Use, variability, and justification of eligibility criteria for phase II and III clinical trials in acute leukemia

Andrew Hantel,[1,2,3] Marlise R. Luskin,[3] Irum Khan,[4] Elizabeth Warner,[2] Anand A. Patel,[5] Thomas P. Walsh,[1] Daniel J. DeAngelo,[3] Christopher S. Lathan[1,6] and Gregory A. Abel[1,2,3]

[1]Division of Population Sciences, Dana-Farber Cancer Institute, Boston, MA; [2]Center for Bioethics, Harvard Medical School, Boston, MA; [3]Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA; [4]Division of Hematology/Oncology, Department of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; [5]Section of Hematology-Oncology, Department of Medicine, The University of Chicago, Chicago, IL and [6]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Correspondence: A. Hantel
andrew_hantel@dfci.harvard.edu

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Supplemental Appendix

Supplemental Methods

ClinicalTrials.gov Search Terms:

Condition or Disease: Acute Myeloid Leukemia OR Acute Lymphoblastic Leukemia

Study Type: Interventional Studies (Clinical Trials)

Age: Adults (18-64) and/or Older Adults (65+)

Phase: Phase 2, Phase 3

Start Dates: 1/1/2010-12/31/2019

Eligibility Criteria Selection and Coding:

Verbatim criteria were abstracted according to this list, and criteria without pre-specified variables were iteratively included when used by at least three trials. Numerical criteria were transformed to a common unit when possible, with laboratory value parameters at Dana-Farber Cancer Institute used to define normal limits, as needed. Broad or blanket criteria (e.g., "adequate organ function") were not counted as specific exclusions. A single set of criteria were created for trials with multiple cohorts to maintain a constant unit of analysis and as this set of criteria would reflect the entire population able to participate in the trial.

Drug Safety Data Selection and Coding:

Drugs were identified by their labeling as "Interventions" in the ClinicalTrials.gov study listing. For drugs FDA-approved at the time of study initiation, the FDA labels was

reviewed for dosing, pharmacology, and safety data; Lexicomp and clinical trials cited were reviewed if the necessary data were not listed in the label.[9] For drugs not FDA-approved at the time of study initiation, the study protocol listed on ClinicalTrials.gov and publication(s) listed in the protocol associated with previously conducted investigational studies were reviewed for safety data. PubMed.gov was also queried using the investigational agent name(s), as listed on ClinicalTrials.gov, to identify study protocols and study results; the first 20 search results (sorted by "Best Match") were reviewed to identify additional safety data. Sources were documented and binary safety signals were assigned if review identified Common Terminology Criteria for Adverse Events (CTCAE) any grade ≥3 toxicity related to the eligibility criteria of interest, and/or any grade toxicity in ≥10% of participants, and/or renal/hepatic elimination ≥10%.[10,11] Drugs associated with viral reactivation and moderate/major substrates of metabolic processes relevant to antiviral medications (e.g., CYP, p-GP, UGT) were catalogued.[12] Drug safety signals and limits were then assigned to trials according to the therapies tested; when multiple limits for the same criterion were present, the most conservative value was used.

Supplemental Table 1. Clinical Trial Enrollment Criteria Variables and Codes

Category	Variable	Response Type	Response Options	Abstractor Instructions
Trial Characteristics	Year	Numerical	Number	Year of study start date.
	Phase II	Binary	Yes, No	"Yes" if there was a Phase II component.
	Phase III	Binary	Yes, No	"Yes" if there was a Phase III component.
	Number of Participants	Numerical	Number	Number of study subjects listed.
	Academic Investigator/Institution Sponsor	Binary	Yes, No	"Yes" if there was an academic investigator/institution listed as study sponsor.
Sponsor	NIH Sponsor	Binary	Yes, No	"Yes" if the NIH was listed as study sponsor.
	Industry Sponsor	Binary	Yes, No	"Yes" if a pharmaceutical company or other medical industry company listed as study sponsor.
	Randomization	Binary	Yes, No	"Yes" if participants were randomized to a treatment arm.
Demographics	Older Adult Age Demarcation	Numerical	Number	Age (in years) listed to demarcate older from younger adults, to restrict the trial to older adults, or to restrict from the inclusion of older adults. Leave blank if not mentioned.
	ECOG Performance Status Limit	Numerical	Number	Upper limit of performance status. Leave blank for trials and/or cohorts that require participants to have poor performance status. Leave blank if not mentioned.
	Life Expectancy	Numerical	Number	Time (in years) listed denoting the minimum life expectancy an individual should have to be eligible to participate. Leave blank if not mentioned.
Comorbidities	Restriction for Prior Malignancy	Binary	Yes, No	"Yes" if there is a restriction for persons with a prior malignancy diagnosis.
	Exception for Prior Malignancy Based on Time Since Remission	Binary	Yes, No	"Yes" if there is an exception to the prior malignancy restriction based on years in remission from prior malignancy
	Time Since Remission of Prior Malignancy	Numerical	Number	List the number of years required to have passed since documented remission from prior malignancy for the individual to be allowed to participate. Leave blank if not mentioned.
	HIV Restriction	Categorical	Not allowed, Allowed, Allowed with restriction	Note if the trial allows, does not allow, or allows HIV with restriction (e.g., allows controlled but not active HIV). Leave blank if not mentioned.

	Hepatitis B Restriction	Categorical	Not allowed, Allowed, Allowed with restriction	Note if the trial allows, does not allow, or allows Hepatitis B with restriction (e.g., allows controlled but not active infection). Leave blank if not mentioned.
	Hepatitis C Restriction	Categorical	Not allowed, Allowed, Allowed with restriction	Note if the trial allows, does not allow, or allows Hepatitis B with restriction (e.g., allows controlled but not active infection). Leave blank if not mentioned.
Organ Function	Left Ventricular Ejection Fraction Limit	Numerical	Number	Lower percentage limit of ejection fraction. Leave blank for trials and/or cohorts that require participants to have decreased ejection fraction. Leave blank if not mentioned.
	QTc	Numerical	Number	Upper limit of the QTc interval. Leave blank if not mentioned.
	Renal Function Limit	Numerical	Number	Upper limit of creatinine or lower limit of CrCl or eGFR (or other measure). List formula used for calculation if stated. Leave blank for trials and/or cohorts that require participants to have decreased renal function. Leave blank if not mentioned.
	Bilirubin Limit	Numerical	Number	Upper limit of bilirubin with unit of measure. Leave blank for trials and/or cohorts that require participants to have decreased liver function. Leave blank if not mentioned.
	Gilbert's Exception	Binary	Yes, No	"Yes" if there is an exception to the bilirubin limit for suspected or diagnosed Gilbert's disease. Leave blank if no bilirubin limit.
	AST/ALT Limit	Numerical	Number	Upper limit of AST/ALT with units of measure (list both values if they are different). Leave blank for trials and/or cohorts that require participants to have decreased liver function. Leave blank if not mentioned.
	Disease Exception	Binary	Yes, No	"Yes" if there is an exception to the bilirubin and/or AST/ALT limit for suspected elevation due to leukemic involvement. Leave blank if no liver function limits mentioned.
Disease Characteristics	Disease Status	Binary	Active, Remission	Note if the trial is for patients with active disease or in remission.
	CNS Disease	Categorical	Allowed, Not Allowed, Allowed with Restrictions	Note if the trial allows, does not allow, or allows with restriction (e.g., allows history of CNS disease but not active disease). Leave blank if not mentioned.
	WBC Count Upper Limit	Numerical	Number	List the upper limit of the WBC count allowed in 10^9/L. Leave blank if not mentioned.

Treatment Characteristics	Hydrea Cytoreduction	Binary	Yes, No	"Yes" if cytoreduction with hydrea is allowed.
	Leukopheresis Cytoreduction	Binary	Yes, No	"Yes" if cytoreduction with leukopheresis is allowed.
	Cytarabine Cytoreduction	Binary	Yes, No	"Yes" if cytoreduction with cytarabine is allowed.
	Prior Treatment Allowed	Binary	Yes, No	"Yes" if prior treatments for acute myeloid leukemia are allowed.
	Prior Treatment Wash Out Period (days)	Numerical	Number	List the required washout period after prior anti-cancer therapies, if listed in days.
	Prior Treatment Wash Out Period (halflives)	Numerical	Number	List the required washout period after prior anti-cancer therapies, if listed in drug halflives.

NIH: National Institutes of Health; ECOG: Eastern Cooperative Oncology Group; HIV: human immunodeficiency virus; QTc: corrected QT interval; AST/ALT: Aspartate transaminase / alanine aminotransferase; CNS: central nervous system; WBC: white blood cell.

Supplemental Table 2. Drug Safety Review Variables and Codes

Category	Variable	Response Type	Response Options	Abstractor Instructions
Drug	Investigational	Binary	Yes, No	"Yes" if the drug did not have an FDA approval at the study start date.
	Class	Categorical	Anthracycline, Antimetabolite, Purine analogue, etc.	List the drug class. If there is no class identified, list the mechanism(s) of action.
	Sources Reviewed	Categorical	Non-investigational: FDA labels, Lexicomp, and registration trials.	List the sources reviewed from which the data entered was obtained.
			Investigational: phase 0/I/II study protocol, phase 0 and I study result, additional study protocol or results from other setting	List the sources reviewed from which the data entered was obtained.
	Source URLs	Categorical	URL	List the URLs for the sources identified above.
Renal	Elimination	Binary	Yes, No	"Yes" if drug metabolism and/or excretion is listed as ≥10% renal/urinary.
	Toxicity	Binary	Yes, No	"Yes" if the data source lists Common Terminology Criteria for Adverse Events grade ≥3 toxicity and/or any grade toxicity in ≥10% of participants.
	Limit Listed	Binary	Yes, No	"Yes" if there is a suggested limit to renal function listed.
	Limit Value	Numerical	Number	List the renal function limit listed.
	Limit Value Units	Categorical	mg/dl, ml/min, ml/min/1.73m^2	List the units used for the limit value.
Hepatic	Elimination	Binary	Yes, No	"Yes" if drug metabolism and/or excretion is listed as ≥10% hepatic/biliary.
	Toxicity	Binary	Yes, No	"Yes" if the data source lists Common Terminology Criteria for Adverse Events grade ≥3 toxicity and/or any grade toxicity in ≥10% of participants.
	Bilirubin Limit Listed	Binary	Yes, No	"Yes" if there is a suggested limit to the bilirubin listed.
	Bilirubin Limit Value	Numerical	Number	List the bilirubin limit listed.
	Bilirubin Limit Value Units	Categorical	mg/dl, ULN	List the units used for the limit value.
	AST/ALT Limit Listed	Binary	Yes, No	"Yes" if there is a suggested limit to AST/ALT listed. If there are separate limits, list separately.
	AST/ALT Limit Value	Numerical	Number	List the AST/ALT limit listed. If there are separate limits, list separately.

	AST/ALT Limit Value Units	Categorical	mg/dl, ULN	List the units used for the limit value. If there are separate limits, list separately.
Cardiac	QTc Prolongation	Binary	Yes, No	"Yes" if QTc prolongation risk is listed as associated with the drug.
	QTc Limit Listed	Binary	Yes, No	"Yes" if there is a suggested limit to the QTc listed.
	QTc Limit Value	Numerical	Number	List the QTc limit listed.
	QTc Limit Value Units	Categorical	ms	List the units used for the limit value.
	Heart Failure or Cardiomyopathy	Binary	Yes, No	"Yes" if heart failure and/or cardiomyopathy risk is listed as associated with the drug.
	Left Ventricular Ejection Fraction (LVEF) Limit Listed	Binary	Yes, No	"Yes" if there is a suggested limit to the LVEF listed.
	Left Ventricular Ejection Fraction Limit Value	Numerical	Number	List the LVEF limit listed.
	Left Ventricular Ejection Fraction Limit Value Units	Categorical	%	List the units used for the limit value.
Potential Antiviral Drug-Drug Interactions	Moderate or Major CYP3A4, CYP2B6, CYP2C19, CYP2C9 or CYP1A2 Substrate	Binary	Yes, No	“Yes” if the drug is a moderate or major substrate of at least one of the listed CYPs.
	Moderate or Major CYP Substrates	Categorical	CYP3A4, CYP2B6, etc.	List the CYPs for which it is a moderate or major substrate.
	p-glycoprotein Substrate	Binary	Yes, No	“Yes” if the drug is a moderate or major substrate of p-GP.
	UGT Family Substrate	Binary	Yes, No	“Yes” if the drug is a moderate or major substrate of a UGT.
	Other Substrate	Binary	Yes, No	“Yes” if the drug is a moderate or major substrate of another protein/enzyme not listed above.
	Other Substrate List	Categorical	OAT1, OCT1, etc.	List the other protein/enzyme for which it is a moderate or major substrate.
Viral Reactivation	HIV	Binary	Yes, No	"Yes" if HIV reactivation risk is listed as associated with the drug.
	Hepatitis B	Binary	Yes, No	"Yes" if Hepatitis B reactivation risk is listed as associated with the drug.
	Hepatitis C	Binary	Yes, No	"Yes" if Hepatitis C reactivation risk is listed as associated with the drug.

Supplemental Table 3. Drugs Included in the Analysis

33A	Crenolanib	Imatinib	CB-839
9-ING-41	CX-01	IMGN632	Pevonedistat
ABL001	Cyclophosphamide	INCB053914	Pinometostat
Acalabrutinib	Cytarabine	INCB054329	Plerixafor
ADI-PEG 20	Daratumumab	INCB059872	Ponatinib
Alemtuzumab	Dasatinib	Inotuzumab ozogamicin	Pracinostat
Alisertib	Daunorubicin	digoxin	PRI-724
All-trans retinoic acid	DC AML Vaccine	Iomab-B	Quizartinib
Alvocidib	DCLL9718S	Ipilimumab	Rabbit ATG
Anti-Thymocyte Globulin	Decitabine	Irinotecan	Tosedostat
APR-246	Deferasirox	Ivosidenib	Rigosertib
Ascorbic acid	Dexrazoxane	Ixazomib	Rituximab
ASLAN003	DFP-10917	JZP-458	Ruxolitinib
Asparaginase	Doxil	KRT-232	Samalizumab
ASTX727	Doxorubicin	Lenalidomide	Sapacitabine
Atezolizumab	DT388IL3	Lintuzumab-Ac225	Sargramostim
Azacitidine	Durvalumab	Lomustine	Selinexor
AZD1775	E6202	Lorvotuzumab Mertansine (IMGN901)	Sirolimus
Bemcentinib	Eltrombopag	LY3039478	SL-401
Bendamustine	Enasidenib	MEK 162	SNDX-5613
Bexarotene	Entinostat	Melphalan	Sorafenib
BI 836858	Entospletinib	Mercaptopurine	Sunitinib
Birinapant	Erlotinib	Methotrexate	SY-1425 (tamibarotene)
BL-8040	Erwinia asparaginase	MGTA-456	Tacrolimus
Blinatumomab	Erwinia asparaginase (recombinant)-rywn	Midostaurin	Talacotuzumab
BMS-936564	Etoposide	N-803	Talazoparib

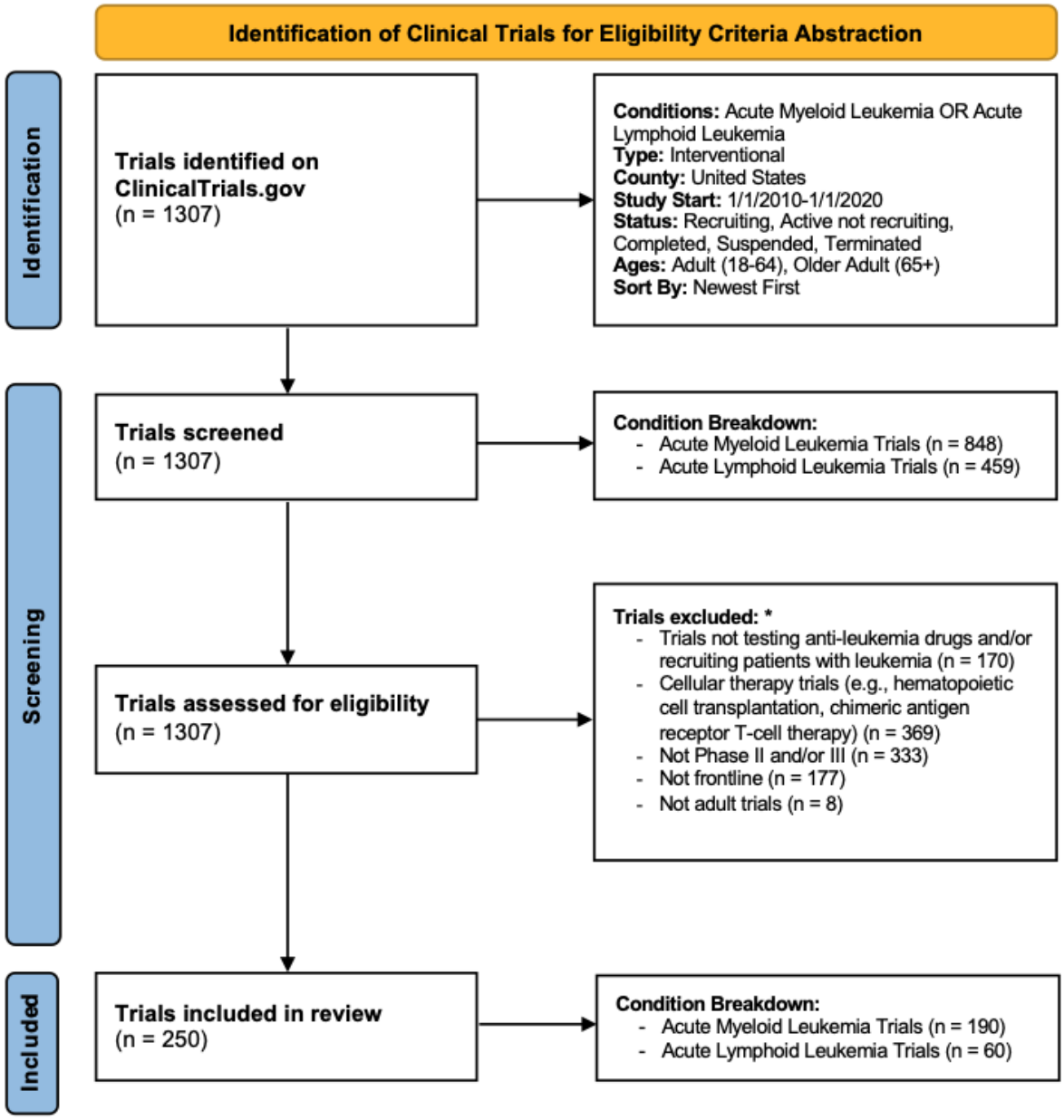
Bortezomib	Fludarabine	Mitoxantrone	Thioguanine
Bosutinib	Galinpepimut-S	Mycophenolate Mofetil	Thiotepa
BP1001	Gemcitabine	Nelarabine	Tipifarnib
CC-486	Gemtuzumab ozogamicin	Nilotinib	Topotecan
Brentuximab Vedotin	Gilteritinib	Nivolumab	Trametinib
BST-236	Glasdegib	NLA-101	Veliparib
Busulfan	GMI-1271	Ofatumumab	Venetoclax
BVD-523	GSK2141795	Omacetaxine	Vincristine
Calaspargase Pegol-mknl	Guadecitabine	Onvansertib	Volasertib
Carboplatin	PF-04449913	Paclitaxel	Vorinostat
Cholecalciferol	Ibrutinib	Pacritinib	Peginterferon Alfa-2a
Cladribine	Idarubicin	Palcociclib	Vosaroxin
Clofarabine	Idasanutlin	PD-616	WT1 peptide vaccine
Co-ArgI-PEG modified human arginase I	Idelalisib	PEG-Asparaginase	
CPX-351	Ifosfamide	Pembrolizumab	

Supplemental Table 4. Odds of Phase III eligibility criteria concordance compared to Phase II.

Criteria	OR Concordance	p-value	OR 95% CI
LVEF Limit	0.54	0.06	0.28,1.05
QTc Limit	0.86	0.63	0.45,1.61
Bilirubin Limit	0.41	0.01	0.21,0.78
AST/ALT Limit	0.43	0.01	0.23,0.83
Renal Function Limit	0.53	0.047	0.28,0.99
HIV Any Excl	0.79	0.46	0.41,1.49
Hepatitis B Any Excl	0.78	0.54	0.41,1.47
Hepatitis C Any Excl	0.85	0.60	0.45,1.61

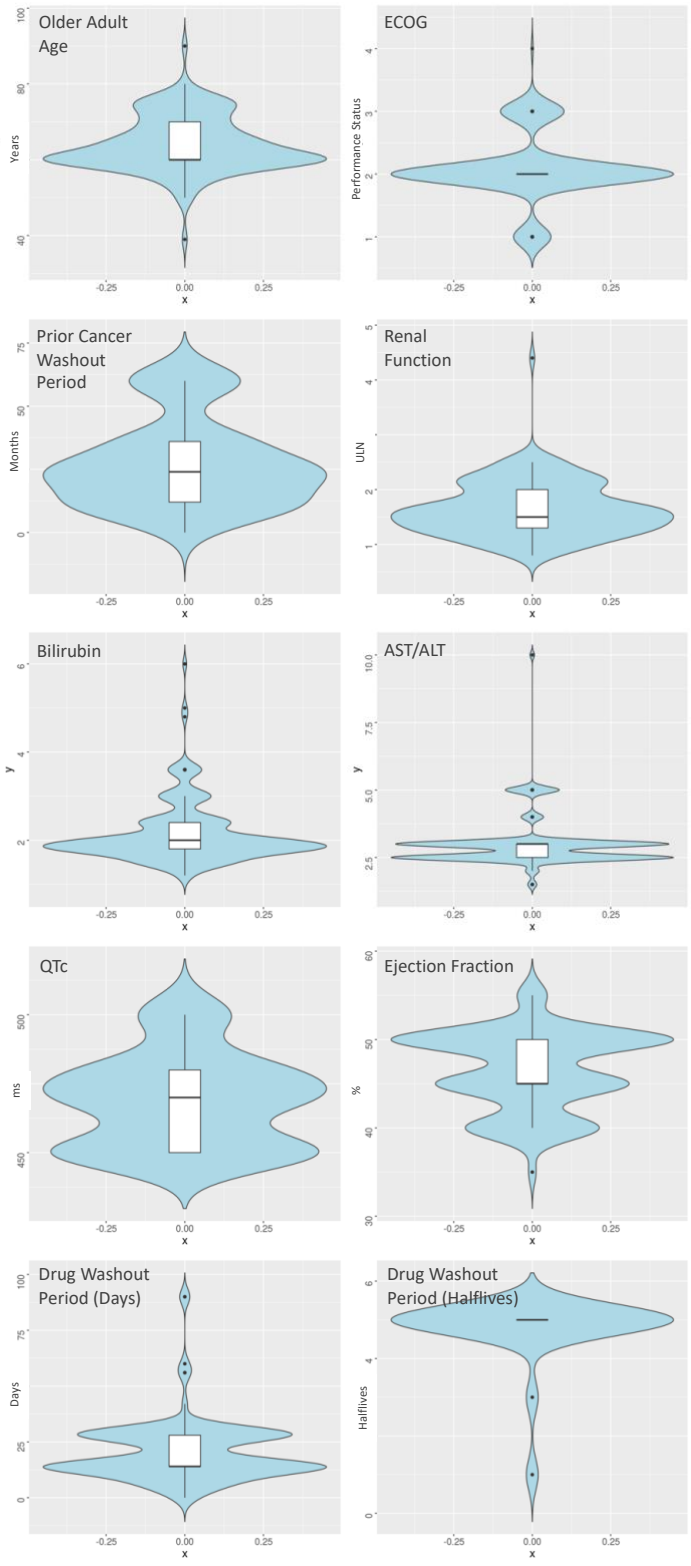
LVEF: left ventricular ejection fraction; QTc: corrected QT interval; AST/ALT: Aspartate transaminase / alanine aminotransferase; HIV: human immunodeficiency virus

Supplemental Figure 1. PRISMA Diagram



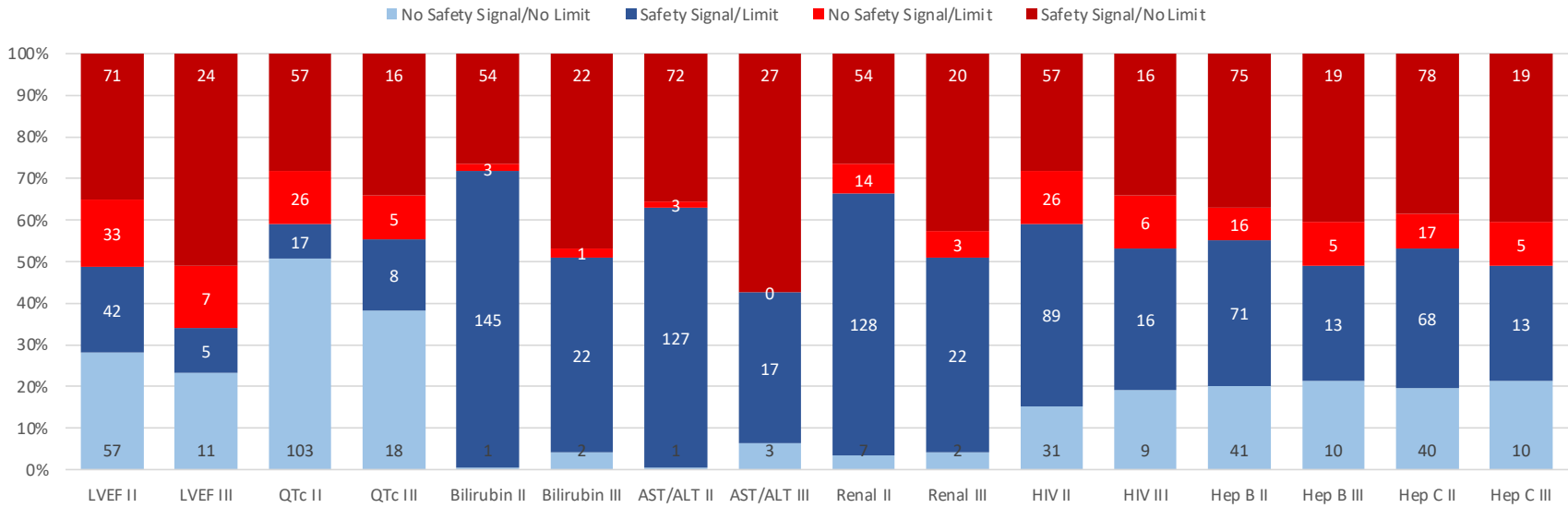
*Trials were reviewed for the listed exclusions in order from top to bottom; trials may have had more than one reason for exclusion but are categorized based on the first exclusion category listed.

Supplemental Figure 2. Violin Plots of Variability for Measures Associated with Enrollment Criteria. All x-axes represent density.



ECOG: Eastern Cooperative Oncology Group; WBC: white blood count; L: liters; ULN: upper limit of normal; AST/ALT: aspartate transaminase / alanine aminotransferase; QTc: corrected QT interval; %: percentage

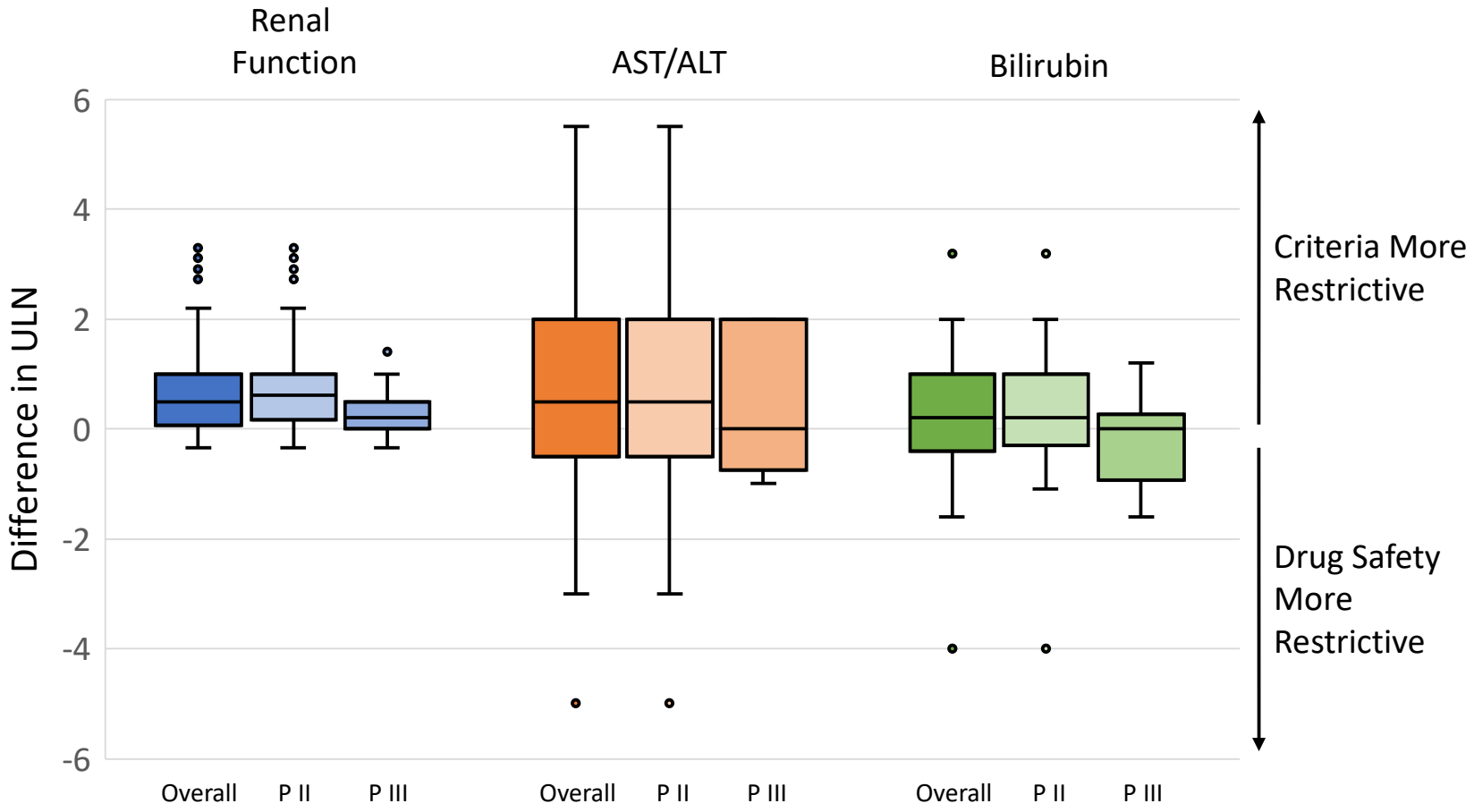
Supplemental Figure 3. Concordance and discordance of eligibility criteria with drug safety signals by trial phase.



Stacked bars show concordance (blue) and discordance (red) of criteria with drug safety signals. For criteria with associated measures, box and whisker plots show median and interquartile ranges based on the presence (red) or absence (blue) of a drug safety signal; outlier points are shown individually. The label "II" refers to phase II trials and "III" to phase III trials.

LVEF: left ventricular ejection fraction; QTc: corrected QT interval; AST/ALT: aspartate transaminase / alanine aminotransferase; HIV: human immunodeficiency virus; Hep: hepatitis

Supplemental Figure 4. Differences between renal and hepatic function limits suggested by drug safety profiles and enrollment criteria stratified by trial phase.



Each box plot shows the difference between the limits suggested by the most conservative safety profile suggested by the drug review and by the trial's enrollment criteria. Positive criteria indicate the trial criteria is more restrictive than the drug safety profile.

AST/ALT: aspartate transaminase / alanine aminotransferase; ULN: upper limit of normal; P II: phase II; P III: phase III