PHASE I SOLID TUMOR TRIALS IN THE ERA OF PRECISION ONCOLOGY – A SYSTEMATIC SURVEY

Shannon Stockton, MD

Hematology/Oncology Fellow

Vanderbilt University Medical Center

Nashville, TN

DISCLOSURES

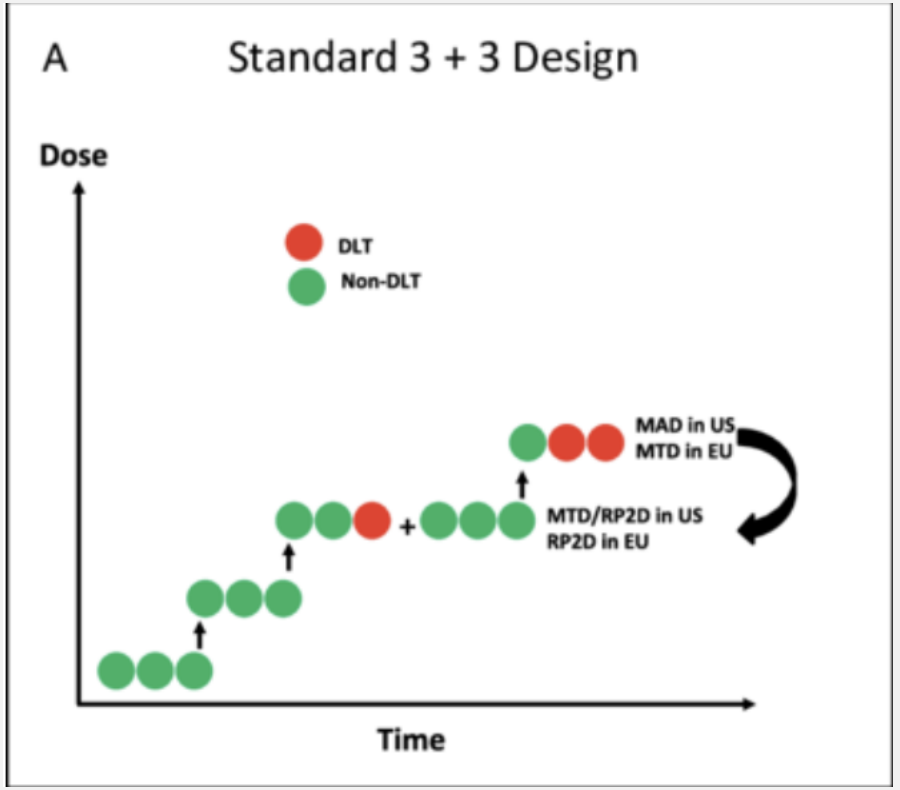
- No relevant disclosures

INTRODUCTION

- While the goal of Phase I clinical trials remains unchanged, the characteristics of therapeutic agents have changed drastically in the era of precision oncology, from cytotoxic chemotherapy to targeted agents, immunotherapy (IO), etc.
- Drug development mechanisms have also shifted, including tissue agnostic approvals and FDA Breakthrough Designation

INTRODUCTION

- Despite the change in the types of agents used and the ways drugs are approved, in it is not clear if trial design has been widely adapted to reflect these changes
- Rule-based dose escalation designs (i.e. 3+3) have traditionally been used in phase I trials (Rogatko JCO 2007), but these designs are based on the premise that there is a linear relationship between drug dose, toxicity and expected response, ie cyototoxic chemotherapy, that may not hold constant for targeted agents/IO (Sachs, Clin cancer res 2016)
- Our study seeks to characterize the evolution (or lack thereof) of Phase I solid tumor trials in the era of precision oncology



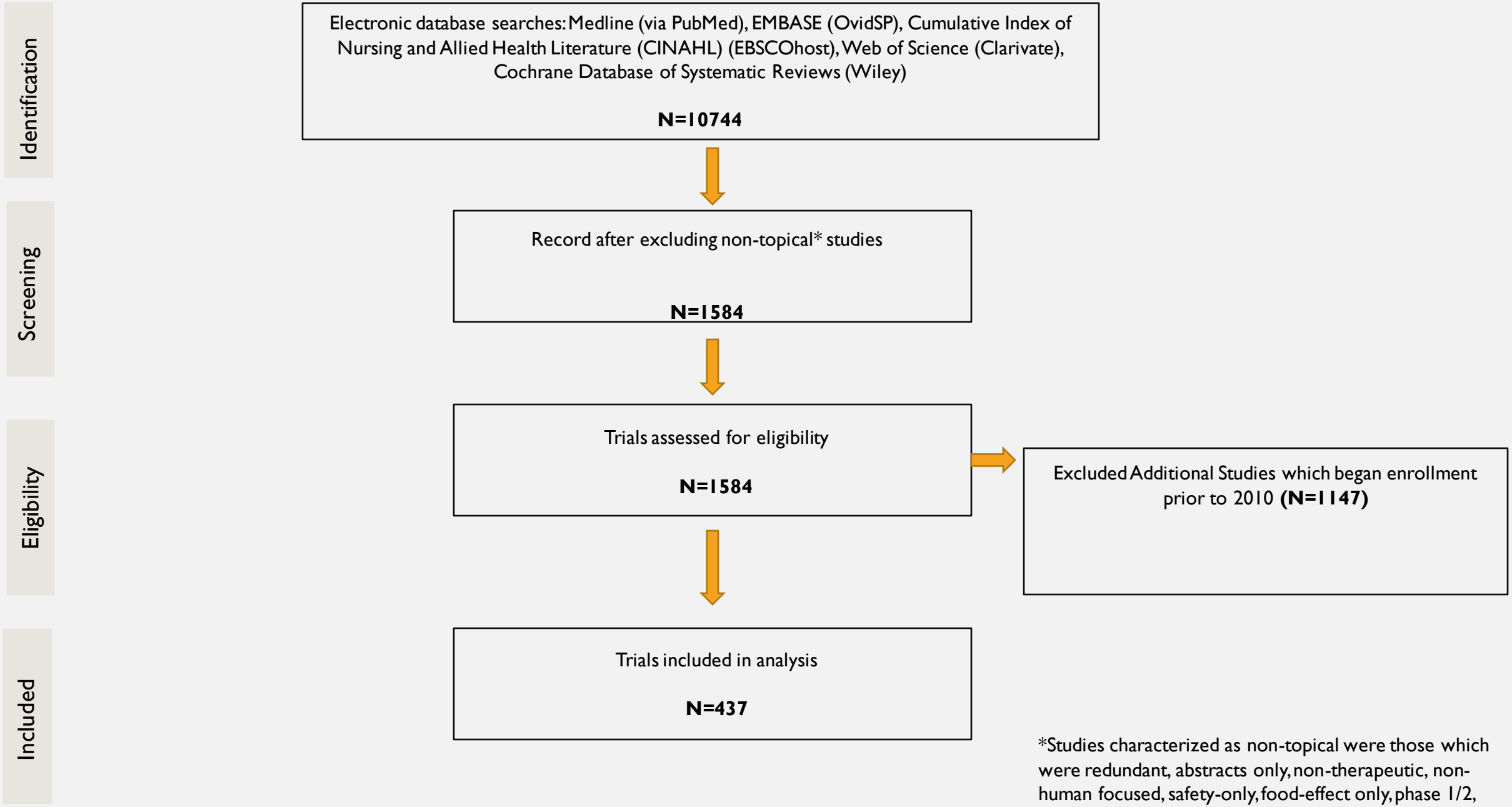
OBJECTIVES

Primary aim:

- Estimate the proportion of phase I trials using rule-based dose escalation schemes (i.e., 3+3 design and variations, including accelerated titration, pharmacologically-guided dose escalation, and rolling 6)

METHODS

- Eligible journals: Annals of Oncology, British Journal of Cancer, Cancer Discovery, Clinical Cancer Research, Investigational New Drugs, JAMA Oncology, Journal of Clinical Oncology, Lancet, Lancet Oncology, Molecular Cancer Therapeutics, The New England Journal of Medicine, and The Oncologist
- Restricted studies included in this analysis to Jan 1, 2010 – Dec 31, 2020 to better capture the era of precision oncology
- Two reviewers reviewed studies for inclusion, with uncertain cases decided by 3rd reviewer. Data abstraction performed by two reviewers with concordance rate of 98.7% established by 3rd reviewer.


Identification
Screening
Eligibility
Included
Electronic database searches: Medline (via PubMed), EMBASE (OvidSP), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (EBSCOhost), Web of Science (Clarivate), Cochrane Database of Systematic Reviews (Wiley)
N=10744
Record after excluding non-topical* studies
N=1584
Trials assessed for eligibility
N=1584
Excluded Additional Studies which began enrollment prior to 2010 (N=1147)
Trials included in analysis
N=437
*Studies characterized as non-topical were those which were redundant, abstracts only, non-therapeutic, non-human focused, safety-only, food-effect only, phase 1/2, radiation therapy focused, included pediatric populations or involved non-systemic treatment modalities

RESULTS

Dose Escalation Class (N=353)	
Rule	314 (89%)
Model	39 (11%)
Dose Escalation Algorithm (N=353)	
3+3	284 (80.5%)
Other	57 (16.1%)
mTPI	6 (1.7%)
TITE-CRM	5 (1.4%)
BOIN	1 (0.3%)

RESULTS

Most Common Drug Classes (N=437)	
Targeted	208 (47.6%)
Immunotherapy	96 (22%)
Other	88 (20.1%)
Chemotherapy	30 (6.9%)
DNA Damage Repair Inhibitor	15 (3.4%)
Use of Expansion Cohorts (N=437)	
Yes	174 (40.1%)
No	260 (59.9%)
Most Common DLTs (N=426)	
Other	275 (64.6%)
Gastrointestinal	72 (16.9%)
Hematologic	54 (12.7%)
Constitutional	25 (5.9%)

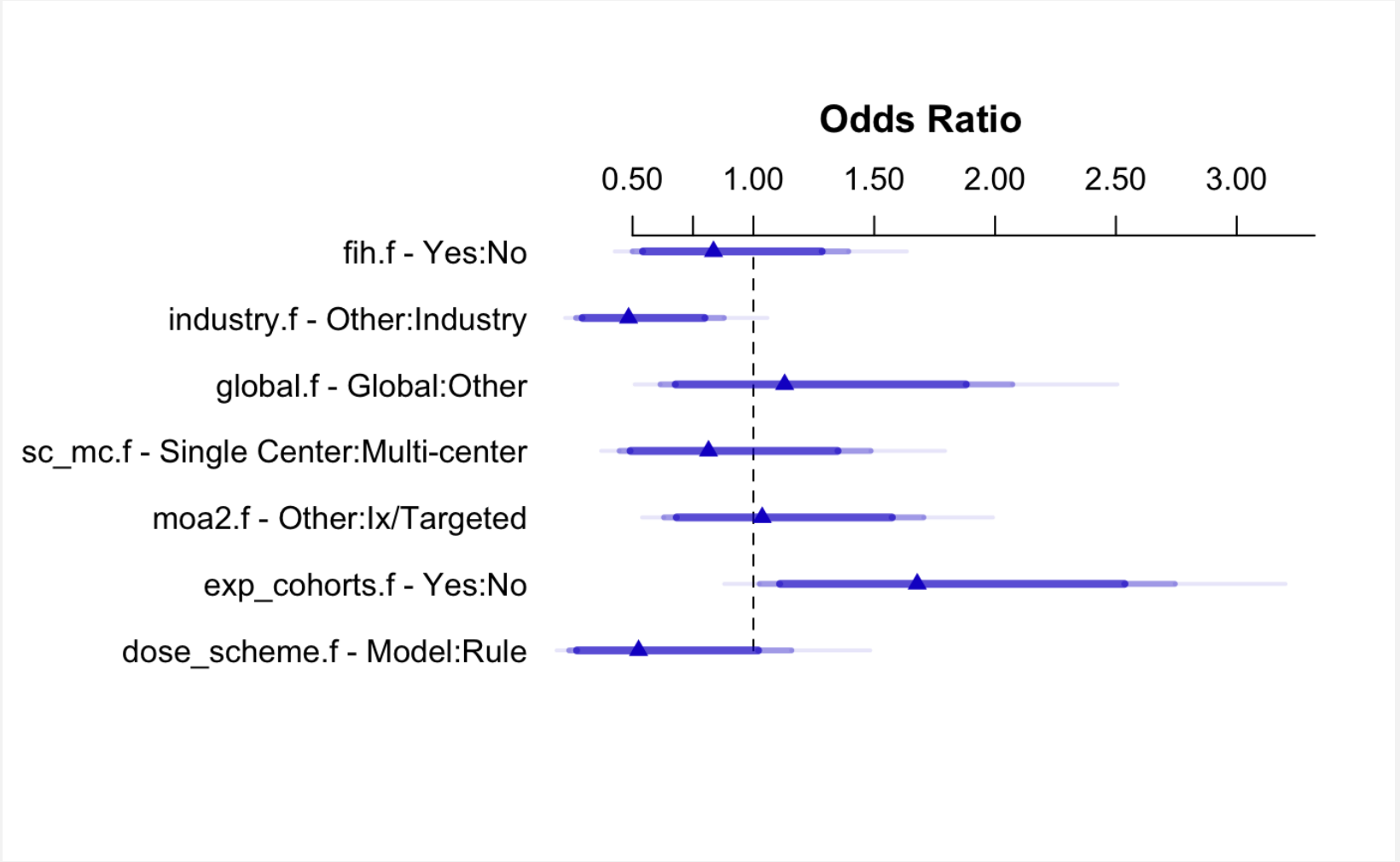
UNIVARIATE ANALYSIS: FACTORS ASSOCIATED WITH PROGRESSION TO PHASE 2

	N	No (N=273)	Yes (N=164)	Overall (N=437)	Test Statistic
First in Human?	437				X^2_1=0.02, P=0.89[2]
No		193/273 (70.7)	117/164 (71.3)	310/437 (70.9)	
Yes		80/273 (29.3)	47/164 (28.7)	127/437 (29.1)	
Study Sponsor	433				X^2_2=21.14, P<0.01[2]
NCI		42/271 (15.5)	7/162 (4.3)	49/433 (11.3)	
Industry		172/271 (63.5)	135/162 (83.3)	307/433 (70.9)	
Other		57/271 (21.0)	20/162 (12.3)	77/433 (17.8)	
Study Sponsor	433				X^2_1=19.39, P<0.01[2]
Other		99/271 (36.5)	27/162 (16.7)	126/433 (29.1)	
Industry		172/271 (63.5)	135/162 (83.3)	307/433 (70.9)	
Study Location	437				X^2_4=22.99, P<0.01[2]
NAmer		147/273 (53.8)	56/164 (34.1)	203/437 (46.5)	
Europe		37/273 (13.6)	18/164 (11.0)	55/437 (12.6)	
Asia		30/273 (11.0)	28/164 (17.1)	58/437 (13.3)	
Global		53/273 (19.4)	59/164 (36.0)	112/437 (25.6)	
Other		6/273 (2.2)	3/164 (1.8)	9/437 (2.1)	
Study Location	437				X^2_1=14.74, P<0.01[2]
Other		220/273 (80.6)	105/164 (64.0)	325/437 (74.4)	
Global		53/273 (19.4)	59/164 (36.0)	112/437 (25.6)	
Multicenter Study?	426				X^2_1=9.62, P<0.01[2]
Single Center		84/265 (31.7)	29/161 (18.0)	113/426 (26.5)	
Multi-center		181/265 (68.3)	132/161 (82.0)	313/426 (73.5)	

UNIVARIATE ANALYSIS: FACTORS ASSOCIATED WITH PROGRESSION TO PHASE 2

	N	No (N=273)	Yes (N=164)	Overall (N=437)	Test Statistic
Drug Action	437				$X^2_4=3.66$, $P=0.45^2$
Cx		17/273 (6.2)	13/164 (7.9)	30/437 (6.9)	
Ix		53/273 (19.4)	43/164 (26.2)	96/437 (22.0)	
Targeted		136/273 (49.8)	72/164 (43.9)	208/437 (47.6)	
DNAdri		10/273 (3.7)	5/164 (3.0)	15/437 (3.4)	
Other		57/273 (20.9)	31/164 (18.9)	88/437 (20.1)	
Therapy Class	437				$X^2_1=0.04$, $P=0.84^2$
Other		84/273 (30.8)	49/164 (29.9)	133/437 (30.4)	
Ix/Targeted		189/273 (69.2)	115/164 (70.1)	304/437 (69.6)	
Expansion Cohorts?	434				$X^2_1=18.43$, $P<0.01^2$
No		183/270 (67.8)	77/164 (47.0)	260/434 (59.9)	
Yes		87/270 (32.2)	87/164 (53.0)	174/434 (40.1)	
Class of Dose Escalation	353				$X^2_1=1.11$, $P=0.29^2$
Rule		207/236 (87.7)	107/117 (91.5)	314/353 (89.0)	
Model		29/236 (12.3)	10/117 (8.5)	39/353 (11.0)	

MULTIVARIATE ANALYSIS: FACTORS ASSOCIATED WITH PROGRESSION TO PHASE 2



CONCLUSIONS

- Rule-based designs still predominate in clinical trials in the era of precision oncology, with 3+3 being most common
- The most common agents tested in Phase I trials are targeted agents, followed by immunotherapy
- Univariate analysis of factors associated with phase 2 testing showed association with whether test was first-in-human, industry funding, global centers, multicenter testing, and use of expansion cohorts
- Multivariate analysis of factors associated with phase 2 testing showed association with industry funding and use of expansion cohorts
- Univariate and multivariate analysis underway to evaluate factors associated with drug regulatory approval - to be updated at ASCO and in manuscript

ACKNOWLEDGEMENTS

- This work was done in collaboration with statistician G. Dan Ayers, my co-fellow Dr. Cody Lee, librarian Heather Laferriere, my mentor Dr. Jordan Berlin, and my co-mentor Dr. Nanu Das

Muffin, the pet who supported this work

REFERENCES

1. Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. *J Clin Oncol*. 2007;25(31):4982-4986. doi:10.1200/JCO.2007.12.1012
2. Sachs JR, Mayawala K, Gadamsetty S, Kang SP, de Alwis DP. Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example. *Clin Cancer Res*. 2016;22(6):1318-1324. doi:10.1158/1078-0432.CCR-15-1295