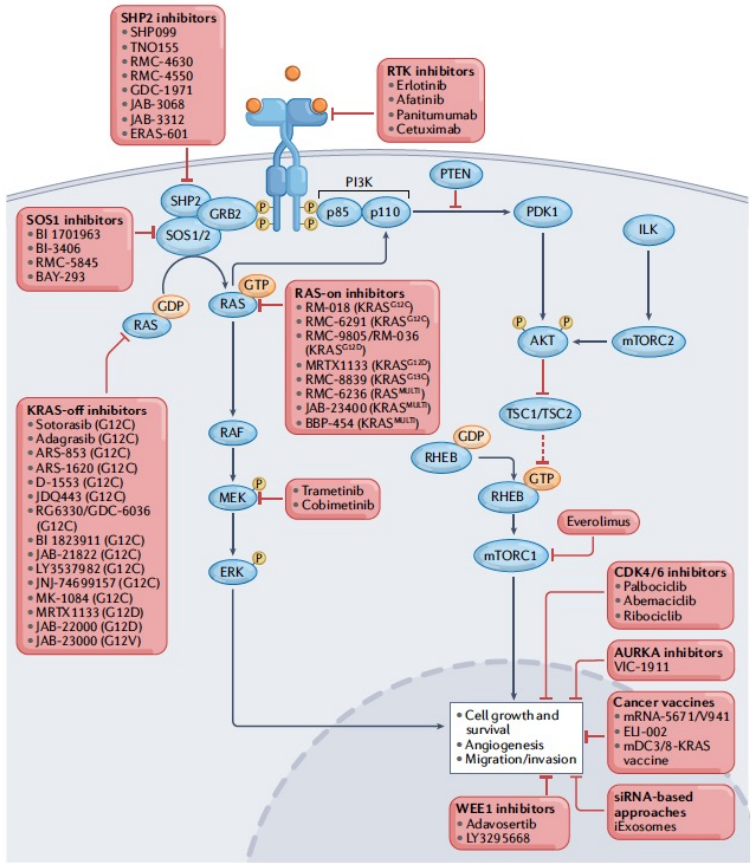
- がんの標的のいくつかは（代表的には、β-カテニン、*RAS*、*TP53*、転写因子 (STAT3、MYCなど)
  - ✓ リガンドと薬物が結合できるアクセス可能な深い疎水性ポケットがない
  - ✓ 酵素活性が欠如している（活性部位がない）ため、「創薬不可能」とされてきた

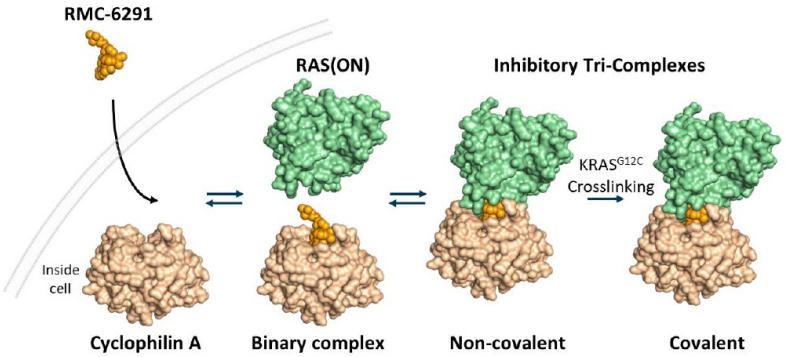
- ➢ 構造生物学の進歩 、三次元化学ライブラリー、分子標的と相互作用の側面を視覚化または予測するための新しい計算手法など、最近の技術進歩により、創薬不可能性の概念が変わってきた

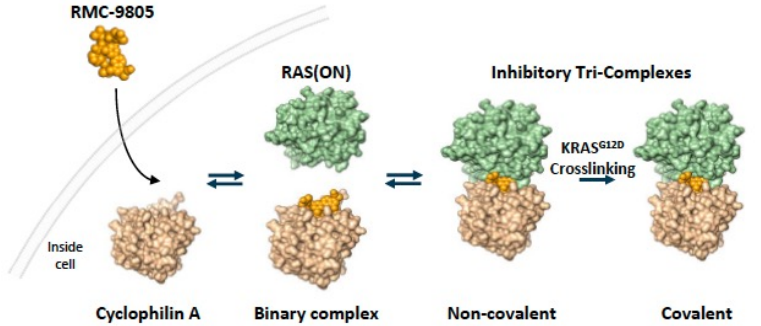
- ➢ さらに、薬理学における進歩も同様であり、治療用抗体および生物学的製剤、特定のタンパク質の選択的分解を可能にする戦略、および核酸ベースの化合物の送達システムの改善などが達成されつつある

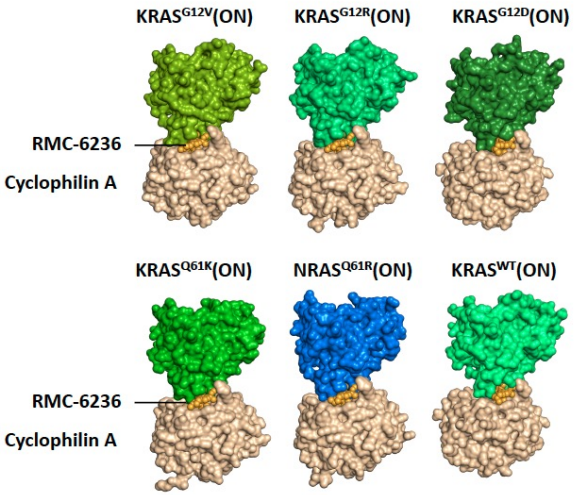
KRAS inhibitor

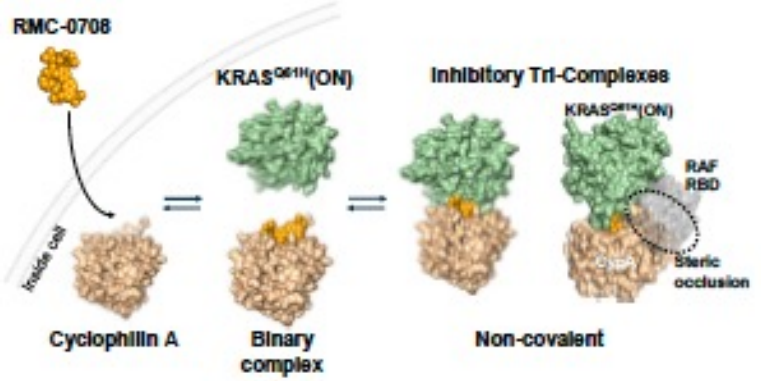
RAS ^{on} 阻害剤など、新たな創薬技術が臨床導入へ









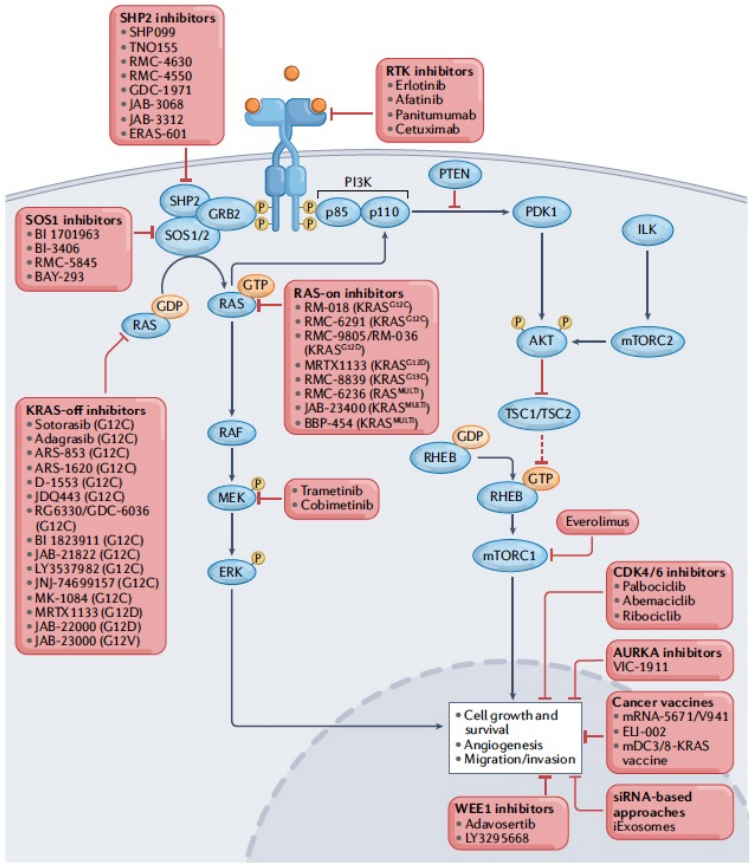


Nat Rev Clin Oncol 2022 Oct;19(10):637-655

https://www.revmed.com/pipeline/rason-inhibitors

KRAS inhibitor

様々なmodalityの薬剤が開発されている

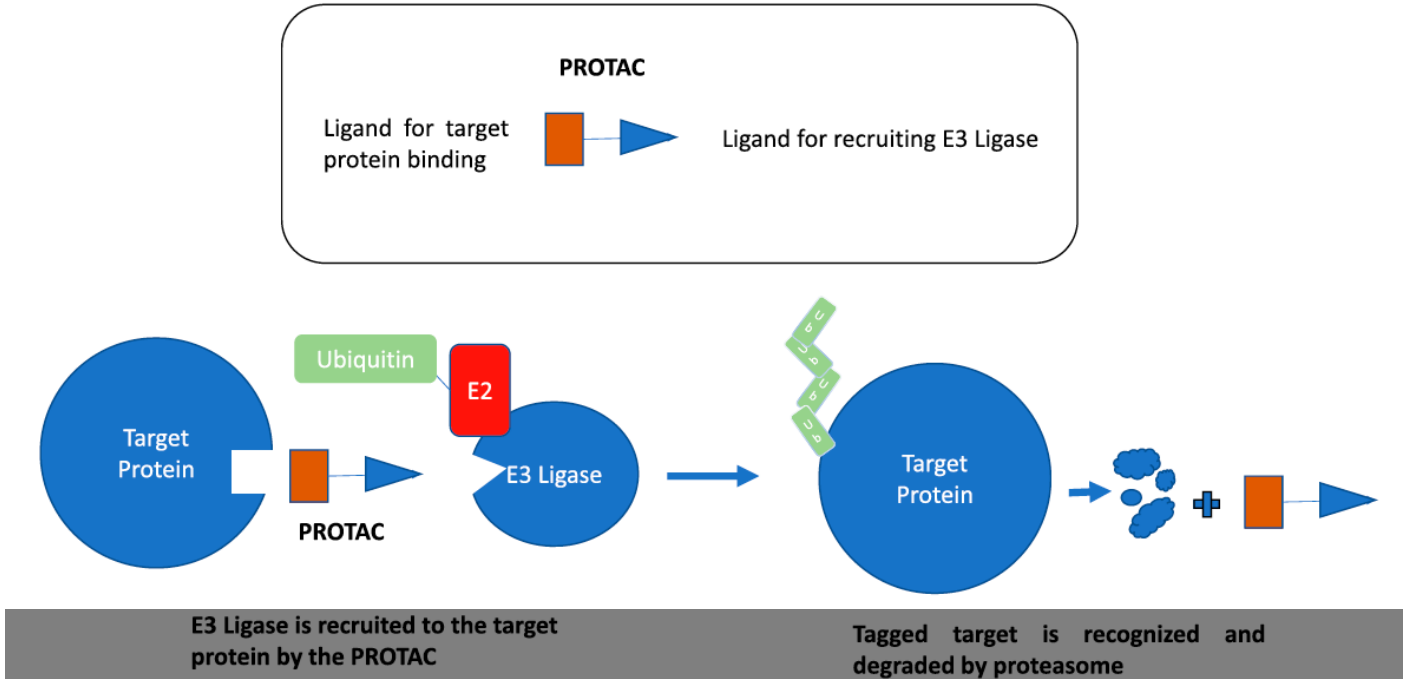


Strategy and target	Agent	Phase of development
RAS degraders		
$KRAS^{G12C}$	LC-2 (PROTAC)	Preclinical studies
$KRAS^{G12C}$, $KRAS^{G12D}$, $KRAS^{G12V}$ and $KRAS^{Q61H}$	K27-SPOP	Preclinical studies
RAS toxins		
Pan-RAS	$RRSP–DT_B$	Preclinical studies
Adoptive cell therapy		
$KRAS^{G12V}$	**Specific TCRs**	Clinical trials (NCT04146298)
$KRAS^{G12D}$	**Specific TCRs**	Preclinical studies
Cancer vaccines		
$KRAS^{G12C}$, $KRAS^{G12D}$, $KRAS^{G12V}$ and $KRAS^{G13D}$	**mRNA-5671/V941**	Clinical trials (NCT03948763)
$KRAS^{G12C}$, $KRAS^{G12V}$, $KRAS^{G12D}$, $KRAS^{G12A}$, $KRAS^{G13D}$ or $KRAS^{G12R}$	**Mutant KRAS-targeted long-peptide vaccine**	Clinical trials (NCT04117087)
$KRAS^{G12C}$, $KRAS^{G12V}$, $KRAS^{G12D}$ or $KRAS^{G12R}$	**mDC3/8-KRAS vaccine**	Clinical trials (NCT03592888)
$KRAS^{G12D}$ or $KRAS^{G12R}$	ELI-002 2P	Clinical trials (NCT04853017)
KRAS siRNAs		
Various mutant KRAS mRNAs	Various nanoparticle-based technologies	Preclinical studies
$KRAS^{G12D}$ mRNA	iExosomes	Clinical trials (NCT03608631)

Nat Rev Clin Oncol 2022 Oct;19(10):637-655

PROTAC

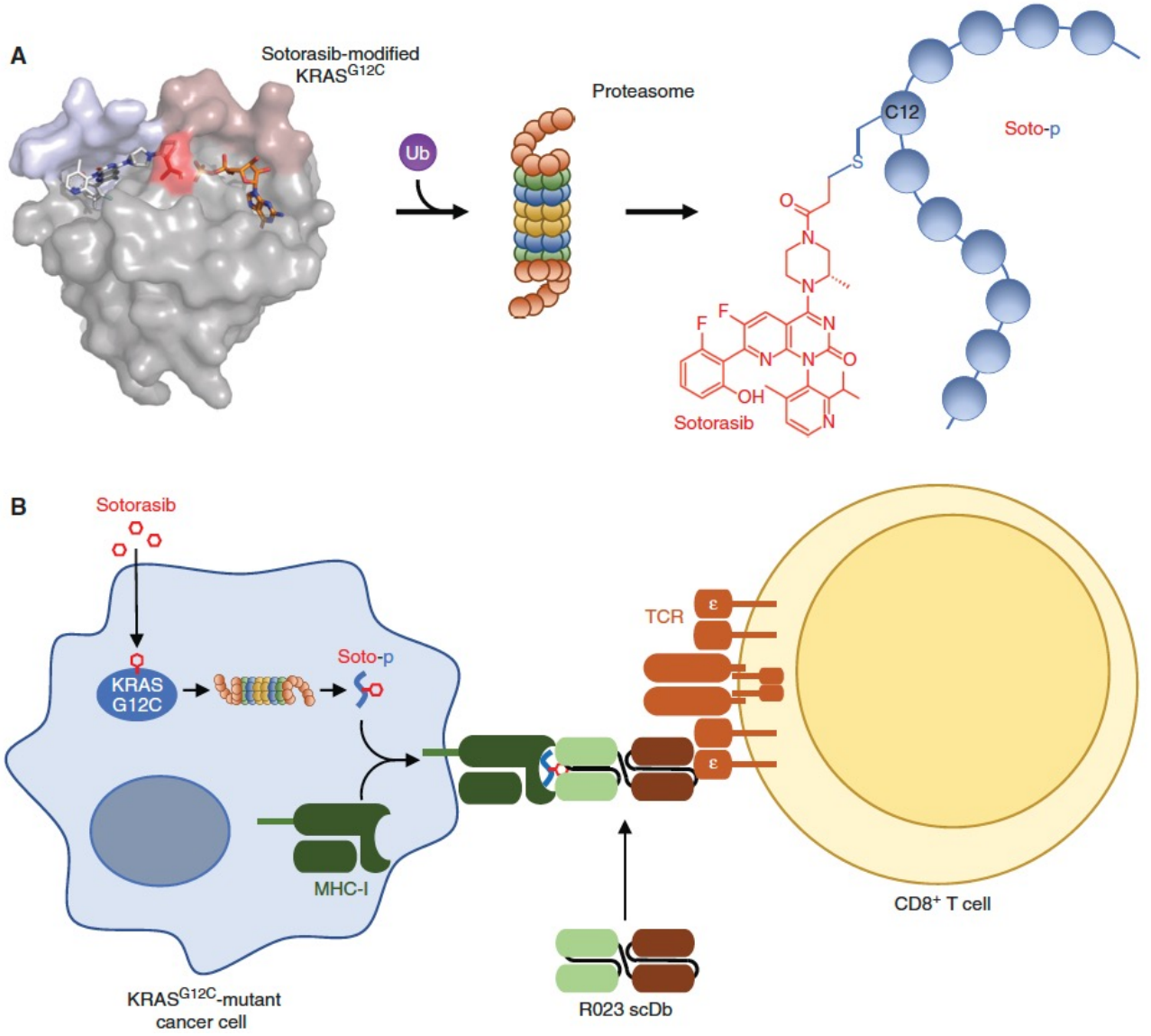
- Proteolysis Targeting Chimera：標的タンパク質分解誘導化合物
- ユビキチン・プロテアソームシステ（UPS）を利用して，細胞内の標的タンパク質の分解を誘導する低分子化合物



Mol Cancer. 2022 Apr 11;21(1):99

Specific TCRs

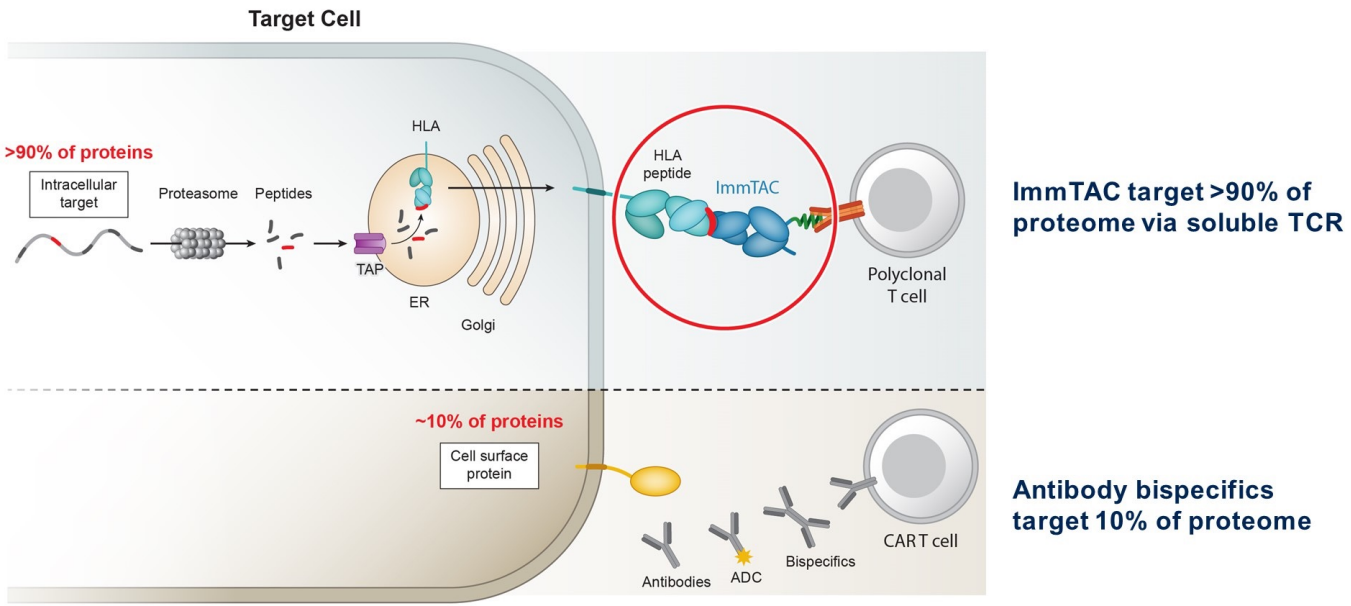
- *KRAS*変異タンパク質の特定のアミノ酸置換が、細胞傷害性T細胞の標的となりうる新抗原として十分な構造差を示すか検討中
- *KRAS G12C*のシステイン置換をsotorasibで共有結合的に修飾すると、*KRAS G12C*単独よりも効果的にMHC提示型のネオアンチゲンとなりうる



Cancer Discov. 2023 Jan 9;13(1):19-22.

BiTE formulation Specific TCR Tebentafusp

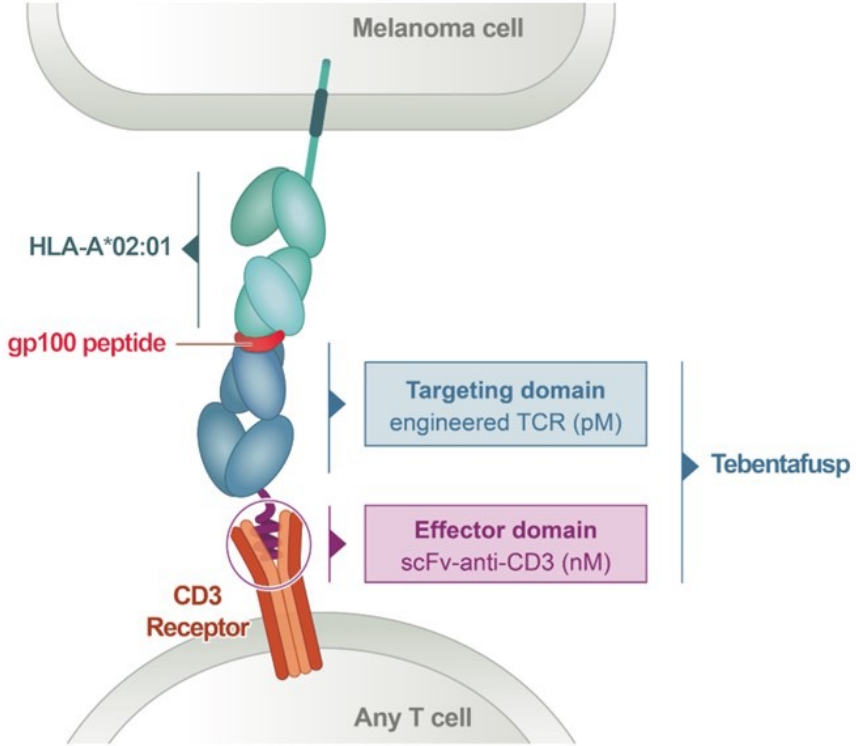
Tebentafusp is a first-in-class, bispecific gp100 peptide-HLA-A*02:01 directed T cell receptor CD3 T cell engager



ImmTAC target >90% of proteome via soluble TCR

Antibody bispecifics target 10% of proteome

ImmTAC, Immune mobilizing T cell receptor Against Cancer



ImmTAC, Immune mobilizing monoclonal T cell receptor Against Cancer

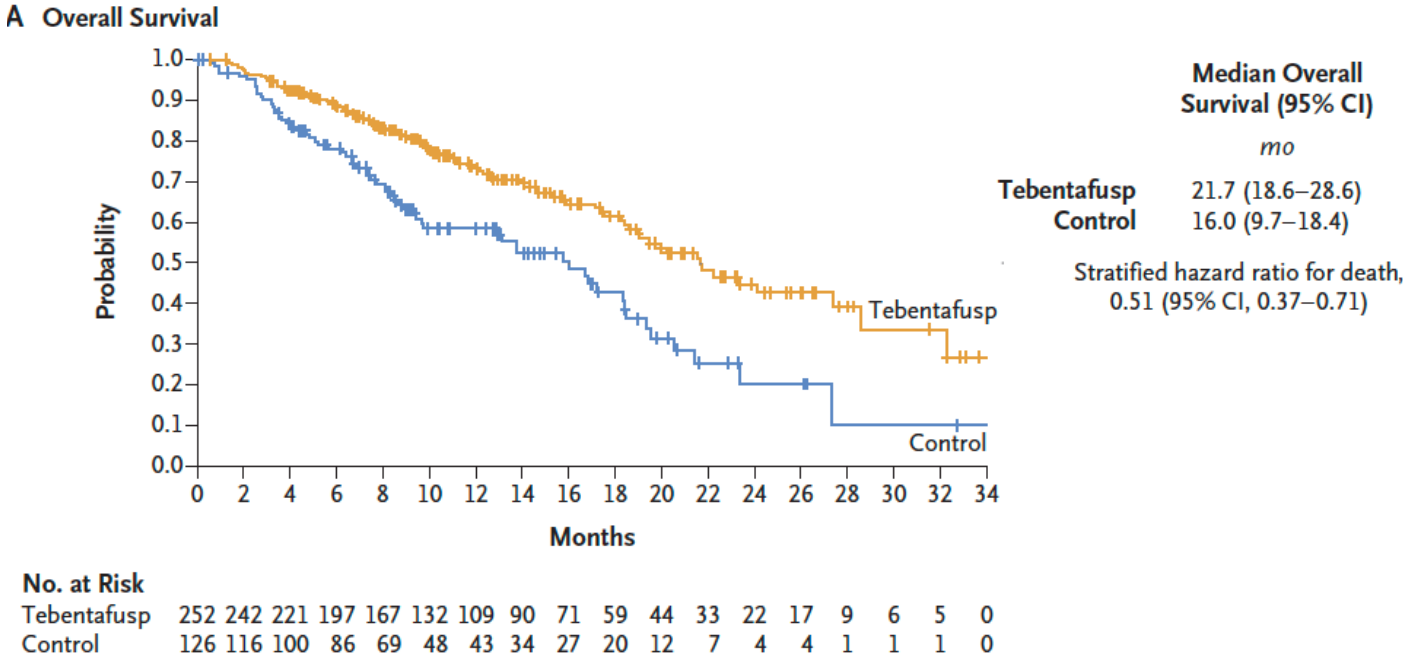
1. Nathan P, et al. *N Engl J Med* 2021;385:1196-206; 2. Middleton MR, et al. Clin Cancer Res 2020; 26: 5869-78

Journal of Clinical Oncology 40, no. 16_suppl (June 01, 2022) 104-104.

Tebentafusp

RECIST response rate and PFS underestimate OS

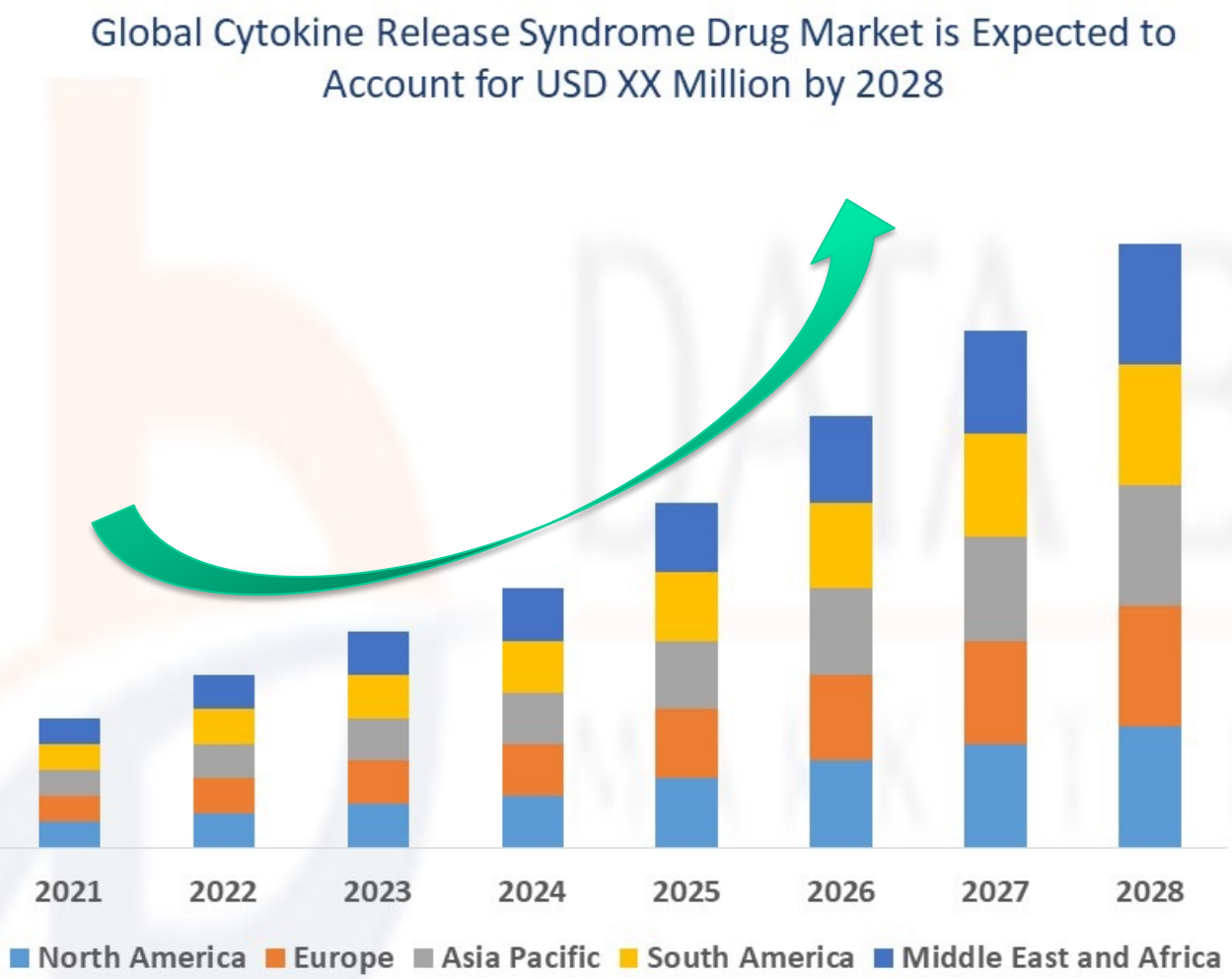
	Tebentafusp vs Investigator Choice (IC)
RECIST response rate	9% vs 5%
Tumor shrinkage*	39% vs 24%
PFS (HR)	0.73 (95% CI: 0.58, 0.94)



Recently approved by FDA

N Engl J Med . 2021 Sep 23;385(13):1196-1206.

市場拡大する新規がん免疫療法



Global Cytokine Release Syndrome Drug Market, By Regions, 2021 to 2028

2021

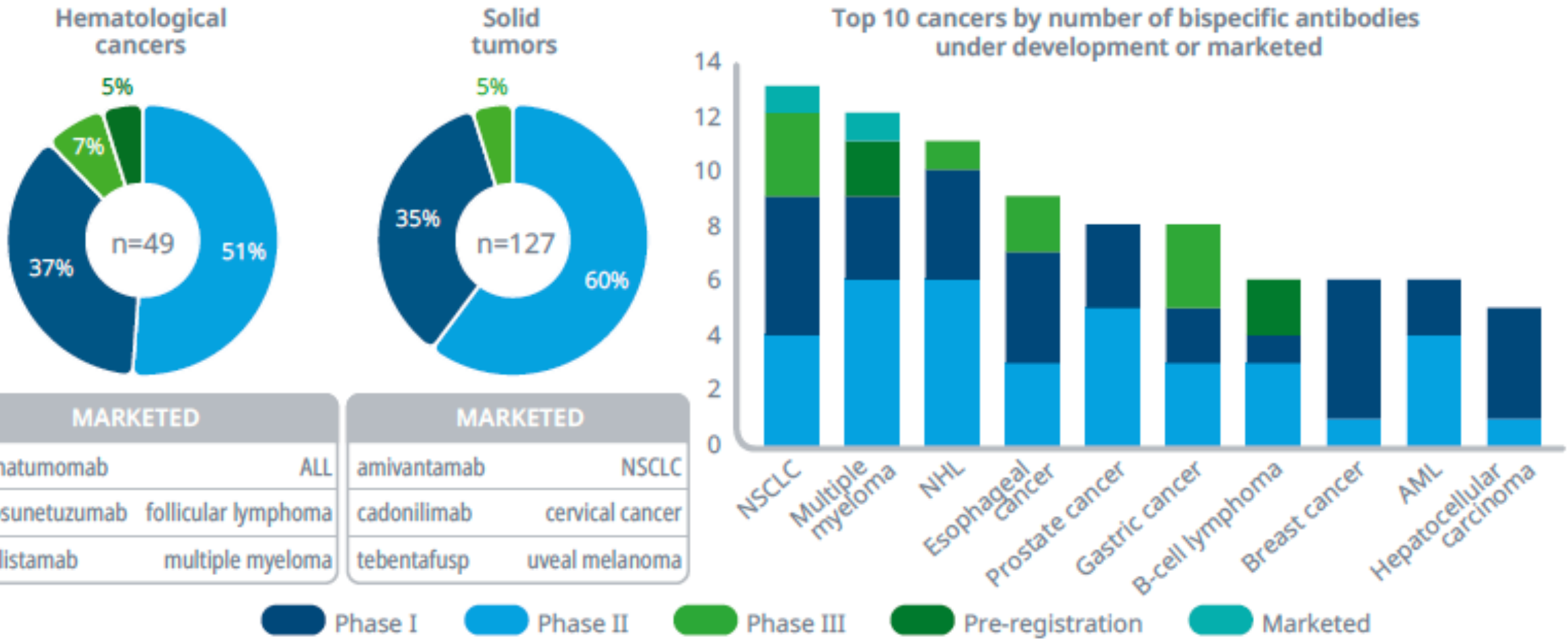
2028

DATA BRIDGE MARKET RESEARCH

DATA BRIDGE
MARKET RESEARCH

6 bispecific antibodies are marketed globally for oncology with many in development for rare hematological cancers

Exhibit 7: Bispecific antibody pipeline by tumor and phase, 2022



MARKETED	
blinatumomab	ALL
mosunetuzumab	follicular lymphoma
teclistamab	multiple myeloma

MARKETED	
amivantamab	NSCLC
cadonilimab	cervical cancer
tebentafusp	uveal melanoma

Global Trends in R&D 2023

国立がん研究センター東病院における早期開発薬剤の変遷
(固形がん)

投与患者数割合

	2017年度	2018年度	2019年度	2020年度	2021年度
IO	42.4%	50.8%	41.6%	40.2%	27.2%
T-cell engagers	0.8%	0.0%	2.2%	9.3%	12.6%
ゲノム関連	27.2%	19.5%	27.7%	15.9%	30.5%
ADC	4.0%	5.1%	9.5%	17.8%	17.2%
抗体	7.2%	3.4%	2.9%	3.7%	4.0%
低分子	12.8%	9.3%	2.9%	5.6%	8.6%
殺細胞薬	5.6%	11.9%	13.1%	5.6%	0.0%

Vaccine

- mRNAワクチンを中心に活発にチャレンジが始まっている
- TSAを標的としたmRNAではmelanomaでpositiveな結果が発表されている

Oncology Pipeline: Significant Progress and Expansion in 2022

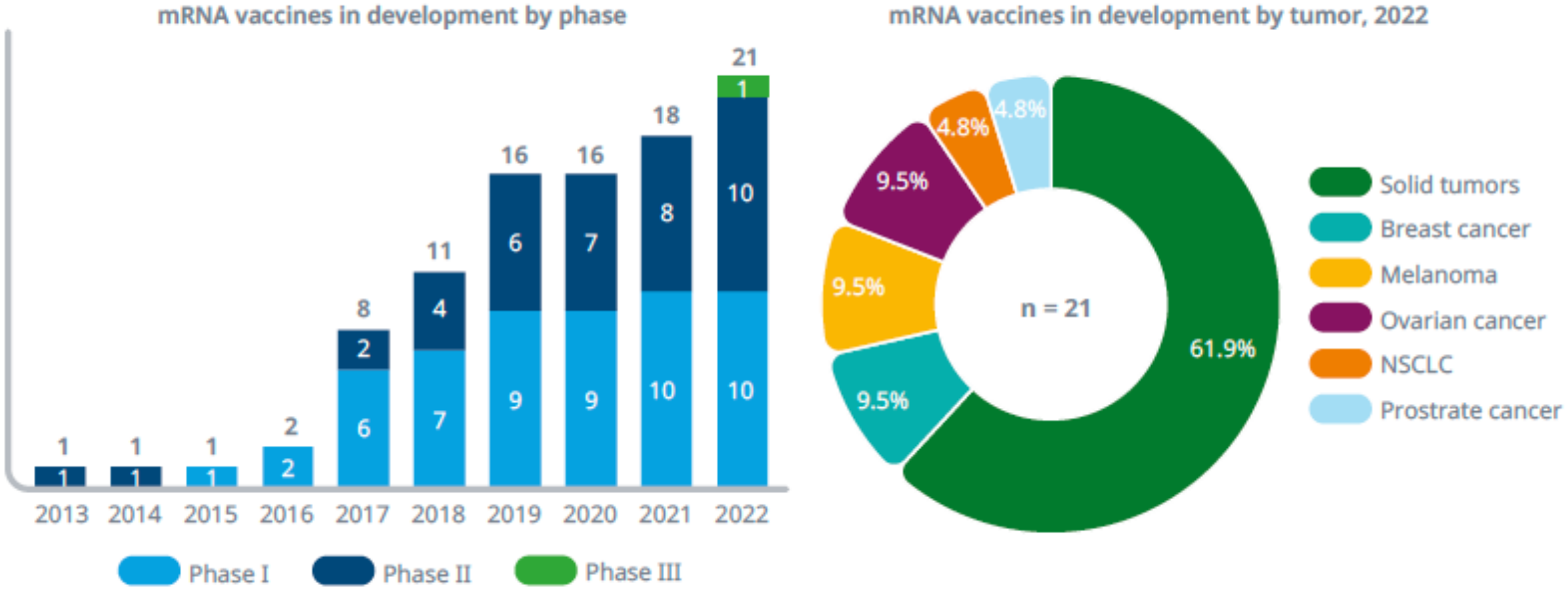
Drug class	Platform	Product candidate	Indication (targets)	Pre-clinical	Phase 1	Phase 2	Phase 3	Milestones
mRNA	FixVac	BNT111	Advanced and R/R melanoma					
		BNT112	Prostate cancer					
		BNT113	HPV16+ head and neck cancer					
		BNT116	NSCLC 2L+					FPD in July 2022 ✓
	iNeST	Autogene cevumeran (BNT122)[1]	1L melanoma					Data update exp. 1H 2023
			Adjuvant colorectal cancer					
			Solid tumors					
			Adjuvant pancreatic ductal adenocarcinoma[2]					Data update June 2022 ✓
	Intratumoral immunotherapy	SAR441000 (BNT131)	Solid tumors (IL-12sc, IL15-sushi, GM-CSF, IFNα)					
	RiboMabs	BNT141	Multiple solid tumors (CLDN18.2)					FPD in Jan. 2022 ✓
		BNT142	Multiple solid tumors (CD3×CLDN6)					FPD in July 2022 ✓
	RiboCytokines	BNT151	Multiple solid tumors (optimized IL-2)					
		BNT152, BNT153	Multiple solid tumors (IL-7, IL-2)					

mRNA-4157 vaccine (V940)

2023 ASCO Annual Meeting
Journal of Clinical Oncology 41, no. 17_suppl (June 10, 2023) LBA9503-LBA9503.

Development of mRNA vaccines for cancer has more than doubled since 2017 with focus on solid tumors

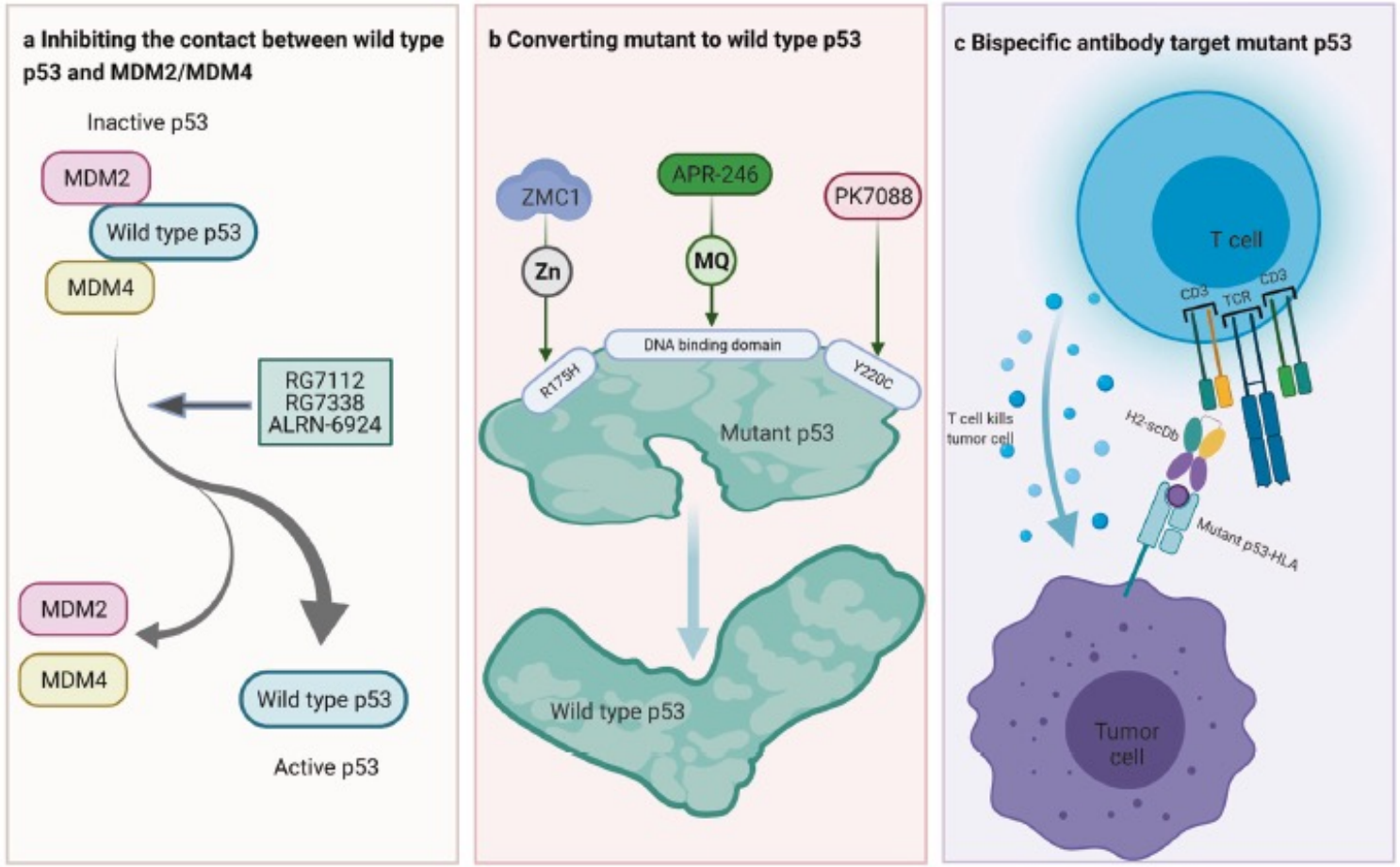
Exhibit 10: Oncology mRNA vaccines in development by phase and tumor



Global Trends in R&D 2023

Approaches to *p53*

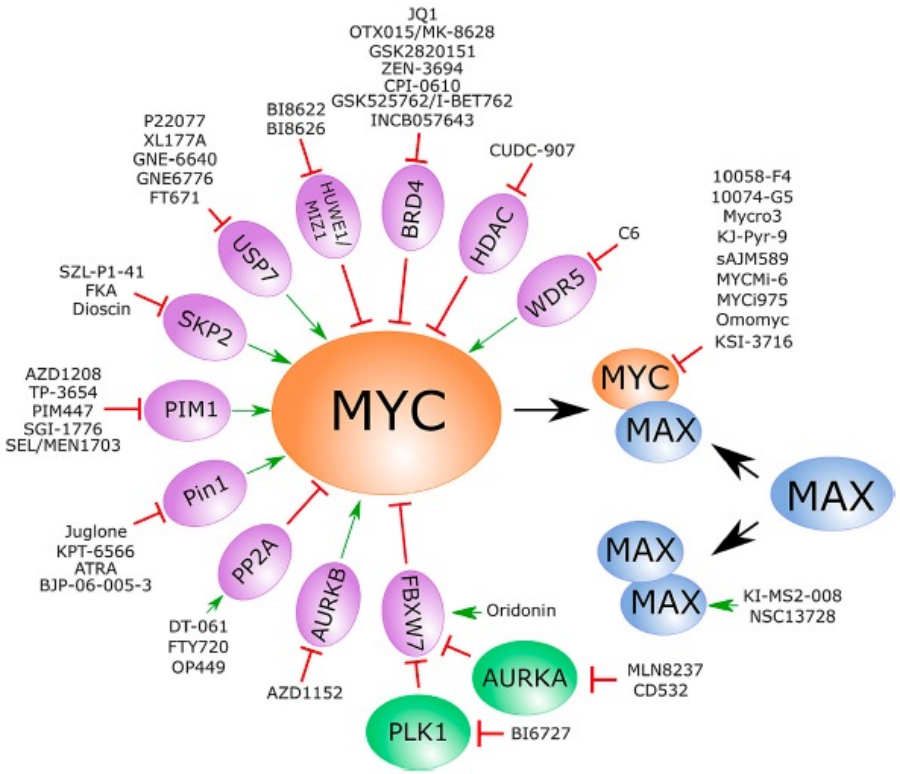
様々なmodalityの薬剤が開発されている

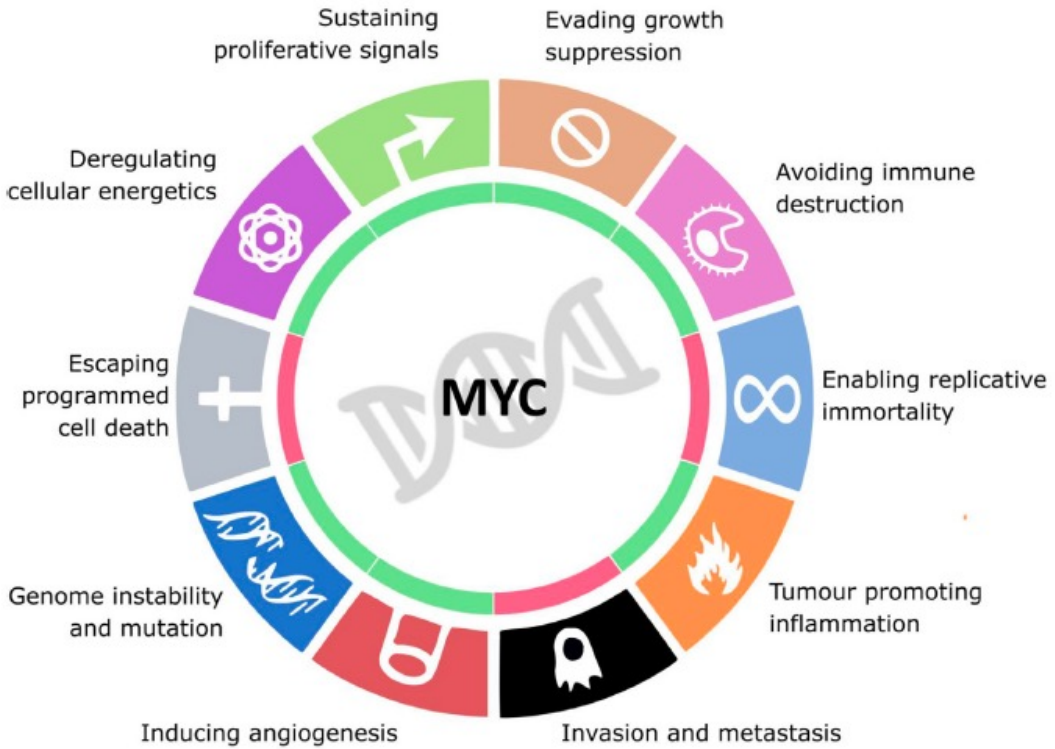


Cancers (Basel). 2023 Jan 9;15(2):429.

Approaches to MYC

- MYCは、酵素的に活性な部位がなく、ドラッグデザインが難しい。さらに、MYCとそのパートナーMAXとの間の高親和性相互作用、異なるMYCファミリーメンバーの部分的な機能重複性、核局在性のために、有効な阻害剤設計にとって永遠の障害とされてきた





EBioMedicine. 2022 Jan;75:103756.

Undruggable no more　？

- Undruggable target = 「創薬不可能」 または、「治療不可能な」標的

➢ もはや、「創薬不可能」 という標的はないのかもしれない
➢ むしろ、 「創薬可能」 「治療可能な」な標的・評価を探索へ

✓ 「治療不可能」か「治療可能」かは、今後の臨床開発の結果次第

では、これらの薬剤開発は日本で、どれほど行われているのか？

- RAS ^{on}
- mRNA vaccine
- TP53
- MYC

Japan no more　？

- Undruggable target ＝「創薬不可能」 または、「治療不可能な」標的

➢ もはや、「創薬不可能」 という標的はないのかもしれない

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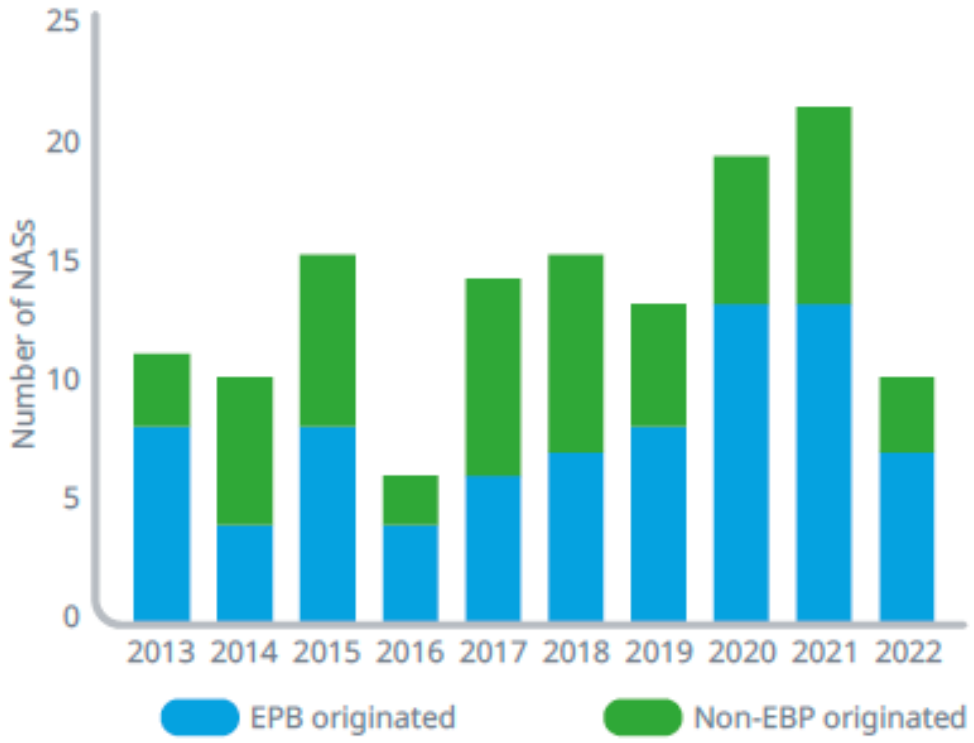
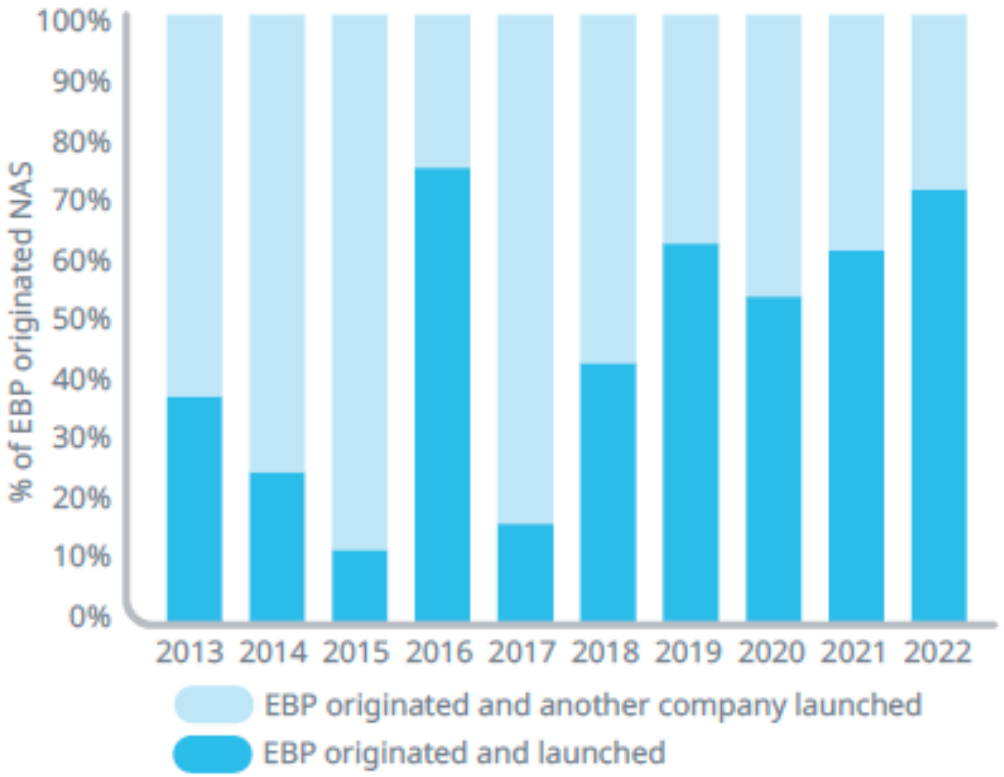
では、これらの薬剤開発は日本で、どれほど行われているのか？

~~• RAS on~~
~~• mRNA vaccine~~
~~• TP53~~
~~• MYC~~

Emerging biopharma companies originated 70% of new oncology drugs in 2022 and launched 71% of their own products

Exhibit 33: Companies originating and filing FDA regulatory submissions for oncology NASs and percent of launches by NAS launch year

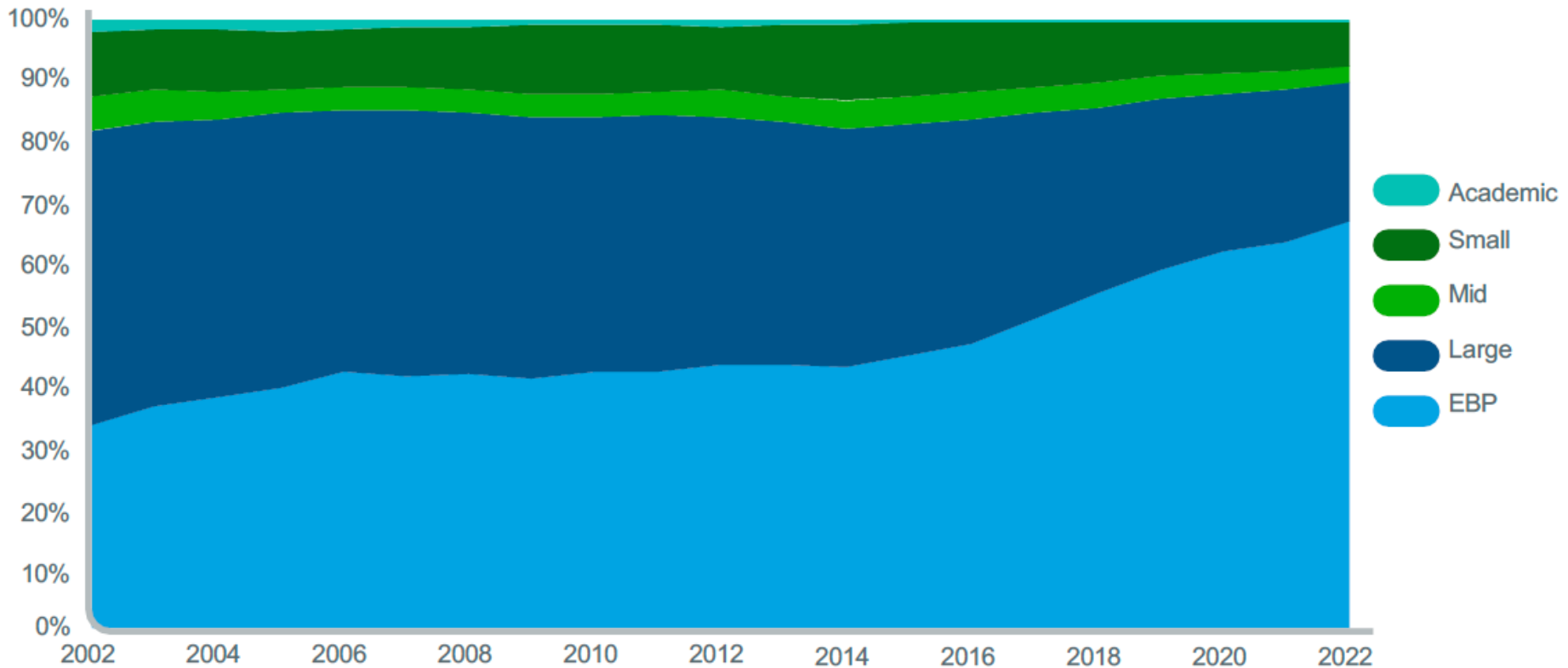




Source: IQVIA Institute, Apr 2023

Emerging biopharma companies are responsible for two-thirds of the R&D pipeline, with their share continuing to grow

Exhibit 16: Share of Phase I to regulatory submission pipeline by company segment, 2002–2022



Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

CLDN18.2 Targeted treatments

Reported	Drug name	Types	Company/Developer	Phase	Trial No.
✓	Zolbetuximab, IMAB362	MAB	Astellas Pharma Global Development Inc	III	NCT03504397, NCT03653507, NCT03505320
✓	AB011	MAB	Carsgen Therapeutics, Ltd.	I	NCT04400383
✓	MIL93	MAB	Beijing Mabworks Biotech Co., Ltd.	I	NCT04671875
✓	TST001	MAB	Mabspace Biosciences (Suzhou) Co., Ltd.→Transcenta Therapeutics	I	NCT04495296, NCT04396821
	SPX-101	MAB	SparX Biotech(Jiangsu) Co., Ltd.	I	NCT05231733
	LM-102	MAB	LaNova Medicines Limited	I	NCT04735796, NCT05008445
	DR30303	MAB	Zhejiang Doer Biologics Co., Ltd.	I	NCT05639153
	ZL-1211	MAB	Zai Biopharmaceutical (Suzhou) Co., Ltd.	I	NCT05065710
✓	CT-041	CAR-T	Carsgen Therapeutics, Ltd.	I	NCT04404595, NCT04581473, NCT03159819, NCT03874897
	CT-048	CAR-T	Carsgen Therapeutics, Ltd.	I	NCT05393986
	LCAR-C18S	CAR-T	Shanghai Oriental Hospital	I	NCT04467853
	LY011	CAR-T	Shanghai Longyao Biotechnology Inc., Ltd.	I	NCT04966143, NCT04977193
	IMC002	CAR-T	Suzhou Immunofoco Biotechnology	I	NCT05472857
	LB1908	CAR-T	Legend Biotech USA Inc	I	NCT05539430
	HEC-016	CAR-T	Shenzhen Fifth People's Hospital	I	NCT05277987
	KD-496	CAR-T	KAEDI	I	NCT05583201
	IBI345	CAR-T	Innovent Biologics (Suzhou) Co. Ltd.	I	NCT05199519
	Iy011	CAR-T	Shanghai Longyao Biotechnology Inc., Ltd.	I	NCT04977193
	AMG910	BITE	Amgen	I (terminated)	NCT04260191
	ASP2138	BITE	Astellas Pharma Global Development Inc	I	NCT05365581
	QLS31905	BITE	QLS31905	I	NCT05278832
✓	Q-1802	Bispecific (CLDN-PDL1)	QureBio Ltd	I	NCT04856150
	TJ-CD4B	Bispecific (CLDN-41BB)	I-MAB Biopharma Co., Ltd	preclinical	-
	PT886	Bispecific (CLDN-CD47)	Phanes Therapeutics	I	NCT05482893
	TPX-4589/LM-302	ADC	Turning Point Therapeutics, Inc.→BMS	I	NCT05001516
	SYSA1801	ADC	CSPC ZhongQi Pharmaceutical Technology Co., Ltd.→Elevation Oncology	I	NCT05009966
✓	CMG901	ADC	Keymed Biosciences Co.Ltd	I	NCT04805307
	RC118	ADC	RemeGen Co., Ltd.	I	NCT04914117, NCT05205850
	CPO102	ADC	Conjupro Biotherapeutics, Inc.	I	NCT05043987
	SKB315	ADC	Sichuan Kelun Pharmaceutical Research Institute Co., Ltd→MSD	I	NCT05367635
	SOT102	ADC	SOTIO Biotech	I	NCT05525286
	BNT141	mRNA-encoded antibody	BioNTech	I/II	NCT04683939

Clinical Trial Gov accessed on Feb 7, 2023

Healthcare policy initiatives over the last 10 years have positively impact development and launch timelines, and Patient access to innovation

However, proposed pricing measures and pricing reform designed to manage pharmaceutical spend will potentially impact growth

Potential pricing measure changes being discussed

- Expansion in scope of Repricing measures including Cost Effectiveness Assessment and HTA
- Increase in frequency of Repricing measures including Cost Effectiveness Assessment and HTA
- Revision to eligibility criteria for price protection under “Price Maintenance Premium” syste

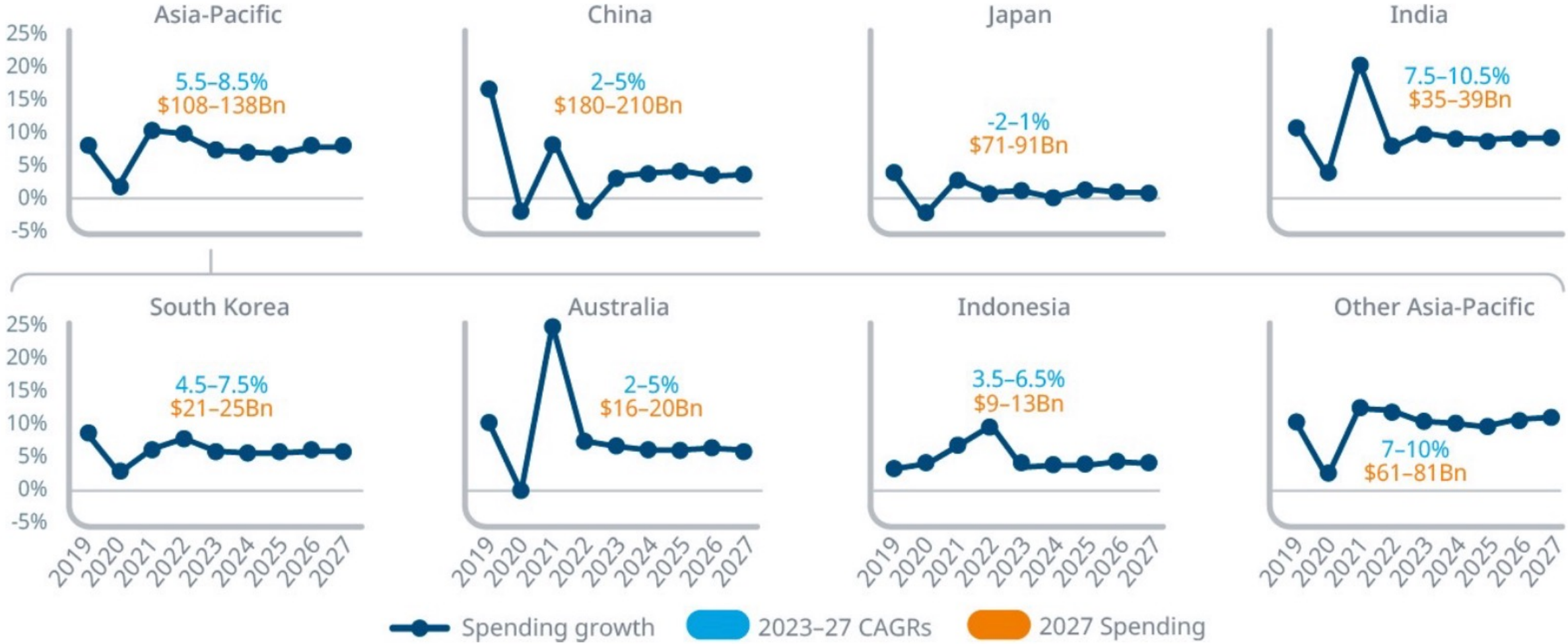
Already assumed in IQVIA’s Outlook to 2027 forecast due to trial implementation in 2021 and 2023

- “Out-of-Cycle” / “Off-Year” NHI Price revisions in odd-numbered years (in addition to current biennial revisions in even-numbered years)

Source: IQVIA Solutions Japan K.K. Japan Thought Leadership analysis.

Japan is the 2nd largest Asia-Pacific market behind China (and 3rd globally) but with lower top-line growth through 2027

Spending growth in select Asia-Pacific countries 2019–2027, total market, const US$



Source: IQVIA Market Prognosis, Sep 2022; IQVIA Institute, Nov 2022
Notes: 2019 is included to show the impacts of the pandemic on spending growth. Asia-Pacific excludes China, India and Japan which are shown separately.
Report: The Global Use of Medicines 2023: Outlook to 2027. IQVIA Institute for Human Data Science. January 2023

IQVIA INSTITUTE

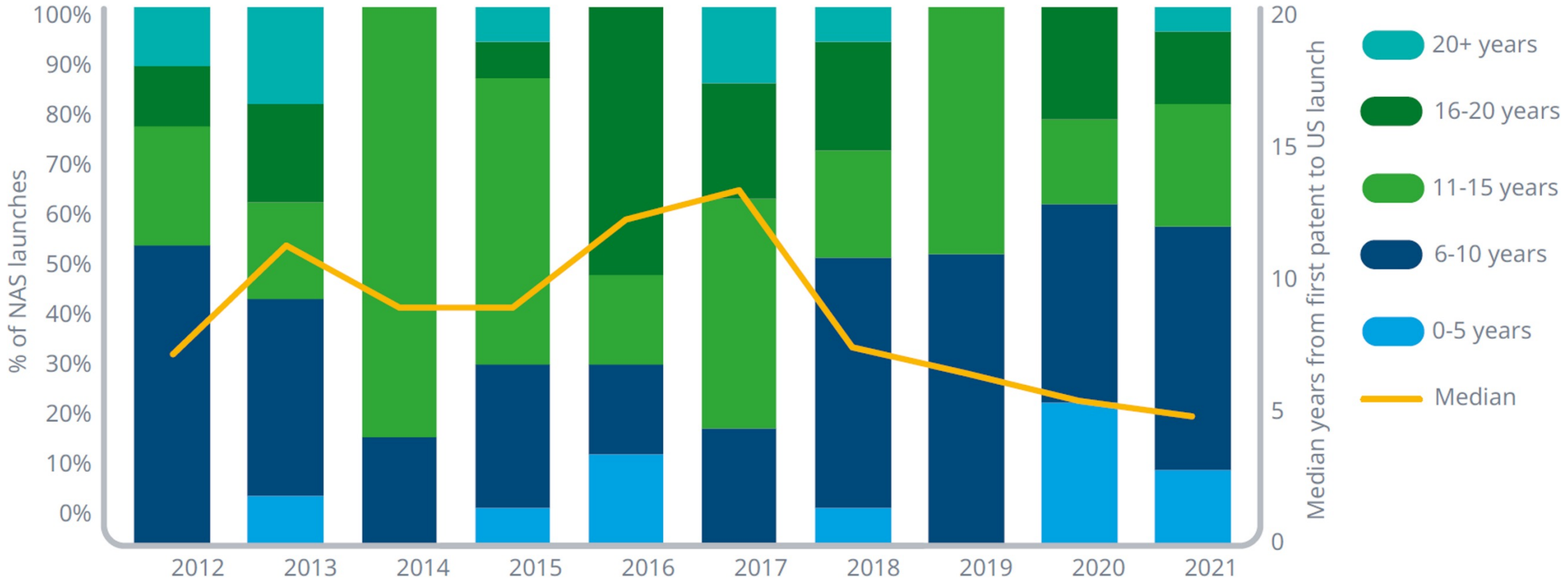
(from IQVIA the Global Use of Medicines 2022 OUTLOOK to 2026)

	2016年		2021年		2026年予測	
1	米国	100.0	米国	100.0	米国	100.0
2	中国	27.6	中国	29.2	中国	29.3
3	日本	19.2	日本	14.7	ドイツ	12.3
4	ドイツ	10.5	ドイツ	11.1	日本	11.9
5	フランス	7.9	フランス	7.2	フランス	7.1
6	イタリア	6.9	英国	6.3	ブラジル	7.0
7	英国	6.0	イタリア	6.3	英国	6.8
8	スペイン	5.0	ブラジル	5.5	イタリア	6.2
9	カナダ	4.7	スペイン	5.1	インド	5.6
10	ブラジル	4.0	カナダ	4.7	スペイン	5.0
11	インド	3.3	インド	4.3	カナダ	4.8
12	オーストラリア	3.1	ロシア	3.2	ロシア	4.1
13	韓国	2.9	韓国	3.2	韓国	3.3
14	ロシア	2.4	オーストラリア	2.5	メキシコ	2.5
15	メキシコ	1.9	メキシコ	2.1	トルコ	2.4
16	アルゼンチン	1.6	ポーランド	1.6	オーストラリア	2.4
17	ポーランド	1.6	サウジアラビア	1.5	アルゼンチン	1.8
18	サウジアラビア	1.5	ベルギー	1.5	ポーランド	1.6
19	スイス	1.3	トルコ	1.4	サウジアラビア	1.6
20	オランダ	1.3	アルゼンチン	1.3	ベルギー	1.5

日本の市場規模は未だ第三位

抗がん剤の開発期間は短縮化

- **Time from first patent filing and U.S. launch for novel active substances (NASs), 2012–2021**



(from IQVIA institute Global Oncology Trends 2022)

なぜ日本での臨床開発参入が少ないのか

➢ 日本を知らない

1. 日本での承認には、未だ10%ルールが必要と思っている

2. そもそもの治験届までの手順さえわからない（治験薬輸入へのプロセス・CMCレポート提出の有無など）

3. 日本に関するコンサルト会社がイけていない

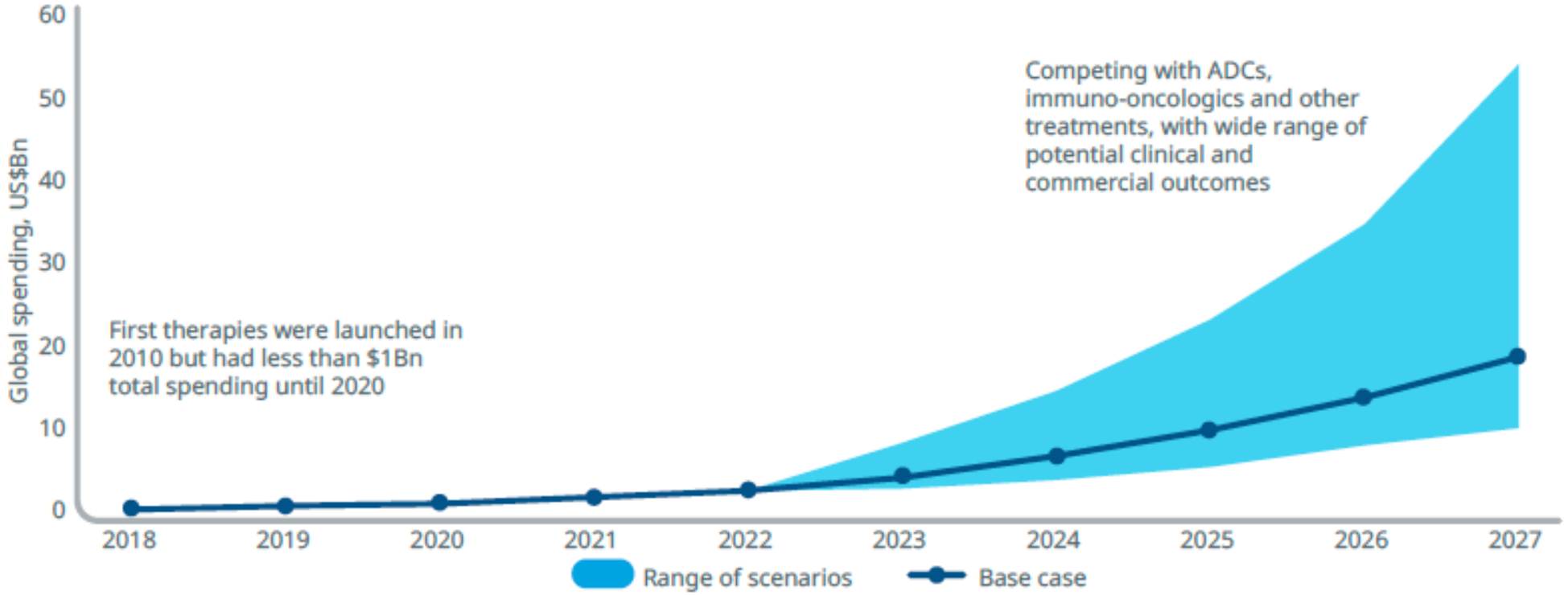
➢ 日本における開発コスト

1. 治験国内管理人になるCRO委託費が高い
・主にCRA費が高くなる（参加施設が多い、on-siteモニタリングの回数など）

2. 施設のコストが高い
- FMVによるBMC型費用算定導入が少ない
- SMO 3者契約によるCRC費用
- IRB業務数が多く、効率も悪く、人件費がかかる

The outlook for next-generation biotherapeutics in oncology includes significantly uncertain clinical and commercial success

Exhibit 55: Cell, gene and RNA therapeutics

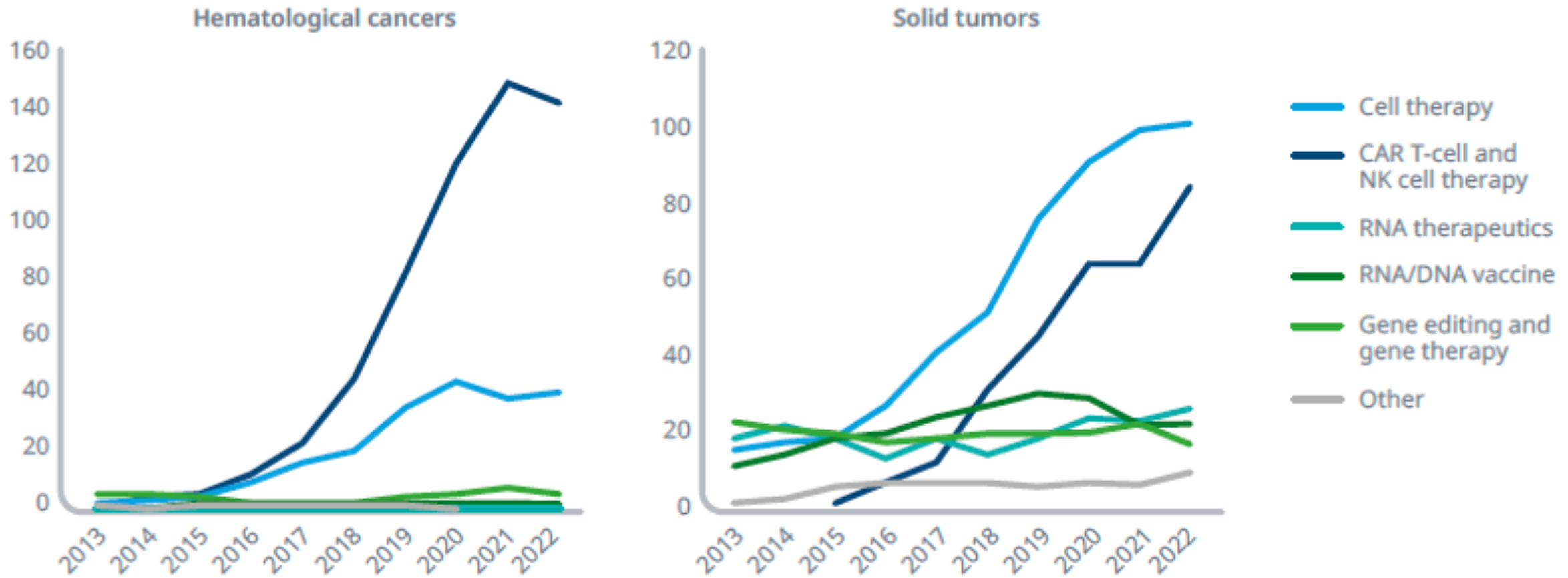


Source: Company Financials, IQVIA Institute, Apr 2023.

(from IQVIA institute Global Oncology Trends 2022)

The next-generation biotherapeutic pipeline is focused on cell therapies, particularly CAR T in hematological cancers

Exhibit 8: Oncology next-generation biotherapeutics Phase I to regulatory submission by mechanism, 2013–2022



(from IQVIA institute Global Oncology Trends 2022)

Teijin's CDO located in Kashiwanoha platform:

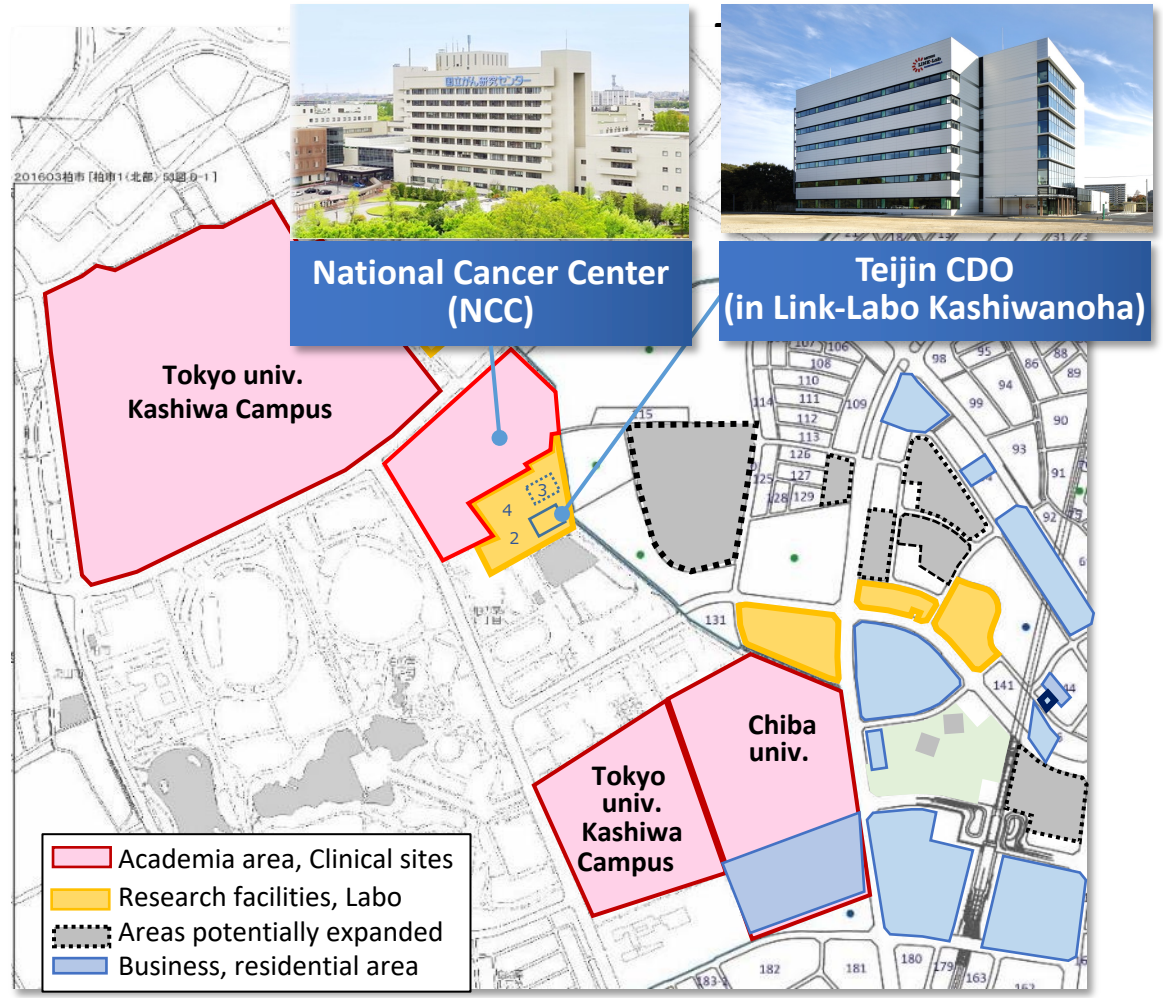
◆ Kashiwanoha is One of the bio-clusters invested by Japan Cabinet Office

Greater Tokyo Bio-community (GTB)

Kashiwanoha is one of the components of GTB, which is invested by Japan Cabinet Office as innovation platforms

Kashiwanoha platform, Bio-cluster area

Teijin CDO is co-located with "National Cancer Center", which is one of the biggest and leading medical institutes of oncology



Kashiwanoha Regenerative Medicine Platform (RMPF): Overview

Teijin CDMO

- Product development, clinical supply
- Supports for commercialization

Seeds from Academia/Biotech

CROs, Analytical vendors*

Pharma

Hospitals, Medical Institutes

Venture Capitals

Join/Collaboration

Join

Join

Join

Join

Kashiwanoha Platform
Mitsui Fudousan (Real-estate company,office function)

Innovative Treatments

Commercialization

Patients, Hospitals

Regenerative Medicine Market

National Cancer Center (NCC)

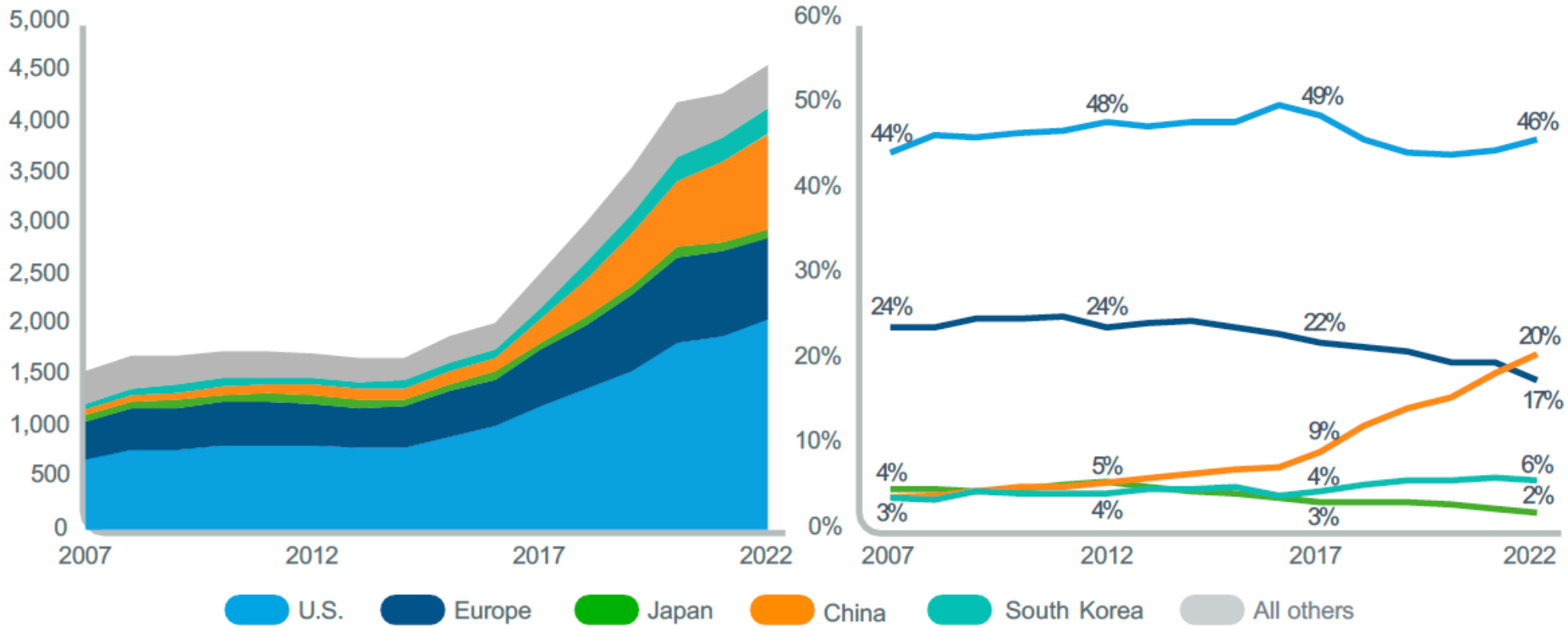
- Medical supports as KOLs
- Initiation of clinical researches/trials

Teijin/J-TEC (as CDMO):	Manufacturing from process development to commercialization as a pioneer
National Cancer Center (as Clinical facilitator):	Clinical supports and consultations based on the cutting-edge oncology research
Mitsui-Fudousan (as Coordinator):	Activation of the community to promote innovation

* H.U. group holdings/H.U. Cells (under H.U. group): Start “Supporting of development in Regenerative Medicine -services related to quality tests-” in collaboration with National Cancer Center at Kashiwanoha https://www.hugp.com/resources/file/pdf/20220921%20News_final%20%20kk.pdf (Japanese only)

Emerging biopharma drug development is rising rapidly, particularly in China, whose share now exceeds that of Europe

Exhibit 17: Number of drugs and country share of emerging biopharma pipeline Phase I to regulatory submission based on company headquarter location, 2007–2022



Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

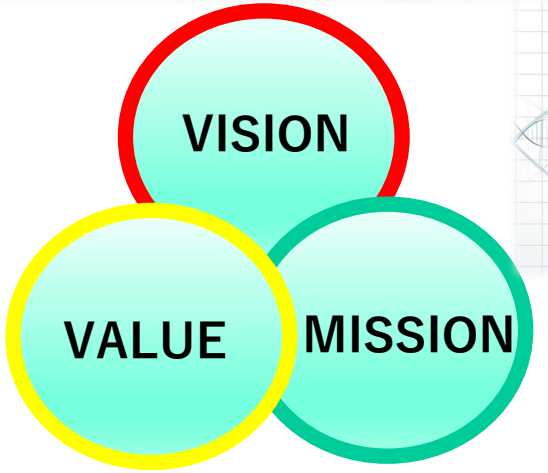
本日のまとめ

- Undruggable な標的は、もう存在しないかもしれない（まだ知らないdruggableを見つけにいく方向へ?）
- 様々なモダリティー、MoAの薬剤が臨床導入されており、適応する施設体制整備と規制への理解が必要
- 新薬開発はEBPが多くの開発を担っており、日本への参入を、CRO/規制当局/施設（PI)とともに日本への理解の継続的な努力と、治験環境の効率化を促進する必要がある
- 新たなモダリティーやプラットフォームを受け入れる基盤を構築し、日本が選ばれる環境にすると同時に、日本からの創薬をpush-upする必要がある

Biological agnostic To Platform agnostic

Department of Experimental Therapeutics
国立がん研究センター東病院　先端医療科

Welcome to National Cancer Center Hospital East



- ✓新規抗癌剤の早期開発
- ✓臓器横断的ながん診療
- ✓TR研究の推進