Master Protocols – FDA Oncology Experience

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Outline

- Regulations
- FDA Experience with Basket, Umbrella and Platform Master protocols
- Concluding Remarks

Regulatory support for good statistical practices

- Substantial evidence of effectiveness

"…Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling…"

Section 505(d) FD&C Act of 1962
as amended

Regulatory Evidence Standard

- Traditionally interpreted as:
  - Results observed in at least two independent studies
  - Probability of one-sided type I error controlled at 0.025 level in each study
  - Clinically meaningful treatment effect
  - Acceptable risk/benefit profile

* Section 505(d) FD&C Act of 1962 as amended

Regulatory Approval Pathways

- Regular Approval (RA): based on Clinical benefit (Survival benefit/patient benefit, or benefit in a validated surrogate marker)
  - Should be better than placebo
  - RCT or single arm studies
- Accelerated Approval (AA) in serious or life-threatening disease: based on ”surrogate” endpoint reasonably likely to predict clinical benefit; improvement over available therapy; required confirmation of clinical benefit
  - Comparative efficacy
  - Single arm studies or RCT

Challenges and Opportunities in Single Arm Studies

- Difficult to attribute safety concerns
- Long-term safety unknown as survival is generally short
- Biomarker defined population – biomarker prognostic marker or predictive marker?
- Randomization not feasible in very rare populations

Master Protocols

- One overarching protocol that includes one or more of the following:
  - Multiple diseases
  - Multiple treatments
  - Multiple molecular markers
- Other names:
  - Platform Trials
  - Umbrella Trials

  Examples: BATTLE 1, ISPY 2, LUNG-MAP, etc.
  - Basket Trials: Examples: Vbasket, Imatinib study, NCI MATCH, etc.

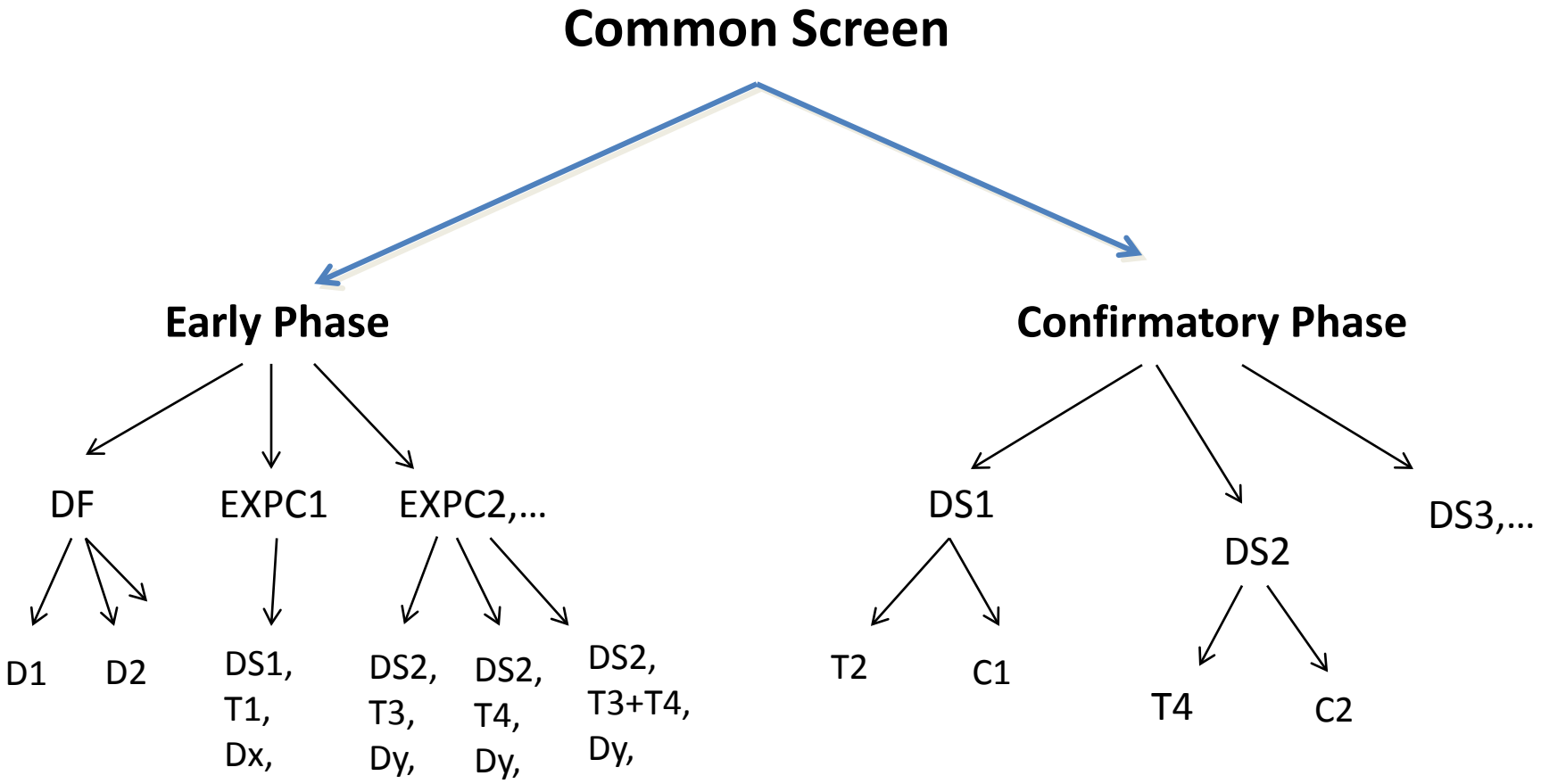
Advantages

- Potential save of resources: centralized governance structure – central IRB, standing DMC, central labs with QA oversight
- Infrastructure advantages: streamlined enrollment, central electronic data capture system, common case report form, etc
- Potential for data sharing: useful in future design of trials – Bayesian priors, historical/external control, etc

Clinical Trial with Common Control: Resources can be saved!

- 5 concurrently run studies in advanced RCC
- In each of the 5 studies control arm is Sunitinib:
  - Checkmate 214: Ipi + Nivo →Nivo vs. Sunitinib
  - Keynote 426: Pembro + Axitinib vs. Sunitinib
  - Javelin Renal 001: Avelumab + Axitinib vs. Sunitinib
  - NCT02420821: Atezo + Bev vs. Sunitinib
  - NCT02811861: Lenvatinib + everolimus vs. Lenvatinib + pembro vs. Sunitinib
- Could have saved precious patient resource in one study with a common control!

Hypothetical Seamless Drug Development



DF=dose-finding, EXPC=expansion cohort, D=dose, DS=disease, T=treatment

Phase 1/2 Expansion Cohort Studies

- Start with a dose escalation study in all solid tumors or hematological malignancies
- Amend protocol to start expansion cohorts in specific diseases, with different dosing regimens, single arm and randomized studies
- Central Governance

Things to consider:

- Pre-specified starting and stopping criteria and maximum sample size needed
- Patient protection – exposing patients to unknown safety risk
- Data tracking, Data dissemination, IRB involvement, etc.

Example: KEYNOTE 001 pembrolizumab study

Example 1: Keynote-001: Phase I Trial of Patients with Advanced Solid Tumors (N=1255)

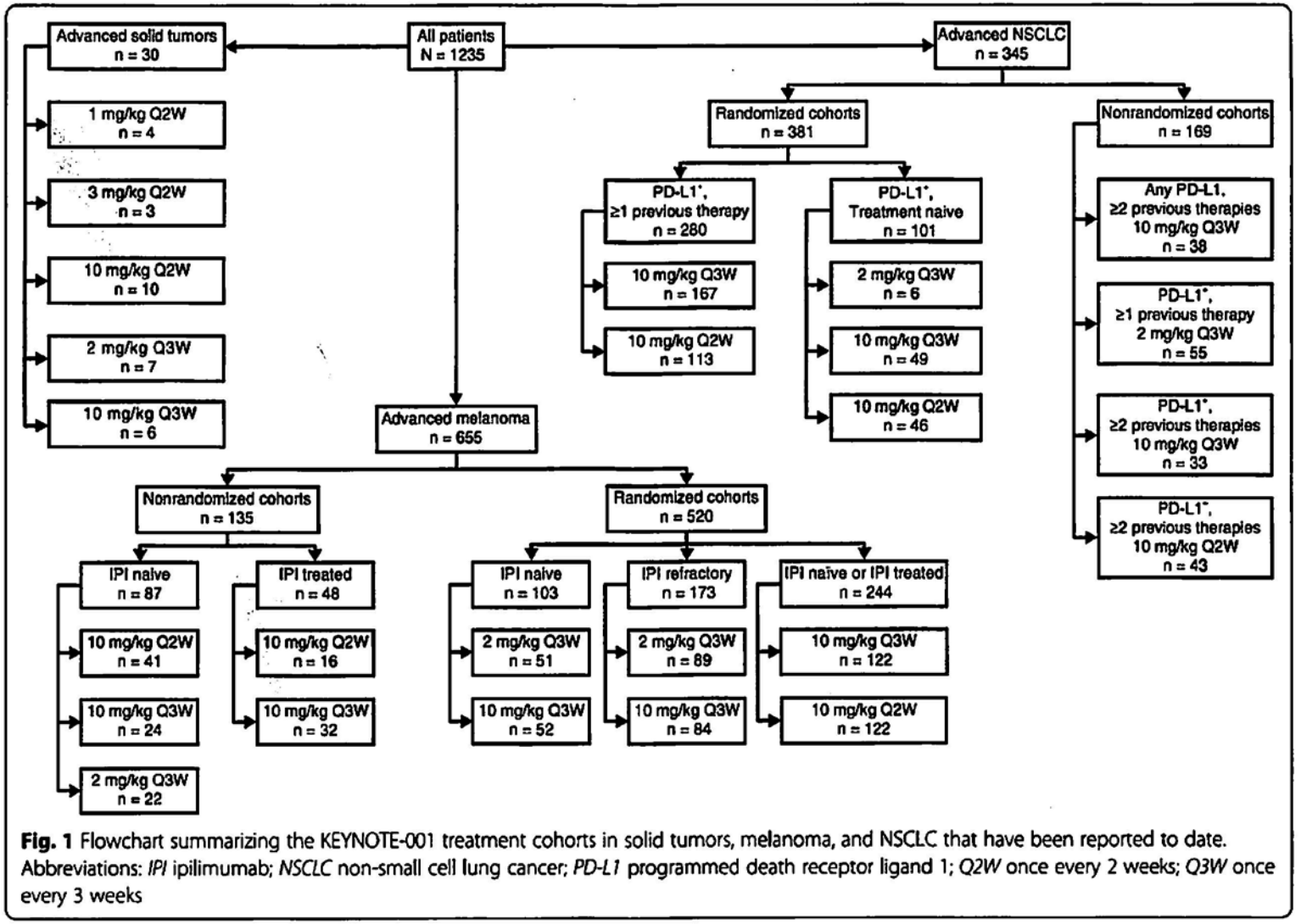


Fig. 1 Flowchart summarizing the KEYNOTE-001 treatment cohorts in solid tumors, melanoma, and NSCLC that have been reported to date. Abbreviations: *IPI* ipilimumab; *NSCLC* non-small cell lung cancer; *PD-L1* programmed death receptor ligand 1; *Q2W* once every 2 weeks; *Q3W* once every 3 weeks

Khoja et.al., J of Immuno Therapy of cancer 2015

Basket Trials

Histology-Agnostic Clinical Trial Designs

Single arm or randomized controlled clinical trials to:

- Evaluate One treatment for one molecular target in multiple disease sites or histology

- Evaluate Multiple treatments for one molecular target with single/multiple disease sites or histology

Example 2: Imatinib – common molecular driver

- Imatinib Target Exploration Consortium Study evaluating imatinib mesylate for the treatment of 40 different malignancies all sharing a common molecular driver BCR-ABL translocation
- Existing large body of data on safety and efficacy of imatinib in other diseases
- Imatinib mesylate was approved for five supplemental indications, myelodysplastic/myeloproliferative diseases, aggressive systemic mastocytosis, hyper eosinophilic syndrome, chronic eosinophilic leukemia, and dermatofibrosarcoma pertuberans - individually, all these diseases are extremely rare. These were based on ORR

Example 3: Pembrolizumab – Tissue Agnostic Approval

Approved for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient

- Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

Agnostic to Cancer Site

- Mismatch repair (MMR) deficiency refers to deficiency in proteins responsible for DNA MMR: MSH2, MSH6, MLH1, PMS2
- MMR deficiency leads to the MSI-H phenotype
- MMR deficient/MSI-H cancers harbor thousands of mutations (i.e., high mutational burden; hypermutated phenotype)
- The hypothesis is that MSI-H cancer represents a unique, biomarker-identified disease with a common immunobiology
- Most common recurrent MSI-H/MMRd malignancies have dismal prognosis

MSI-H/MMRd biology

- MSI-H/MMRd tumors share common pathological characteristics
- MSI-H/MMRd results in increased mutation load which increases neo-antigen burden
- MSI-H/MMRd selection does not appear to result in higher PD-L1 expression
- Mutation load / neoantigen burden is associated with improved outcomes to immunotherapy in different tumors

15 Different Cancer Types Included in the Submission

Cancer type	(n)
Colorectal	90
Esophageal	1
Gastric	9
Ampullary / Biliary	11
Pancreatic	6
Small Intestine	8
Breast	2
Endometrial	14
Thyroid	1
SCLC	1
Bladder	1
Kidney	1
Prostate	2
Sarcoma	1
Retroperitoneal	1

Table 23: MSI-H Trials (Product Label)

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
KEYNOTE-016 NCT01876511	• prospective, investigator- initiated • 6 sites • patients with CRC and other tumors	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164 NCT02460198	• prospective international multi- center • CRC	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
KEYNOTE-012 NCT01848834	• retrospectively identified patients with PD-L1-positive gastric, bladder, or triple- negative breast cancer	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-028 NCT02054806	• retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KEYNOTE-158 NCT02628067	• prospective international multi- center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		149			

CRC = colorectal cancer; PCR = polymerase chain reaction; IHC = immunohistochemistry

Table 24: Efficacy Results for Patients with MSI-H/dMMR Cancer (product label)

Endpoint	N = 149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Response duration	
Median in months (range)	NR(1.6+, 22.7+)
% with duration ≥ 6 months	78%

Table 25: Response by Tumor Type (product label)

	N	Objective response rate n (%) 95% CI		DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

Example 4: Clinical Trial NCT02034110

- A Phase II, open-label, study in subjects with BRAF V600E-mutated rare cancers with several histologies to investigate the clinical efficacy and safety of the combination therapy of dabrafenib and trametinib

Study Design

Histology	Overall Incidence Rates in US (2011)	BRAF V^{600E} Mutation Rate
Anaplastic thyroid cancer (ATC)	0.10/100,000	24%
Biliary Tract Cancer (BTC)	0.6/100,000	7 - 30%
Diffuse Large B Cell Lymphoma (DLBCL)	9.17/100,000	4%
Gastrointestinal stromal tumor (GIST)	0.7 - 1.1/100,000	2 - 5%
Germ Cell Tumor (GCT) (~50% non-seminomatous)	6.31/100,000 (white males) 1.38/100,000 (black males)	3%
High-Grade Cerebral Glioma (HGG)	2 - 4/100,000	~3% (GBM)
Hairy Cell Leukemia (HCL)	0.33/100,000	90 - 100%
Multiple Myeloma (MM)	5.579/100,000	4%
Adenocarcinoma of Small Intestine	0.073/100,000	~10%

Study Design

- Primary endpoint is ORR
- Each cohort of tumor type of a given histology will enroll a maximum of 15 subjects
- A Bayesian hierarchical design 'dynamically' borrows information across histologic cohorts – shrinkage estimates
- Interim analyses for efficacy and safety

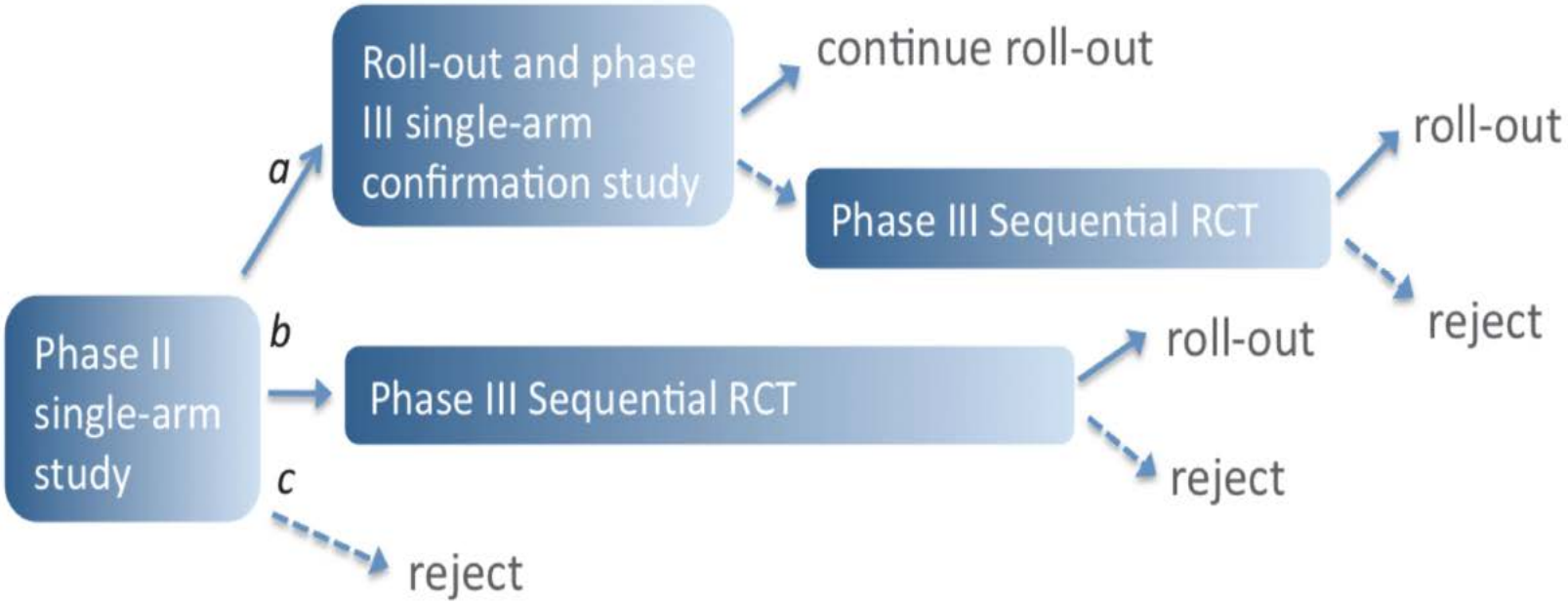
Review Consideration

- Typically compare with historical control data. The proposed Bayesian model formally includes historical response rate as a factor in the model, although what is considered as historical control rates (prior) needs discussion – changing over time
- Exchangeability?
- Trial is still ongoing. ATC results published http://ascopubs.org/doi/pdf/10.1200/JCO.2013.51.1766. When there is new info, will this be updated?
- Recently approved for the treatment of advanced/metastatic anaplastic thyroid cancer

Other Examples

- Basket trials: Pharmaceutical Trials (Eg: Signature, My Pathway), Institution Trials, MPACT, MATCH
- Umbrella/Platform trials: Breast (SAFIR-01, I-SPY2), Colon (FOCUS-4, ASSIGN), Melanoma (GEMM), Lung (Lung-MAP, BATTLE, MATRIX, SAFIR-02, ALCHEMIST), Rare tumors (DART), Institution Trials, VIKTORY screening protocol in gastric cancer, AML (BEAT trial)
- Registries: TAPUR, etc

Example outside of Oncology: "Single-Arm to RCT" (Cooper et al)



(Cooper, et al Evaluating clinical trial designs for investigational treatments of Ebola Virus Disease. PLoS Med 2015; 12(4):e1001815)

Key Questions

- Objective: Screening patients or Screening drug products, Assess activity *vs.* Confirm efficacy
- Disease defined by molecular signature only vs. site of disease, histology and molecular signature
- Prevalence of each sub-population
- Knowledge of natural history of the disease in each of the sub-population
- Available data from Phase 1 and Phase 2 studies: appropriate dose and preliminary information on activity
- Known targets?
- Feasibility of execution of the study

Considerations

- Challenges
  - Could be logistically challenging, Varying clinical experience and development phases between drugs, Transparency and cooperation between pharma
  - Assay platform selection, central vs. local testing, agent selection

- Lessons from master protocol
  - Possibility of change of the standard care due to new approvals
  - Willing to and plan adapt when necessary

Remarks

- Targeted therapy can be beneficial across various diseases in a target population – Agnostic to disease site
- Need for Drug and Device development in parallel
- Supplemental vs. new molecular entity
- Opportunities to conduct clinical trials with innovative designs
- Challenges in the complexity of the designs, analyses and interpretation of the results
- FDA encourages use of Master protocols where appropriate; Guidance is under development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