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BEST PRACTICE

BASKET TRIALS

A well-used format of master protocols in modern drug development

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DISCLOSURES

Nadia Harbeck has reported:

Consulting honoraria: Agendia, BMS, Celgene, Genomic Health, Odonate, Sandoz/Hexal. Lectures honoraria: Amgen.

Consulting and lectures honoraria: AstraZeneca, Daiichi-Sankyo, Eli Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Seattle and Genetics.

West German Study Group: minority ownership academic study group. Role in AGO breast commission (Germany).

Benedikt Westphalen has reported:

Honoraria for Advisory Boards, Travel support: Bayer, Celgene, RedHill. Honoraria for Advisory Boards: Rafael Pharmaceuticals, Shire/Baxalta. Speakers fee-Ipsen. Honoraria for Advisory Boards, Travel support, Speakers' fee: Roche, Servier. Travel support, Speakers fee:Taiho.

AIO in DKG: Member since 2013; steering committee pancreatic cancer, cancer of unknown primary, translational and molecular oncology.

Christian Dittrich has reported:

Honoraria for role as advisory board member/scientific advisor: Novartis Pharma, Merck Serono, Roche Austria, Bristol-Myers Squibb, Ipsen Pharma, Eli Lilly Austria, sanofi-aventis / Ellipses; Honoraria for role as chair/speaker: Novartis Pharma, Roche Austria, Eli Lilly Austria, AstraZeneca Österreich; Honoraria for role as IDMC Member: Institut Jules Bordet, Merck Serono; Travel expenses: Roche Austria, Servier Pharma, Merck Austria, sanofi-aventis, Bayer Austria, Takeda.

Institutional 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

President, Angewandte Krebsforschung - Institution für Translationale Forschung Wien (ACR-ITR VIEnna)

KEY POINTS

- Background
- Actionability
- Molecular profiling: Feasibility, matching of therapy, outcome
- Basket trials: Rationale, definition, characteristics, design, potential, types, aims, and categorisation
- Tumour agnostic basket trials
- Tissue context *versus* tissue agnosis
- Achievements reached with basket trials
- On-going novel basket trial initiatives: BOB, PIPELINE
- Reasons why basket trials may fail
- Potential solutions to make basket trials more successful

BACKGROUND

Report by the Institute of Medicine (2010) calling for restructuring of the U.S. Clinical Trials System

Goals: To increase efficiency

To lower the attrition rate of clinical trials

To reduce costs

Measures: To increase efficiency by economising trial procedures by means of "master protocols"

- centralised screening platforms
- common protocol format
- increase of likelihood of eligibility criteria leading to enhanced patient participation

Result: Detection of only large efficacy signals (in single-arm cohorts)

Renfro A, Sargent DJ. Ann Oncol 2017;28:34–43.

ANTICIPATION OF MASTER PROTOCOLS

A concept of transformative clinical trial designs for a more efficient process has been elaborated, thereby considering the possibility of molecular profiling (MP) that results in consecutive smaller numbers of patients eligible per stratum

Sleijfer S, *et al.* J Clin Oncol 2013;31:1834–41.

TARGETED THERAPY

Dependency of the necessary number of patients on the prevalence of the therapeutic target required to be randomised to reach a certain envisaged therapeutic benefit in the era of targeted therapy

% patients with target in study	Hazard ratio for benefit in patients with target		
	1.3	1.5	2.0
10	32000	11000	3900
30	3600	1800	600
50	1700	780	280
70	900	400	150

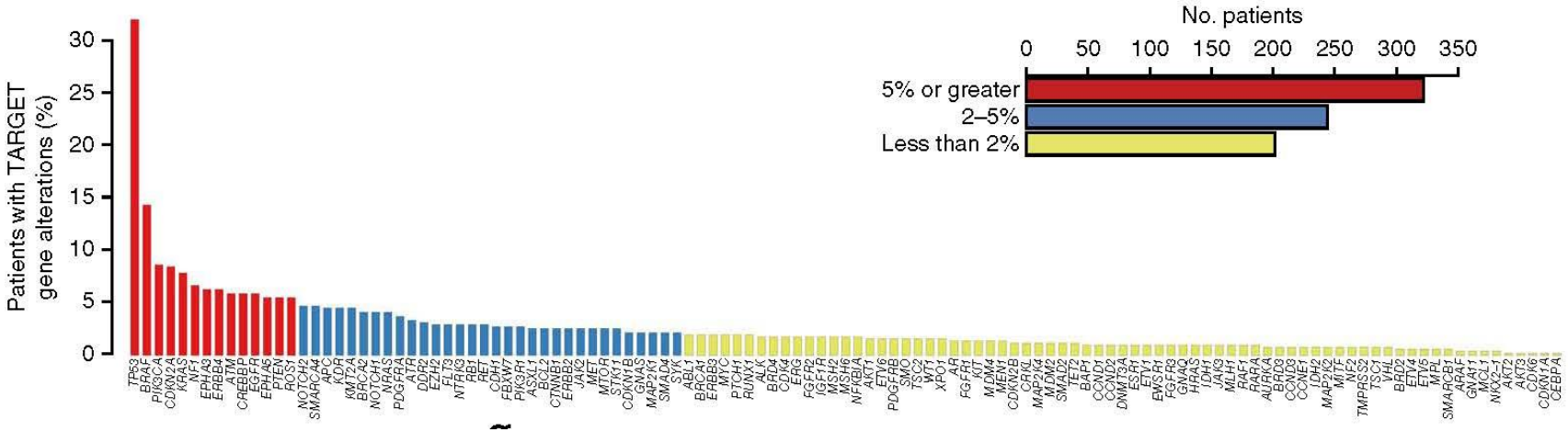
Adapted from Dancey JE, Freidlin B. Lancet 2003;362:62–4.

THE TARGET DATABASE OF POTENTIAL CLINICAL ACTIONABILITY

Ultimate prevalences of potential therapeutic targets in the era of molecularly defined therapy

Long tail of potentially clinically relevant alterations in TARGET genes

Majority of events occur in genes that individually are altered in less than 2% of the overall cohort



Van Allen EM, *et al.* Nat Med 2014;20:682-8. Reprinted by permission from Springer Nature, Nature Medicine. Whole-exome sequencing and clinical interpretation of formalin-fixed, paraffin-embedded tumor samples to guide precision cancer medicine, Van Allen EM, *et al.* copyright 2014.

ACTIONABILITY

The ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) A classification of targets for use in precision cancer medicine based on clinical evidence of utility		
ESCAT	Evidence	Clinical Application
Tier I	Ready for routine use	Standard of care
Tier II	Investigational	Treatment to be considered (preferably in registry or clinical trials)
Tier III/IV	Hypothetical target	Treatment only in clinical trials
Tier V	Combination development	Treatment only in trials testing drug combinations
Tier X	Lack of evidence of actionability	Treatment not to be used for clinical decisions

Adapted from Mateo J, *et al*. Ann Oncol 2018;29:1895–902.

FEASIBILITY OF MOLECULAR PROFILING AND MATCHING THERAPY

In 18 selected screening trials

Patients entered	Actionable genomic alterations in % patients	Matched drug therapy in % patients with actionable genomic alterations	Matched drug therapy in % patients eligible	Matched drug therapy in % patients entered
18 Trials	16 Trials	16 Trials	15 Trials	15 Trials
40,607	Median 56% Range 26–90%	Median 24% Range 2–62%	Median 15% Range 1–56%	Median 13% Range 1–39%

Adapted from Dittrich C. Cancer Treat Rev 2020;90:102082.

OUTCOME OF MOLECULAR PROFILING

In 18 selected screening trials

Patients entered	Clinical benefit rates in patients with actionable genomic alterations	Clinical benefit rates in all patients eligible	Clinical benefit rates in all patients entered	Objective response rates in patients with actionable genomic alterations	Objective response rates in all patients eligible	Objective response rates in all patients entered
18 Trials	7 Trials	6 Trials	7 Trials	7 Trials	7 Trials	7 Trials
40,607	Median 30% Range 16–52%	Median 6% Range 1–11%	Median 5% Range 1–7%	Median 14% Range 6–19%	Median 1% Range 1–9%	Median 1% Range 0.5–6%

Adapted from Dittrich C. Cancer Treat Rev 2020;90:102082.

REASONS FOR DIFFICULTIES IN EXPLOITING MOLECULAR PROFILING FOR THE CLINICAL ROUTINE

Lack of available clinical trials	Lack of patients' availability to trials
Meric-Bernstam F, *et al.* J Clin Oncol 2015 Le Tourneau C, *et al*. Lancet Oncol 2015 Hirshfield KM, *et al*. The Oncologist 2016 Stockley TL, *et al*. Genome Med 2016 Dalton WB, *et al*. JCO Precis Oncol 2017 Zehir A, *et al*. Nat Med 2017 Tsimberidou AM, *et al*. JCO Precis Oncol 2017	Tannock IF, Hickman JA, N Engl J Med 2016 Zehir A, *et al.* Nat Med 2017 Jordan EJ, *et al*. Cancer Discov 2017
Lack of availability of novel therapeutics	**Poor clinical status of patients**
André F, *et al*. Lancet Oncol 2014 Hirshfield KM, *et al*. The Oncologist 2016 Holch JW, *et al.* Eur J Cancer 2017 Jordan EJ, *et al*. Cancer Discov 2017 Moorcraft SY, *et al*. Ann Oncol 2018	Hirshfield KM, *et al*. The Oncologist 2016 Joffe S, *et al*. J Clin Oncol 2017
Lack of adequate tumour samples for analysis	**Failure of successful sequencing of tumour material**
Tannock IF, Hickman JA, N Engl J Med 2016 Hyman DM, *et al*. Cell 2017 Renfro LA, Mandrekar SJ, J Biopharm Stat 2018	Moorcraft SY, *et al.* Ann Oncol 2018

RATIONALE OF BASKET TRIALS

Cancers arising from different organs can dispose on similar mutational profiles and may respond similarly to targeted therapies

This cross-cancer similarity represents a rationale to base the trial concept of basket trials thereupon

Ciriello G, *et al*. Nat Genet 2013;45:1127–33.

PRECISION MEDICINE TRIALS

Master protocols: To answer more questions more efficiently in less time

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Adapted from Woodcock J, LaVange LM. N Engl J Med 2017;377:62–70.

CHARACTERISTICS OF BASKET TRIALS

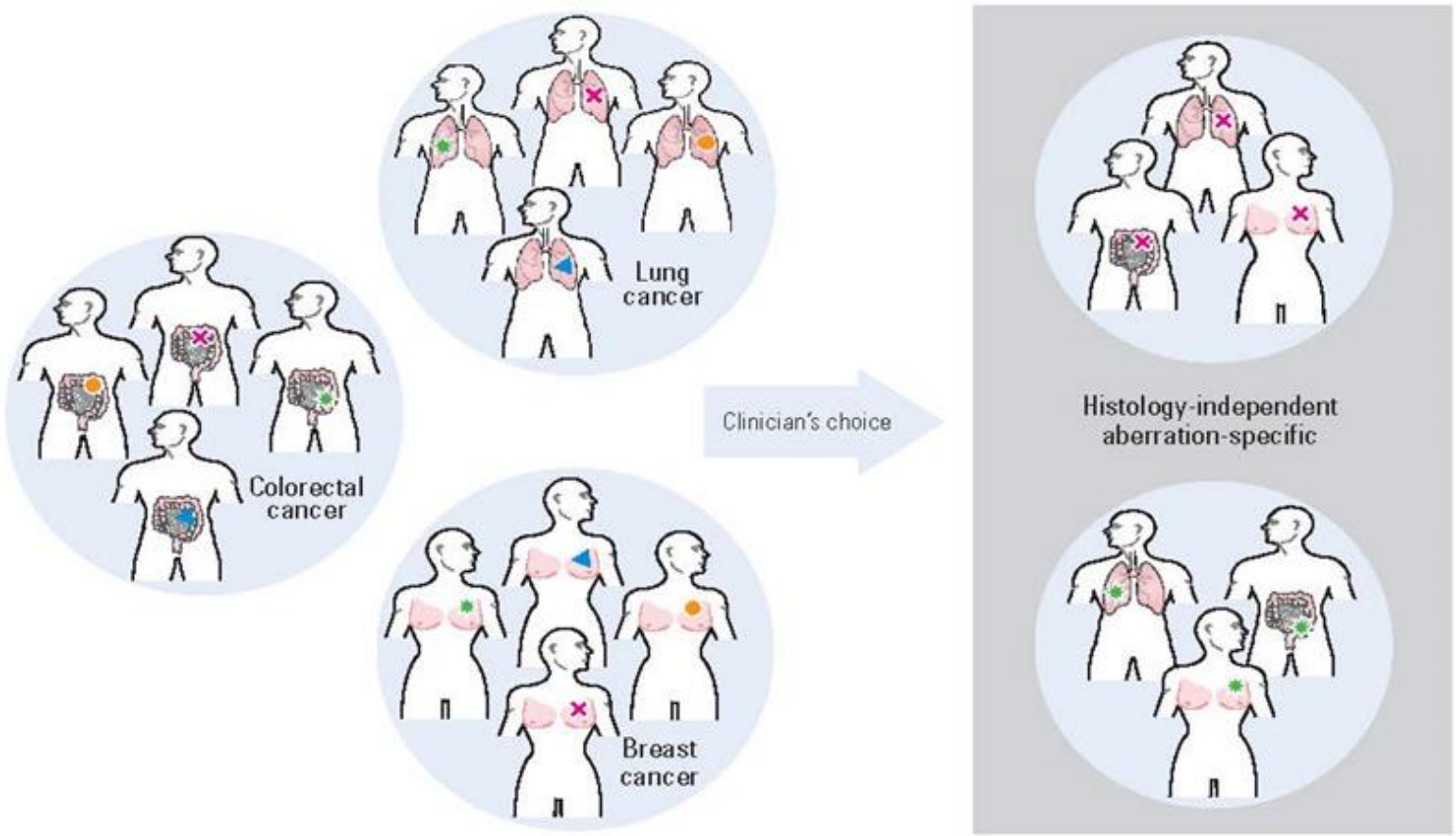
Basket trials group patients by the genomic alterations present in their tumours, thereby reflecting an increasingly accepted reclassification of human cancers, which is not based on the organ of their origin, but on the molecular abnormalities that drive their growth and progression

Basket trials are testing experimental agents across multiple patient populations in one cohesive design

Hoadley KA, *et al.* Cell 2014;158:929–44; Hyman DM, *et al.* Cell 2017;168:584–99; Mandrekar S, *et al.* Am Soc Clin Oncol Educ Book 2015;e141–7.

DESIGN OF BASKET TRIALS

Histology-independent, aberration-specific clinical trial design



Sleijfer S, *et al.* J Clin Oncol 2013;31(15):1834–41. Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.

POTENTIAL OF BASKET TRIALS

- To test a defined biological hypothesis that a particular mutation predicts response to a targeted drug independent of the tumour histology

  Baselga J. Ann Oncol 2013;24:1956–7.

- To resolve the uncertainty whether a particular mutation in a tumour of a particular histologic type should be considered actionable for treatment with a given drug

  Mandrekar SJ, *et al.* Am Soc Clin Oncol Educ Book 2015;e141–7.

- To validate targets as biomarkers

  Redig A, Jänne P. J Clin Oncol 2015;33:975–7.

- To study targeted therapies in low frequency mutations across multiple tumour types

  Hyman DM, Solit D. J Clin Oncol 2015;33:2725–6.

TYPES OF BASKET TRIALS

Basket Trials

To study a single targeted therapy
in the context of a single molecular subtype
in multiple clinical diseases

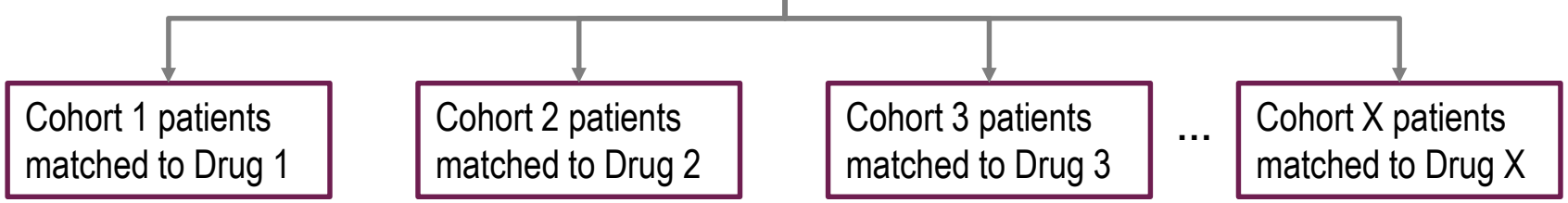
Multiple / Parallel Basket Trials

To study multiple targeted therapies
in the context of several molecular subtypes
in multiple clinical diseases

MULTIPLE / PARALLEL BASKET TRIAL DESIGN

Schematic representation

- Single protocol infrastructure
- Enrol to multiple cohorts defined by genetic mutation and/or cancer type
- Centralised screening and patient identification according to cohort eligibility criteria
- Single-arm statistical designs to support relatively exploratory or early drug development hypotheses



Mandrekar S, *et al*. Am Soc Clin Oncol Educ Book 2015;e141–7.

INTERCHANGEABLE DENOMINATIONS OF MASTER PROTOCOL TRIALS

Umbrella trials
ALCHEMIST
BATTLE-1
BATTLE-2
FOCUS 4
I-SPY 2
Lung-MAP
NCI-MATCH
SAFIR02 Lung/Breast
WINTHER

Algorithm-based randomised strategy trials
ALCHEMIST
Lung-MAP
NCI-MPACT
SAFIR02 Lung/Breast
SHIVA

ALCHEMIST
BATTLE-1
BATTLE-2
FOCUS 4
I-SPY 2
Lung-MAP
NCI-MPACT
NCI-MATCH
SAFIR02 Lung/Breast
SHIVA
WINTHER

Basket trials / multiple parallel basket trials
NCI-MPACT
NCI-MATCH
SHIVA

Algorithm-based non-randomised strategy trials
WINTHER

Platform trials
BATTLE-1
BATTLE-2
FOCUS 4
I-SPY 2
Lung-MAP
NCI-MPACT
NCI-MATCH

DESIGN OF BASKET TRIALS

- Generally single-arm trials
- Usually based on short-term endpoints (overall response)
- Hypothesis generating: explorative character (“trials designed to learn”)
- Need for validation by confirmatory trials (e.g. small randomised phase 2 trials) (“trials designed to conclude”)

DESIGN OF BASKET TRIALS
(CONTINUED)

- Generally dispose on small numbers of patients only
- The predictive value of a test (e.g. for a mutation) is lower, where the prevalence of the target (e.g. that mutation) is low
- Small single-arm discovery trials, thus requiring confirmation to prove that their outcome is due to a true treatment effect and not due to chance difference
- Cost-effectiveness of targeted therapy as in basket trials is directly related to the positive predictive value (PPV) of the test

Adapted from Ramsey SD, *et al.* J Clin Oncol 2019;37:3472–4;
Qin B-D, *et al.* Front Oncol 2019;9:229.

AIMS OF BASKET TRIALS

- To seek for a signal of anti-tumour activity (Example: NCI-MATCH trial)
  (mainly testing of novel agents in uncommon or rare tumours or scarce subcohorts of common tumours; preponderant design: single-stage)

  Conley BA, Doroshow JH. Semin Oncol 2014;41:297–9; Abrams J, *et al.* Am Soc Clin Oncol Educ Book 2014;34:71–6; Flaherty KT, *et al.* J Natl Cancer Inst 2020;112:1021–9.

- To determine antitumour effectiveness (Example: TAPUR study)
  (mainly testing of already registered drugs off-label in scarce subcohorts of common, uncommon or rare tumours; preponderant design: two-stage)

  Mangat PK, *et al.* JCO Precis Oncol 2018;2. https://doi.org/10.1200/PO.18.00122.

- To investigate whether drug selection based on molecular profiling (MP) results in better outcome than drug selection not based on MP (Example: SHIVA trial)

  Le Tourneau C, *et al.* Lancet Oncol 2015;16:1324–34.

SUBTYPES OF BASKET TRIALS

One drug — one oncokinase — multiple diseases

- Example: Vemurafenib-BT (Hyman DM, *et al.* New Engl J Med 2015;373:726–36)

One drug — multiple oncokinases — multiple diseases

- Example: CREATE trial (Péron J, *et al.* Eur J Cancer 2019;109:192–5)

Multiple drugs — multiple oncokinases — multiple diseases

- Example: CUSTOM trial (Lopez-Chavez A, *et al.* J Clin Oncol 2015;33:1000–7)

Cunanan KM, *et al.* J Clin Oncol 2017;35:271-3.

CATEGORISATION OF BASKET TRIALS

According to the degree of dependency of or independency from histology

GNOSTIC All tumour types are prespecified	Examples: CUSTOM trial (Lopez-Chavez A, *et al.* J Clin Oncol 2015) CREATE EORTC 90101 trial (Schöffski P, *et al.* Eur J Cancer 2018) TAPUR study (Mangat PK, *et al*. JCO Precis Oncol 2018)
SEMI-GNOSTIC At least one tumour type is prespecified	Examples: Olaparib (Kaufman PA, *et al.* J Clin Oncol 2015) Vemurafenib (Hyman DM, *et al.* New Engl J Med 2015) Entrectinib (Doebele RC, *et al.* Lancet Oncol 2020)
AGNOSTIC No tumour type is prespecified	Examples: Imatinib Target Exploration Consortium Study B2225 (Heinrich MC, *et al*. Clin Cancer Res 2008) Larotrectinib (Drilon A, *et al.* New Engl J Med 2018) NCI-MATCH trial (Flaherty KT, *et al.* J Natl Cancer Inst 2020)

Adapted from Dittrich C. Cancer Treat Rev 2020;90:102082.

TUMOUR AGNOSIS AS INITIAL CONCEPT OF BASKET TRIALS

Some pathways carry a driving role in multiple tumour types that leads to a pan-tumour approach

Cancer Genome Atlas Research Network; Weinstein JN, *et al.* Nat Genet 2013;45:1113–20.

SELECTION OF TUMOUR AGNOSTIC BASKET TRIALS

Basket Trial	Reference
Imatinib Target Exploration Consortium Study B2225	Heinrich MC, *et al.* Clin Cancer Res 2008
SIGNATURE	Kang BP, *et al.* Clin Pharmacol Ther 2015 Slosberg ED, *et al.* Oncotarget 2018
MyPathway	Hainsworth JD, *et al.* J Clin Oncol 2018
NCI-MATCH (National Cancer Institute-Molecular Analysis for Therapy Choice) Trial	Flaherty KT, *et al.* J Natl Cancer Inst 2020
AcSé Program (Secured Access to Innovative Therapies)	Buzyn A, *et al.* Nat Rev Clin Oncol 2016
DRUP (Drug Rediscovery Protocol)	Van der Velden DL, *et al.* Nature 2019
SCOUT/NAVIGATE	Drilon A, *et al.* New Engl J Med 2018 Hong DS, *et al.* Lancet Oncol 2020
STARTRK-1/STARTRK-2/ALKA-372-001	Doebele RC, *et al.* Lancet Oncol 2020
CodeBreak 100	Hong DS, *et al.* New Engl J Med 2020
ARROW	Subbiah V, *et al.* J Clin Oncol (Suppl) 2020; Abstract 109
KEYNOTE-158	Marabelle A, *et al.* J Clin Oncol 2020

REQUIREMENTS FOR AGNOSTIC BASKET TRIALS

- Need to be based on a strong biological rationale
- Knowledge that similar alterations in different histologies have a comparable biological significance and can be successfully targeted with the same agents
- Targets / biomarkers must be validated in the tumour entities in which they are to be tested
- Knowledge about the natural history of the disease

HYPOTHESES

At the beginning of the development of immune checkpoint inhibitors as tumour agnostic therapeutics

- Mismatch repair deficient tumours stimulate the immune system

  Bodmer W, *et al.* Nat Genet 1994;6:217–9.

- Tumours with a large number of somatic mutations due to mismatch repair deficiency may be susceptible to immune checkpoint blockade

  Le DT, *et al.* N Engl J Med 2015;372:2509–20.

- Tumours with a high tumour mutational burden (TMB-H; defined as ≥10 mutations/Mb assessed in FFPE tumour samples using the Foundation One CDx® assay) may be susceptible to immune checkpoint blockade with pembrolizumab

  Marabelle A, *et al.* Ann Oncol 2019;30(Suppl 5):v477(Abstract 11920).

PD-1 BLOCKADE IN TUMOURS WITH MISMATCH REPAIR DEFICIENCY

Pembrolizumab 10 mg/kg intravenous infusions q14 days

Objective responses according to RECIST criteria

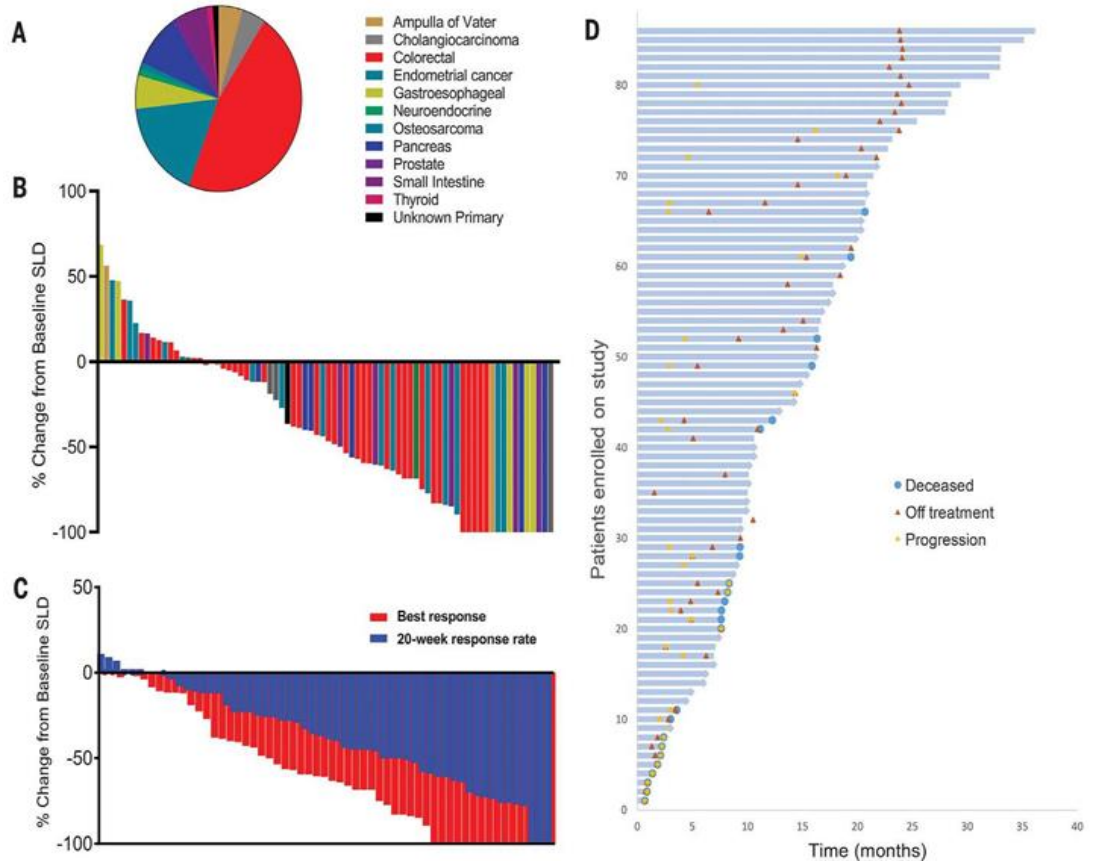
Type of response	Mismatch repair-deficient colorectal cancer (n=10)	Mismatch repair-proficient colorectal cancer (n=18)	Mismatch repair-deficient noncolorectal cancer (n=7)
Complete response, n (%)	0	0	1 (14)*
Partial response, n (%)	4 (40)	0	4 (57)†
Stable disease at Week 12, n (%)	5 (50)	2 (11)	0
Progressive disease, n (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated, n (%)°	0	5 (28)	0
Objective response rate, % (95% CI)	40 (12, 74)	0 (0, 19)	71 (29, 96)
Disease control rate, %§ (95% CI)	90 (55, 100)	11 (1, 35)	71 (29, 96)
Median duration of response, wk	Not reached	NA¶	Not reached
Median time to response, wk (range)	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks
† One patient had a partial response at 12 weeks
° Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair - proficient colorectal cancer

Le DT, *et al.* N Engl J Med 2015;372:2509–20.

MISMATCH REPAIR DEFICIENCY AND RESPONSE OF SOLID TUMOURS TO PD-1 BLOCKADE

This phase 2 trial (KEYNOTE-016) was continued and finally yielded clinical response to pembrolizumab across 12 different tumour types with mismatch repair deficiency



From Le DT, *et al*. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357(6349):409–13. Reprinted with permission from AAAS (available at: https://science.sciencemag.org/content/357/6349/409.long; accessed Nov 2020).

TUMOUR TYPE AGNOSTIC DRUG DEVELOPMENT

- Is appropriate if drug — target combinations demonstrate very high activity across multiple tumour types
- Is appropriate for targets where actionability is not conditioned by tumour lineage
- Risks delaying drug development if effects are differing across tumour types
- May be inappropriate if a drug is most effective in combination regimens
- Is only appropriate if knowledge about natural history of the disease is available
- Is only appropriate if the target is validated in the respective disease

Flaherty K, *et al.* Am Soc Clin Oncol Educ Book 2017;37:222–30;
Hyman DM, *et al.* Cell 2017;168:584–99; André F. N Engl J Med 2018;378:763–5;
André F, *et al.* Ann Oncol 2014;25:2295–303.

POTENTIAL BIOMARKERS FOR TUMOUR AGNOSTIC TREATMENT / TREATMENT DEVELOPMENTS (SELECTION)

AKT1 mutations	HER2 mutations	PDGFRA/B fusions
ALK fusions	HER3 mutations	PD-L1 overexpression
APOEC	KIT mutations	PD-L1 amplification
BRAF mutations	KRAS mutations	PIK3CA mutations
BRCAness	MET alterations	POLE mutations
dMMR	MSI-high*	RET alterations
EZH2 mutations	NRG1 alterations	ROS1 alterations
FGFR alterations	NTRK1/2/3 fusions*	TMB-high*

* Biomarker with established tumour agnostic approval

Hyman DM, *et al.* Cell 2017;168:584–99; Garber K. Nat Rev Drug Discov 2018;17:227–9;
IQVIA. https://www.iqvia.com/insights/the-iqvia-institute/reports/supporting-precision-oncology (accessed Nov 2020).

DEPENDENCY OF TARGETED THERAPY ON THE DISTINCT TYPE OF THE MOLECULAR ALTERATION

Efficacy of pemigatinib in cholangiocarcinoma

	CR (%)	PR (%)	SD (%)	Median PFS Months
FGFR2 gene fusions / rearrangements	2.8	32.7	46.7	6.9
Other FGF/FGFR gene alterations	0	0	40.0	2.1
No FGF/FGFR gene alterations	0	0	22.2	1.7

Vogel A, *et al.* Ann Oncol 2019;30(Suppl 5):v876;abstract LBA40.

TUMOUR TYPE AGNOSTIC APPROVALS

Pembrolizumab (Keytruda®) – PD-1 checkpoint inhibitor

- FDA: Approval (on the basis of the MSI-high or dMMR biomarker)
- FDA: Accelerated approval (on the basis of the tumour mutational burden-high (TMB-H) biomarker)

Larotrectinib (Vitrakvi®) – First-in-class highly selective pan-TRK inhibitor

- FDA: Approval
- EMA: Approval

Entrectinib (Rozlytrek®) – Multi-targeted pan-TRK / ROS-1 / ALK inhibitor

- Japan: Approval
- FDA: Approval
- EMA: Conditional approval

Most genomic alterations will not predict for tumour type agnostic efficacy

Hyman DM *et al*; Nature 2018;554:189-94.

TISSUE CONTEXT *VERSUS* TISSUE AGNOSIS

Does matching drug and mutation outweigh tissue of origin?

Response rates to vemurafenib

in melanomas with BRAF $V600E^{mut}$:	80%
in colorectal cancer with BRAF $V600E^{mut}$:	5%

The unresponsiveness of colon cancer with the same molecular aberration is explained by a rapid feedback activation of EGFR

Melanoma cells express low levels of EGFR and are therefore not subject to this feedback activation

→ Tissue context matters

Prahallad A, *et al.* Nature 2012;483:100–3.

THE BEACON CRC TRIAL IN BRAF V600E^{MUT} COLORECTAL CANCER

Providing clinical evidence for the correctness of the explanations by Prahallad A, *et al*. Nature 2012

Encorafenib Binimetinib Cetuximab	Randomisation Encorafenib Cetuximab	Cetuximab / Irinotecan or Cetuximab / FOLFIRI
N=224	N=220	N=221
Prespecified interim analyis		
N=111	N=113	N=107
Median overall survival p<0.001		
9.0 months	8.4 months	5.4 months
Overall response rate p<0.001		
26%	20%	2%
Median progression-free survival p<0.001		
4.3 months	4.2 months	1.5 months

Adapted from Kopetz S, *et al.* N Engl J Med 2019;381:1632–43.

TUMOUR AGNOSTIC DRUG DEVELOPMENT

Examples demonstrating that tumour type matters

Trial name	Agent	Molecular alteration Expression	Results	Reference
Imatinib Target Exploration Consortium Study B2225	Imatinib	Protein expression of imatinib-sensitive tyrosine kinases: KIT, PDGFRA/B (IHC-based)	Confirmed response in: Solid tumours 9% Haematologic malignancies 28%	Heinrich MC, *et al.* Clin Cancer Res 2008
MyPathway	Trastuzumab + pertuzumab	HER2 amplification / overexpression	Colorectal cancer: ORR 38% (PR) Non-small cell lung cancer: ORR 13% (PR)	Hainsworth JD, *et al.* J Clin Oncol 2018
	Vemurafenib	BRAF V600E mutant	Non-small cell lung cancer: ORR 43% Ovarian cancer: ORR 50% Other 3 sites: ORR 0%	

SUCCESS OF BASKET TRIALS

Expectable only if

- Tumour depends on targeted pathway
- Targeted therapy reliably inhibits the target

ACHIEVEMENTS REACHED WITH BASKET TRIALS

Basket trials have

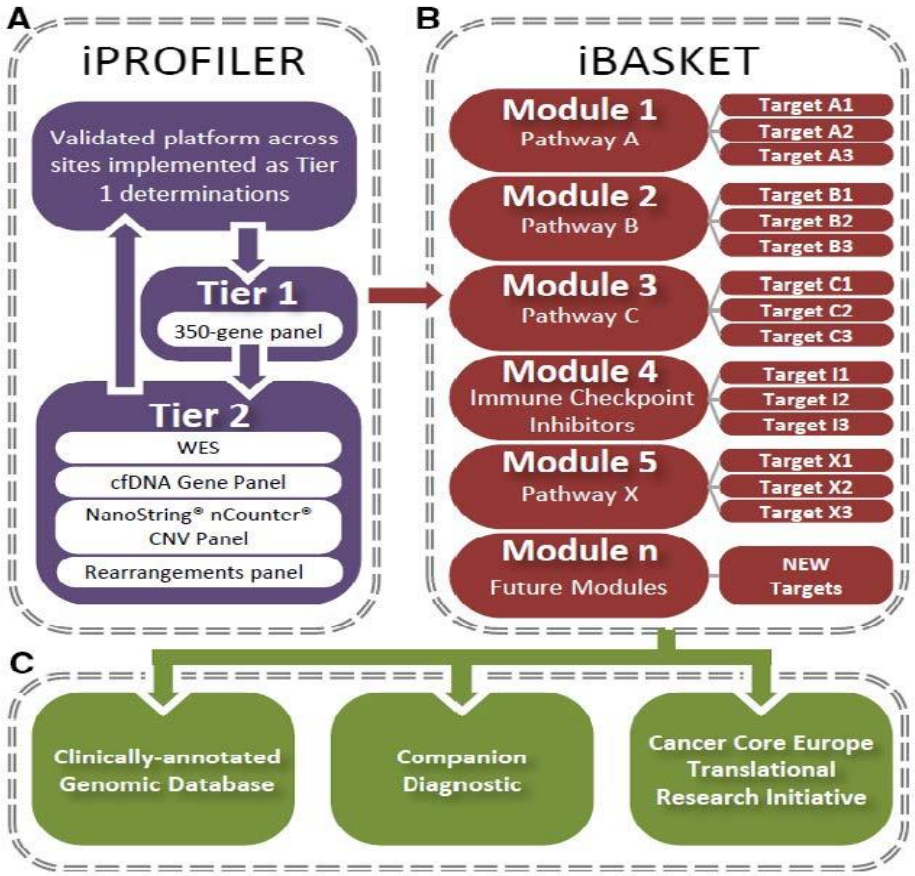
- substantially contributed to modern drug development
- resulted in multiple drug approvals
- resulted in the first tumour agnostic drug approvals of EMA, FDA, and PMDA
- a much higher than proportional impact on drug approval in paediatric patients
- a high impact on drug approval in rare cancers
- contributed to the validation of targets as biomarkers
  (such as microsatellite instability-high (MSI-H) in metastatic colorectal cancer, or tumour mutational burden-high (TMB-H) in solid tumours, or fibroblast growth factor receptor (FGFR)1/2/3/4 alterations in intra-hepatic cholangiocarcinoma)

BASKET OF BASKETS (BOB) CLINICAL TRIAL

Ongoing Novel Basket Trial Initiative

The BOB trial is a project of the collaborative basket framework of the Cancer Core Europe (CCE).

Its goal is to evaluate the antitumour activity of matched therapies most efficiently in small CCE patient populations, thereby respecting integrated translational research considerations.



The Basket of Baskets Clinical Trial process

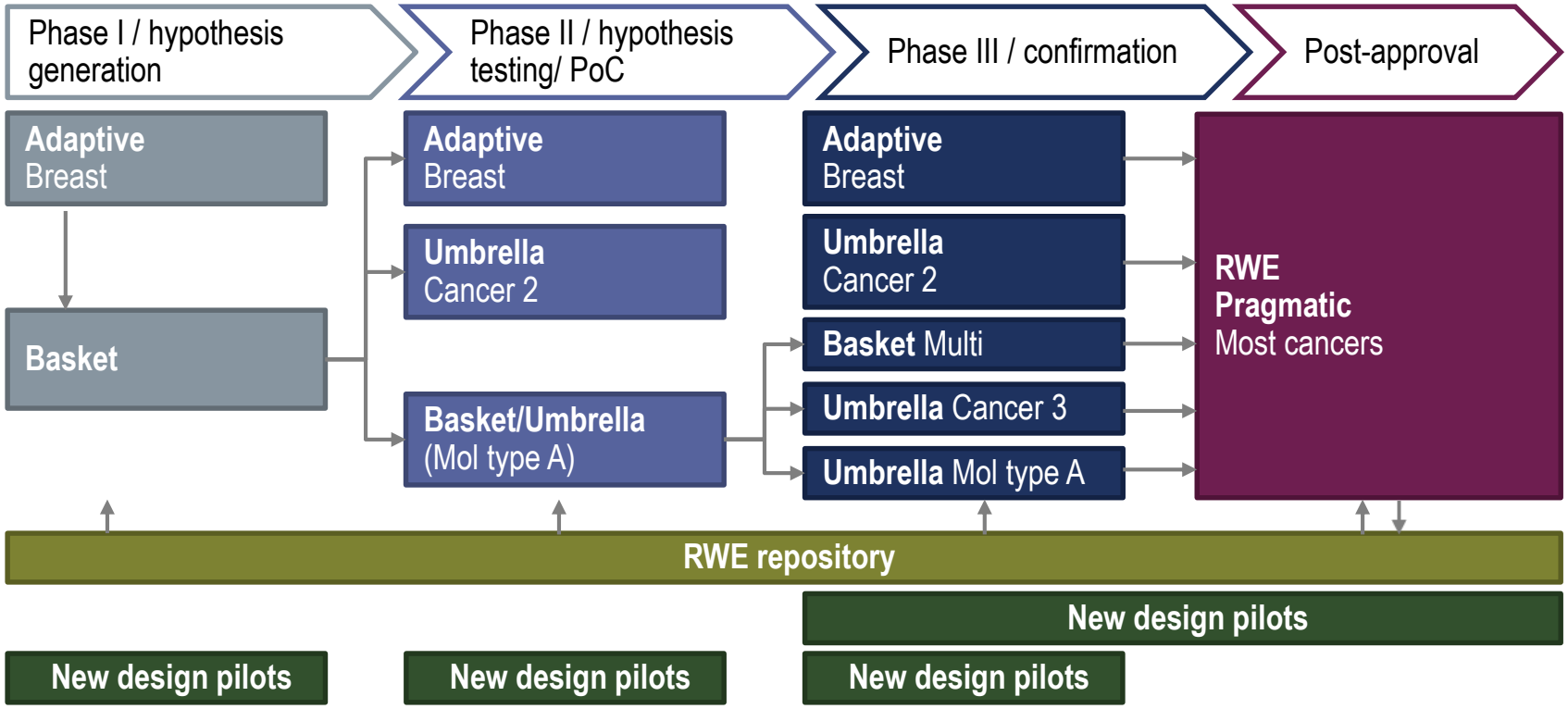
(A) iPROFILER: a 2-tier process of increasing resolution to identify potential candidate and determine their molecular signature

(B) iBASKET: the array of modules in the trial process, each of which focuses on a different pathway. Within each module, there are several arms that target specific components of the modules pathway

(C) The outcomes of BOB

PIPELINE (PORTFOLIO OF INNOVATIVE PLATFORM ENGINES, LONGITUDINAL INVESTIGATIONS AND NOVEL EFFECTIVENESS)

Ongoing Novel Basket Trial Initiative



Whether the integration of basket trials as inaugural part of the multi-master protocol network PIPELINE will lead to better outcome more efficiently has to be temporised

Trusheim MR, *et al.* Clin Pharmacol Ther 2016;100:713–29.

REASONS WHY BASKET TRIALS MAY FAIL

- Tumour-biology inherent
  - intratumour heterogeneity
  - intrinsic/de novo drug resistance
- Inefficacy of an agent tested independent from the trial conditions
- Patient selection based on a not validated target/biomarker
- Acquired drug resistance caused by patient pretreatment
- Impossibility to distinguish whether an effect is due to the treatment tested or due to the patient selection by means of the target/biomarker selection used because lack of randomisation does not allow to differentiate between predictive and prognostic features
- Restriction of patient/tumour selection based exclusively on molecular profiling in form of genotyping, thereby neglecting other impacting parameters such as gene expression
- Gene expression but not mutation is a molecular feature that best predicts differential sensitivity

Tsherniak A, *et al.* Cell 2017;170:564–76.

POTENTIAL SOLUTIONS TO MAKE BASKET TRIALS MORE SUCCESSFUL

- Up-front use of combinatorial therapies to avoid or overcome drug resistance in heterogeneous tumours
- Drug selection based on an algorithm for prioritising the right drugs at the most appropriate sequence in case of multiple molecular alterations
- Combinatorial drug selection by means of systems biology

POTENTIAL SOLUTIONS TO MAKE BASKET TRIALS MORE SUCCESSFUL (CONTINUED)

- Combination of functional characterisation of tumour drivers beyond genotyping because of the complex intratumour inter-dependencies, including epigenomics, proteomics, immune-profiling, and functional diagnostics
- Interdisciplinary treatment approach because of partly organ-dependent organisation of oncologic departments
- Focus on endpoints with intermediate- to long-term impact (DOR, PFS, TTF) instead of mainly short-term impact (ORR) to better assess the more important parameters reflecting tumour trunk alterations