Cancer Core Europe
CDDF Cancer Drug Development Forum
CDDF MULTI-STAKEHOLDER WORKSHOP
INNOVATION IN ONCOLOGY CLINICAL TRIAL DESIGN
12 - 13 June 2017
Frankfurt, Germany
CDDF Cancer Drug Development Forum

Relevance of Innovative Trial Design Today

Basket of Baskets and other Innovative Clinical Trials

CAMBRIDGE Cancer CENTRE
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Karolinska Institutet
NETHERLANDS CANCER INSTITUTE ANTONI VAN LEEUWENHOEK
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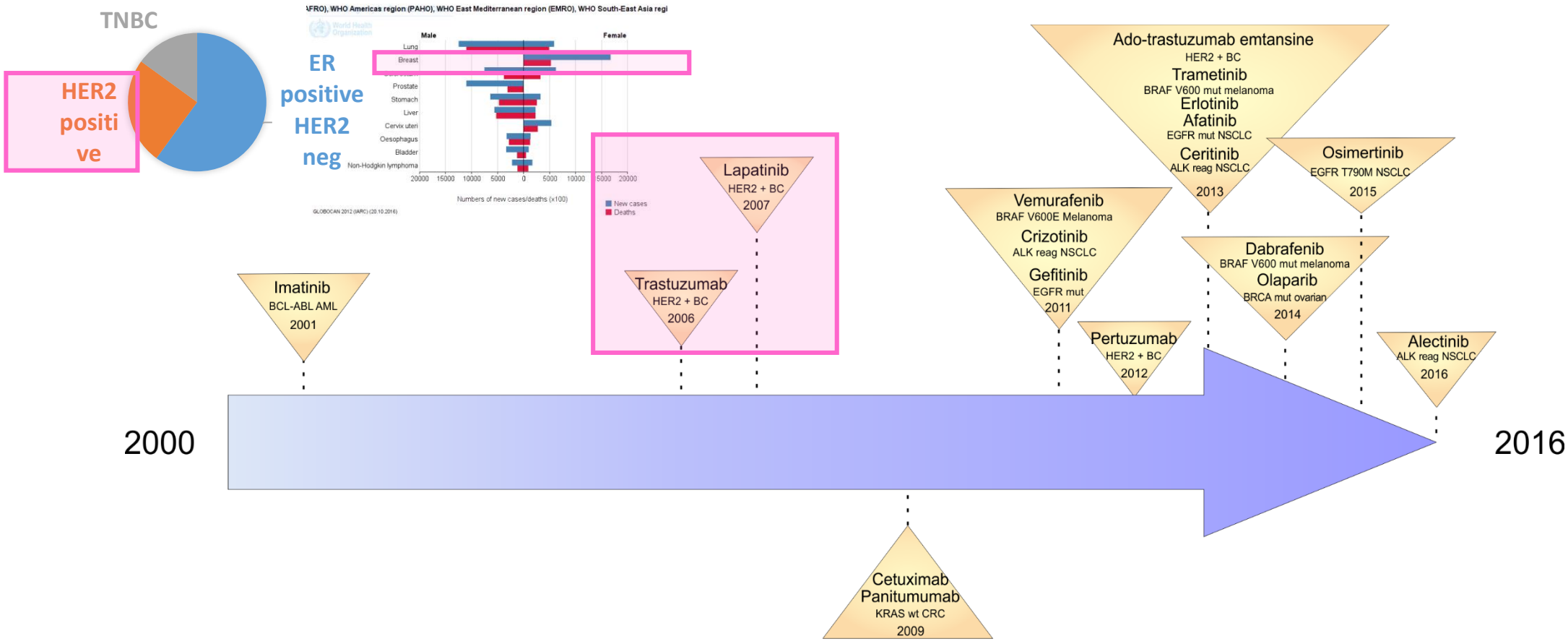
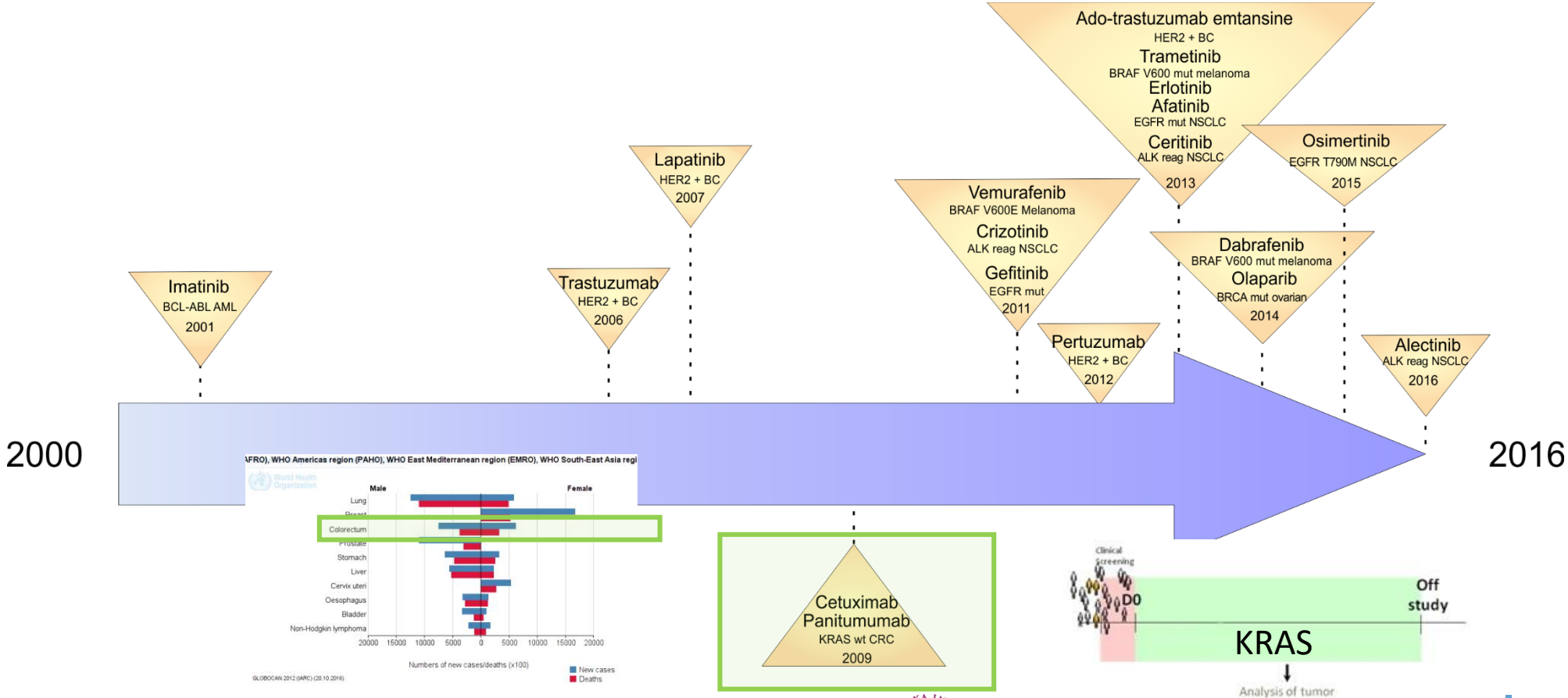
Outline

- Precision Medicine Clinical Trials – Evolving Field
  - “Classic” industry-sponsored design:
    - single drug, single disease type, central biomarker analysis
  - Basket Studies
    - Vemurafenib in non-melanoma BRAF V600E mutant tumors
    - Larotrectinib in adult and pediatric NTRK fusion cancers
  - Molecular selection programs – multiplexed biomarker analysis
  - Examples of academic studies with novel designs
    - WINTHER Study / LUNG-Matrix / NCI-MATCH
  - Basket of Baskets

Precision Medicine Clinical Trials Evolving Field

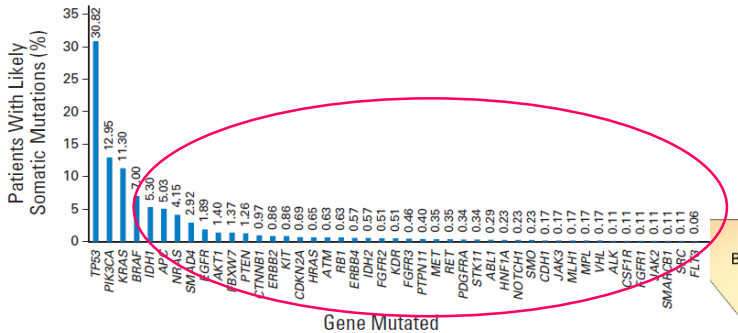


Precision Medicine Clinical Trials Evolving Field



Precision Medicine Clinical Trials Evolving Field

Long Tail Distribution



Imatinib
BCL-ABL AML
2001

Trastuzumab
HER2 + BC
2006

Cetuximab
Panitumumab
KRAS wt CRC
2009

Vemurafenib
BRAF V600E Melanoma
Crizotinib
ALK reag NSCLC
Gefitinib
EGFR mut
2011

Pertuzumab
HER2 + BC
2012

Ado-trastuzumab emtansine
HER2 + BC
Trametinib
BRAF V600 mut melanoma
Erlotinib
Afatinib
EGFR mut NSCLC
Ceritinib
ALK reag NSCLC
2013

Dabrafenib
BRAF V600 mut melanoma
Olaparib
BRCA mut ovarian
2014

Osimertinib
EGFR T790M NSCLC
2015

Alectinib
ALK reag NSCLC
2016

2000

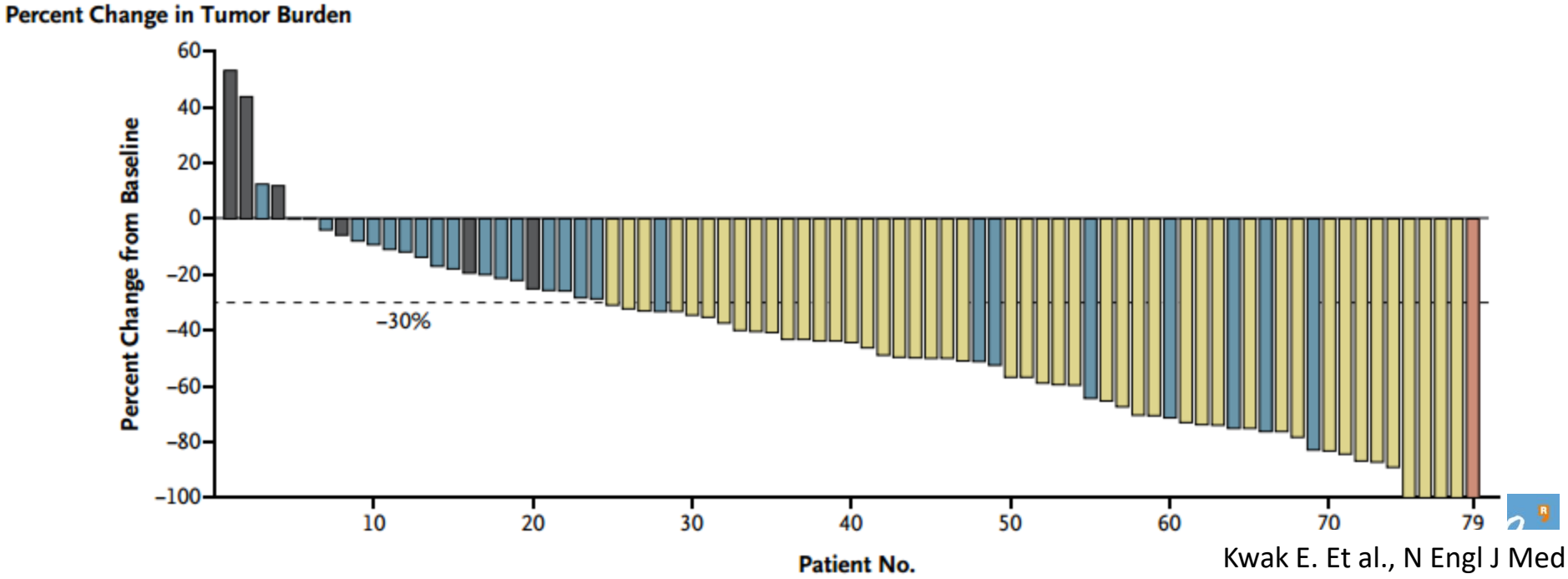
2016

"Classic" Precision Medicine in Oncology Study: Single drug, Single disease type, Central biomarker analysis

Crizotinib in ALK-translocated NSCLC

- Approx. 1500 patients – Screened
- 82 patients - Treated

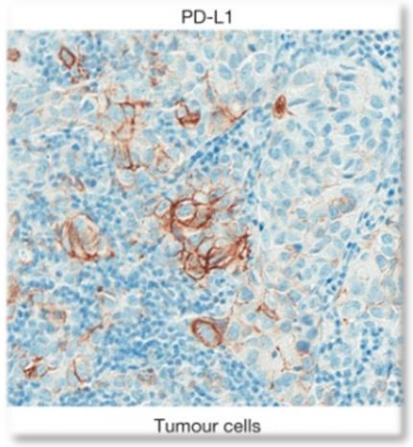
High Attrition

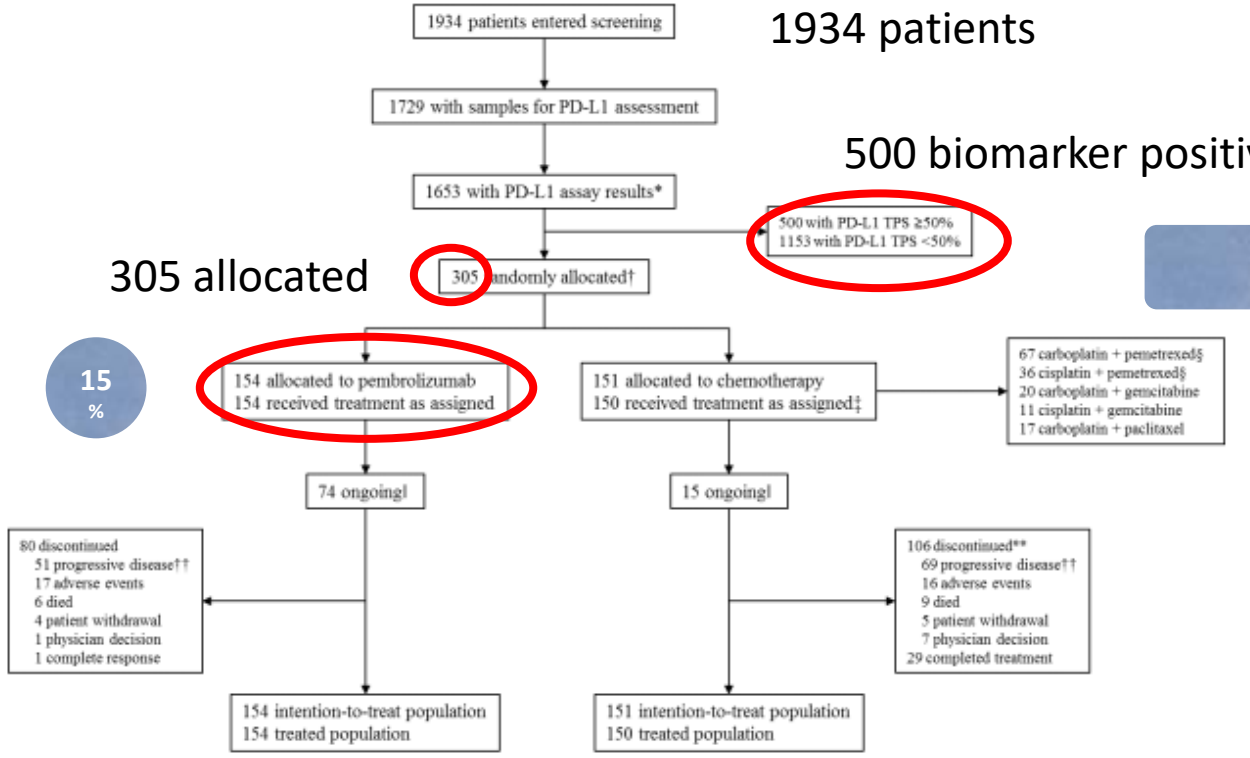


Kwak E. Et al., N Engl J Med. 2010;363(18):1693-703

"Classic" Precision Medicine in Oncology Study
Turn Around Time - Patient Clinical Deterioration

KEYNOTE-024: Phase III study of pembrolizumab vs Chemotherapy as first line for PD-L1-Positive Non-Small-Cell Lung Cancer.





1934 patients

500 biomarker positive not randomized

305 allocated

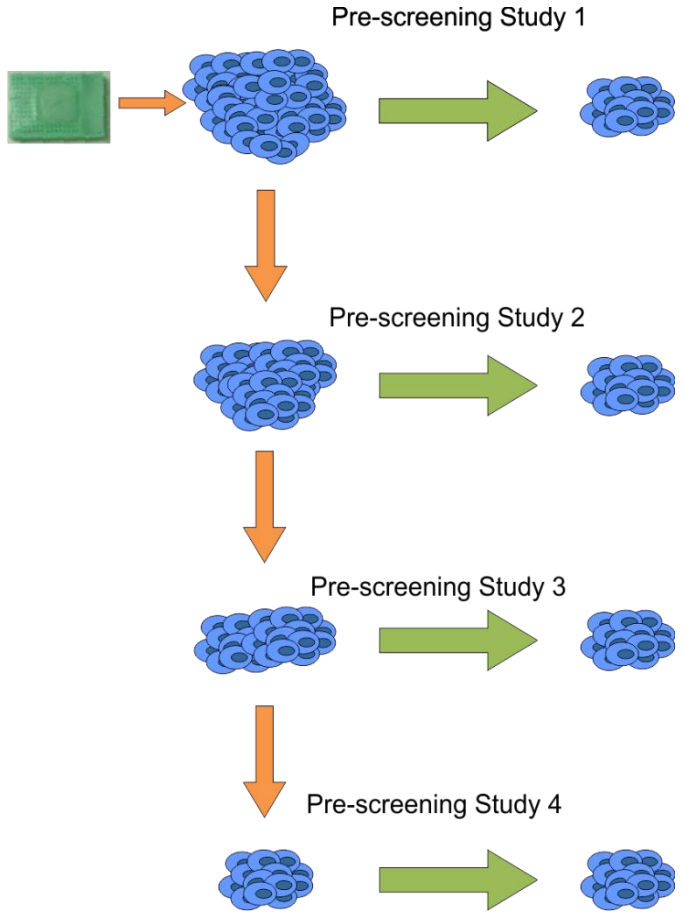
39 % ATTRITION

15 %

Reck M. et al.; N Engl J Med. 2016 Oct 8.

“Classic” Industry-Sponsored Design – Issues
Sample Exhaustion

- Subsequent central testing
  - Sample Exhaustion
- Particularly challenge
  - Small biopsies



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Molecular Selection Programs

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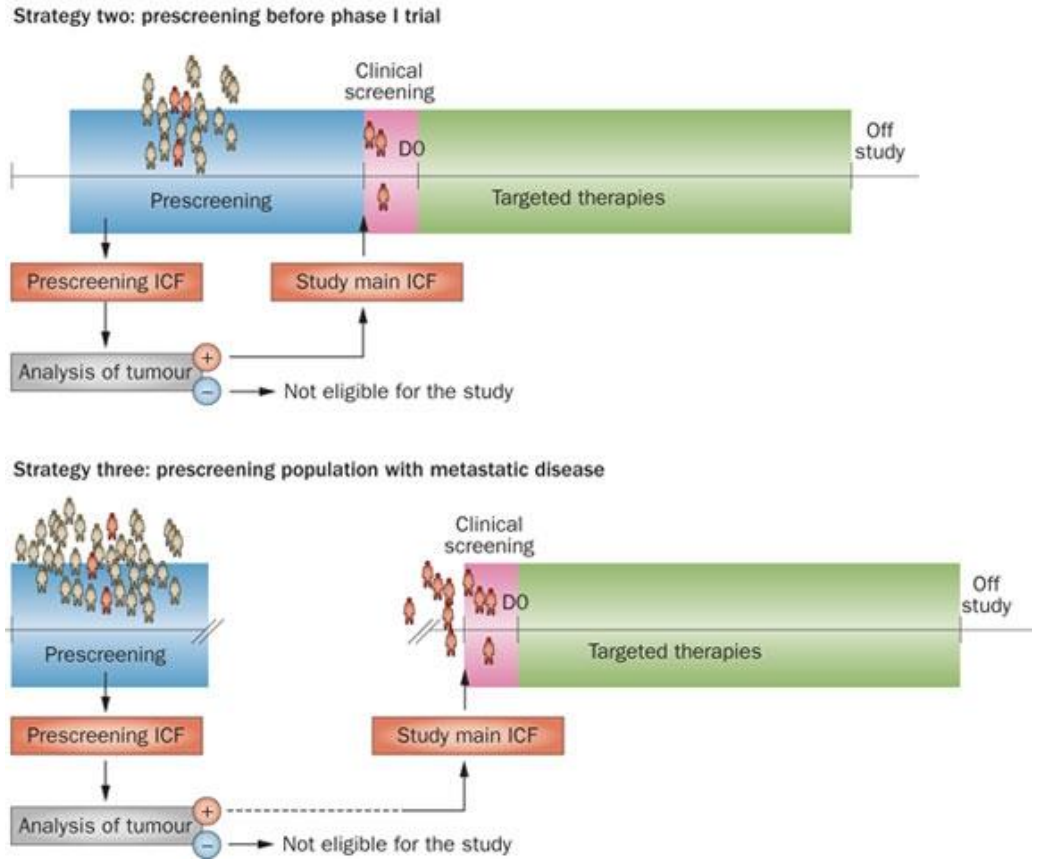
Molecular Selection Programs
Multiplexed Biomarker Analysis

- Multiplexed biomarker analysis
- Performed locally
- Short turn-around time
- Patient's tumor characterized by the time of requiring participation in a clinical trial
- Customizable
- Cost issues



Molecular Selection Programs

	IMPACT *(NCT01505400)* *Princess Margaret Cancer Centre*	MD Anderson Cancer Center	MOSCATO Institute Gustave Roussy
Patients Enrolled	N=678	N=2601	N=708
Enrollment Period	Mar 2012 – April 2013	May 2012 – Jul 2013	--
Sample not analyzed	75 (11 %)	601 (23 %)	66 (9%)
Patients >= 1 mutation	176	1203	--
Patients actionable alteration	43	627	290
Patients receiving matched targeted agent	23 (clinical trial)	123 [83 clinical trial + 40 off label]	140

3 %

5 %

20 %

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Basket Studies

Single Drug, Histology Agnostic Approach

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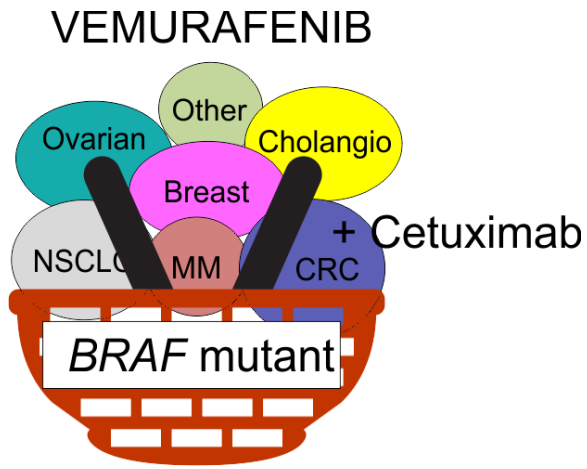
Basket Studies

Vemurafenib in non-melanoma BRAF V600E mutant tumors

- Same Drug (single agent or in combination)
- Patients selected by a common molecular alteration
- Different tumor types

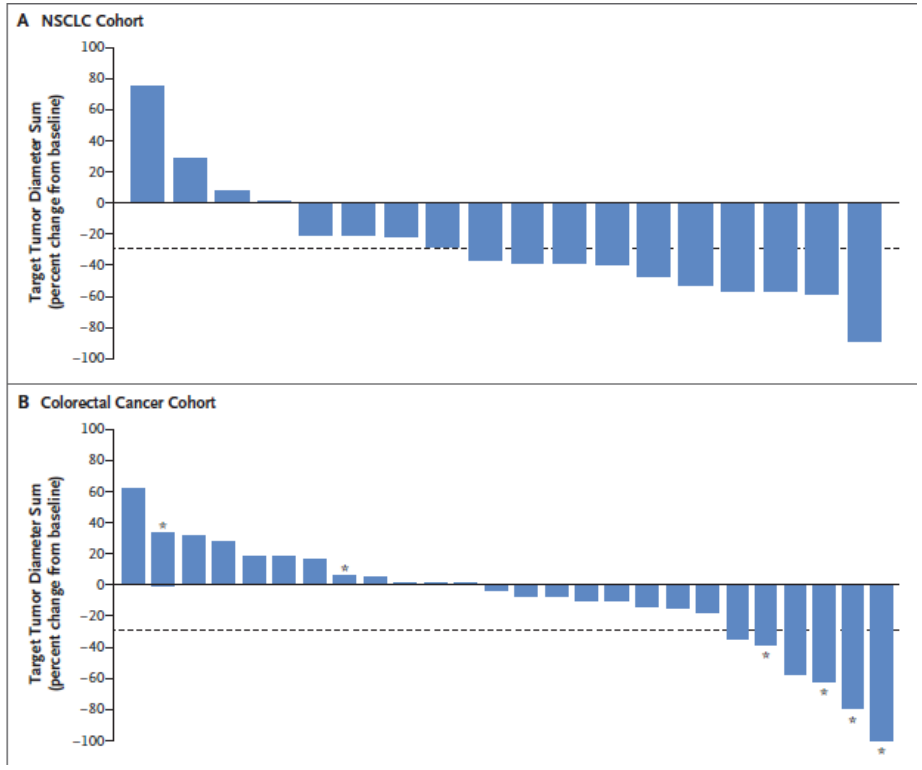
Arm 1	Non-Small Cell Lung Cancer
Arm 2	Ovarian Cancer
Arm 3	Colorectal Cancer
Arm 4	Cholangiocarcinoma
Arm 5	Breast Cancer
Arm 6	Multiple Myeloma
Arm 7	Others

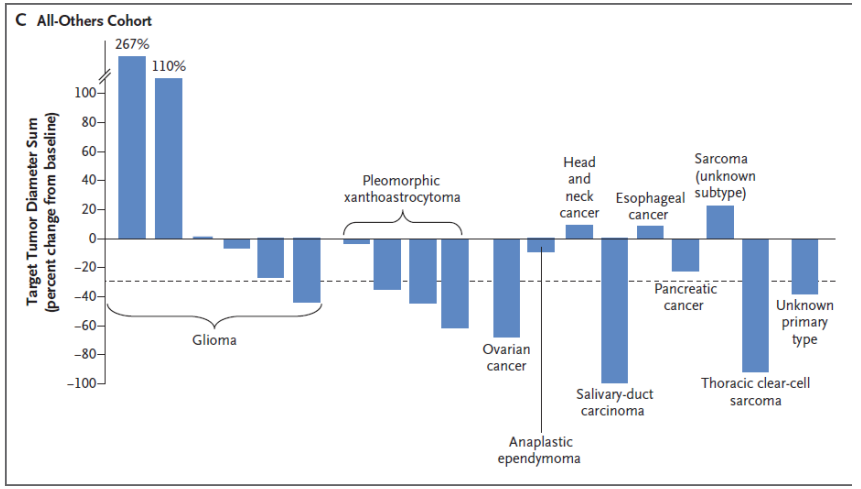


Hyman DM et al. N Engl J Med (2015) 373:726-736

Basket Studies

Vemurafenib in non-melanoma BRAF V600E mutant tumors





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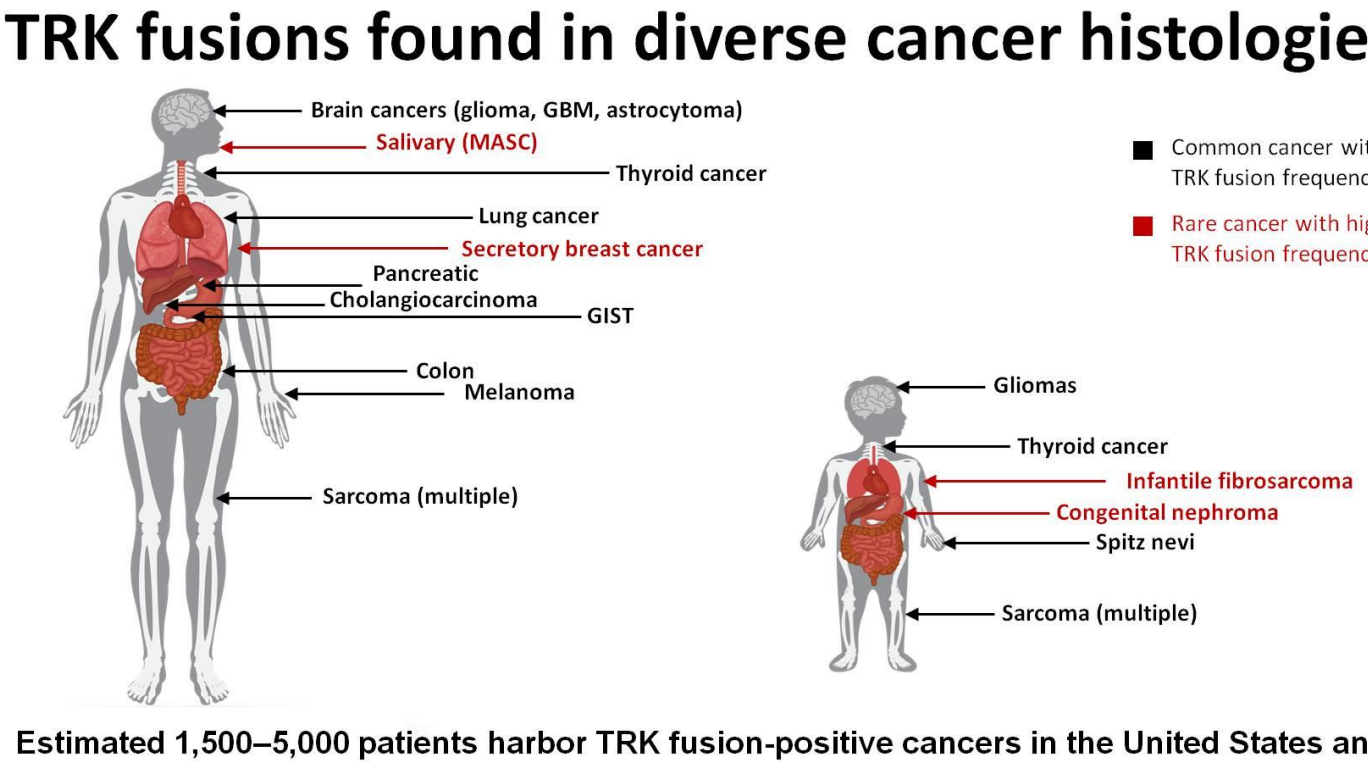
Basket Studies

Larotrectinib in Adults and Pediatric NTRK Fusion Tumors



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Basket Studies

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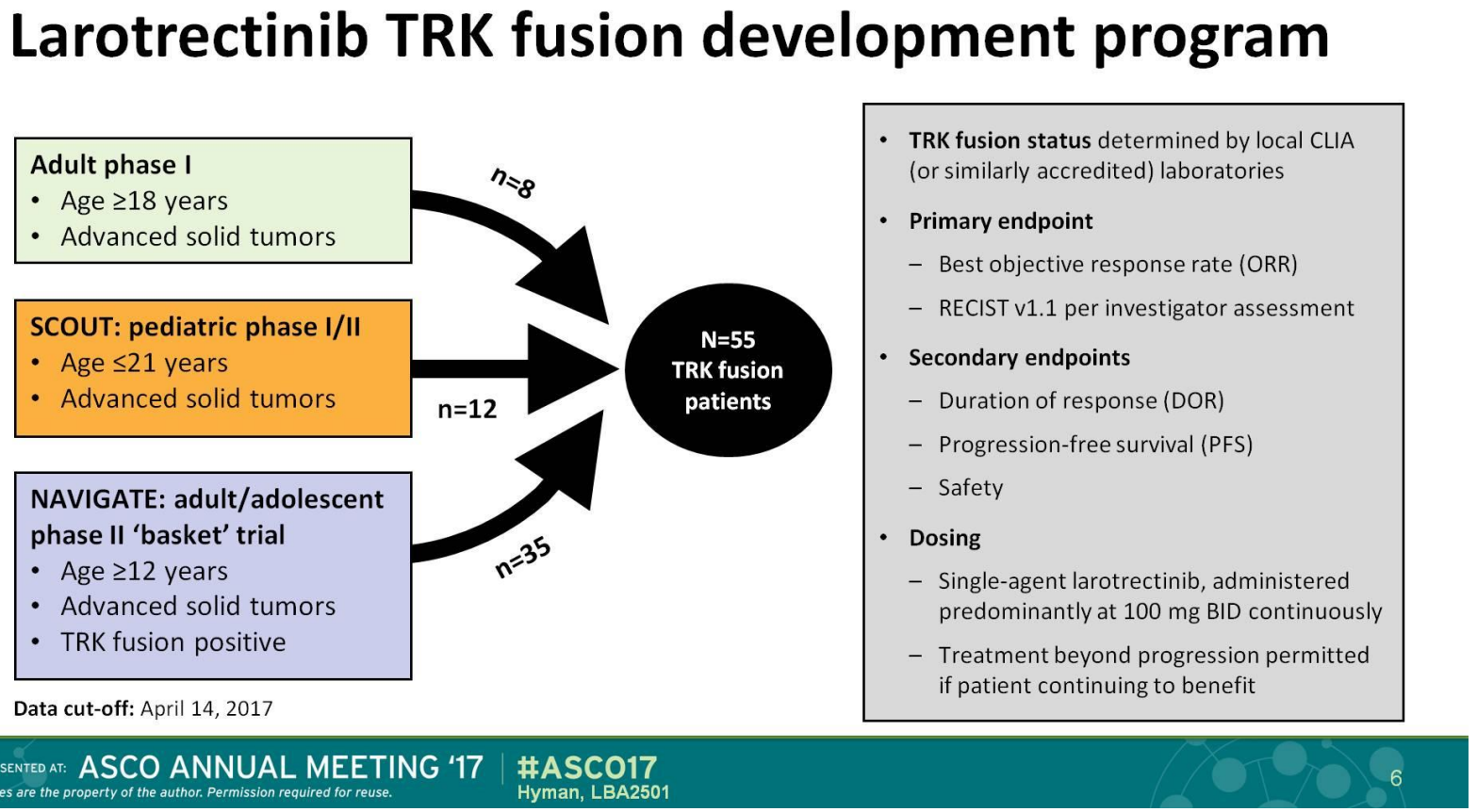

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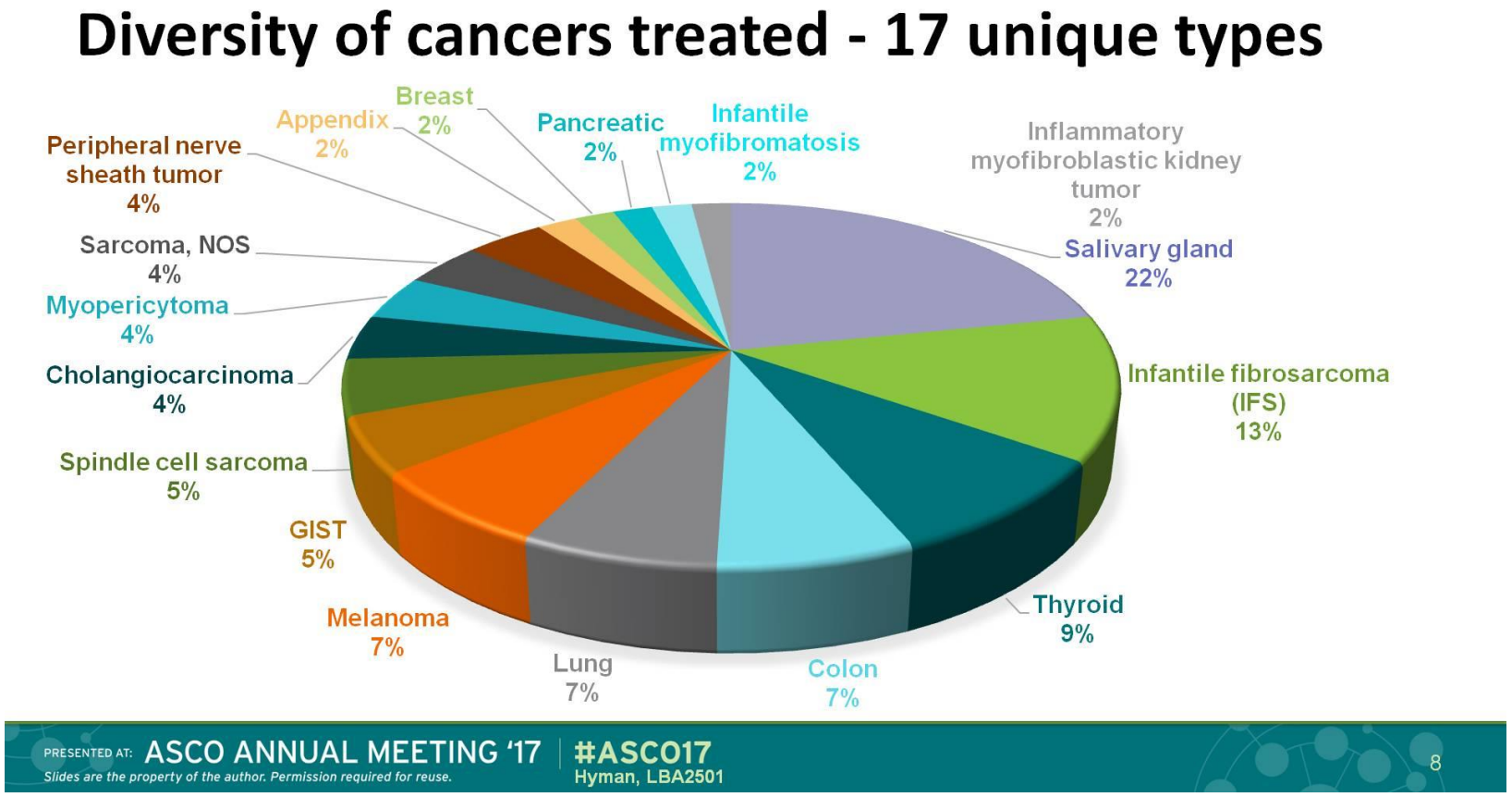
Basket Studies

Larotrectinib in Adults and Pediatric NTRK Fusion Tumors



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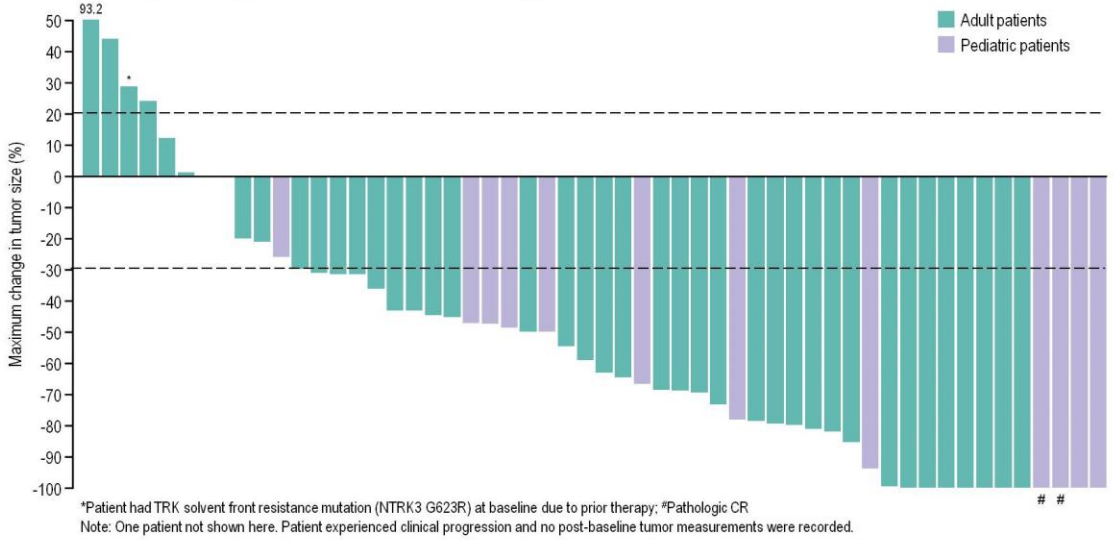
Basket Studies

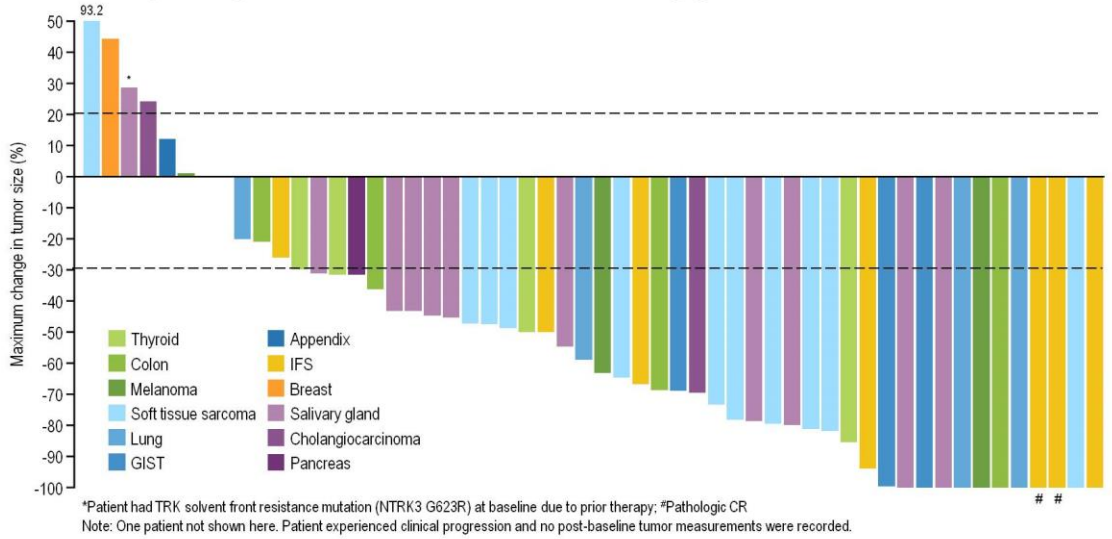
Larotrectinib in Adults and Pediatric NTRK Fusion Tumors

Efficacy regardless of age



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Efficacy regardless of tumor type



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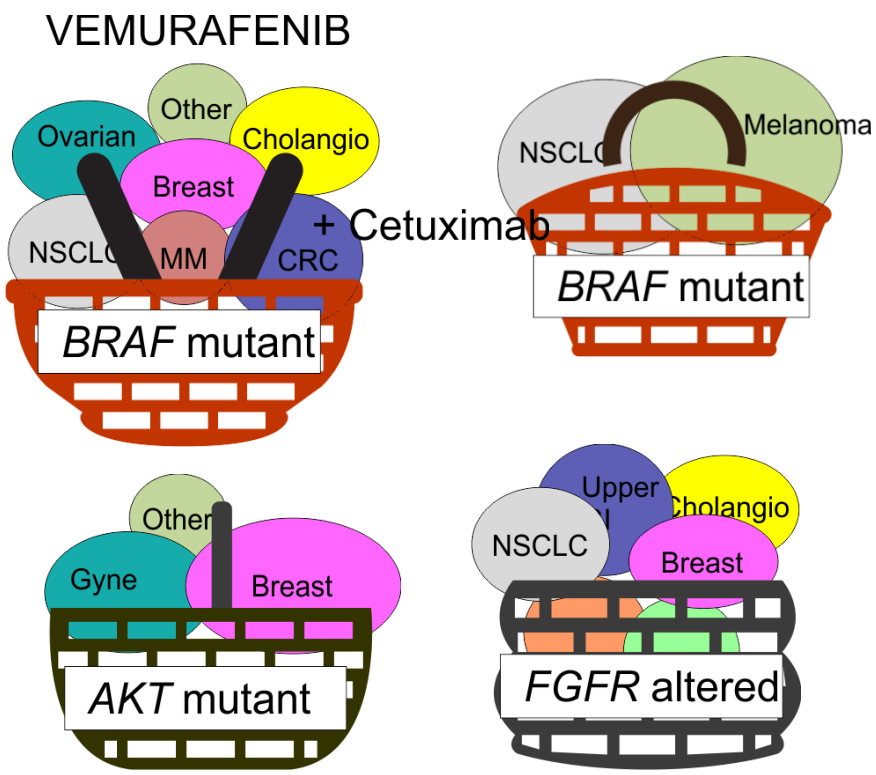
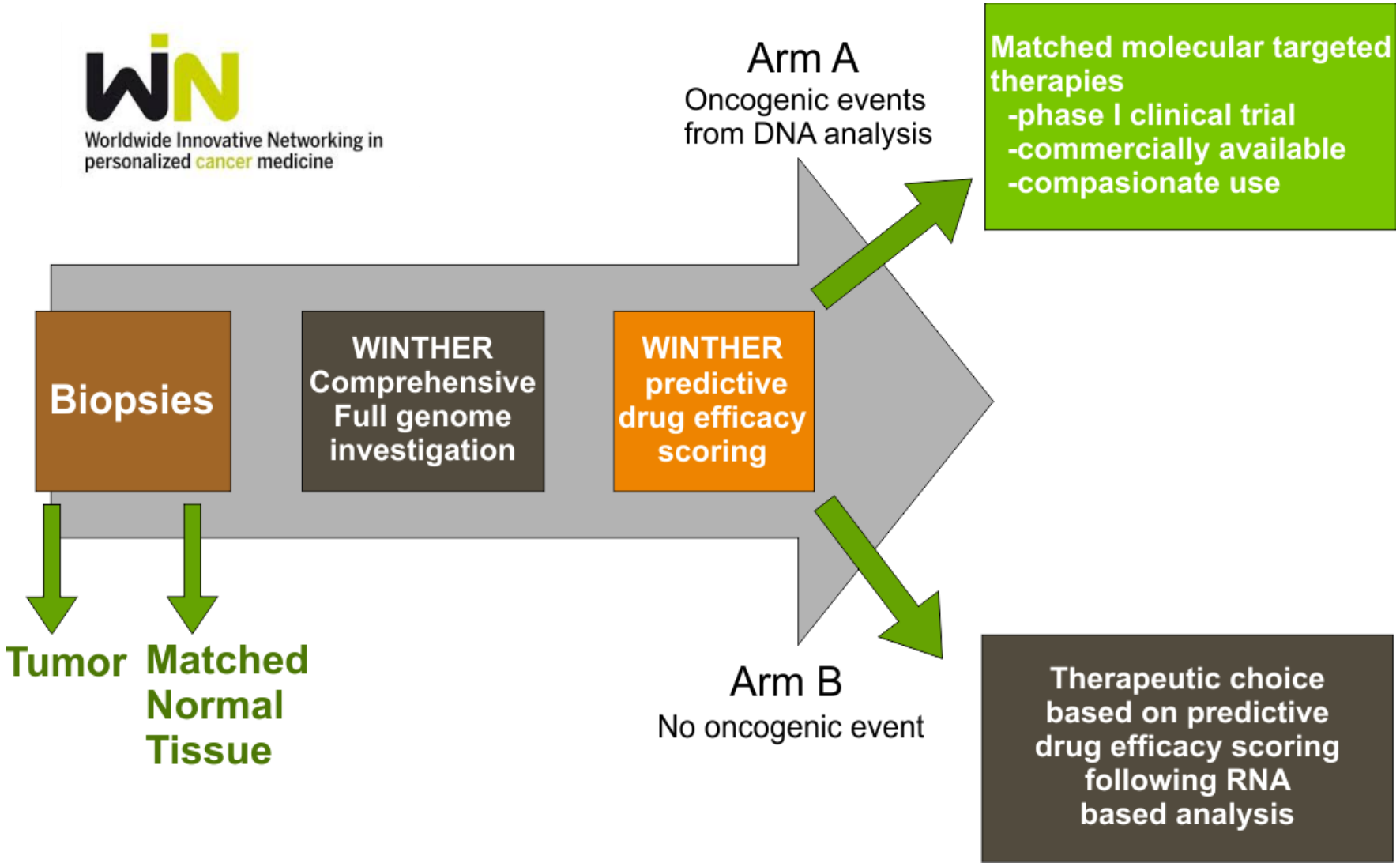
Basket Studies: Challenges

- Different protocols co-existing
- Design not easily adaptable
- Different molecular selection methods
- Tumor sample exhaustion
- Molecular selection program cost
- Rare mutations / rare populations
  - Difficult to find in a single institution
  - Cost-effectiveness issues

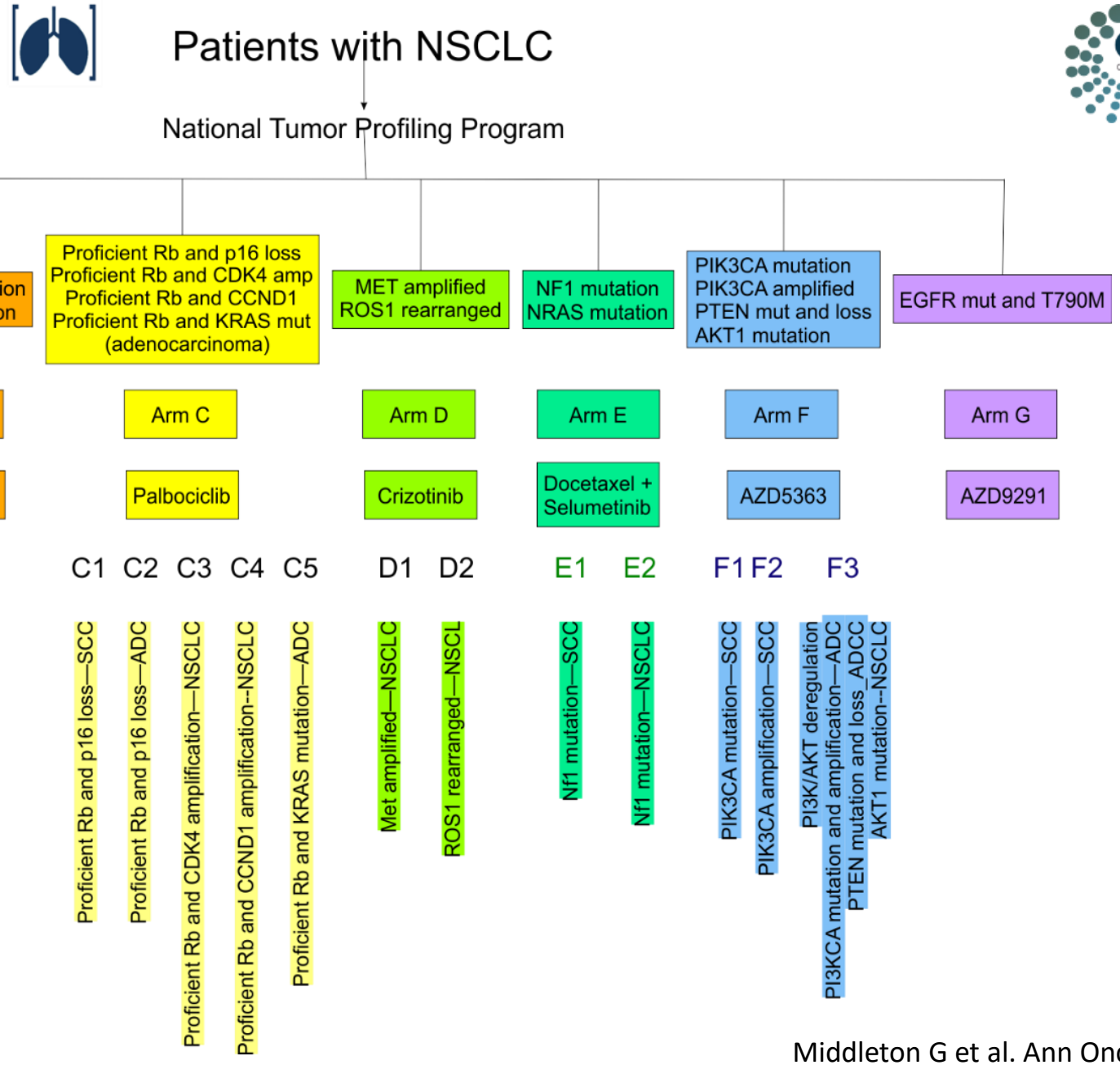


Examples of Academic Studies with Novel Designs

WINTHER Study

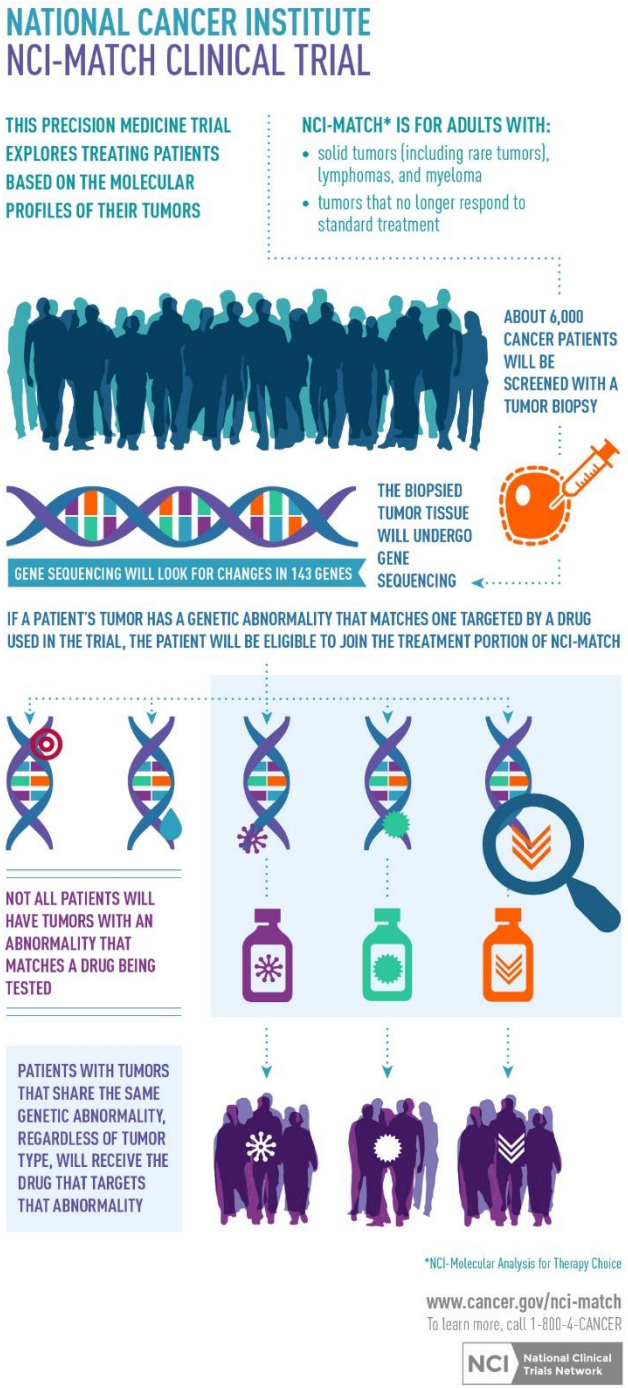


LUNG-MATRIX



National Lung Matrix Trial

Middleton G et al. Ann Oncol 2015; 2464



NCI-MATCH

Arm	Drug	Alteration
A	Afatinib	EGFR mutation
B	Afatinib	HER2 mutations
C1	Crizotinib	MET mutation
C2	Crizotinib	MET 14 exón
E	Osimertinib	EGFR T790M
F	Crizotinib	ALK transloc
G	Crizotinib	ROS1 transloc
H	Dabrafenib + Trametinib	BRAF V600E or V600K
J	Trastuzumab + Pertuzumab	HER2 amplification
L	TAK228	mTOR mutation
M	TAK228	TSC1 or TSC2
R	Trametinib	BRAF fusions or Other BRAF mut

Arm	Drug	Alteration
S1	Trametinib	NF1 mutations
S2	Trametinib	GNAQ or GNA11 m
T	Vismodegib	SMO / PTCH1 m
U	Defactinib	NF2 loss
V	Sunitinib	cKIT mutations
X	Dasatinib	DDR2 mutation
Y	AZD5363	AKT mutation
W	AZD4547	FGFR alterations
Z1B	Palbociclib	CCND1, 2 and 3 ampl
Z1C	Palbociclib	CDK4 or CDK6 ampl
Z1E	Larotrectinib	NTRK fusions
Z1I	AZD1775	BRCA1 or BRCA2 mutations

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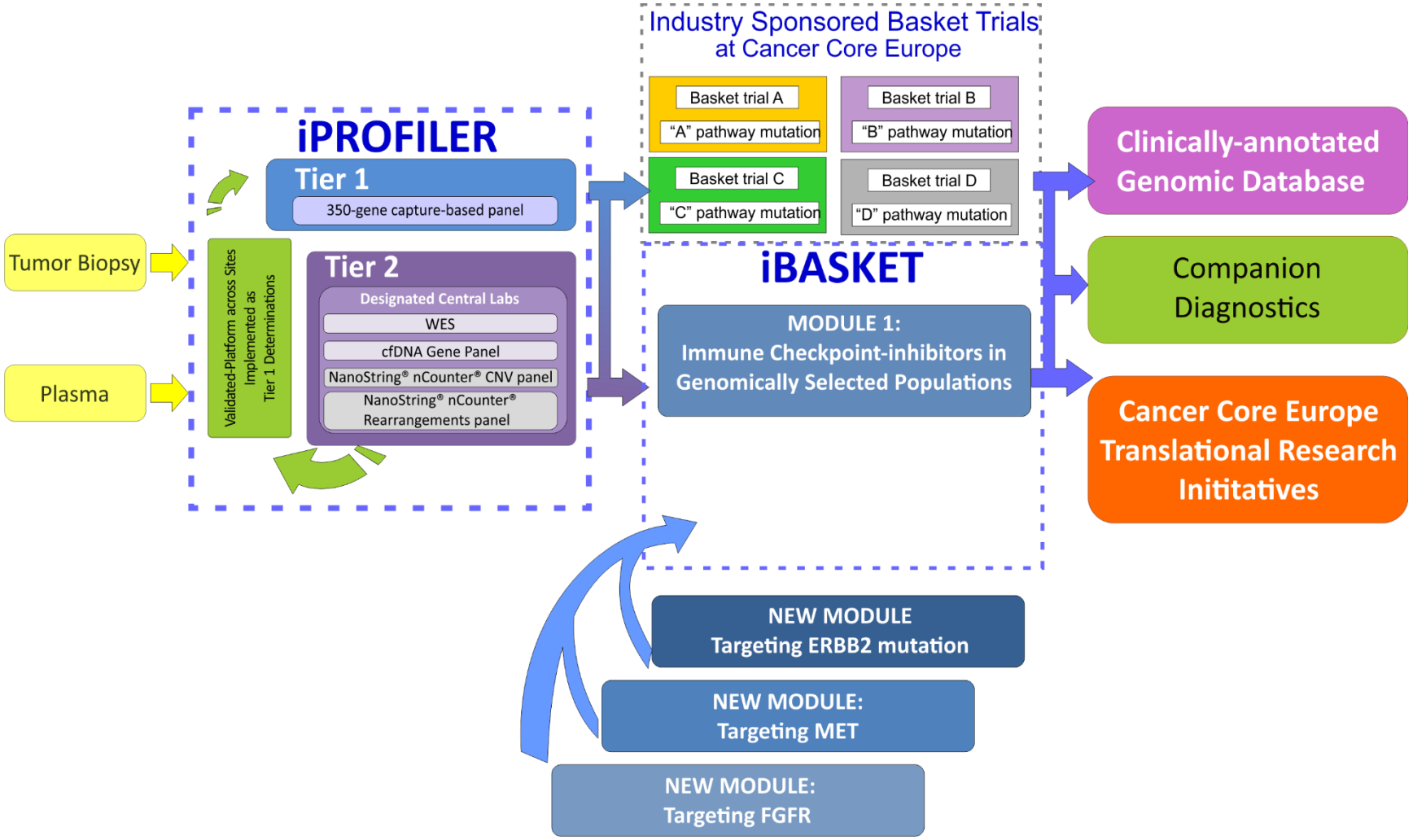
Basket of Baskets (BoB)

A modular multi-Basket trial to improve personalize medicine in cancer patients

Basket of Baskets: Study Design



Basket of Baskets: iPROFILER

Multiplexed NGS platform

Sample optimization

Two tiers

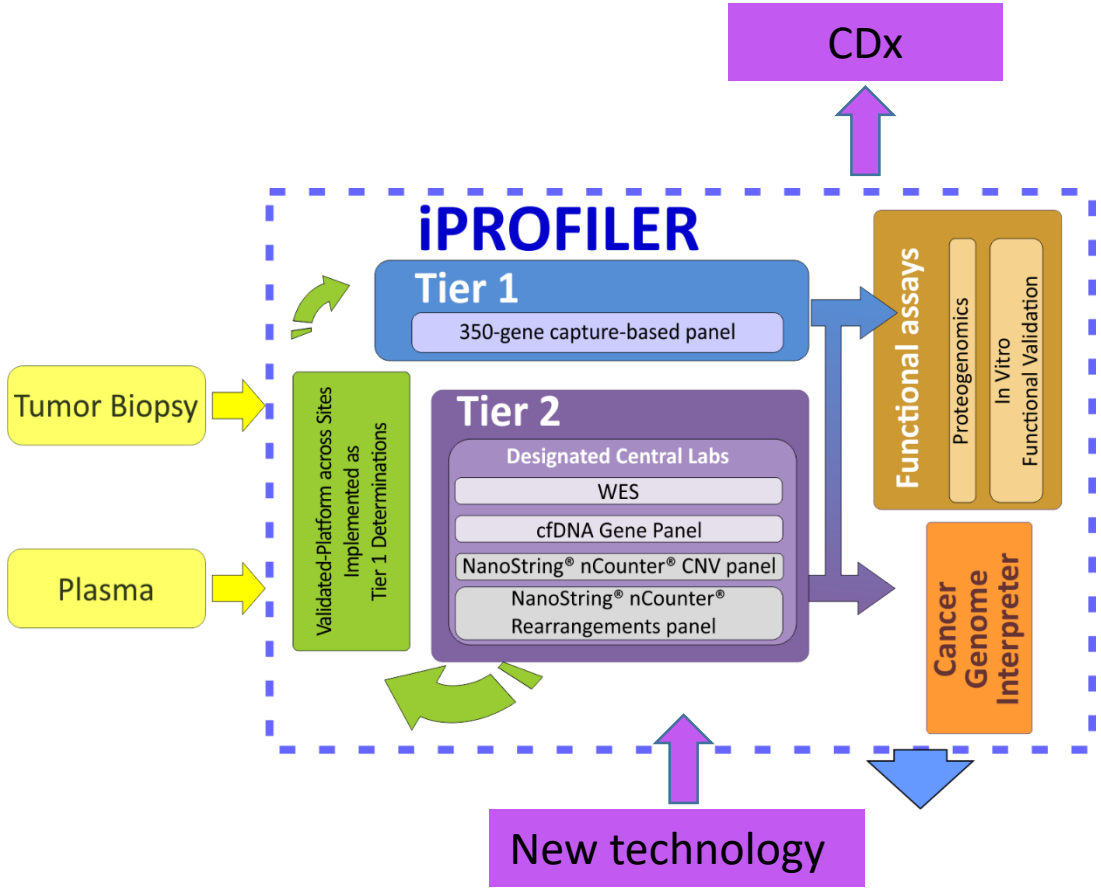
<u>Tier 1:</u> customized, certified NGS panels in each center

- Rapid turnover
  - Diminishing patient attrition
- Companion Diagnostic (CDx) co-development

<u>Tier 2:</u> Centralized.

Whole exomeSeq, mRNA analysis, cfDNA

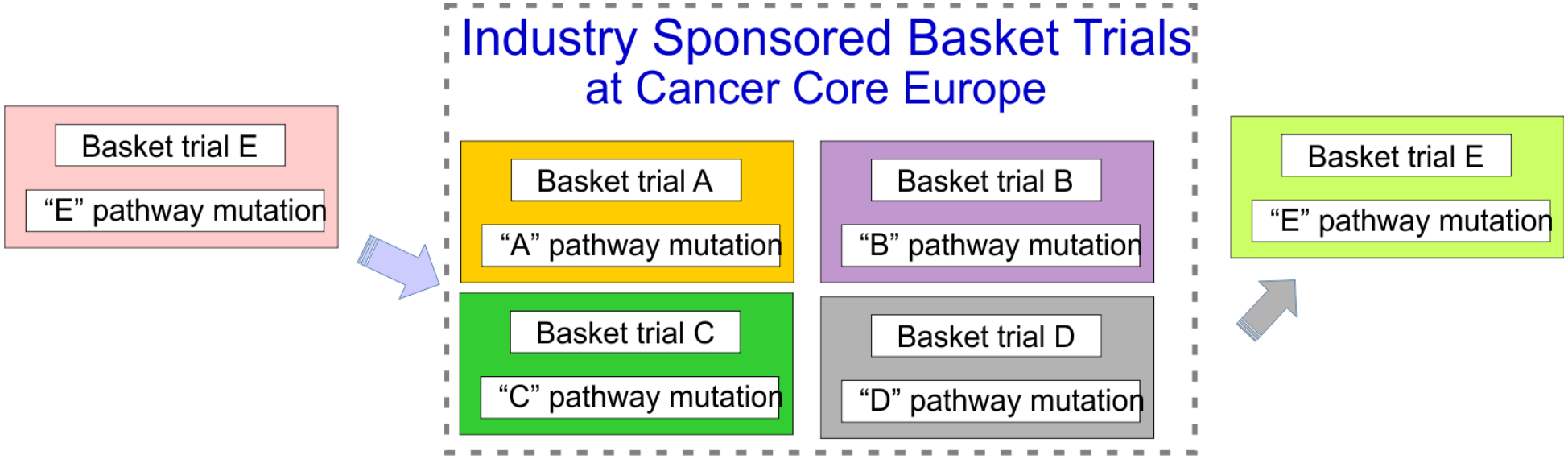
Subsequent validation across sites to become Tier 1 test



✓ Flexibility to incorporate new platforms and biomarkers

✓ Allow development of Multimarker CDx

Basket of Baskets: Industry Sponsored Basket Trials

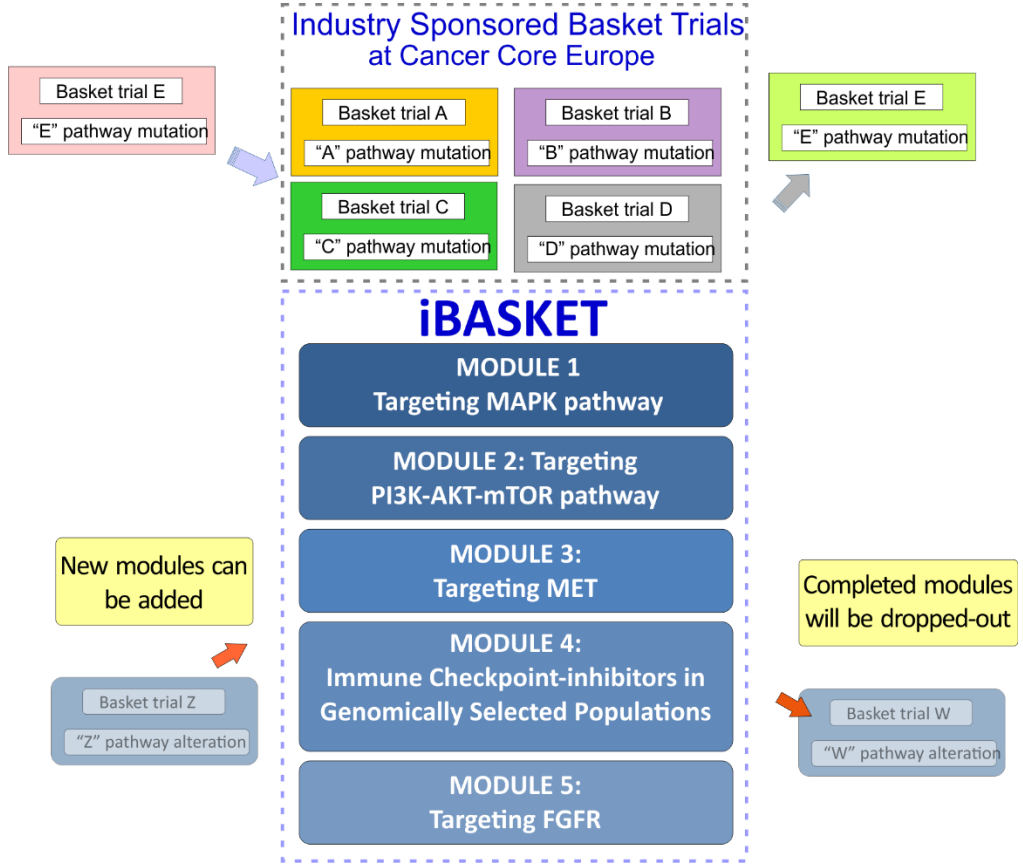


- Access to a large number of patients with molecularly profiled tumors (iPROFILER)
- Common contract/budgeting policy
- Companion Diagnostic Validation
- Open to collaboration – open to include new basket trials

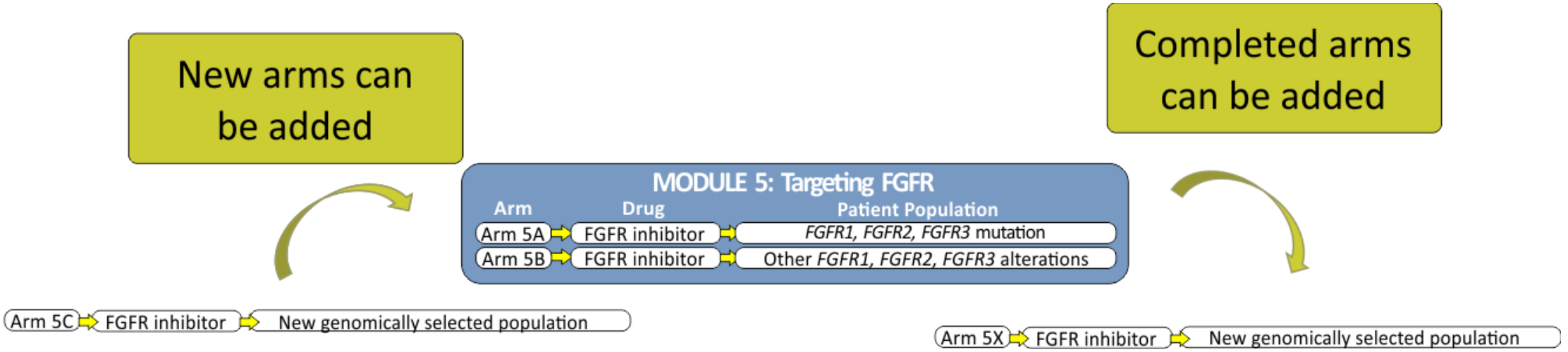
Basket of Baskets
iBASKET

iBASKET – Investigator Initiated

- Umbrella protocol
- Multi-modular
- Modules can be added or dropped-out based on the results
- Each module has individual arms in genomically selected populations



Arm Structure

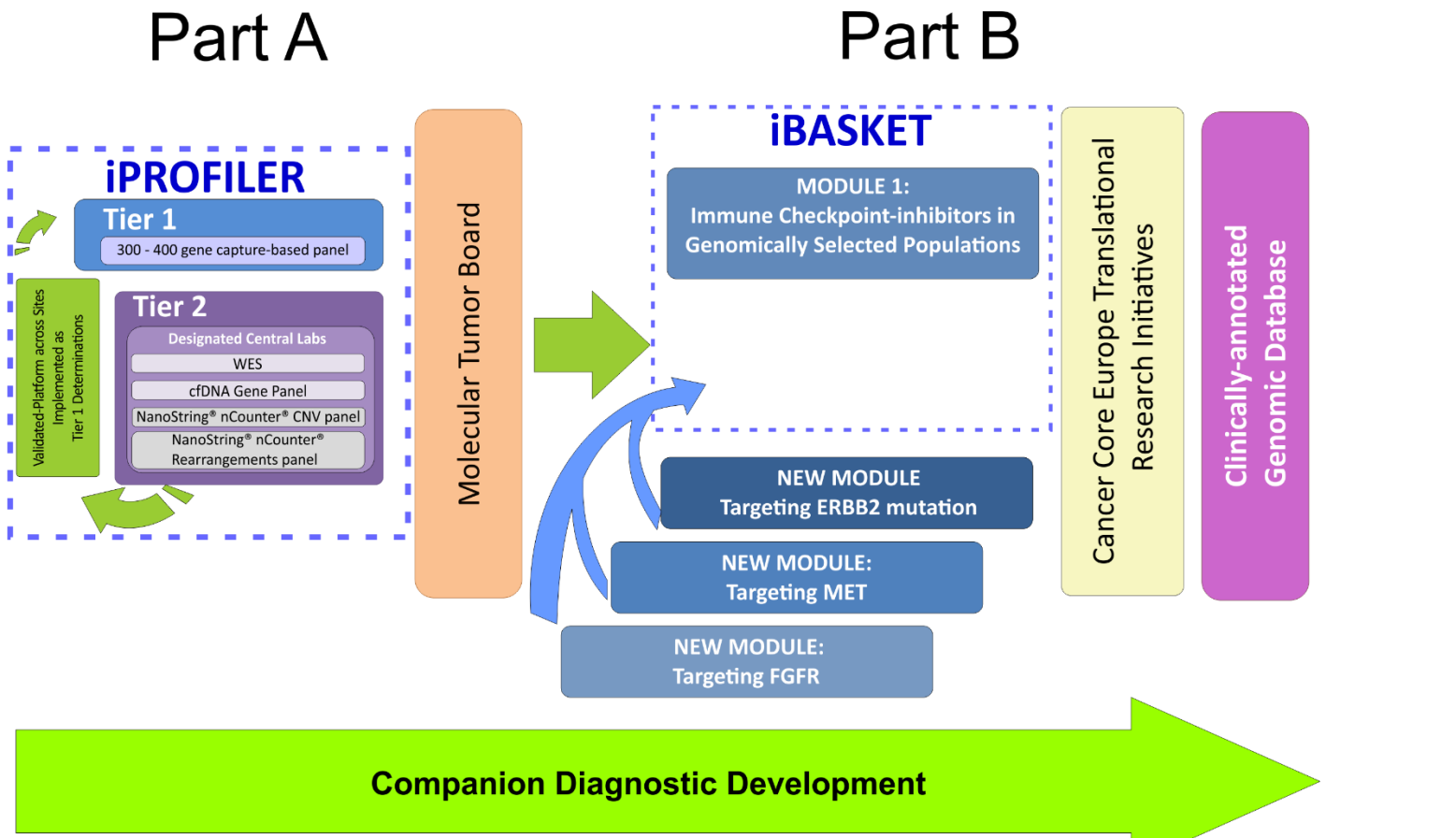


Potential use of different statistical designs per module or treatment arm

Module 1

- Bayesian model
  - Provides flexibility in case the number of patients identified by iPROFILER and enrolled in module 1 differs from the estimated number at the time of treatment design
- Adaptative design
  - To evaluate the most appropriate cut-off for arms evaluating continuous variables (such as CNA)

Basket of Baskets: Outcomes



Key Inclusion/Exclusion

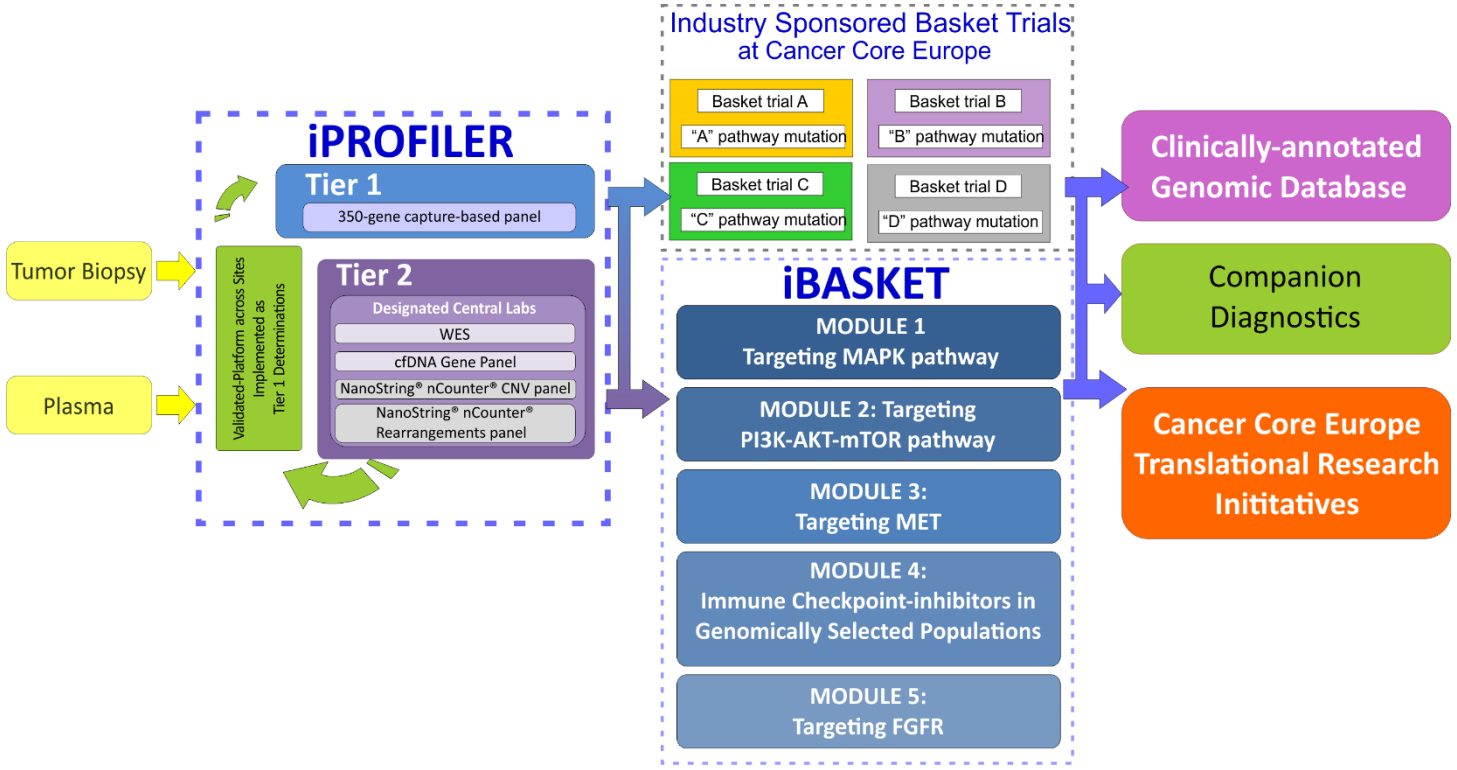
- Patients must have histologically or cytological confirmed malignancy that is metastatic or unresectable who have progressed to standard therapy, who are receiving a standard anticancer treatment but no subsequent approved treatment would be available upon progression, who are unable to receive standard therapy, or for whom standard therapy does not exist.
- Patient must have ECOG performance status of 0 or 1.
- Patients must be 18 year-old or older.
- Patients must have measurable disease according to RECIST 1.1. (see section 16.1 for details)
- **Patients must have enough tumor tissue for molecular analysis:**
  - **Patients providing fresh frozen tissue must provide 4 core biopsies or equivalent. Fresh frozen tissue must be preferentially collected from a tumor biopsy; hence, patients must have disease amenable to be biopsied. Otherwise, the patient should have fresh frozen tumor tissue stored in a biobank or biorepository.**
  - **Patients providing formalin-fixed paraffin embedded tissue (FFPE) must provide a minimum amount of tissue ranging from 20 to 28 slides depending on the sample tumor cellularity. If there is not enough archival tissue to meet this criterion, the patient must undergo a tumor biopsy.**
  - **Efforts will be made to provide fresh frozen tissue in at least one quarter of the participating patients. The proportion of patients that might provide fresh frozen tissue might change based on the results from the molecular analysis.**
- Adequate organ function
- Women of child-bearing potential and men must agree to use adequate contraception

iPROFILER Schema

	Screening					MTB Tier 1	Results discussion Visit	MTB Tier 2
	Informed consent signature	Screening visit	<= 5 days from sample reception	< 72 h prior tumor biopsy	Tumor biopsy			
Informed consent [1]	X							
Medical history		X						
Cancer history [2]		X						
Demographics [3]		X						
ECOG PS		X					X	
Symptoms		X					X	
Height, weight		X						
Physical exam		X						
CBC [4]		X						
Biochemistry [4]		X						
Coagulation [4]		X						
Serum pregnancy test		X						
Blood collection for germline DNA assessment		X						
Review eligibility criteria	<----------X---------->							
Additional criterion for patients providing archival tissue (fresh frozen or FFPE)								
Tumor quality assessment[5]			X					
Additional criteria for patients undergoing tumor biopsy								
CBC [6]				X				
Tumor biopsy [7]					X			
All patients								
Tier 1 Report MTB discussion						X		
Tier 1 Report review with patient							X	
Tier 2 Report MTB discussion								(X) [8]
Tier 2 Report review with patient								(X) [8]

Cancer Core Europe – Basket of Baskets

- Taskforces integration:
  - Clinical Trials
  - Genomics
  - Data Sharing
  - Imaging
  - Immunotherary
  - Education
  - Legal - Contracts



Conclusions

- More patients accesing to anti-cancer personalized therapy
- Cost-efficient plattform:
  - Evaluate anticancer activity
  - Expedite drug development
- Creating genomically annotated clinical database
- Platform for translational research
- Flexibility
- Long-lasting Project

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- Elena Chavarria
- Susana Muñoz

Genomics Group

- Ana Vivancos

Cancer Immunotherapy Group

- Alena Gros

ODysSey Group

- Rodrigo Dienstmann

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