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REGULATORY ONCOLOGY DRUG APPROVALS BASED ON THE NEW CLINICAL RESEARCH LANDSCAPE

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KEY POINTS

- Explosion of available promising drugs (targeted, agents, antibody drug conjugates, immunotherapies)
- Regulatory pathways for faster approval
- The Immune checkpoint inhibitor paradigm
- The role of accelerated approval: speed, post-market safety and clinical benefit evidence
- Suggestions for improvement
- Novel Designs

SHIFT IN CLASSIFICATION OF CANCER, 2000…

→ parallel shift in how new cancer drugs are developed

Cancer Treatment

Chemotherapy

↓

TARGETED therapies

↓

IMMUNOTHERAPY

Novel clinical trial designs are needed for the molecular age

BEFORE: Large, randomised trials as standard approach to investigate new drugs with *cytotoxic* effects,

NOW: novel *cytostatic* therapies to:

- interrupt cancer cell growth and division along one or more of a set of cellular "pathways" (targeted therapies), or
- unleash the patient's own immune system against the tumour (*immunotherapies*)

→ development of **smaller**, **more focused** trials, **both within and across disease types**

Renfro LA and Mandrekar SJ, J Biopharm Stat 2017

FDA TAKES NEW STEPS

To broaden patient participation in cancer clinical trials

For far too long, certain patients have been unnecessarily excluded from the chance to be a part of a clinical trial (i.e. paediatric patients, patients with HIV, hepatitis B or C, brain metastases, organ dysfunction, and prior or concurrent malignancies)
– Scott Gottlieb MD, FDA Commissioner

Broadening eligibility criteria → Clinical Trials more representative of the patient population:

- Maximise the generalisability of the trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to receive the drug

https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm633202.htm

FDA APPROVALS

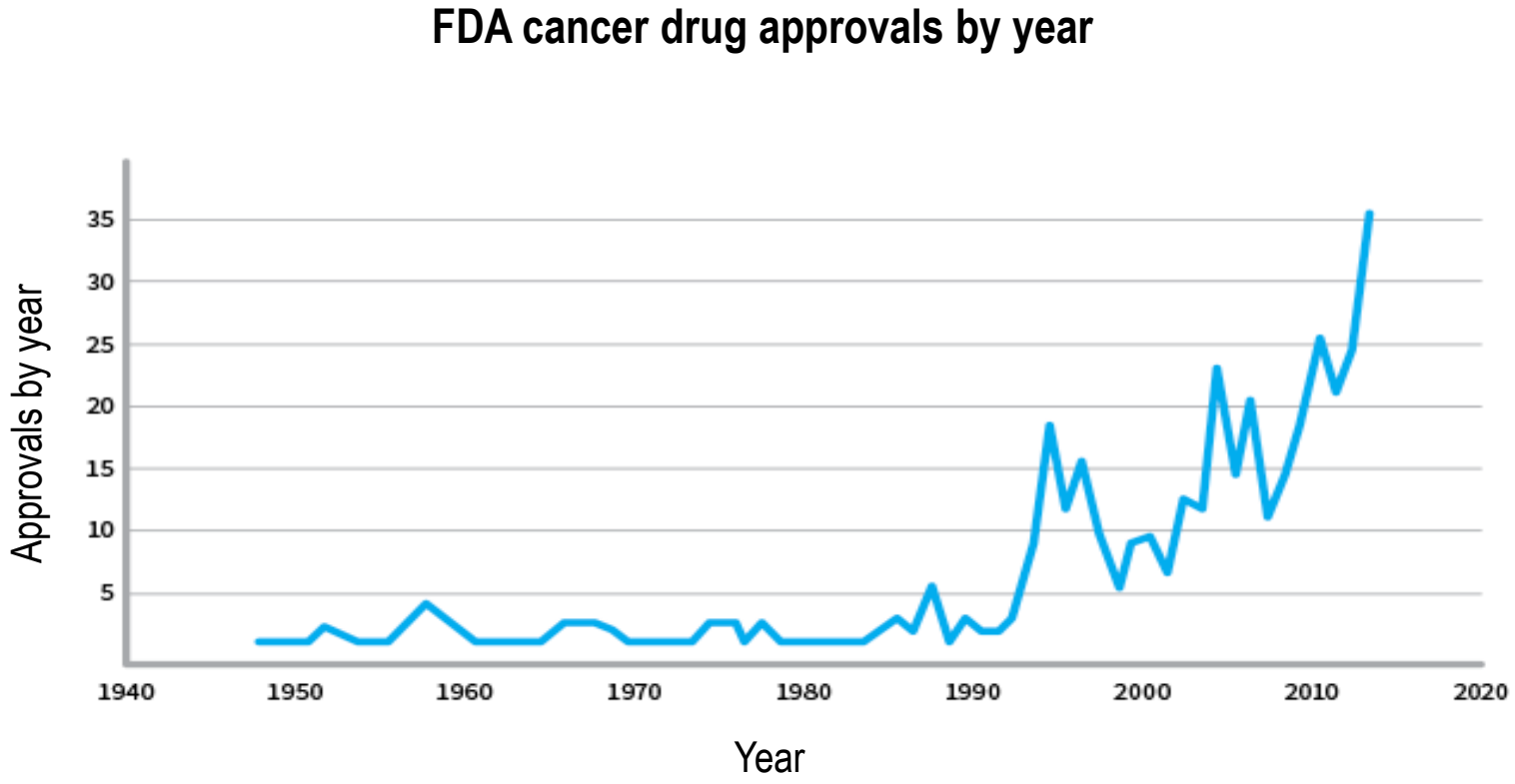
Traditional Approvals[1]

Expedited Approvals[2]

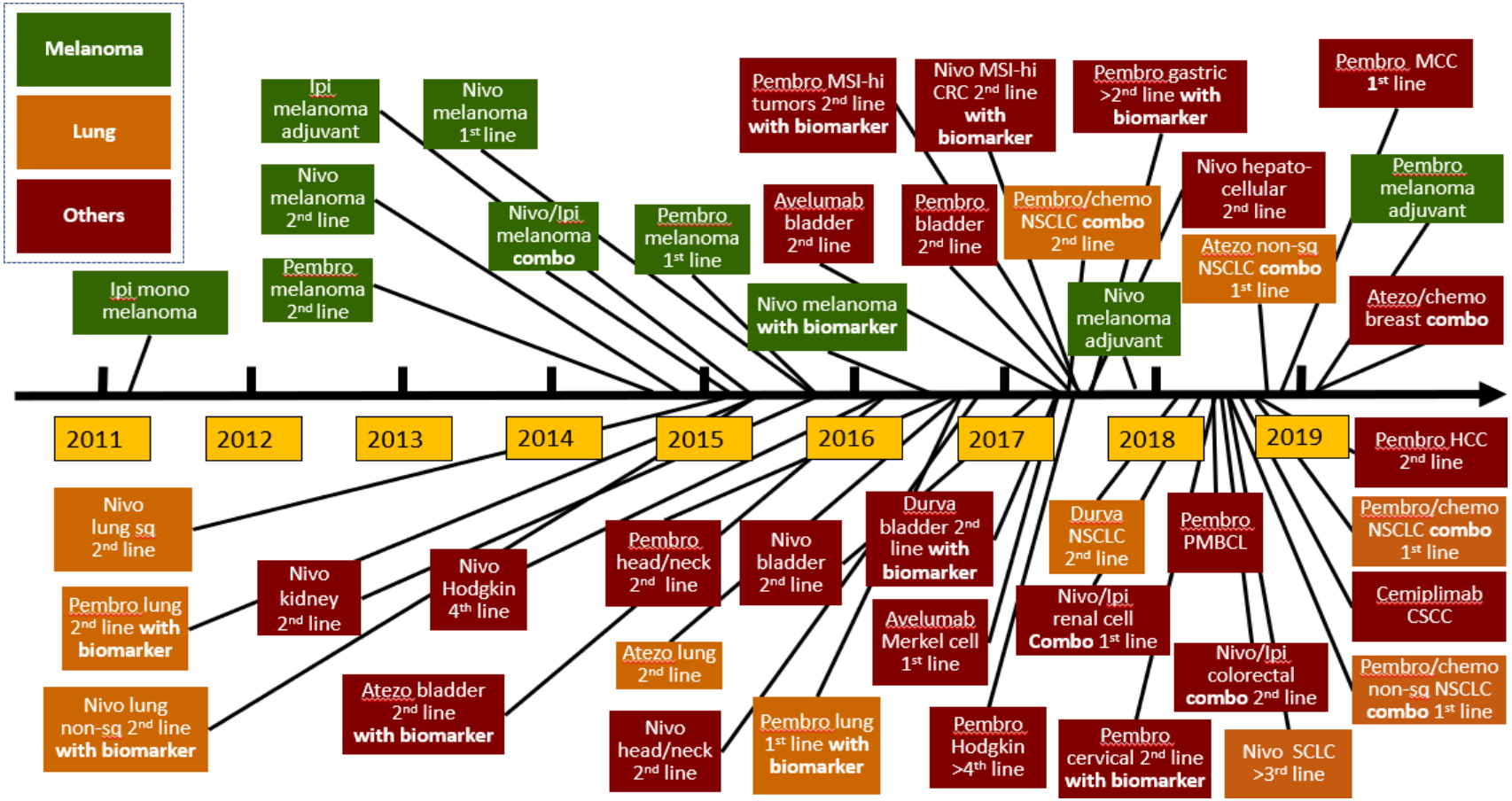
- Priority Review (FDA to take action on an application within 6 months) – 1992
- Accelerated Approval (for drugs that treat serious conditions and fill an unmet need – provisional approval based on **a surrogate endpoint**) – 1992
- Fast Track (for drugs that treat serious conditions and fill an unmet need) – 1997
- Breakthrough Therapy (for drugs that demonstrate substantial improvement over available therapy) – 2012

1. https://www.fda.gov/drugs/resourcesforyou/consumers/ucm295473.htm
2. US Food and Drug Administration. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics; 2014; https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

THE EXPLOSION OF CANCER THERAPEUTIC OPTIONS



(44) FDA APPROVALS FOR IMMUNE CHECKPOINT BLOCKERS



Updated March 2019: Modified from Topalian SL, ESMO 2017 and Peters S, 2017

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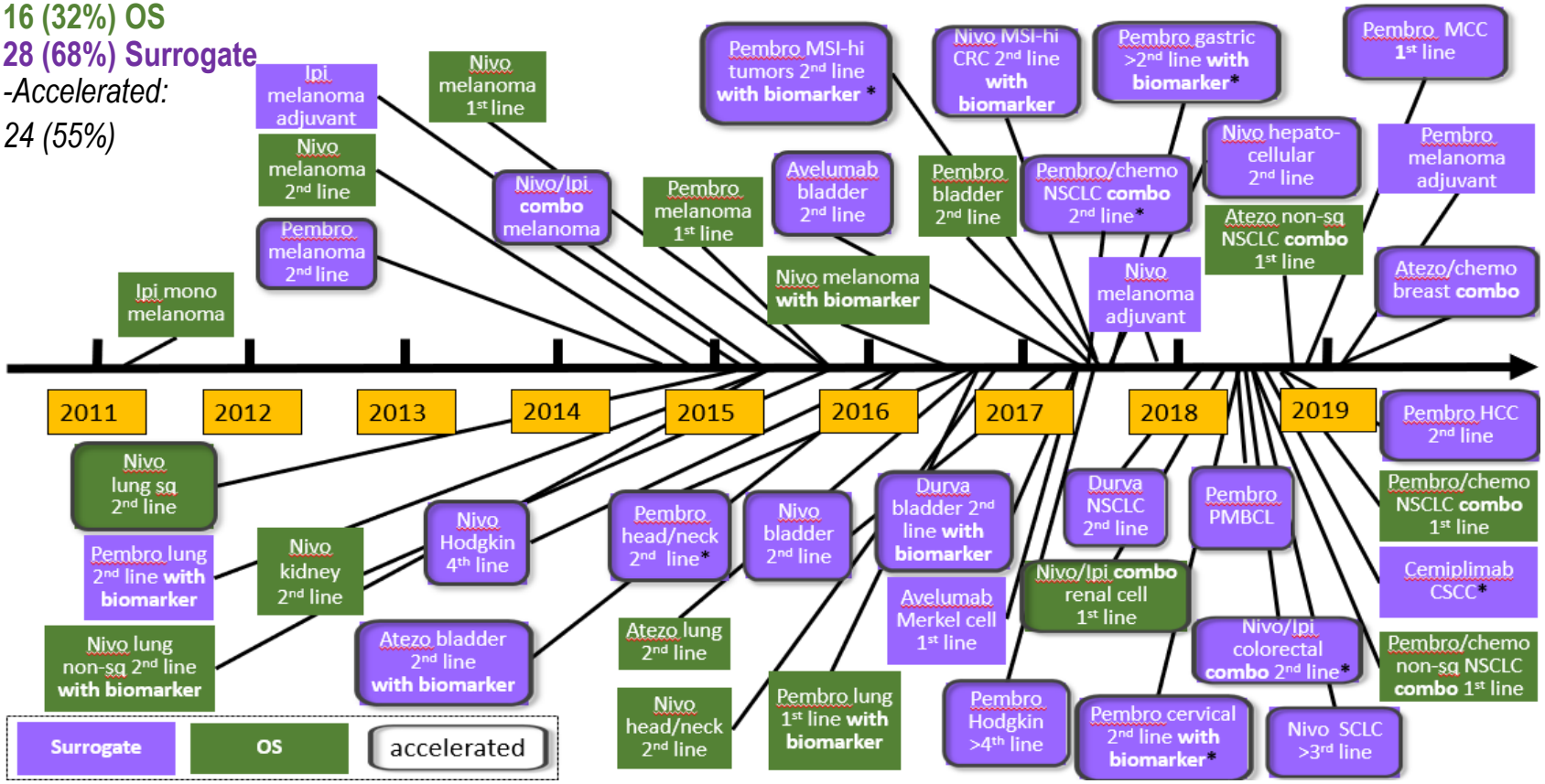
(44) FDA APPROVALS FOR IMMUNE CHECKPOINT BLOCKERS

Among 44 approvals:
16 (32%) OS
28 (68%) Surrogate
-Accelerated:
24 (55%)



*: multi-cohort
Updated March 2019: Modified from Topalian SL, ESMO 2017 and Peters S, 2017.

FDA OVERALL EXPEDITED APPROVALS

How many? How fast?

Agency	Period	Total approved	Expedited programs		
			Any	Accelerated	Priority review
FDA	2001-2010	222		28 (13%)	77 (35%)
FDA	2012-2016	174	105 (60%)	26 (15%)	90 (52%)
FDA	Median **time (years) to FDA approval**: ◆ 7.1 (any expedited program) *vs*. 8 (non-expedited) (p=0.04) ◆ **4.8 (breakthrough)** *vs*. 8 (non-breakthrough) (p<0.001)				

Downing NS, *et al.* JAMA 2017.

FDA OVERALL EXPEDITED APPROVALS

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			Any	Accelerated	Priority review
FDA	2001-2010	222		28 (13%)	77 (35%)
	Follow-up 2001-2015	123 postmarket safety events in 71/222 (32.0%) 11.7 yrs median FU Accelerated: more frequent events (multivariable analysis)			

"The high frequency of postmarket safety events highlights the need for continuous monitoring of the safety of novel therapeutics throughout their life cycle"

Downing NS, *et al.* JAMA 2017.

FDA ACCELERATED APPROVALS

A 25-year experience

Time period: December 11, 1992 – May 31, 2017

FDA granted accelerated approval (AA) to **64** malignant haematology and oncology products for **93** new indications. Of these, 53 were for new molecular entities (NME).

Single-arm trial designs provided the data for 67 (72%) of the initial AA indications.

Beaver JA, *et al*. JAMA Oncol 2018;4(6):849–56

FDA ACCELERATED APPROVALS

A 25-year experience

Agency	Period	Accelerated approvals (AAs)	Regular approvals (initially AA)	Initial regular approvals
FDA	1992-2017	93	51 (55%) 37(40%) pending 5 (5%) withdrawn	174
Endpoint – n (%)				
Response Rate		81 (87%)	13 (26%)	43 (25%)
Progression-Free Survival/ Time To Progression		8 (9%)	20 (39%)	59 (34%)
Disease-Free Survival/ Recurrence-Free Survival		4 (4%)	3 (6%)	3 (2%)
Overall Survival		-	15 (29%)	60 (35%)

Beaver JA, *et al*. JAMA Oncol 2018;4(6):849–56

FDA ACCELERATED APPROVALS

A 25-year experience

Agency	Period	Accelerated approvals (AAs) - N=93	
		Fulfilled postmarket req./ verified benefit	Trial(s) not completed / no verified benefit
FDA	1992-2017	51 (55%)*	37 (40%)**
Time from AA to benefit OR cut-off date (yrs)			
	Median (Min-Max)	3.4 (0.5-12.6)	1.5 (0.1-12.4)

***Median time from AA to verified benefit= 3.1 *vs.* 5.5 years**,
for indications with **ongoing trials** vs. those **without ongoing trials** (9 indications).

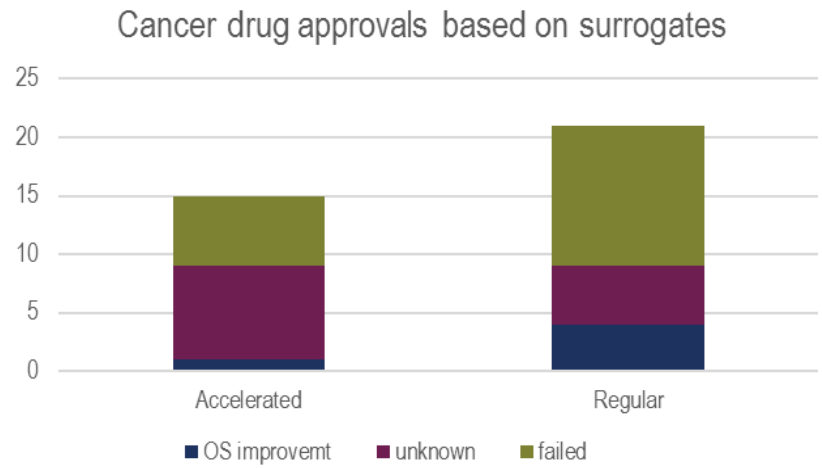
****Not yet verified benefit:** **>5y: 8 indications (22%), <3y: 26 (70%), <2y: 20 (54%)**

Note: 5 (5%) have been withdrawn from the market

Beaver JA, *et al.* JAMA Oncol 2018;4(6):849–56

CANCER DRUG APPROVALS BASED ON SURROGATES

FDA 2008-2012 (med f-up 4.4 y)



Evidence on OS

- 67% (36 of 54) based on surrogates
- **14% verified OS improvement**

Kim C, Prasad V. JAMA Intern Med 2015;175(12):1992–4

EMA 2009-2013 (med f-up 5.4 y):

Among 68 approvals for cancer indications

- 44 no evidence of OS benefit at the time of market approval,
- Postmarket:
  - **Evidence for OS gain: 3/44 (7%)**

Davis C, et al, BMJ 2017*;359:j4530*

FDA 2009-2013 (min f-up 4 y):

- 19 accelerated approvals in cancer
  - **Fulfilled postmarket req: 42%**

Naci H, *et al.* JAMA 2017; 318(7):626-636

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PIVOTAL TRIAL ENDPOINTS AND OUTCOMES

Of US FDA-designated breakthrough *versus* no breakthrough cancer drugs, 2012-2017

End Point or Outcome	Breakthrough-Designated Drugs (n = 25)	Nonbreakthrough Drugs (n = 33)	*P*
Primary trial end point, No. (%)			
Response rate	16 (64)	12 (36)	.03
Progression-free survival	8 (32)	11 (33)	
Invasive disease-free survival	0 (0)	1 (3)	
Overall survival	1 (4)	9 (27)	
Efficacy§			
Response rate, %			
Median (IQR)	38 (24-54)	43 (34-47)	.73
Pooled estimate (IQR)	37 (26-49)	39 (30-50)	.74
Progression-free survival			
Gain, months, median (IQR)	8.6 (4.5-11.9)	4.0 (3.0-6.0)	.11
Pooled hazard ratio (IQR)	0.43 (0.27-0.59)	0.51 (0.40-0.63)	.28
Clinically meaningful improvement, No. (%)	5 (83)	9 (75)	.99
Novelty			
Novel mechanism of action, No. (%)	9 (36)	13 (39)	1.00
Safety			
Serious adverse events, No. patients (%)	2,586 of 6,857 (38)	4,347 of 11,933 (36)	.93
Deaths not caused by progression, No. patients (%)	347 of 6,265 (6)	517 of 12,188 (4)	.99

SUGGESTIONS FOR IMPROVEMENTS

to the accelerated pathway for cancer drug approvals

Confirmatory post marketing studies for accelerated drug approvals should include both OS and QoL outcomes because these are the 2 facets of clinical benefit currently being used by the FDA.

Preapproved QoL measures should be published for specific drug classes.

Anticipated or clinically significant changes in OS and in QoL measures should be defined a priori to facilitate the identification of drugs whose "postmarketing clinical study fails to verify clinical benefit."

These are design parameters that should be set from the start of the accelerated path trial

Bauer SR & Redberg RF, JAMA Intern Med. 2017;177(2):278.

CAUTIONARY NOTE

FDA's various expedited pathways are:

- Less stringent: only 1 pivotal trial, fewer patients, shorter follow-up, **surrogate endpoints**[1]

Requirement: Postmarket studies that evaluate OS or QoL

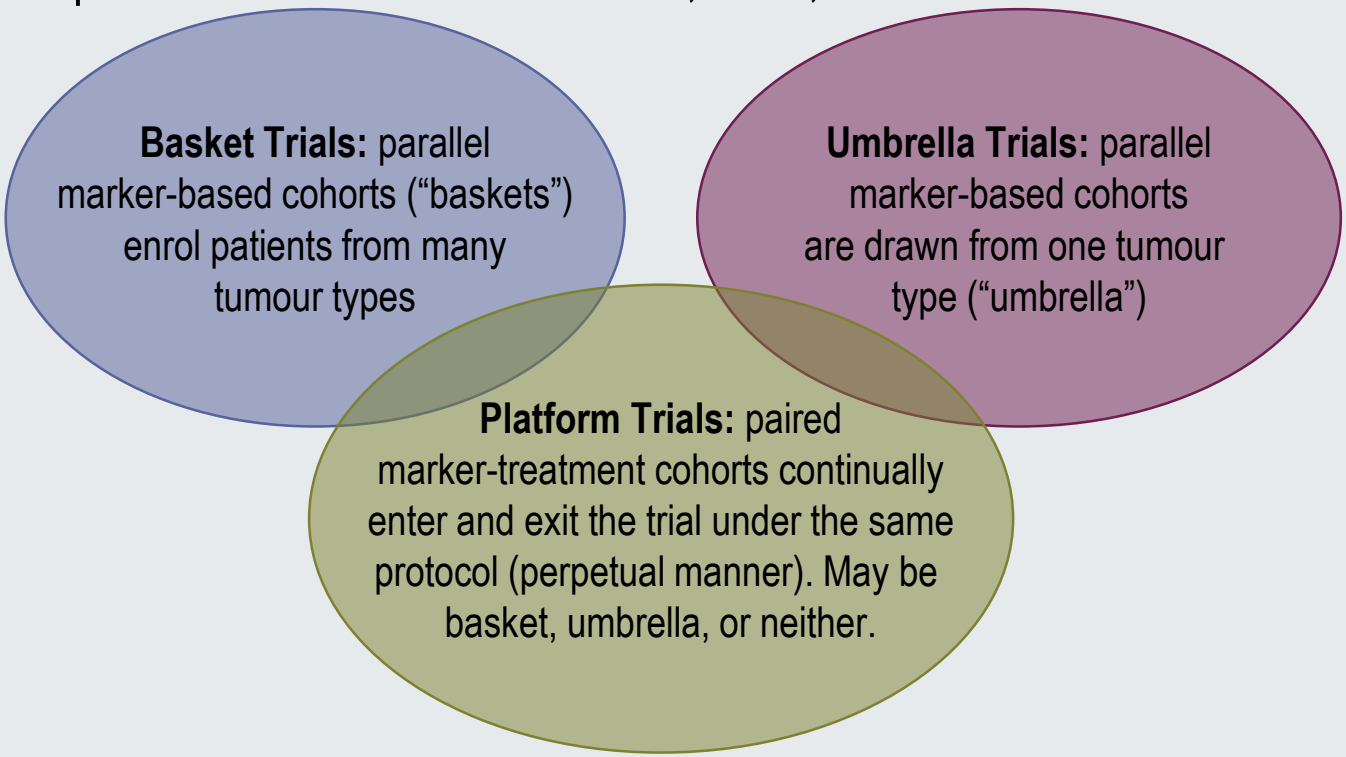
Problems:

- Crossover, Post-hoc analyses (inherently subject to confounding),
- Published results: OS or QoL verification reported only in 7% to 42% (EMA or FDA) after considerable time on market

Importantly, many of the surrogate outcomes are poorly correlated with survival, or the strength of the correlation is untested

1.Rupp T, Zuckerman D, JAMA Intern Med. 2017;177(2):276-277; 2. Prasad V, BMJ 2017;359:j4528

Master Protocols: Over-arching clinical trial protocols comprised of parallel marker-based sub-trials, arms, or cohorts



Adapted from Renfro LA and Mandrekar SJ, J Biopharm Stat 2017

CHALLENGES IN MASTER PROTOCOLS

Goal of precision medicine is conducting

“trials designed to learn”

This aim addressed by master protocols

A. basket trials, platform trials, and phase II portions of phase II/III umbrella trials

→ **“trials designed to confirm”**

B. potential expansions by phase III portions of phase II/III umbrella trials

Menis J, *et al.,* Eur Respir Rev 2014; Burock S, *et al.,* Eur J Cancer 2013; Renfro LA and Sargent DJ, Ann Onc 2016; Woodcock J and LaVange LM, NEJM 2017.

DESIGN FOR IMMUNOTHERAPY TRIALS

Regulatory bodies now approve trials based on novel protocols (e.g. Phase I trials based on single-arm designs, not randomised). Other novelties in the clinical trial design setting:

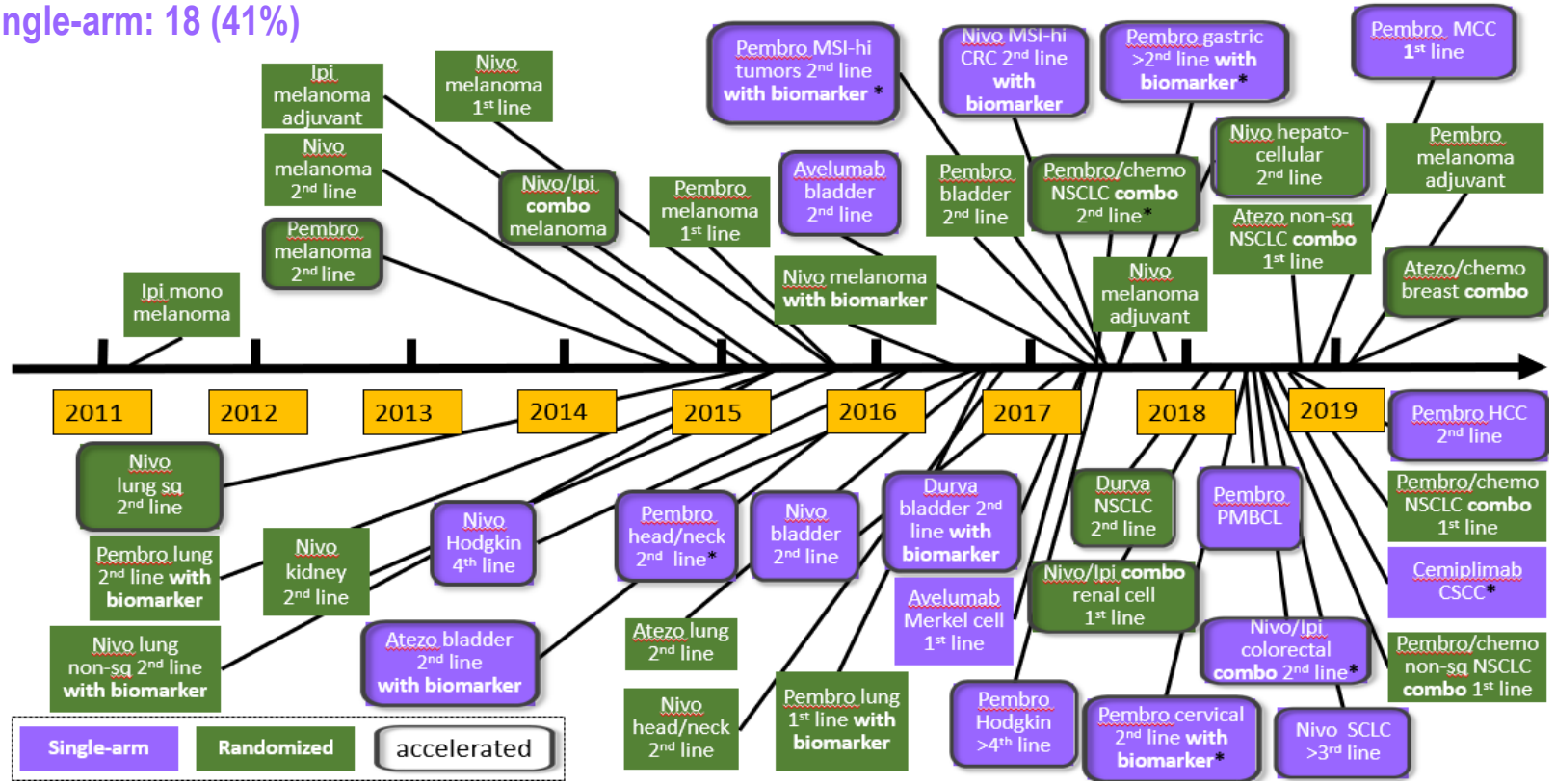
- Advantage of using new designs developed and tested on targeted therapies (basket, umbrella, multiple endpoints/cohorts, platforms, adaptive)
- Inclusion of immunotherapy arm in these trials when no target exists
- Change in the paradigm of Phase I
  - → expansion cohorts – efficacy evaluation
- Adaptation (co-primary endpoints; interim) possible due to substantial improvements targeted AND OBSERVED (use of lower alpha limits)
- No verdict yet on definite predictive biomarker (PD-L1, TMB)
- Favoured primary endpoints:
  - ORR (RECIST 1.1) & OS, milestone survival

(44) FDA APPROVALS FOR IMMUNE CHECKPOINT BLOCKERS

Among 44 approvals:

Randomised: 26 (59%)

Single-arm: 18 (41%)



*: multi-cohort. Updated March 2019: Modified from Topalian SL, ESMO 2017 and Peters S, 2017

“DRAMATIC EFFECT” (ICH E10; 2001)

- Use of the external control design is restricted to situations in which the effect of treatment **is dramatic** and the usual course of the disease highly predictable;
- Start with externally controlled trial and switch to RCT (or stop) if effect not dramatic;

What is the threshold for “dramatic”?
Based on what parameter? ORR

Pignatti F, Casali P, EMA-ESMO workshop 2016.

EMA-APPROVED DRUGS – SINGLE ARM STUDIES

- Studies (pub. 2006-2016) which led to EMA-approved drugs graded by MCBS (N=93):
- 10 single-arm trials (11%)
  - **4 immunotherapy 40%**
  - 6 targeted 60%

Drug	Cancer
AZD9291 (Osimertinib)*	Lung
Ceritinib*	Lung
Crizotinib	Lung
Alectinib	Lung
Olaparib	Ovarian
Everolimus	Brain
Nivolumab	Hodgkin's Lymphoma
Atezolizumab	Urothelial
Pembrolizumab	Head and Neck
Pembrolizumab	Colorectal

Single arm EMA-approved immunotherapy trials N=4 (11%)

*Trials with results stratified by subgroup. Osimertinib MUT/WT and Ceritinib with prior Crizotinib/No prior Crizotinib.
Cherny N, Ann Oncol, 2015; Cherny N, Ann Oncol, 2017

CAR T-CELL IMMUNOTHERAPY APPROVED BY THE FDA

- On August 30, 2017, the FDA granted regular approval to tisagenlecleucel for patients with relapsed or refractory paediatric precursor B-cell ALL
- **The first chimeric antigen receptor (CAR) T-cell immunotherapy approved by the FDA**
- Approval was based on a single-arm trial of 63 patients, among them:
  - confirmed overall remission rate was 82.5% (95% CI 70.9, 91.0)
    - 63% with complete remission
    - 19% with complete remission with incomplete haematological recovery
  - Median remission duration was not reached (range: 1.2 to 14.1+ months)

FDA'S ACCELERATED APPROVAL TO PEMBROLIZUMAB

For first tissue/site agnostic indication

On May 23, 2017, the FDA granted accelerated approval to pembrolizumab for unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours

First approval of a **cancer treatment based on a common biomarker** without regard to the tumour's original location

- Basis: 149 patients with MSI-H or dMMR cancers across **five uncontrolled, multi-cohort, single-arm clinical trials**
- Major efficacy outcome: ORR – Response duration

Further study is ongoing to confirm clinical benefits

https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm560040.htm

FDA'S ACCELERATED APPROVAL TO PEMBROLIZUMAB

For first tissue/site agnostic indication

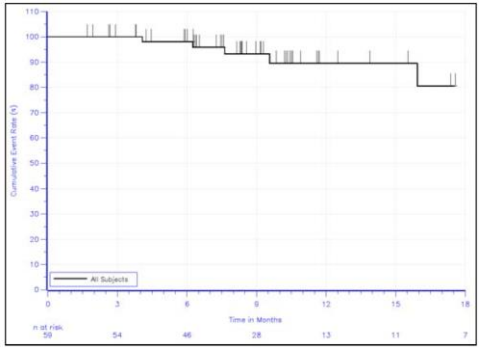
The pivotal data for the approval included patients from the:

- KEYNOTE-016 (n=58)
- KEYNOTE-164 (n=61)
- KEYNOTE-012 (n=6)
- KEYNOTE-028 (n=5)
- KEYNOTE-158 (n=19)

Not even basket-trial!

Clinical data that supported the approval of pembrolizumab

	N	Objective response rate n (%)	95% CI
CRC	90	32 (36%)	(26%, 46%)
Non-CRC	59	27 (46%)	(33%, 59%)
Endometrial cancer	14	5 (36%)	(13%, 65%)
Biliary cancer	11	3 (27%)	(6%, 61%)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)
Pancreatic cancer	6	5 (83%)	(36%, 100%)
Small intestinal cancer	8	3 (38%)	(9%, 76%)
Breast cancer	2	PR, PR	
Prostate cancer	2	PR, SD	
Bladder cancer	1	NE	
Esophageal cancer	1	PR	
Sarcoma	1	PD	
Thyroid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	
Small cell lung cancer	1	CR	
Renal cell cancer	1	PD	



Duration of response in 59 responding patients

Source: Keytruda Approval Package. .S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/125514Orig1s014.pdf. Accessed Dec 2019
Presented By Steven Lemery at 2017 ASCO Annual Meeting.
Courtesy of Dr Steven Lemery

EMA APPROVAL

- Standard Marketing Authorisation (MA) based on comprehensive data
- Non-standard Marketing Authorisation
  - Conditional Marketing Authorisation (CMA)
    - Before comprehensive data are available
  - Marketing Authorisation under exceptional circumstances
    - Comprehensive data not expected

CONDITIONAL MARKETING AUTHORISATION (CMA)

- MA before comprehensive data are available
- Requirements
  - Comprehensive data expected post-approval (e.g. confirmative phase III trial) within defined timeframes
  - Fulfil unmet medical need
  - Benefit to public health
  - Annual renewals based on fulfilment of specific obligations
- 10-year experience with CMA (2006-16)
  - 17 anticancer drugs were granted CMA
  - No CMAs were revoked or suspended
  - CMAs were converted to conventional MA with 4 years

MARKETING AUTHORISATION (MA) UNDER EXCEPTIONAL CIRCUMSTANCES

- Comprehensive data are not expected due to
  - Rare indications
  - Current state of scientific knowledge
  - Ethical issues

- Annual re-assessment of benefit/risk ratios according to specific obligations
  - Post-marketing safety studies
  - Cohort studies
  - Registries

LOW-VALUE APPROVALS AND HIGH PRICES MIGHT INCENTIVISE INEFFECTIVE DRUG DEVELOPMENT

The FDA and finally also the EMA have shown a willingness to approve anticancer drugs based on a single randomised trial achieving statistical significance, even if the magnitude of benefit is marginal or only quantified using a surrogate outcome

Neratinib for patients with HER2- positive breast cancer based on a 2.3% improvement in invasive disease-free survival (DFS), a surrogate end point, in a single randomised trial (approved by FDA and EMA)

Sunitinib for adjuvant treatment of RCC based on the results of one positive randomised trial showing an improvement in DFS, despite a second cooperative group trial failing to show a DFS benefit - **neither trial showed an improvement in overall survival** (approved by FDA and not by EMA)

Pharmaceutical companies could, hypothetically, turn a profit by testing inert chemical compounds in phase III trials

Prasad V, McCabe C and Mailankody S, Nature Reviews, Clinical Oncology,2018; 15(7):399-400

EXAMPLE TO AVOID

A risky phase III trial in the absence of a strong rationale

The EVOLVE-1 study:

- Everolimus as a second-line treatment of hepatocellular carcinoma.
- A phase III trial with over 500 accrued patients that revealed no significant difference in the efficacy of everolimus *versus* best supportive care in this setting.

Authors disclosure: The rationale supporting the phase III trial was limited to phase I data, and biological plausibility derived through laboratory studies, but that no dedicated phase II trial had been conducted!

Prasad V, McCabe C and Mailankody S, Nature Reviews, Clinical Oncology,2018; 15(7):399-400

SUGGESTION

The current situation could be remedied either

- By demanding a minimum of two independent randomised trials to support approval decisions (minimising false positive rates), as is the norm in areas of medicine outside of oncology
- and/or changing the financial incentives relating to the use of anticancer drugs, such that prices or reimbursement of drugs are based on their **clinical benefit**, according to robust value frameworks, and not mere statistical significance

Prasad V, McCabe C and Mailankody S, Nature Reviews, Clinical Oncology,2018; 15(7):399-400

PROGRESS AGAINST CANCER

Depends on efficient drug approval system that brings safe, effective treatments to patients

The Accelerated Approval process may lead to delivery of exciting and promising new drugs earlier than waiting for the more extensive trial to be completed.

Rationale:

Biomarker-driven clinical cancer care is proven to work and have saved time, money, and lives.

Common cancers = rare cancers when divided into narrow subsets according to their genomics → smaller trials are often the only way forward.

Hayes K, ASCO Perspectives; 11 June 2018.

PROGRESS AGAINST CANCER

Depends on efficient drug approval system that brings safe, effective treatments to patients

EMA and FDA efforts to streamline continuously adapt the approval process for progress in drug development

Novel and pragmatic trial designs

Cleverly designed trials, with collection of biospecimens for (secondary) tumour biomarker test analyses

→

New therapeutic agents to the right patients at the right time,

More efficient use of novel drugs

EXPECTATIONS OF FUTURE DIRECTIONS OF DEVELOPMENTS AND CAVEATS

- Increased use with more nuanced assignment of patients to matched treatments
- Handling of 'Exceptional responders'
- **Regulatory approvals based on single-arm trials with a small number of patients**[1]
- High-stakes competition for the **combination of therapies** in registration studies[2]

The accelerated approach has the potential to validate a novel combination faster

BUT

the potential for negative consequences is real

Evaluation of Clinical Benefit will become more and more important

- Harmonisation of HTA, pricing, and reimbursement decisions across all European countries to balance accessibility of new drugs for all European patients

1. Renfro LA and Mandrekar SJ, J Biopharm Stat 2017; 2. Garon EB, Comment 2016; 17(3): 259-260 on Antonia S, *et al,* Lancet Oncol, 2016.

THANK YOU!

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DISCLOSURES

- **Urania Dafni** has reported no conflict of interest
- **Zoi Tsourti** has reported no conflict of interest
- **Panagiota Zygoura** has reported no conflict of interest
- **Alex A. Adjei** has reported no conflict of interest
- **Dirk Arnold** has reported: Honoraria for Advisory Boards: Bayer Healthcare, Amgen, Merck Sharp & Dhome, Merck Serono, Eli Lilly, Bristol Myers Squibb, Servier, Roche, Terumo, Sirtex, Boston Scientific. Honoraria for presentations: Bayer Healthcare, Amgen, Servier, Roche, Terumo, Astellas, Biocompatibles, Sirtex, ArtTempi Media, Prime Oncology, TRM Oncology. Support for congress travel: Bristol Myers Squibb, Roche, Sanofi. Consulting board role IQVIA (paid to his Institution). Research Funding: Documentation fees with clinical trials, paid to his Institution by Sanofi, AstraZeneca, Incyte, Merck Sharp & Dohme. Non- financial interests: Flatiron. Principal Investigator of phase III trial with MOLOGEN. Planned as principal investigator with SFJ, Pleasanton (acting as trial sponsor for Merck Serono). Planned as principal investigator with Oncolytics. Scientific Advisory Board for Oncolytics, Biotech, SFJ, Munich Biotech. Leadership roles/Membership: ECCO Member of the Executive Board2015-2017 (on behalf of ESMO), membership of the Finance Committee. AIO in DKG: Member since 2003, Chairperson of Colorectal Cancer Working Group 2010-2018, membership in other steering committees. EORTC: Member of GI Cancer Group, Steering Committee Member since 2008; Task Force lead for Rectal Cancer and Anal Group since 2016.

DISCLOSURES

- **Ahmad Awada** has reported advisory role, research grants to his institute. Speaker for Roche, Lilly, Amgen, EISAI, BMS, Pfizer, Novartis, MSD, Genomic Health, Ipsen, AstraZeneca, Bayer, Leo Pharma.

- **Christian Dittrich** has reported honoraria for role as speaker/chair and advisory board/IDMC member as well as travel expenses – AstraZeneca Österreich, Bayer Austria, Bristol-Myers Squibb, Ellipses, Eli Lilly Austria, Ipsen Pharma, Merck Austria, Merck Serono, Novartis Pharma, Roche Austria, Sanofi- Aventis, Servier Pharma, Takeda. Research grants/educational grant – Amgen, AstraZeneca Österreich, Bayer Austria, EISAI, Boehringer Ingelheim, Merck Austria, Mundipharma, Novartis Pharma, Pfizer Corporation Austria, PharmaMar, Pierre-Fabre, Roche Austria, sanofi-Aventis, Janssen-Cilag Pharma. IDMC member-Institut Jules Bordet, Scientific Committee Member-Institut National du Cancer (INCa).

- **Denis Lacombe** has reported no conflict of interest

- **Paul Morten Mau-Sørensen** has reported advisory boards for Roche and Genmab. He has received research grant from Karyopharm. He has conduced sponsored trials with AstraZeneca, Bioclin, BMS, Cantargia, Genmab, Incyte, Loxo, Merck, Novartis, Pfizer, Puma biotechnology,Roche, Symphogen, Alligator Bioscience, Karyopharm, MSD, AbbVie, Sanofi-Aventis, Orion, Eli Lilly, (financial support paid directly to his institution).