



CHALLENGES, NOVEL DESIGNS AND FUTURE VISIONS IN EARLY PHASE CLINICAL TRIALS

Dr. Angela Bischoff

CLINICAL TRIALS SYMPOSIUM

OCTOBER 11, 2019. BUCHAREST, ROMANIA

ARENSIA LOCATIONS

Romania, Bucharest (3 Units)

Moldova, Chisinau (2 Units)

Georgia, Tbilisi (1 Unit)

Ukraine, Kiev (2 Units)



ARENSIA OVERVIEW

NO. OF UNITS - EACH BASED IN LARGE HOSPITALS-	LOCATION	THERAPEUTIC AREAS SERVED
3 EXPLORATORY MEDICINE UNITS	BUCHAREST, ROMANIA	IMMUNO-INFLAMMATORY, ONCOLOGY, PULMONOLOGY, CARDIOLOGY, METABOLIC/DIABETES, NEPHROLOGY, GASTROENTEROLOGY, DERMATOLOGY, INFECTIOUS DISEASES (HCV/HBV/HIV), NEUROLOGY
2 EXPLORATORY MEDICINE UNITS	CHISINAU, MOLDOVA	IMMUNO-INFLAMMATORY, ONCOLOGY/HEMATOLOGY, METABOLIC/DIABETES, CARDIOLOGY, GASTROENTEROLOGY, UROLOGY, NEPHROLOGY, DERMATOLOGY, OPHTHALMOLOGY, HEPATOLOGY, INFECTIOUS DISEASES (HCV/HBV), PSYCHIATRY, NEUROLOGY
1 EXPLORATORY MEDICINE UNIT	TBILISI, GEORGIA	ONCOLOGY/HEMATOLOGY, IMMUNO-INFLAMMATORY, DERMATOLOGY, GASTROENTEROLOGY, CARDIOLOGY/METABOLIC, GYNECOLOGY, GASTROENTEROLOGY, INFECTIOUS DISEASES (HBV/HIV), NEUROLOGY
2 EXPLORATORY MEDICINE UNITS	KIEV, UKRAINE	ONCOLOGY/HEMATOLOGY, IMMUNO-INFLAMMATORY, DERMATOLOGY, GASTROENTEROLOGY, INFECTIOUS DISEASES (HCV/HBV), METABOLIC/DIABETES, CARDIOLOGY, GYNECOLOGY, UROLOGY, OPHTHALMOLOGY

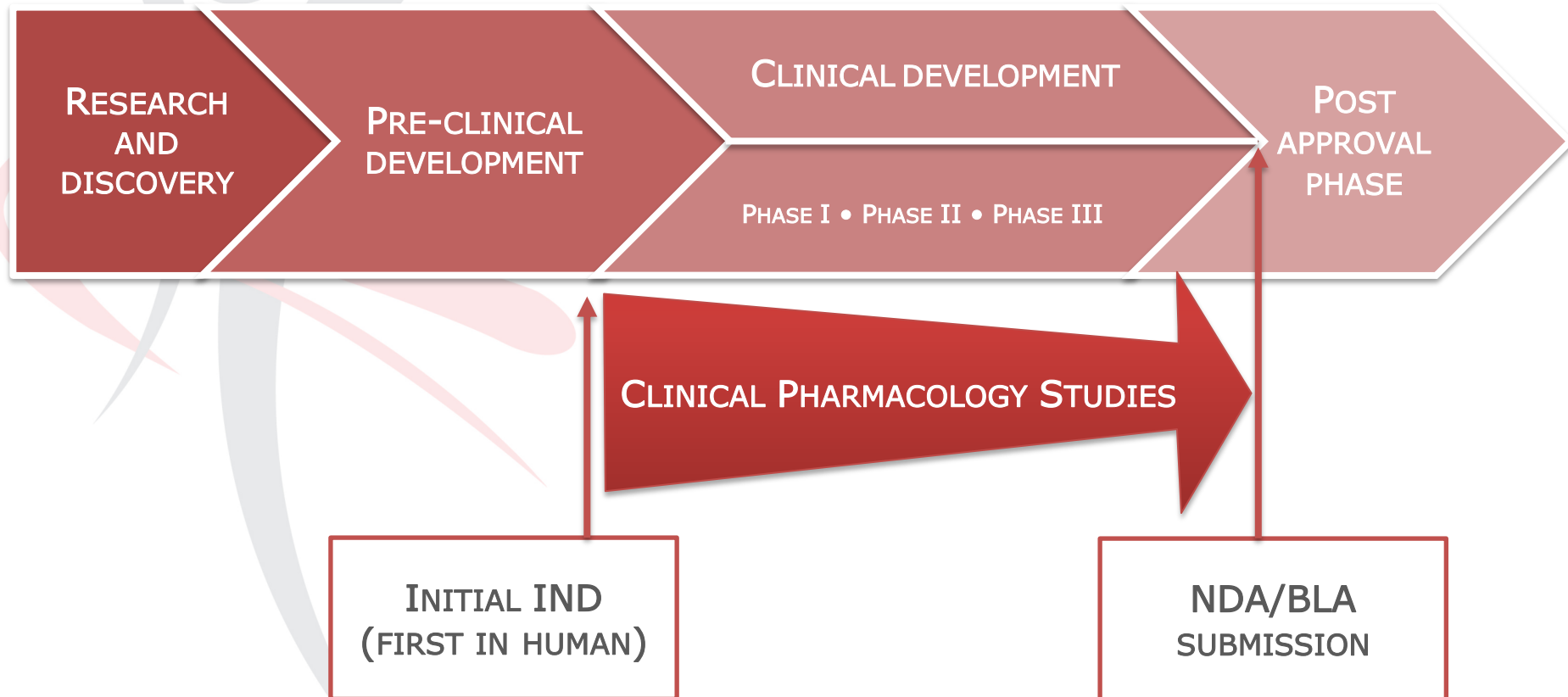
CLINICAL RESEARCH STATUS QUO

- STATE OF THE ART RESEARCH: ONE INDICATION, ONE MOLECULE
- "CLASSIC" INVESTIGATOR AND SITE TEAM
- "CLASSIC" PROJECT MANAGEMENT APPROACH
- "CLASSIC" REGULATORY APPROACH

„CLASSICAL“ CLINICAL RESEARCH

- **PHASE I:** DETERMINES WHETHER DRUG IS SAFE TO CHECK FOR EFFICACY
- **PHASE II:** DETERMINES WHETHER DRUG CAN HAVE ANY EFFICACY
- **PHASE III:** DETERMINES A DRUG'S THERAPEUTIC EFFECT
- **POST MARKETING SURVEILLANCE OR PHASE IV:** WATCH DRUG'S LONG TERM EFFECTS

„CLASSICAL“ CLINICAL RESEARCH



ARENSIA EXPERTISE

HIGH DEGREE OF SCIENTIFIC AND LOGISTICAL EXPERTISE
FOR PHASE Ib/IIa AND PROOF OF CONCEPT PATIENT
STUDIES:

- FIRST-INTO-PATIENTS SAD/MAD ADAPTIVE DESIGN WITH NOVEL COMPOUNDS
- SAFETY, EFFICACY, DOSE FINDING
- BE / DDI / QTc
- PK IN RENAL & HEPATIC IMPAIRMENT (ALL STAGES) VS.
MATCHING HEALTHY VOLUNTEERS

MASTER PROTOCOLS

- **BASKET TRIALS:** ONE TREATMENT, MANY INDICATIONS
- **UMBRELLA TRIALS:** ONE BIOMARKER, MANY TREATMENTS
- **PLATFORM TRIALS:** MANY BIOMARKERS, MANY TREATMENTS

TRENDS IN EARLY DEVELOPMENT

LATEST TRIAL DESIGNS



Traditional Design

Drug 1	
	Indication 1

- Single treatment
- Single indication



Umbrella Design

Drug 1	
Drug 2	Indication 1
....	
Drug n	

- Multiple treatments
 - Fixed # treatment arms or add/delete treatment arms
- Single indication



Basket Design

Drug 1	
	Indication 1
	Indication 2
	
	Indication n

- Single treatment
- Multiple indications
 - Genomic information
 - Severity
 - Lines of therapy
 - Background Characteristics



Platform Design

Drug 1	Indication 1
Drug 2	Indication 2
....	
Drug n	Indication n

- Multiple treatments
 - Fixed # treatment arms or add/delete treatment arms
- Multiple indications
 - Fixed # indications or add/delete indications

UMBRELLA VS. BASKET TRIALS

UMBRELLA DESIGN



MULTIPLE DRUGS



ONE INDICATION (E.G. LUNG)

MULTIPLE ALTERATIONS



BASKET/BUCKET DESIGN



ONE DRUG



MULTIPLE INDICATIONS (E.G. LUNG, BREAST, COLON...)

ONE ALTERATION



BASKET TRIAL DESIGN



BASKET TRIAL DESIGN: WHY?

- MANY MOLECULAR SUBTYPES OF PATHOLOGY DISCOVERED → NARROW “NICHE” INDICATIONS WITH UNIQUE TARGETS
- ENROLLMENT IS A CHALLENGE IN ORPHAN/NICHE INDICATIONS → LACK OF POSSIBILITY TO ENROLL ENOUGH SUBJECTS WITH SPECIFIC DISEASE SUBTYPE
- “ONE INDICATION AT A TIME” NOT FEASIBLE AND NOT EFFECTIVE
- ORIGINAL BASKET TRIAL DESIGN: IMATINIB B2225

BASKET TRIAL DESIGN: **HOW?**

- TO PAIR TARGETED THERAPY WITH A TARGETABLE MUTATION, IRRESPECTIVE OF CANCER DIAGNOSIS
- CONDITIONS WITH SAME PREDICTIVE BIOMARKERS ARE SELECTED
- MULTIPLE TUMOR TYPES WITH ONE DRUG AND PREDICTIVE BIOMARKER
- USES POOLED POPULATION FOR INITIAL ANALYSIS

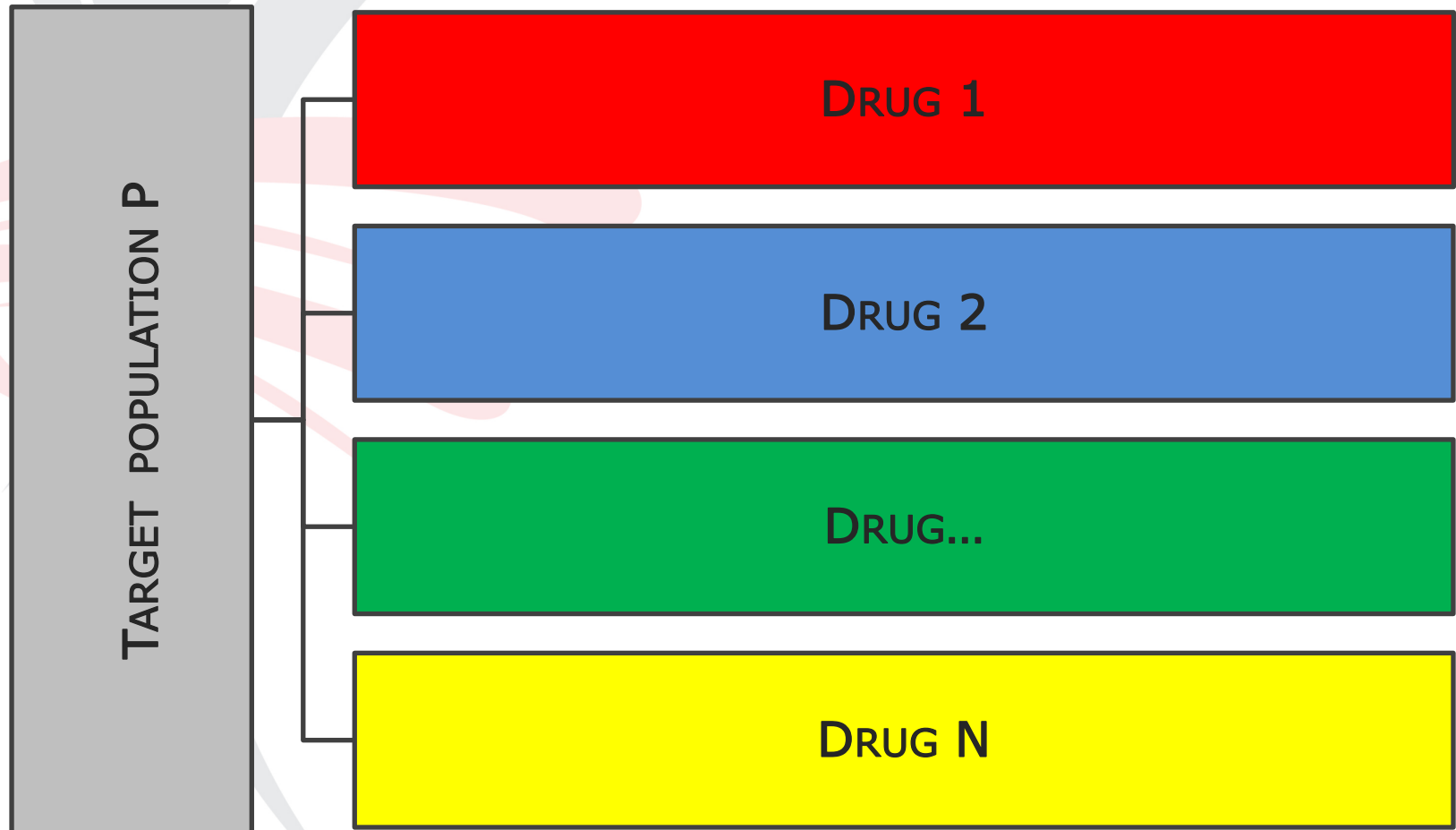
BASKET TRIAL DESIGN: **BENEFITS**

- INCREASED AND EARLIER PATIENT ACCESS TO TARGETED THERAPIES FOR SMALL SUBGROUPS
- HYPOTHESIS-DRIVEN MECHANISM OF COMBINING PRECISION MEDICINE WITH CLINICAL TRIAL DESIGN
- VALIDATION OF CLINICAL TARGET
- COST-EFFECTIVE METHODS FOR SPONSORS TO DEVELOP TARGETED AGENTS IN SMALL SUBGROUPS
- DATASETS FOR HEALTH AUTHORITIES TO ASSESS BENEFIT-RISK IN THESE SMALL PATIENT GROUPS

BASKET TRIAL DESIGN: **EXAMPLES**

- 2015: NATIONAL CANCER INSTITUTE US: NCI-MATCH TRIAL (MOLECULAR ANALYSIS FOR THERAPY CHOICE), WITH PLANS TO SCREEN UP TO 3,000 PATIENTS WITH ENROLLMENT OF AT LEAST 1,000 INDIVIDUALS TO A TARGETED DRUG COMBINATION, INDEPENDENT OF TUMOR HISTOLOGY
- NCI-IMPACT TRIAL (MOLECULAR PROFILING-BASED ASSIGNMENT OF CANCER T
- CUSTOM (MOLECULAR PROFILING AND TARGETED THERAPIES IN ADVANCED THORACIC MALIGNANCIES) TRIAL THERAPY

UMBRELLA TRIAL DESIGN



UMBRELLA TRIAL DESIGN: **WHY?**

- SCOPE: TO TEST THE IMPACT OF DIFFERENT DRUGS ON DIFFERENT MUTATIONS IN A SINGLE TYPE OF CANCER ('UNDER THE UMBRELLA OF ONE DISEASE').
- PERSONALIZED APPROACH FOR TRIAL SUBJECTS → BIGGER SUCCESS RATES
- THE TRIALS ALLOW RESEARCHERS TO TEST A NUMBER OF DIFFERENT MEDICINES IN PATIENTS WITH A SIMILAR DISEASE
- QUICKER IDENTIFICATION OF PATIENT SUBGROUPS WHO WOULD MOST BENEFIT FROM TESTED MEDICINES

UMBRELLA TRIAL DESIGN: **HOW?**

- ONE TUMOR TYPE OR ONE HISTOLOGY TYPE WITH MULTIPLE DRUGS AND PREDICTIVE BIOMARKERS
- PATIENTS ARE MATCHED TO DRUGS BASED ON PREDICTIVE BIOMARKERS → EXPOSURE IS VERY SELECTIVE AND HIGHLY JUSTIFIED (UNNECESSARY EXPOSURE IS AVOIDED)
- COOPERATION AMONG MULTIPLE SPONSORS: COMPOUNDS COULD COME FROM DIFFERENT COMPANIES!

UMBRELLA TRIAL DESIGN: **EXAMPLES**

- BATTLE (BIOMARKER-INTEGRATED APPROACHES OF TARGETED THERAPY FOR LUNG CANCER ELIMINATION) TRIAL
- WINTHER (A STUDY TO SELECT RATIONAL THERAPEUTICS BASED ON THE ANALYSIS OF MATCHED TUMOR AND NORMAL BIOPSIES IN SUBJECTS WITH ADVANCED MALIGNANCIES)
- MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE) TRIAL

PLATFORM TRIAL DESIGN: DEFINITION

- A PLATFORM TRIAL IS A CLINICAL TRIAL WITH A SINGLE MASTER PROTOCOL IN WHICH MULTIPLE TREATMENTS ARE EVALUATED IN PARALLEL
- ADAPTIVE PLATFORM DESIGNS OFFER FLEXIBLE FEATURES:
 - DROPPING OR ADDING/REPLACEMENT OF TREATMENTS
 - DECLARING ONE OR MORE TREATMENTS AS SUPERIOR

PLATFORM TRIAL DESIGN

	DRUG A	DRUG B	DRUG C	...	DRUG K	...
TYPE 1	BASKET					
TYPE 2						
...						
TYPE N						
...						

	DRUG A	DRUG B	DRUG C	...	DRUG K	...
TYPE 1	UMBRELLA					
TYPE 2						
...						
TYPE N						
...						

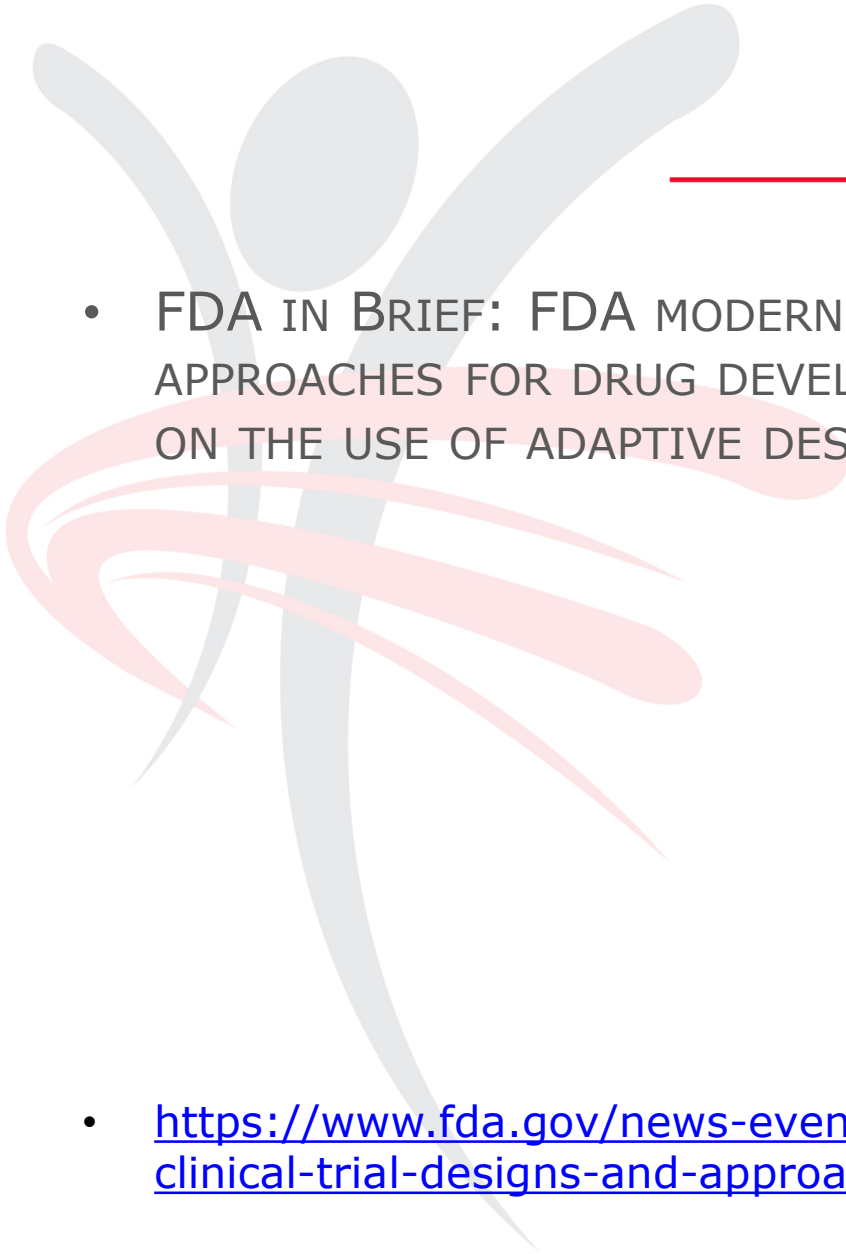
	DRUG A	DRUG B	DRUG C	...	DRUG K	...
TYPE 1	PLATFORM					
TYPE 2						
...						
TYPE N						
...						

PLATFORM TRIAL DESIGN: **WHY**

- PLATFORM TRIALS CAN FIND BENEFICIAL TREATMENTS WITH FEWER PATIENTS, FEWER PATIENT FAILURES, LESS TIME, AND WITH GREATER PROBABILITY OF SUCCESS THAN A TRADITIONAL TWO-ARM STRATEGY.
- OBJECTIVE IS GO-NO-GO DECISION OF NEW TREATMENT
- ESCALATION TO PHASE 2A TO PHASE 2B IN EARLY DRUG DEVELOPMENT
- CONSOLIDATED INFORMATION ON DISEASE AS WELL AS TREATMENT

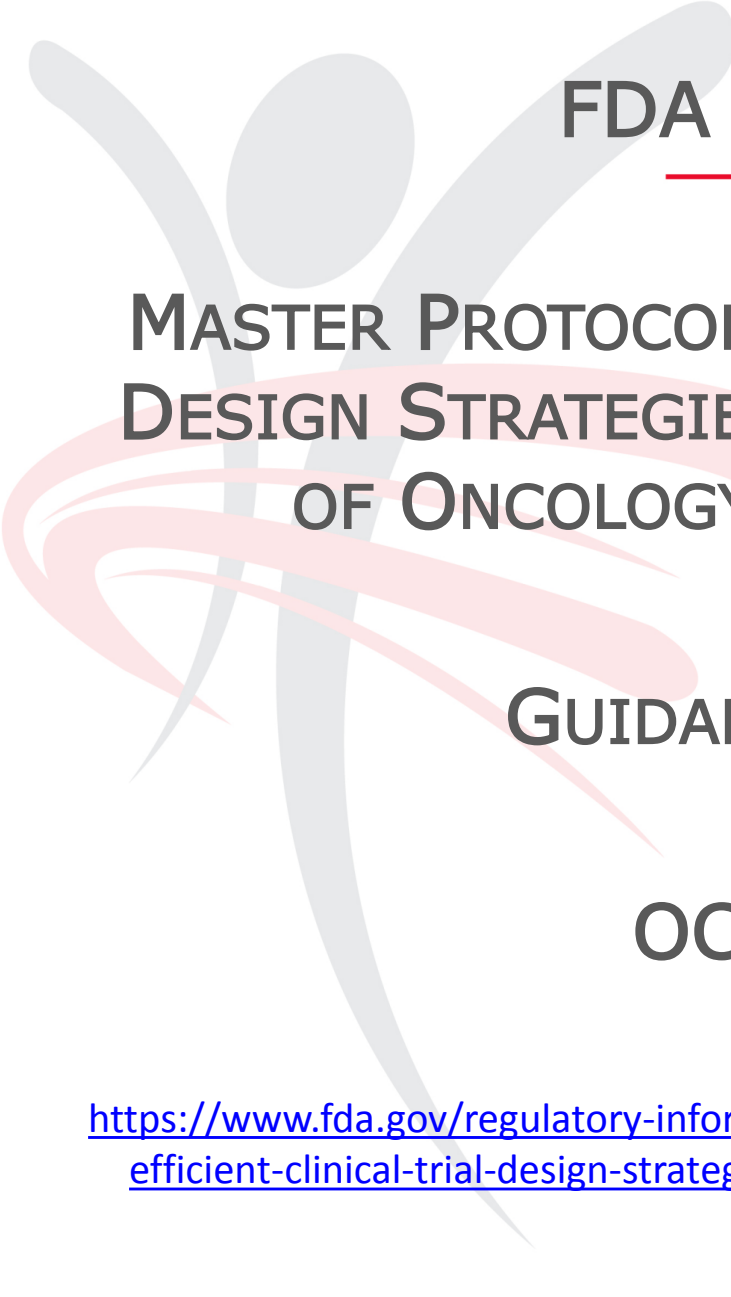
PLATFORM TRIAL DESIGN: **EXAMPLES**

- **I-SPY 2** ([HTTPS://CLINICALTRIALS.GOV/CT2/SHOW/NCT01042379?TERM=I-SPY2&RANK=1](https://clinicaltrials.gov/ct2/show/NCT01042379?term=I-SPY2&rank=1))
 - **INDICATION:** EARLY HIGH RISK BREAST CANCER, 1920 PATIENTS
 - **DESIGN:** PHASE 2, MULTICENTER, ADAPTIVE, RANDOMISED
 - **IMPs:** 19 DIFFERENT TREATMENT, EITHER SINGLE OR COMBINED
 - PEMBROLIZUMAB, TRASTUZUMAB, PERTUZUMAB, NERATINIB
 - AND MORE...
 - **TUMOR CHARACTERISTICS:** MAMMAPRINT HIGH, ANY ER STATUS, ANY HER2 STATUS, OR MAMMAPRINT LOW, ER NEGATIVE (<5%), ANY HER2 STATUS, OR MAMMAPRINT LOW, ER POSITIVE, HER2/NEU POSITIVE



FDA PRESS RELEASE

- **FDA IN BRIEF: FDA MODERNIZES CLINICAL TRIAL DESIGNS AND APPROACHES FOR DRUG DEVELOPMENT, PROPOSING NEW GUIDANCE ON THE USE OF ADAPTIVE DESIGNS AND MASTER PROTOCOLS**
- <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-modernizes-clinical-trial-designs-and-approaches-drug-development-proposing-new>



FDA MASTER PROTOCOLS ADVOCATE

MASTER PROTOCOLS: EFFICIENT CLINICAL TRIAL DESIGN STRATEGIES TO EXPEDITE DEVELOPMENT OF ONCOLOGY DRUGS AND BIOLOGICS

GUIDANCE FOR INDUSTRY

OCTOBER 2018

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and-biologics>

FDA APPROVALS

- 2017: **PEMBROLIZUMAB (KEYTRUDA)**
FOR AN EXPANDED INDICATION TO TREAT
MICROSATELLITE INSTABILITY-HIGH CANCER BASED
ONLY ON GENETIC ABNORMALITY, **REGARDLESS OF
ORIGIN OR LOCATION**
- 2018: **LAROTRECTINIB (VITRAKVI)**
- FOR ADULT AND PEDIATRIC PATIENTS WITH **SOLID
TUMORS** THAT HAVE A NEUROTROPHIC RECEPTOR
TYROSINE KINASE (NTRK) GENE FUSION WITHOUT A
KNOWN ACQUIRED RESISTANCE MUTATION

DR. JANET WOODCOCK



[N Engl J Med](#). 2017 Jul 6;377(1):62-70. doi: 10.1056/NEJMra1510062.

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both.

[Woodcock J¹](#), [LaVange LM¹](#).

Author information

1 From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

REFERENCES

- <https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/fda-modernizes-clinical-trials-master-protocols-february-26-2019-issue>
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and>



THANK YOU!

FOR ANY QUESTIONS PLEASE CONTACT:

ANGELA BISCHOFF

CELL: +49 152 51920 475

ANGELA.BISCHOFF@ARENSIA-EM.COM

WWW.ARENSIA-EM.COM