Criteria to assess cancer immunotherapy combinations in early-phase clinical trials and the types of efficient clinical trial designs needed for regulatory approval: An industry perspective

Alexandra Snyder, M.D.

Disclosures & Disclaimers

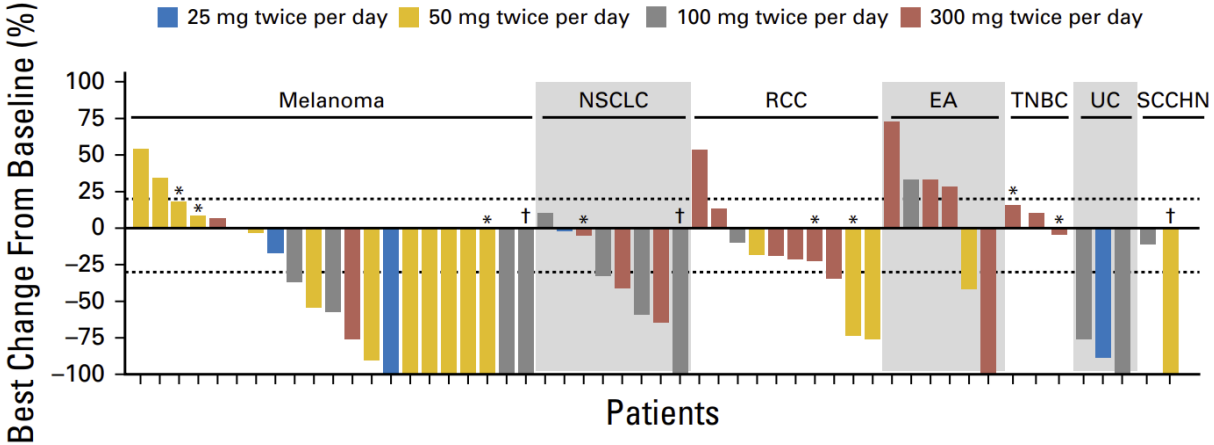
- Employee of Generate Biomedicines
- Owns stock in Merck and Allogene
- I am representing my own opinions as an individual, not those of any company or industry body

Agenda

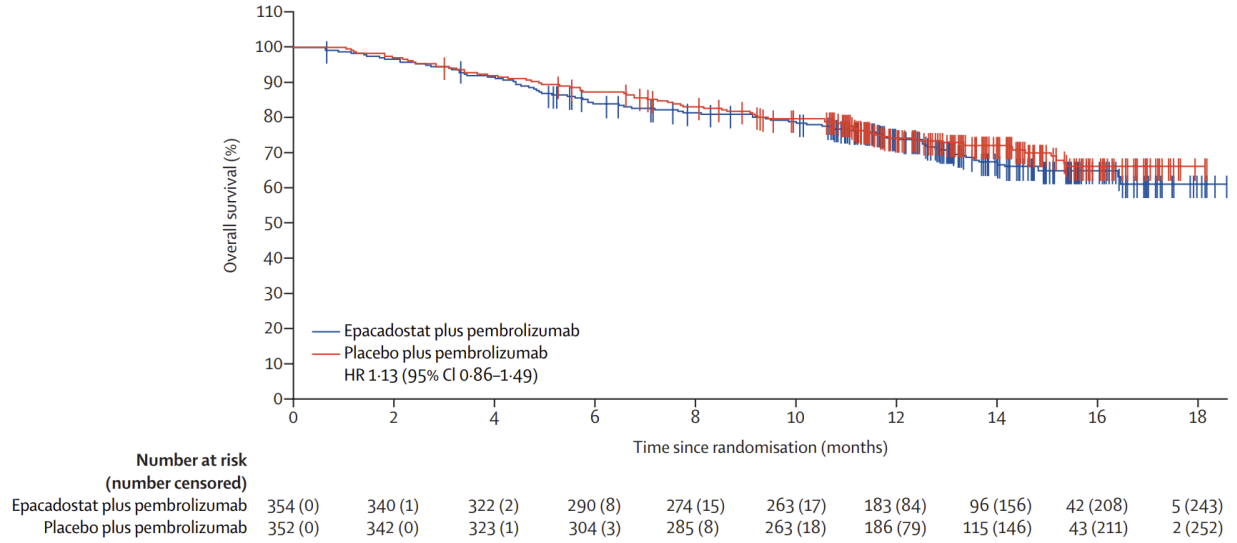
- Biology, trial results and impact
- What next?

Biology, trial results and impact: IDO

- Strong preclinical rationale
- No objective response as a single agent (Beatty GL et al., 2017); SD ≥ 16 weeks in 7/52 patients
- ORR for pembrolizumab in KEYNOTE-001 in melanoma: 33% (Kang SP et al Annals Onc 2017)
- ORR for epacadostat + pembrolizumab in Phase 1 melanoma: 55% (12/22) (Mitchell T et al JCO 2019)
- Randomized Phase 3 trial of pembrolizumab ± epacadostat showed overlapping PFS and OS curves
- Potential reasons for this outcome discussed by Dr. Luke



Mitchell T et al JCO 2019



Long GV Lancet Oncol 2019

Biology, trial results and impact: IDO

Merck, Incyte IDO inhibitor fails late-stage trial

Result casts shadow over other similar-acting cancer immunotherapy drug candidates

by *Lisa M. Jarvis*

April 13, 2018 | A version of this story appeared in **Volume 96, Issue 16**

The failure of the epacadostat-Keytruda trial has cast a shadow over all of those programs, especially since melanoma is considered the most likely tumor type to benefit from such combinations. Following the news, Incyte's stock fell by more than 20%; NewLink saw its stock price tumble by roughly 45%.

Genentech Kills IDO Inhibitor Pact with NewLink Genetics

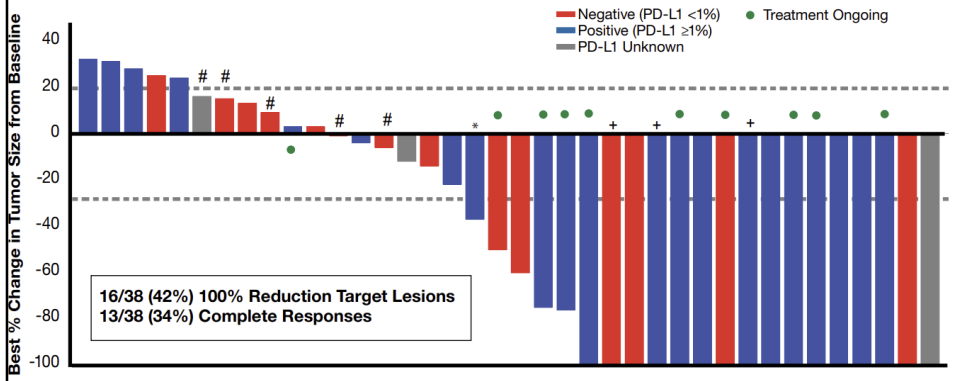
Published: May 16, 2018 | By Mark Terry

On April 6, 2018, **Incyte** and **Merck announced** that their own IDO1 inhibitor, epacadostat, which was being evaluated in combination with Merck's Keytruda in unresectable or metastatic melanoma, failed in a Phase III trial. And then on May 2, **Bristol-Myers Squibb** dropped two Phase III clinical trials of the IDO1 inhibitor it acquired when it bought **Flexus Biosciences** for $1.25 billion in 2015. Bristol-Myers was evaluating BMS-86205 and its checkpoint inhibitor Opdivo in patients with non-small cell lung cancer or head and neck cancer.

NewLink has two drugs in its pipeline, IDO inhibitor indoximod and a variant of indoximod. But after the Merck-Incyte failure, the company **indicated** it planned to reevaluate its programs and end its Phase III trial of indoximod and a PD-1 inhibitor.

Biology, trial results and impact: IL-2

- Extensive preclinical and some clinical validation of anti-tumor effects of IL-2
- NKTR-214 Phase 1 showed deep and frequent responses in melanoma and a potential signal in other tumor types
- Phase 3 study did not show outcome advantage for nivolumab + NKTR-214 over nivolumab alone



1L Melanoma (n=38 Efficacy Evaluable**)	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	13 (34%)
DCR (CR+PR+SD)	28 (74%)
PD-L1 negative (n=14)	6 (43%)
PD-L1 positive (n=21)	13 (62%)
PD-L1 unknown (n=3)	1 (33%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)

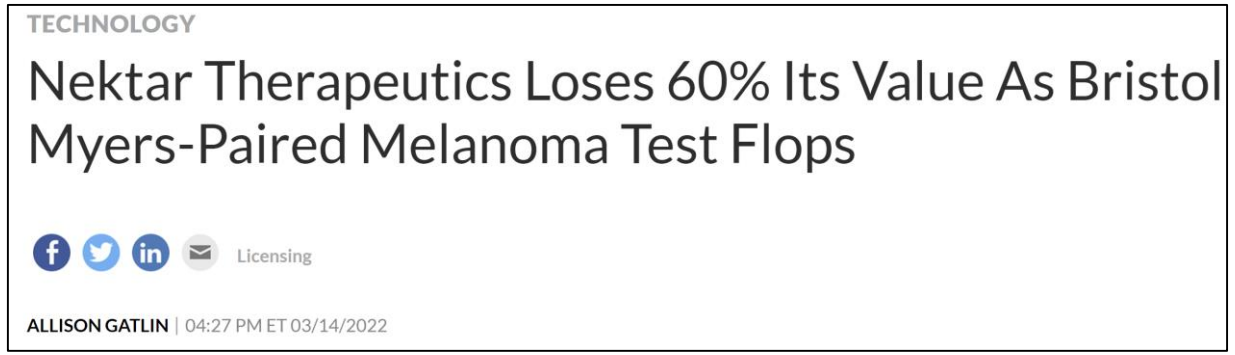
#Best overall response is PD due to non-target lesion progression or presence of new lesion. *Best overall response is SD. +Best overall response is PR. CR for target lesion(s). Non-target lesion(s) still present.
**Efficacy evaluable population includes patients who have measurable disease (per RECIST 1.1) at baseline and also have at least one post-baseline tumor assessment.
ITT = 41: 3 patients are excluded because they are not response evaluable:1 patient discontinued treatment after 1 dose due to unrelated adverse event (MI); 1 patient discontinued treatment after 1 dose due to patient decision; 1 patient discontinued treatment after 3 doses due to patient decision.

Hurwitz M et al ASCO 2019

Outcome	BEMPEG+NIVO (N=391)	NIVO (N=392)
ORR	27.7%	36.0%
DCR	56.1%	58.5%
Median PFS	4.17 mo (95% CI, 3.52–5.55)	4.99 mo (4.14–7.82)
Median OS	29.67 mo (95% CI, 22.14–NR)	28.88 mo (21.32–NR)
Gr 3-4 AEs	21.7%	11.5%
SAEs	10.1%	5.5%

Table adapted from Diab A et al ESMO 2022

Biology, trial results and impact: IL-2


TECHNOLOGY

Nektar Therapeutics Loses 60% Its Value As Bristol Myers-Paired Melanoma Test Flops

Licensing

ALLISON GATLIN | 04:27 PM ET 03/14/2022


DIVE BRIEF

Nektar begins sweeping layoffs after $2B Bristol Myers deal falls apart

Published April 26, 2022

Jonathan Gardner
Senior Reporter

Nektar lays of 70% of its workers…


Industry's IL-2 Struggles Continue as Sanofi Drops Program

Published: Oct 28, 2022 | By Kaley Lefevre


Alkermes joins Bristol Myers in IL-2 exit with oncology business spinoff

By Kevin Dunleavy • Nov 2, 2022 11:08am

Biology, trial results and impact: Lessons learned

- Preclinical outcomes in IO+IO combinations often do not translate in clinical trials
  - However, the relative impact of variables such as a molecule's features, dose, indication and patient selection (or lack thereof) on negative outcomes is often uncertain
- A negative clinical trial result for one member of a drug class or modulator of a mechanism can have a negative domino effect on others in the class *despite significant differences between molecules*
- A negative clinical trial can inflict a substantial adverse effect on the biotech sponsor's ability to continue operations, thereby limiting other research into novel areas that may be occurring and unrelated to the failed study
  - Since ~80% of novel drugs originate in biotech, this insecurity and flux can in theory harm the advancement of novel therapies
- Publication of retrospective translational research from failed studies is not standard

Biology, trial results and impact: Questions for the field

- What are the implications of the limited translatability of preclinical data to IO outcomes in patients with cancer?
  - How does this impact the pathway to IND and the design of Phase 1 studies?
- Is there a way to mitigate the “domino effect” within a class or mechanism?
- Should the field study tumor and/or blood samples from studies that did not reach their primary endpoints?
  - What are the incentives and rationale for and against performing such studies?
- Are we selecting the patients most likely to benefit from therapies that invoke a specific immunomodulatory mechanism?
  - Given the time, regulatory and operational complexity of developing selection biomarkers, how can such selection methods best be developed?

What Next?

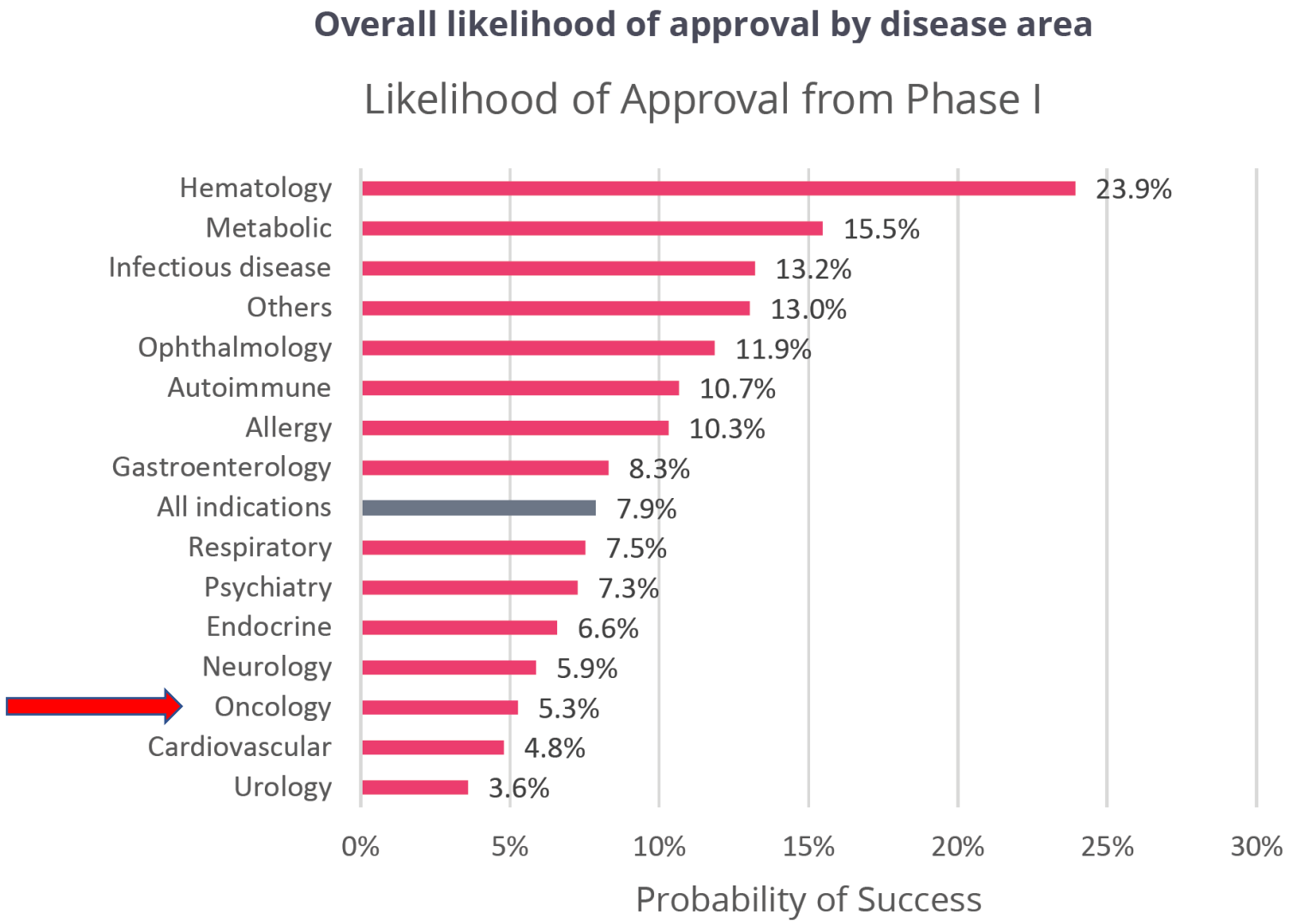
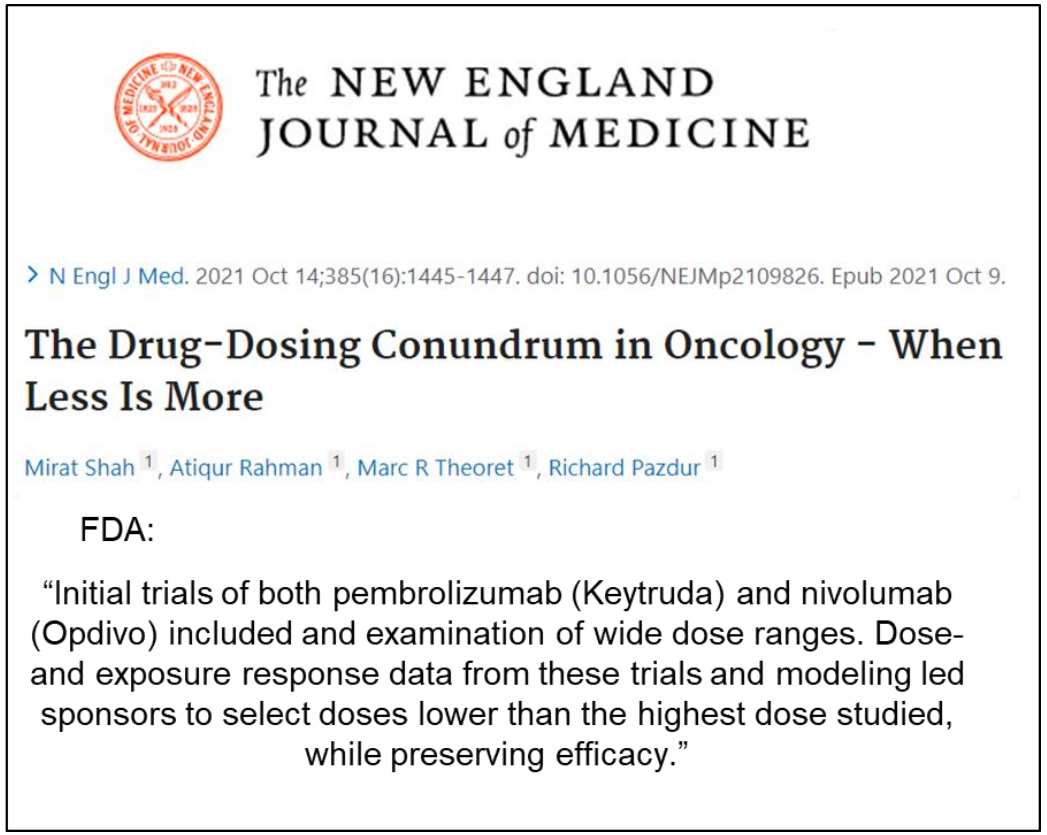


Figure 5a: Chart of LOA from Phase I, displayed highest to lowest by disease area. Source: Biomedtracker® and Pharmapremia®, 2020

What next? Biologically effective dose and, where appropriate, randomized dose finding

Use pharmacodynamics to choose the biologically effective dose (further discussed by Dr. Wolchok)



What next? Pivoting and diversifying

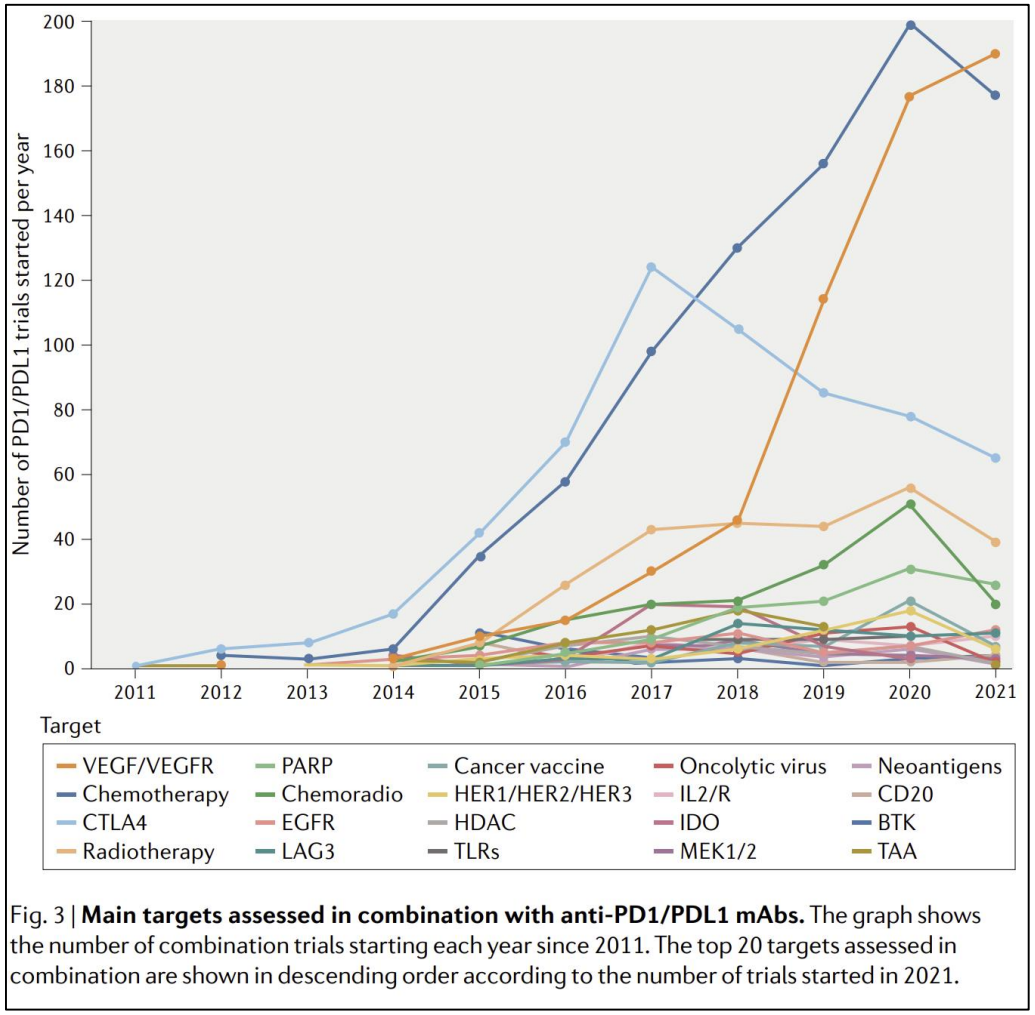
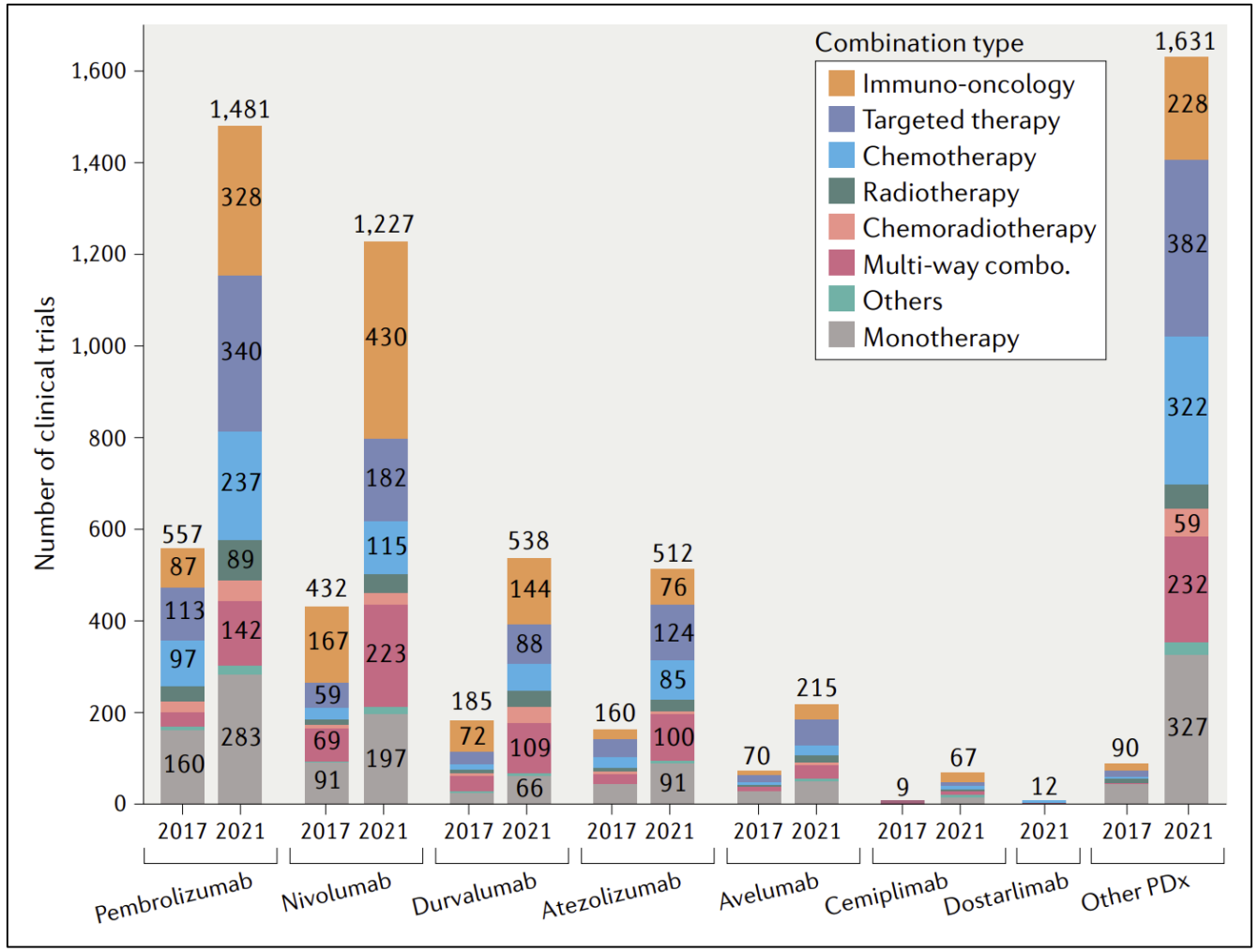


Fig. 3 | **Main targets assessed in combination with anti-PD1/PDL1 mAbs.** The graph shows the number of combination trials starting each year since 2011. The top 20 targets assessed in combination are shown in descending order according to the number of trials started in 2021.



Upadhaya S et al Nat Rev Drug Discovery 2022

What next? Pivoting and diversifying 2022 FDA approvals in oncology

Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date
Tecvayli	teclistamab-cqyv	10/25/2022	To treat relapsed or refractory multiple myeloma among adults who have received at least four specific lines of therapy
Imjudo	tremelimumab	10/21/2022	To treat unresectable hepatocellular carcinoma
Lytgobi	futibatinib	9/30/2022	To treat intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements
Pluvicto	lutetium (177Lu) vipivotide tetraxetan	3/23/2022	To treat prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer following other therapies
Opdualag	nivolumab and relatlimab-rmbw	3/18/2022	To treat unresectable or metastatic melanoma
Kimmtrak	tebentafusp-tebn	1/25/2022	To treat unresectable or metastatic uveal melanoma

What Next? Strategic variables to weigh

Perennial variables

- Focus resources vs. diversification of risk
- Experience of team in relevant space
- Runway ($)
- Overall market dynamics

IO combos & current environment

- Invest in BED to increase likelihood of eventual approval vs. small-as-possible Ph 1 and shift risk onto later development
- Randomized studies against SOC early in development powered for tumor size change vs. waiting and using registrable endpoint
- Risks/benefits to "going it alone" vs. master protocol vs. basket/umbrella studies
- Negative and positive impact of “class effects” from other companies’ results

Conclusions & future directions

- The field has learned considerably from IO+IO combination drug development, however, there is more to learn
  - When studies "fail" - have we tested the right target-modality-dose-patient combination?
  - Judicious use of tools such PD markers, surrogate biomarkers (e.g. tumor size, ctDNA) and model-informed drug development can deepen the understanding of drug activity in a small clinical trial
  - Consider translational examination of failed studies and ongoing studies
- Financial and other pressures from “domino effects” can compel sponsors, especially small biotechs, to make choices that limit exploration of complex or challenging biology
  - Can public-private partnerships and discussions help to address these realities?

Acknowledgements

Discussions with colleagues at MSKCC, Merck, Two River and Generate Biomedicines

Patients and their families

Site study staff