Supplement

Table 1: Performance Status Inclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
ECOG 0	1				
ECOG 0-1	8	3	1	1	
ECOG 0-2	53	36	33	4	15
ECOG 0-1, include 2 if due to disease	1				
ECOG 0-3	1	2	16		
ECOG 0-2, 3 allowed if due to disease			1		
If <75 YO, ECOG 0-3; If ≥75 YO, ECOG 0-2		2			
ECOG 3-4			1		
KPS ≥ 60	3	3	1		
WHO Performance Status 0-2			1		
WHO Performance Status 0-2 if ≥ 75 YO			1		
WHO Performance Status 0-3 if ≥ 60-74 YO			1		
Zubrod Performance Status 0-2			1		
Adequate					1

Table 2: Patient Age Inclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
18 or older	37	34	30	1	10
20 or older	1	1	1		
21 or older			1		
18-65		1		1	
18-70	1	1			
18-75	2	1	1		
<65				1	
≥60	1	2	3	1	

Table 3: MDS Risk Group Inclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
IPSS ≥ 1.5	1	4			
IPSS: ≥3			1		
IPSS: >4.5			1		
IPSS: very low, low, intermediate					
IPSS: low or intermediate-1	3	2	3	1	2
IPSS: low, intermediate-1, intermediate-2, high	1				
IPSS: intermediate			1		
IPSS: intermediate, high risk	1	3	1		1
IPSS: intermediate, high, very high	1	1	1		
IPSS: intermediate-2			1		

IPSS: intermediate-2, high risk	4	3	4	1	
IPSS: intermediate-2, high, very high		1	1		
IPSS-R: 1.5-4.5				1	
IPSS-R≤ 3			1		
IPSS-R >3	1	2	1		1
IPSS-R ≤ 3.5	1		8		
IPSS-R ≥ 3.5	1	4	1		1
IPSS-R ≥ 4			1		
IPSS-R ≤ 4.5			1		
IPSS-R ≥ 4.5	2		3		
IPSS-R: very low, low, intermediate	3	2	6		3
IPSS-R: intermediate					1
IPSS-R: intermediate or high	1	1			
IPSS-R: intermediate to very high	7	6	4		4
IPSS-R: intermediate-2 or higher			1		
IPSS-R: high	1	2			
IPSS-R: high or very high	6		2		
IPSS-R: very low, low, high, very high	1				
IPSS-R: any risk	2	1	1		

Table 4: Prior Treatments Inclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
No prior cytotoxic therapy or HMA		4	2	1	2
No prior lenalidomide			1		
No prior vorinostat		1	1		
No prior targeted therapy					1
No prior investigational agent				1	
No prior anti-PD-1, anti-PD-L1				1	
No prior cytarabine			1		
No prior midostaurin				1	
Refractory/intolerant/ineligible for ESA	6	1	7		3
Received at least 8 weeks of ESA				1	
Refractory after 12 weeks of ESA			1		
Refractory to TPO-RA	1				
Refractory/intolerant/contraindication for luspatercept	1		1		
Ineligible/refractory to HMA	7	4	5		2
No response/progression/relapse after 3 cycles of HMA	1				
No response/progression/relapse after 4 cycles of HMA	7	9	5		
No response/progression/relapse after 6 cycles of HMA		2	6		
Relapse/refractory after 6 cycles of azacitidine or 4 cycles of decitabine	2		2		1
Minimum of 2, maximum of 8 prior DNMTi cycles		1			

Refractory to 2 cycles of HMA+venetoclax			2		
Prior cytarabine dose >20 mg/m^2/day			1		
Refractory to lenalidomide	4	1	2		1
Refractory to lenalidomide after at least 16 weeks					1
1 prior IDH inhibitor	1				
Refractory/intolerant/ineligible for standard approved MDS treatments	6	3	4		
1 prior therapy	1	1	1		
1 or 2 prior therapies	1	2			
2-3 prior therapies		1			
1-4 prior therapies	1	3			

Table 5: Expected Survival Inclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
At least 4 weeks	1	1	1		
≥ 6 weeks	1				
> 2 months	2	1			
≥ 12 weeks	16	12	6	1	1
≥ 4 months	1				
> 6 months		1			1
≥ 12 months	1				

Table 6: Prior Transplantation Status Inclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
Not a candidate/unable/unwilling to receive	10	1	8		3
Transplant candidate	1		3	2	3
Prior transplant required if eligible		1			
Prior transplant allowed	3	1	2	2	
No prior transplant allowed			2		
At least 8 weeks post HSCT	1				
At least 3 months post HSCT	2				
At least 6 months post HSCT	2		1		

Table 7: Bone Marrow Blasts Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
<5%		1	6	2	4
≥ 5%	3	1	3		1
<10%	2				
>10%	2	2	3		
10-19%	1		1		
<20%	2	3	2		2
Blast count ≤ 30 × 10^9 cells/L	1	1			

Table 8: Transfusion Requirements Inclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
No RBC transfusion dependence			3		1
No RBC transfusions within 8 weeks			1		
No transfusion dependence, <3 RBC transfusions in 16 weeks		1	1		
RBC transfusion permitted				1	
RBC transfusions required (no specific thresholds)	3				1
At least 1 unit in two consecutive 8 weeks					1
1-3 units in 8 weeks			1		
RBC transfusion dependence, 1 unit in 8 weeks			1		
Low RBC transfusion burden, <3 units in 16 weeks			1		
Low RBC transfusion burden, 3-7 in 16 weeks, <4 in 8 weeks			2		
RBC transfusion dependence, transfusion within 28 days	1				
RBC transfusion dependence, ≥2 units		1			
RBC transfusion dependence, ≥2 units/month for 2 months					1
RBC transfusion dependence, ≥2 units/month for 3 months	1				
RBC transfusion dependence, ≥2 units in 8 weeks			1		
RBC transfusion dependence, ≥2 units/8 weeks for minimum of 16 weeks		2	2		1
RBC transfusion dependence, ≥3 units over 16 weeks	1	2	1		
High transfusion burden, ≥4 units over 8 weeks			1		
High transfusion burden, ≥8 units over 16 weeks, >4 in 8 weeks			2		
High transfusion burden, ≥8 units over 16 weeks, >4 in 8 weeks for 16 weeks				1	
<4 RBC transfusions over 4 months			1		
2-4 units over 8 weeks					1
2-6 units over 8 weeks					1
Platelet transfusion dependence			1		
Platelet transfusion dependence, 2 units/month for 3 months	1				
Not refractory to platelet transfusions		2	1		

Table 9: Washout Periods Inclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
Should not have received standard chemotherapy within 1 week of administration of study drug	1				
At least 1 week from cytotoxic or non-cytotoxic (immunotherapy) agents.		1			
Off all other treatments for MDS for at least 2 weeks			1		
≥ 2 weeks from prior cancer treatment			1		
>2 weeks from hematopoietic growth factors			2		
≥ 2 weeks from prior chemotherapy	2	1	2		

≥ 2 weeks from targeted therapy		1			
≥ 2 weeks from other investigational cancer therapy	2		1		
≥3 weeks from HMA			1		
Completed any chemotherapy or biologic therapy specific to their myeloid neoplasm ≥ 2 weeks or 5 half-lives (whichever is longer)	1				
At least 2 weeks for cytotoxic agents or at least 5 half-lives for cytotoxic/noncytotoxic agents.		2			
An investigational oral agent within 2 weeks or 5 half-lives (whichever is shorter).	1				
Previous cytotoxic chemotherapy must have been completed at least 3 weeks			1		
No HMA use within 4 weeks					3
No cytotoxic chemotherapy within 4 weeks				1	
≥ 4 weeks from other investigational anticancer therapy	1				
An investigational biologic or an investigational device within 4 weeks or 5 half-lives (whichever is longer)	1				
Prior therapy must have been completed >4 weeks or, if known, ≥ 5 half-lives of the prior agent (whichever is shorter) prior to treatment		1			
No treatment with G-CSF, GM-CSF, or other hematopoietic growth factors within one month		1	3		1
No ESA use within 4 weeks					3
Lenalidomide must have been discontinued ≥ 4 weeks prior to date of screening			1		1
No ESA use within 8 weeks					1
Prior treatment with chimeric antigen receptor T cells (CAR-T cells) should be discontinued for at least 12 weeks after initial dosing		1			
Off immunosuppression for 2 weeks	1			1	
No hormonal therapy for any kind of within 2 weeks prior to participating in this study		1			
No strong inducers/inhibitors of CYP3A4 within 2 weeks	1		1		
No corticosteroids, interferon or retinoids within one month prior to study		1			
No treatment with organic anion transporting polypeptide (OATP) and breast cancer resistance protein (BCRP) inhibitors within 14 days prior	1				

Table 10: Baseline Platelet Count Inclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
Transfusion refractory, platelets<10K with transfusion		2			
>10K without significant bleeding, transfusion allowed	1				
>10K	1				
≥ 20K		1			
≥ 20K, transfusions allowed	1	1			
<30K			1		
<30K or significant bleeding/bruising and <50K	1				

>30K	1		3		1
>30K (transfusion acceptable)					
<50K		1	2		
>50K, without transfusions					1
>50K	1				
≥75K			1		
≤ 75K	1		1		
<100K		1			
<100K with evidence of bleeding			1		
>450K or <30K			1		
Sustained thrombocytopenia for at least 21 days					1

Table 11: Cardiac Disease Exclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
Significant, active cardiac disease	5	3	4		
Active cardiac disease in last 6 months					4
Current or prior heart condition	1				
Uncontrolled hypertension	9	6	6		3
Uncontrolled hypotension					1
Change in antihypertensive within 6 weeks from consent		1			
History of hypertensive crisis or hypertensive encephalopathy	1				
SBP ≥ 180 mmHg, DBP ≥ 100 mmHg despite adequate treatment		3			
SBP ≥ 180 mmHg, DBP ≥ 95 mmHg	2		2		
SBP ≥ 140 mmHg, DBP ≥ 90 mmHg		1			
SBP ≥ 150 mmHg, DBP ≥ 100 mmHg		1			
SBP ≥ 160 mmHg, DBP ≥ 100 mmHg despite adequate treatment	1		1	1	
SBP ≥ 160 mmHg, DBP ≥ 90 mmHg despite adequate treatment		1			
SBP ≥ 160 mmHg, DBP ≥ 110 mmHg despite adequate treatment			1		
SBP ≥ 150 mmHg, DBP ≥ 100 mmHg despite adequate treatment	1				1
SBP ≥ 150 mmHg, DBP ≥ 80 mmHg despite adequate treatment	1				
SBP ≥ 135 mmHg or DBP ≥ 85 mmHg	1				
Diastolic BP > 100 mmHg		1	3		1
Relative hypotension (<90/60 mmHg)	1				
EF <35% within 6 months			1		1
EF<40%		2	1		
EF<40% within 28 days of start		1	1		3
EF<45%	4	1			
EF <50%	6	5	3		

NYHA Class ≥ II	7	5	2	1	
NYHA Class III/IV	15	17	19		7
NYHA Class IV		1	2		
Uncontrolled heart failure	16	7	8	1	3
≥ grade 2 CHF	1				
Moderate/severe aortic or mitral stenosis or other valvulopathy		1			1
Uncontrolled arrythmia	23	17	24	1	2
Arrythmia associated with hemodynamic instability					1
Uncontrolled atrial fibrillation	2	2			
Atrial fibrillation within prior 2 weeks		3			
Persistent atrial fibrillation (continuous for 6 months)	1				
Atrial fibrillation requiring cardioversion in last 4 weeks	2	1			
Atrial fibrillation requiring ablation in last 6 months	1	1			
Acute coronary syndrome in 6 months	1		2		
Unstable angina	29	22	21	1	7
History of MI	3	1	4	1	
Recent MI	1				
≥ grade 2 MI	1				
MI in 3 months	1	1	4		1
MI in 6 months	11	13	15		6
MI in 12 months	1	3			
CABG or peripheral artery bypass surgery within 3 months		1			
CABG or stent within 6 months	4	1	2		
Myocarditis	1				
Clinically significant pericardial disease	1	1	1		
Symptomatic cardiomyopathy	1	1	2		
Amyloidosis		1			
QTc ≥ 440 ms for males, QTc ≥ 450 ms for females	1				
QTc ≥ 450 ms	2	12	2		2
QTc ≥ 470 ms	3	4	1	1	1
QTc ≥ 470 ms for females, QTc ≥ 450 ms for males	5		1		1
QTc ≥ 480 ms for females, QTc ≥ 450 ms for males		1			
QTc ≥ 480 ms	7	1	4		
QTc ≥ 500 ms	1	1	3		
Congenital long QT	2	7	3	1	
Family history of long QT	2	3	2	1	5
History of QT prolongation or torsades		1	2		
Receives drugs with potential to prolong QTc or cause torsade de pointes	4	1			

Implantable pacemaker or automatic implantable cardiac defibrillator				1	
Family history of sudden unexpected death		1		1	1

Table 12: Uncontrolled Infection Exclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
Active uncontrolled infection	32	18	21	2	7
Uncontrolled infection requiring hospitalization					1
Active uncontrolled infection within 7 days	1				
Active uncontrolled infection within 2 weeks	1				
Severe infection	2	1	1		
Life threatening infection	1		1		
Severely infected within last 4 weeks		1			
CTCAE grade 2 infection	2	1			
Active infection not improved with appropriate therapy	4	4	9	1	
Requiring therapy	4	6	2		1
Infection requiring therapy within 7 days		1			
Requiring oral antibiotics within 14 days			1		
Requiring IV antibiotics	1	1	1	1	
Requiring IV antibiotics within 28 days			1		
Frequent hospitalizations for infections (average >1 hospitalization per month in last 6 months)		1			
Active pulmonary TB	3			1	
History of active pulmonary TB				1	
Active or latent TB		1	1		
Syphilis infection	1	1			
Active COVID-19 infection	1	2			
Fungal disease stable for 2 weeks				1	
Bacteremia without negative blood cultures				1	
Fever within 48 hours prior to first dose			1		
Unexplained fever during screening	4	1			
Chronic Infection	1				

Table 13: Creatinine or Creatinine Clearance Exclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
Creatinine within normal institutional limits permitted		1			
Cr ≥ 1.5 mg/dL	3	2	4		
Cr ≥ 1.8 mg/dL		2			
Cr ≥ 2.0 mg/dL	2	1	6	1	
Cr ≥ 2.5 mg/dL			1		
Cr ≥ 1.5x ULN	8	6	6		2
Cr ≥ 2x ULN	4	5	5		1
Cr ≥ 2.5x ULN		1	1		

> Grade 1 serum creatinine	1				
CrCl ≤ 10 ml/min			1		
CrCl ≤ 20 ml/min			1		
CrCl ≤ 30 ml/min	9	8	11		4
CrCl ≤ 40 ml/min	3	4	5		5
CrCl ≤ 45 ml/min	2	1	5		
CrCl ≤ 50 ml/min	4	5	2	1	1
CrCl ≤ 60 ml/min	10	6	4		1
CrCl ≥ 1.5x ULN	2				
CrCl ≥ 2x ULN			1		
CrCl ≥ 2.5x ULN				1	
Dialysis			1		

Table 14: Liver Function Tests Exclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
Abnormal AST/ALT/Total bilirubin			1		1
No severe impairment					
ALT/AST ≥ 1.5 x ULN	1	2	1		
ALT/AST ≥ 2x ULN	2		5		1
ALT/AST ≥ 2.5x ULN	11	8	12	3	1
AST/ALT ≥ 3x ULN	22	19	20		8
AST/ALT ≥ 4x ULN					
AST/ALT ≥ 5x ULN	1		1		
Bilirubin > ULN	1		1		1
Grade 1 total bilirubin	1				
Bilirubin ≥ 1.8 mg/dL		2			
Bilirubin ≥ 3 mg/dL	1				
Bilirubin ≥ 35 umol / L	1		1		
Total bilirubin ≥ 1.5x ULN	21	12	15	1	3
Total bilirubin ≥ 2x ULN	11	7	15	1	1
Total bilirubin ≥ 2.5x ULN	1	4	2		3
Total bilirubin ≥ 3x ULN		5	4	1	2
Direct bilirubin ≥ 2x ULN				1	

Table 15: Pregnancy/Breastfeeding Exclusion Criteria

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
Breastfeeding	39	26	36		9
Unwilling to avoid breastfeeding during and 2 months after study		1			
Pregnancy	37	33	38	1	7
Expecting to conceive/fertility planning	3	1			1
Women of childbearing potential who do not practice contraception during the duration of the trial		3			

Males/Females who do not use effective contraception during the trial	5	4	11		
Male/Females who do not avoid pregnancy for 30 days after last dose on trial			1		
Potentially fertile males/females who have not agreed to avoid pregnancy during and 3 months after trial	3		4		
Unwilling to avoid pregnancy during and 4 months after the trial			1		
Females of childbearing potential who do not use contraception for 6 months after study drug			1		
Males who will not use contraception for 3 months after study and woman who will not use for 6 months after study	1				
Males who will not use contraception for 4 months after study and woman who will not use for 6 months after study		1			

Table 16: Chronic Viral Illness Exclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
HIV	32	35	29	1	6
Exclude uncontrolled HIV	1				1
Eligible if controlled with HAART			1		
Exclude HIV with CD4+ T cell count <350 cells/uL initiation of antiretroviral therapy within 4 weeks, OR AIDS related infection within 12 months	1				
Exclude HIV with CD4+ T cell count <350 cells/uL,					1
Opportunistic infection within last 12 months					1
HIV with undetectable viral load			1		
HIV with undetectable viral load for 6 months			1		
Hepatitis B and C					1
Active Hep B	26	18	14		3
Chronic Hep B	3	1	1		2
Hep B surface antigen positive	6	5	7		1
Hep B surface antigen and core antibody positive			1		3
Active Hep C	27	17	17		2
Chronic Hep C	2	1	1		
Uncontrolled Hep B and C					1
Hep C RNA detected	5	3	5		
Hep B/C if requiring treatment			2	1	
Hep B/C *allowed* if undetectable viral load	6	13	5		
Hep B/C *allowed* if on viral suppression	1	1	1		
Cured HCV *allowed*	2		1		1

Table 17: Other Malignancies Exclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
Prior malignancy	2	3			
Concurrent active malignancy	9	1	5	1	4
Advanced hepatic malignancy excluded					1

Diagnosis of other malignancy within the previous 6 months			2		
Diagnosis of other malignancy within the previous 12 months	1		2		
Concurrent malignancy requiring anticancer systemic treatment	6	6	9		1
Systemic anticancer treatment within 24 months prior		1			
Risk of clinical relapse within 12 months			1		
Active malignancy in 12 months	6	5	3		1
>30% risk of relapse of second malignancy in 1 year					3
Free for ≤2 years	10	10	4	1	2
Free for ≤3 years	7	1	2	1	3
Free for ≤ 5 years	3	2	8		1
Completed therapy with curative intent at least 6 months prior *permitted*		1	2		
Low risk of recurrence *permitted*	1				
Any in situ *permitted*	7	2	4		1
Basal/SCC skin *permitted*	20	15	23	1	9
in situ cervix *permitted*	17	10	15	1	8
In situ breast *permitted*	8	8	9		7
Localized prostate *permitted*	4	4	9		8
Maintenance hormone therapy for breast or prostate *permitted*	5	6	2		
Superficial bladder *permitted*	1	2	1		
Monoclonal gammopathy of undetermined significance *permitted*	1				
Monoclonal B cell lymphocytosis *permitted*	1				
Adequately treated stage 1 or 2 cancer in complete remission *permitted*	1				
Permitted if considered cured	1				

Table 18: Washout Periods Exclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
GCSF or GMCSF within 7 days	3				
ESA or thrombopoietin mimetics within 7 days or 5 half-lives, whichever is longer	1				
Any therapy or experimental agent within 7 days	1	1			
Any therapy or experimental agent within 7 days or 5 half-lives, whichever is longer	1				
ESA, thrombopoietin mimetics, GCSF, GM-CSF, M-CSF within 2 weeks or 5 half-lives	1				
Use of GCSF within 14 days	1	2	4		
Use of ESA within 14 days	1	1	3		
Luspatercept within 14 days			2		
Use of chemotherapeutic agents with 14 days	1	2	5		
Chemotherapy or monoclonal antibodies within 14 days or 5 half-lives	1				
Chemotherapy within 14 days or 5 half-lives, whichever is shorter		1			

Monoclonal antibody within 14 days or 5 half-lives, whichever is shorter		1			
Targeted small molecule therapy within 2 weeks			1		
Small molecule investigational agent within 14 days or 5 half-lives		1			
Targeted small molecular therapy within 14 days or five half-lives (whichever is shorter)					
Immunotherapy within 2 weeks		1	1		
Immunotherapy within 14 days or 5 half-lives, whichever is shorter		1			
HMA, LDAC or venetoclax within 14 days			2		
IMiD within 14 days			1		
Lenalidomide within 14 days			1		
Oral TKIs within 2 weeks or 5 half-lives, whichever is longer	1				
Agents other than hydroxyurea to control blast counts within 14 days	1				
Agents other than hydroxyurea to control blast counts within 14 days or 5 half-lives, whichever is shorter	1				
Any antineoplastic therapy within 14 days	8	5	3		
Antineoplastic therapy with 14 days or 5 half-lives	5				
Antineoplastic therapy with 14 days or 5 half-lives, whichever is shorter	2	1			
Antineoplastic therapy with 14 days or 5 half-lives, whichever is longer	1				
Use of investigational agent within 14 days	5	2	4		
Any investigational drug within 2 weeks or 5 half-lives, whichever is shorter	2	1			
Any investigational drug within 2 weeks or 5 half-lives, whichever is longer	2			1	
EPO, G-CSF, or GM-CSF within 21 days					1
Chemotherapy within 5 half-lives or 3 weeks prior, whichever is longer	1				
Anticancer therapy within 3 weeks	1	1			
Investigational agent within 3 weeks	3		1		
Use of investigational drug within 5 half-lives or 3 weeks, whichever is shorter		1			
Use of investigational drug within 5 half-lives or 3 weeks, whichever is longer	1				
Any prior systemic anticancer treatment within 3 weeks or 5 half-lives		1			
TSA within 28 days	1		1		1
ESAs within 28 days	1	1	5	1	1
Growth factors within 28 days	1	2	4		1
Cytotoxic chemotherapeutic agent within 28 days	2	2	1	1	1
HMA within 4 weeks		1			
Targeted agent within 28 days					1
Biological agents within 28 days	1				

Agents targeting IL-1 within 28 days		1			
Anti-CD47 targeting agent or CD40 agonist within 28 days	1				
Investigational agent within 28 days	3	4	2		1
Use of investigational drug within 5 half-lives or 4 weeks, whichever is longer	1		5		2
No anticancer therapy within 28 days	2	3			
IDH inhibitor within 30 days	1				
GCSF within 30 days			3		
Thrombopoietin receptor agonists within 1 month			1		
Lenalidomide within 30 days			1		
Cytokine therapy within 4 weeks	1		1		
CAR-T within 28 days	1				
Cellular therapy within 4 weeks	1				
Agents targeting CD33, CD123 or CD70 within 4 weeks		1			
Prior investigational agent within 30 days	5	2	5	1	2
Chemotherapy within 4 weeks		1			
Chemotherapy within 5 half-lives or 4 weeks prior, whichever is longer	1				
Immunotherapy within 4 weeks		2			
Any immunotherapy within 5 half-lives or 4 weeks prior, whichever is longer	1				1
Antineoplastic, biological or chemotherapeutic agents within 4 weeks or 5 half-lives, whichever is shorter	2		2		
Antineoplastic agents within 4 weeks or 5 half-lives, whichever is longer	1				
Use of cytotoxic chemotherapeutic agent within 5 weeks					1
Use of corticosteroid within 5 weeks except on a stable or decreasing dose for >1 week prior					1
Less than 5 half-lives for small molecule targeted drug therapy	1				
Investigational agent within 5 half-lives			1		
Anticancer treatment within 5 weeks			1		
Use of investigational drug within 5 half-lives or 5 weeks, whichever is longer					1
Immunotherapy within 42 days	1				
Lenalidomide within 60 days					1
GCSF within 8 weeks					1
EPO within 8 weeks		1			
Investigational drug within 8 weeks					1
Luspatercept within 8 weeks					
Lenalidomide within 8 weeks					3
IMiD within 8 weeks			1		
HMA within 8 weeks			1		1
Cytotoxic agent within 8 weeks					1

Vitamin B12 therapy within 8 weeks			1		
Luspatercept within 65 days					
Investigational agent within 3 months			1		
Disease-modifying therapy within the last 3 months			1		
CAR-T within 3 months	2				
CD137 agonist or other immune activating therapy such as anti-CD40 antibody within the last 3 months	1				
ESA or GCSF in the last 16 weeks					
Immune checkpoint inhibitors within 4 months		1	1		
Monoclonal antibody within 4 weeks	2		1		
Investigational monoclonal antibody within 6 months			1		
Active treatment for at least 24 weeks (including but not limited to immunotherapy or targeted therapy)				1	
Inducer/inhibitor of CYP3A within 3 days		2	1		
P-glycoprotein inducer within 3 days		1			
H2 receptor inhibitor, proton pump inhibitor, or acid suppressor within 3 days	1	1			
P-glycoprotein within 5 days or 5 half-lives			1		
P-glycoprotein inducers/inhibitors within 7 days		1			
Corticosteroid within 7 days	1				
PPI within 7 days	1				
Immunosuppressive therapy with 7 days	3		1		
Strong/moderate inducers/inhibitors of CYP3A4 within 7 days	3	4	1		
Strong/moderate inducers/inhibitors of CYP3A4 within 7 days or 5 half-lives, whichever is shorter	1				
Corticosteroid within 14 days	2	1			
Androgenic hormones within 14 days					1
Strong/moderate inducers of CYP3A4 within 2 weeks	1	1	1		2
Strong CYP3A4 inducers within 14 days or 3 half-lives, whichever is shorter		1			
Cytarabine, oral fluorouracils or endocrine therapy within 2 weeks	1				
CYP3A4 inducers within 5 half-lives			1		
Significant metabolic enzyme inducers within 14 days	2				
Immunosuppressive therapy within 14 days	6	2	3		
Strong/moderate inducers of CYP3A4 within 3 weeks (5 weeks for phenobarbital)			1		
Calcineurin inhibitor within 4 weeks	2				
Proprietary Chinese medicines with anti-tumor indications within 4 weeks	1				
Immunostimulatory agent within 4 weeks	1				
Immunosuppressive therapy within 4 weeks	4				1
Immunostimulatory agent within 6 weeks or 5 half-lives, whichever is shorter			1		
Immunosuppression within 2 months	1				

Nitrosourea, mitomycin or monoclonal antibody within 6 weeks	1				
Drugs at risk of causing prolonged QTc or TdP within 5 half-lives	1	1			
Drugs at risk of causing prolonged QTc or TdP within 5 half-lives or 2 weeks		1			
Statins within 5 half-lives	1	1			
Digoxin within 5 half-lives		1			
Paclitaxel, warfarin, phenytoin, S-mephenytoin, thioridazine, theophylline and tizanidine within 5 half-lives		1			

Table 19: Prior Treatments Exclusion Criteria

Exclude	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
Prior MDS therapy	2		3		
Prior MDS therapy with intensive chemotherapy			5		5
Current systemic treatment for low risk MDS			1		
Prior treatment other than growth factors			1		
Not yet received or deriving benefit from ESA		1			
Prior ESA			1	1	
Prior luspatercept		1	5		1
Prior sotatercept		1	4		1
Prior lenalidomide		1	4	1	4
More than 2 lines of prior non-intensive therapy			1		
Prior therapy with disease modifying agents for MDS	1		3		
Prior HMA	1	5	13	3	7
≥4 cycles with HMA	1				
Received less than 2 cycles of DNMTi therapy		1			
Prior exposure to the investigational oral formulation of decitabine, or other oral azacitidine derivative at any time in the subject's prior history.			1		
No response to HMA/venetoclax	1		1		
Prior therapy other than HMA or LDAC			2		
Prior therapy other than HMA or lenalidomide					1
Prior BCL2 inhibitor		4	1		
Prior venetoclax		2	1		
Prior anti-CD47 or SIRPalpha Ab	4	5	2		2
Prior CD137 antibody	1				
Prior PD1 or PDL1 or PDL2 antibody therapy	2	1	5		
Prior anti-CTLA4	2		2		
Prior histone deacetylase inhibitors	1	1			
Prior CAR-T	2	1			
Prior canakinumab			1		
Prior cytarabine at dose >20 $mg/m^2/day$			1		

Prior treatment with a FLT3-directed bispecific molecule, or a FLT3-targeted antibody	1				
Prior TIM-3 directed therapy	1	1	2		
Prior CD38 therapies			1		
Prior anti-CD123 therapy	1				
Prior CDK8-targeted therapy	1				
Prior HH inhibitor	1				
Prior systemic MDM2-p53 inhibitor treatment	1	1			
Prior mdm2 or mdm4 inhibitors combined with TIM-3 inhibitors or Bcl-2 inhibitors	1				
Prior belinostat or pevonedistat	1	1			
Prior eltrombopag, romiplostim, or other TPO-RA			1		
Prior imetelstat				1	
Prior BH3 mimetic	1		1		
Prior IDH inhibitors		1	1		
Prior ivosidenib		1			
Prior IDH2 inhibitor			1		
Prior DHODH inhibitor	1				
Prior pyruvate kinase activator			1		
Prior quizartinib		1			
Prior gilteritinib		2			
Prior PARP inhibitor			1		
Prior roxadustat or another hypoxia inducible factor prolyl hydroxylase					1
More than 3 lines of therapy for MDS		1	1		

Table 20: Gastrointestinal Disorder Exclusion Criteria

	Phase I	**Phase I/II**	**Phase II**	**Phase II/III**	**Phase III**
Gastrointestinal disease	2		2		1
Severe gastrointestinal disease		1			
Wilson’s Disease or other copper metabolism disorder	1				
Malabsorption syndrome, Short Gut Syndrome, absorption impairment	9	9	3		3
Limited ingestion/absorption of oral drug	11	6	3		3
Peptic Ulcer Disease or Gastritis	3	1		1	
Diverticulitis	1				
Chronic diarrhea	3				
Hepatic cirrhosis	3		5		1
Child Pugh B or C cirrhosis		1	3		
Active liver disease	6	4	4		2
Acute viral hepatitis			1		
Portal hypertension			1		
Acute liver failure			1		

Chronic liver disease	1		1	1	
Severe liver disease	1				
Previous drug induced liver injury	1				
Dysphagia	3	6	1		2
Gastroparesis	3	2	1		2
IBD	4	4	2		1
Acute pancreatitis	1				
Nausea/vomiting	3	2			
Intestinal obstruction	1	2			
Liver malignancy (including metastases)	1	1	1		
Bowel resection	1	2			
Resection of stomach or small intestine	1	3	2		1
Lactose intolerance		1			
Celiac Disease		1	1		1
Active or chronic gastrointestinal bleeding					1

Supplemental Table 21: List of Drugs Included in Concordance Analysis

6MW3211	CLN-049	Fadraciclib (CYC065)	Olutasidenib (FT-2102)
AB8939	CTX-712	FHD-286	Omacetaxine
ABD-3001	CYAD-02	Fludarabine	Pembrolizumab
Aclarubicin	Plogosertib (CYC140)	Fostamatinib	Pevonedistat (TAK-924, MLN4924)
AG-946	Cyclophosphamide/ Endoxan	Glasdegib	QLF32101
Alrizomadlin (APG-115)	Cytarabine	HuMax-IL8 (BMS-986253)	Quizartinib
Anzurstobart (CC-95251)	Danazol	Ivaltinostat (CG200745 PPA)	R906289 Monosodium
APVO436	Daratumumab	Ivosidenib	Rosuvastatin
Aspacytarabine (BST-236)	Darbepoeitin alfa	Lemzoparlimab (TJ011133)	Roxadustat (FG-4592)
Atorvastatin	Daunorubicin	Lenalidomide	Ruxolitinib
Azacitidine	Daunorubicin-cytarabine (liposome encapsulated)	Ligufalimab (AK117)	RVU120
BC3402	Decitabine	Lisaftoclax (APG 2575)	Sabatolimab (MBG453)
Belinostat	Defactinib (PF-04554878, VS-6063)	LP-108	Seclidemstat (SP-2577)
Bemcentinib (BGB324, R428)	Deferasirox	Luspatercept	SHR-1702
Bexmarilimab (FP-1305)	DFV890	Luxeptinib (CG-806)	Sirolimus
Bezafibrate	DSP107	LY3410738	SL-172154

Bisantrene Dihydrochloride	Durvalumab	LYT-200	Sodium stibogluconate
BLEX 404	E7820	Magrolimab	Sodium Valproate
BS HH 002.SA	Edetate calcium disodium	MAX-40279-01	Sonrotoclax (BGB-11417)
BTX-A51	Eltanexor (ATG-016, KPT-8602)	Medroxyprogesterone	Spartalizumab (PDR001)
Busulfan	Eltrombopag	Metformin	Succimer
BXCL701	Emavusertib (CA-4948)	Midostaurin	SX-682
Canakinumab	Enasidenib	Mitoxantrone	Tamibarotene
CB-5339	Entinostat	MP0533	Tapotoclax (AMG 176)
CC-91633	EP0042	NC525	TQB2618
Cedazuridine and azacitidine (ASTX030)	Epoetin alfa/Eprex	Nerofe	TAK-243
Cedazuridine and decitabine	Etavopivat (FT4202)	NIS793	Venetoclax
Ceralasertib (AZD6738)	Etoposide	Nivolumab	Vitamin C
CFI-400945	Everolimus	NTX-301	Vorinostat
Cladribine	Evorpacept (ALX148)	Olaparib	Vosaroxin (SNS-595, voreloxin)
			XZB-0004

Survey Results

Q1 Name

Answered: 22 Skipped: 0

Q2 Upper Age LimitsBackground: Several trials set upper age limits in the eligibility criteria for this analysis. The icMDS asserts that an upper age limit should be avoided given MDS is a disease mostly of older adults, and this restriction profoundly impacts the generalizability of results. Not all pharmacotherapeutic outcomes that can occur in older patients with MDS can be predicted from trials with upper age restrictions. Furthermore, any exclusion of patients based solely on age is arbitrary since chronological age is not an adequate representation of biological age. A prior study evaluating a pooled patient database for patients with MDS found that patients who participated in trials were significantly younger than nonparticipants (23). Instead of imposing strict upper age limitations on trials, the icMDS encourages clinicians to utilize objective geriatric assessments for frailty and consideration of physiological age when assessing clinical trial candidacy for older adult patients. Recommendation: Upper age limits should be avoided.

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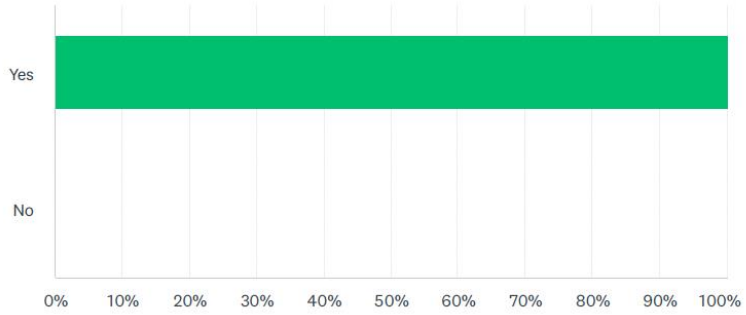

ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q3 Expected SurvivalBackground: Many studies in this analysis had eligibility criteria which required a certain minimum anticipated expected survival; the icMDS recommends avoiding this eligibility criterion. Instead, we recommend prioritizing investigator judgment of whether the patient may potentially benefit the trial (e.g. if the patient has another imminently terminal illness then he or she is is less likely to have the opportunity to benefit from a trial). Patients with MDS have limited therapeutic options resulting in a shorter life expectancy, and this generally should not prohibit them from potentially life-prolonging therapies. Indeed, post-HMA MDS has a life expectancy <6 months, but remains one of the greatest unmet treatment needs. It is well-supported in the medical community that life expectancy is an unnecessary and antiquated criterion because a judgment of life expectancy may be subjective and often incorrect. Other metrics including functional assessments may be more relevant than life expectancy when selecting qualifying study participants. We acknowledge that other terminal illnesses may preclude potential benefits from participation a clinical trial (particularly in patients with LR-MDS), and defer to investigator judgment on enrollment in these scenarios.Recommendation: Minimum expected survival should be avoided with instead prioritization of investigator judgment on whether a patient has the potential to benefit from the trial.

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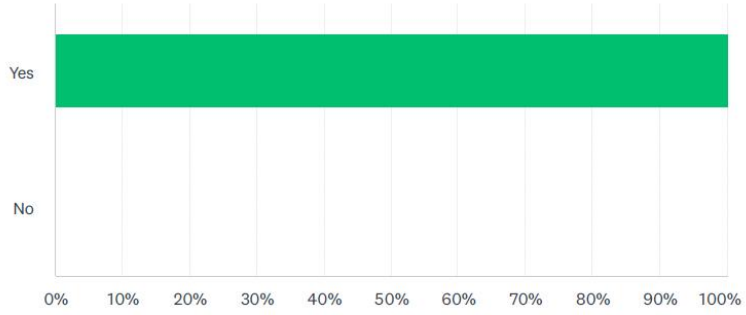

ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q4 Lower Limits for Platelets in HR-MDS TrialsBackground: A few studies focused on HR-MDS in this review exclude patients with platelet levels lower than a certain value (most commonly <50K/mcL). Patients with hematologic malignancies are expected to have hematologic abnormalities at study entry, particularly in HR-MDS. Inclusion criteria for trials focused on HR-MDS should avoid arbitrary lower limits for platelets. This is excessively restrictive given that the disease process itself is characterized by cytopenias. Lower limits for platelets may be more appropriate in LR-MDS trials depending on the therapy; however, we encourage avoiding lower limits in LR-MDS particularly in therapeutics without expected myelosuppression. We encourage language for appropriate transfusion support during the trial.Recommendation: Arbitrary lower limits on platelets threshold should be avoided in trials for HR-MDS.

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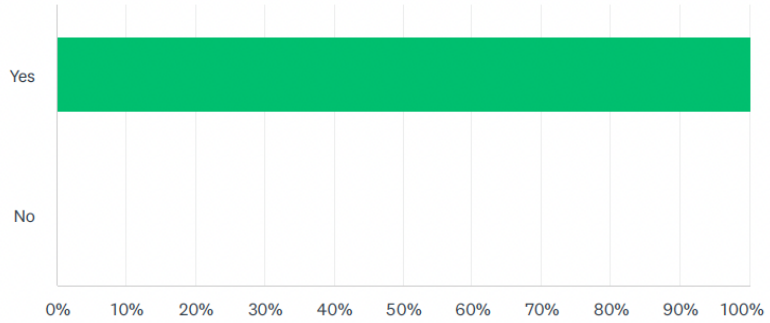

ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q5 Lower Limits for HemoglobinBackground: A few studies in this review excluded patients with hemoglobin levels lower than a certain value (most commonly <9 g/dl). Patients with hematologic malignancies are expected to have hematologic abnormalities at study entry, particularly in bone marrow failure diseases such as MDS. Inclusion criteria should avoid arbitrary lower limits for hemoglobin. This is excessively restrictive given that the disease process itself is characterized by cytopenias. Recommendation: Arbitrary lower limits on hemoglobin thresholds should be avoided.

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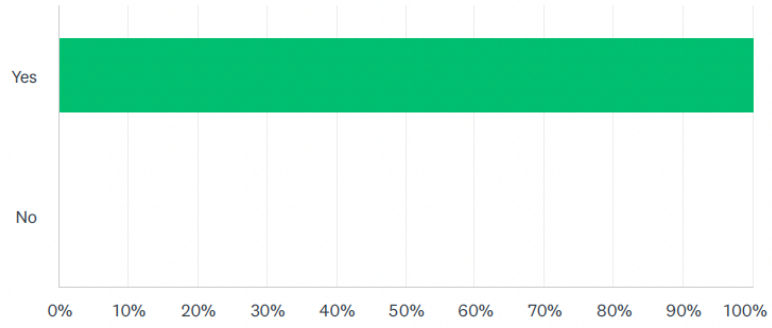

ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q6 Lower Limits for Absolute Neutrophil Count in HR-MDS TrialsBackground: A few trials in this review focused on HR-MDS exclude patients with an absolute neutrophil counts lower than a certain value (most commonly <500/µL). Patients with hematologic malignancies are expected to have hematologic abnormalities at study entry, particularly in HR-MDS. Inclusion criteria should avoid arbitrary lower limits for absolute neutrophil count. We acknowledge that consideration should be given to the specific therapy, and limits may be applicable to therapies with a particularly significant risk of neutropenia. However, absolute neutrophil count limits are often excessively restrictive given that the disease process itself is characterized by cytopenias. We similarly encourage avoiding lower limits in LR-MDS particularly in therapeutics without expected myelosuppression. Inclusion of patients should have language for appropriate supportive care and prophylaxis as a part of the trial.Recommendation: Arbitrary lower limits on absolute neutrophil count should be avoided in trials for HR-MDS.

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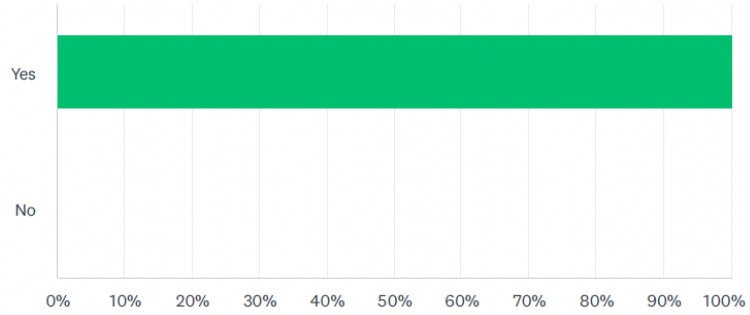

ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q7 Number of Prior TherapiesBackground: Several trials in this analysis restrict patients based on the number of lines of prior therapies (such as greater than 2 lines of therapy). Instead, we recommend that criteria should indicate specific prior exposure as appropriate. For example, it can be a criteria that all patients are required to have prior treatment with an HMA regardless of number of lines of therapy. The icMDS recommends against requirements for a specific number of prior therapies and instead focusing on whether or not there has been exposure to a prior class of therapy or a biosimilar, as relevant to the MDS subtype and risk. Recommendation: Requiring a specific number of prior therapies (such as greater than 2 lines of therapy) should be avoided.

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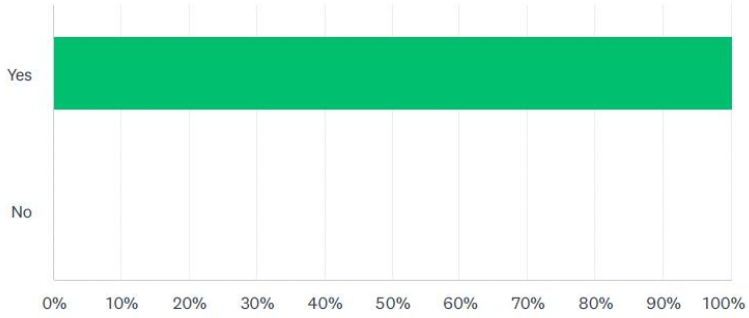
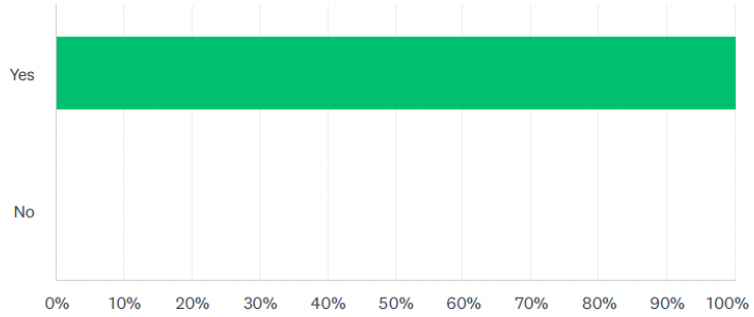


ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q8 Transplant CandidacyBackground: Many trials in this review incorporate criteria on transplant status. In April 2022, the FDA convened a panel of experts in MDS to discuss approaches to improve MDS drug development. This panel noted that a patient's potential for HSCT may be variably interpreted, which can lead to unnecessary exclusion in clinical trials (36). The icMDS similarly advocates that transplant candidacy should not be part of trial exclusion criteria, and may only be relevant when a study occurs peri-transplant by design. This is of interest because imbalance in enrollment between patients who are viewed as potentially transplant eligible and transplant ineligible may impact outcomes in clinical trials.Recommendation: Potential candidacy for stem cell transplant should be avoided (unless study is peri-transplant in design).

Answered: 22 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q9 Renal and Hepatic Laboratory Values in Phase II and III TrialsBackground: Both liver function and renal function tests were common eligibility criteria in this review, and concordance with drug safety signals was low. The icMDS stresses that laboratory parameters should be avoided in phase II and III studies once preliminary adverse events are understood in MDS and do not show safety signals. The icMDS urges concordance between renal and hepatic laboratory values in eligibility criteria and drug safety signals.For renal function, we recommend utilization of Modification of Diet in Renal Disease (MDRD) equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula instead of the Cockcroft-Gault (C-G) equation in MDS clinical trials to best represent true kidney function in older adults. Recommendation: Renal and hepatic laboratory parameters without safety signals should be avoided in later phase trials. We recommend utilization of the MDRD equation or CKD-EPI formula in clinical trials for MDS.

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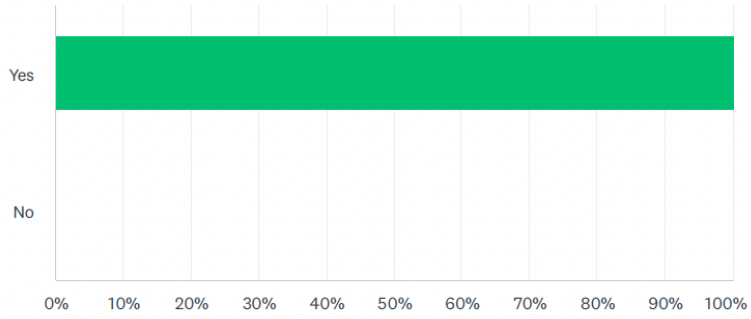

ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q10 Ejection FractionBackground: If an investigational therapy is not known to pose cardiac risks, arbitrary ejection fraction values should not be used to exclude patients from clinical trials. Instead of arbitrary ejection fraction limits that are not concordant with drug safety signals, trials should recommend investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system (e.g., The New York Heart Association [NYHA] functional classification).Recommendation: Arbitrary ejection fraction limits that are not concordant with drug safety signals should be avoided.

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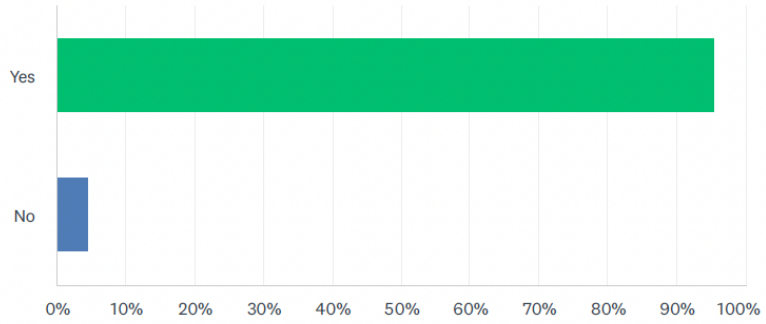

ANSWER CHOICES	RESPONSES	
Yes	95.45%	21
No	4.55%	1
TOTAL		22

Q11 QTc IntervalBackground: The icMDS agrees with recommendations from the FDA that suggests exclusion criteria on QT/QTc interval until the effects of the drug on the QT/QTc interval have been characterized (26). If QTc prolongation is not a safety risk of the drug in early studies, then QTc limits should not be imposed in later phase studies. When QTc limits are used, we recommend use of well-characterized QT correction such as the Fridericia formula.Recommendation: If QTc prolongation is not a safety risk of the drug in early studies, then QTc limits in later phase trials should be avoided.

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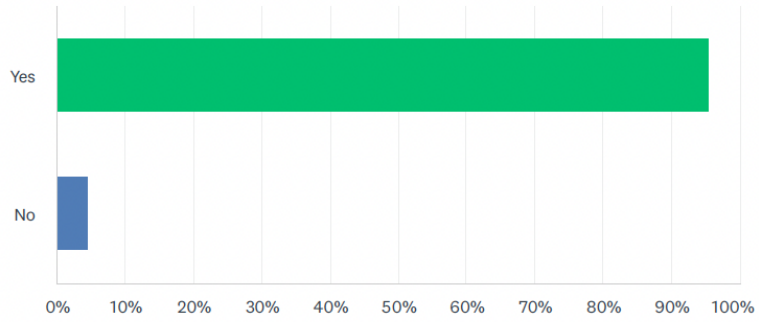
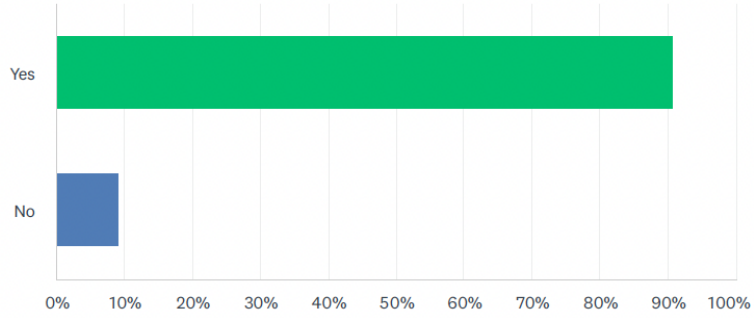


ANSWER CHOICES	RESPONSES	
Yes	95.45%	21
No	4.55%	1
TOTAL		22

Q12 Uncontrolled HypertensionBackground: Several studies include uncontrolled hypertension as an exclusion criterion in this analysis and the range of blood pressures that is considered uncontrolled is widely variable. In the studies of drugs known to increase blood pressure, the icMDS recommends eliminating arbitrary blood pressure limitations with instead focusing on the prevention of “hypertensive urgency,” defined as a systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg, to prevent sequelae.Recommendation: Statements on uncontrolled hypertension with arbitrary blood pressure ranges should be avoided.

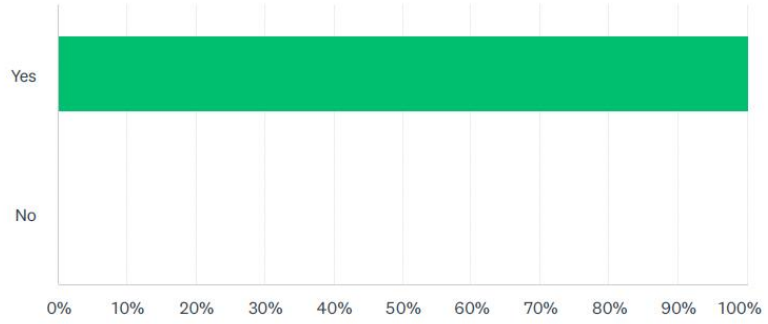
Answered: 22 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	90.91%	20
No	9.09%	2
TOTAL		22

Q13 Other MalignanciesBackground: Many studies in this analysis required patients to be 3 or 5 years from a prior cancer diagnosis. ASCO-Friends and the FDA Administration Working Group noted that patients with prior or concurrent malignancies should be permitted when the risk of the malignancy interfering with either safety or efficacy endpoints is low. The icMDS agrees with this statement. This is particularly relevant to MDS, since the presence of other malignancies may be directly related to the diagnosis of MDS. Indeed, therapy-related MDS (t-MDS) comprises 10% to 20% of all MDS diagnoses, due in part to clonal hematopoietic selection by genotoxic chemotherapy or radiotherapy. However, only 5.7% of trials for MDS include t-MDS. The icMDS asserts that patients with concurrent malignancy should be generally be included if the concurrent cancer is clinically stable and not requiring active tumor-directed therapy within the anticipated study period. This does require consideration of the nature of the particular malignancy. Current malignancies typically require more specific eligibility criteria than prior malignancies. Recommendation: Restrictions on prior or concurrent malignancies should be avoided when the malignancy is stable and the risk of interfering with either safety or efficacy endpoints is low.

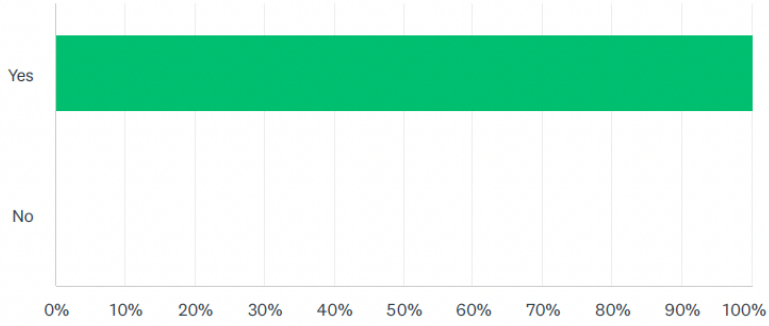
Answered: 22 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q14 Chronic Viral DiseasesBackground: As shown by this review, eligibility criteria can disproportionately exclude potential participants from historically marginalized groups including those with chronic infections such as HIV and hepatitis. Cancer is now a leading cause of mortality in people with HIV; however, many cancer studies exclude this population. The icMDS recommends against broad, blanket statements on the exclusion of HIV and hepatitis without more specific criteria. The icMDS agrees with recommendations from ASCO-Friends and the FDA Working Group that patients with HIV who have low risk of AIDS-related outcomes and are compliant with standard antiretroviral therapy should be included in trials, understanding some drug interactions may impact eligibility but would be accounted for elsewhere. For patients with hepatitis B and C, the icMDS agrees with the criteria developed by the FDA. Active hepatitis B necessitating therapy should require the patient to be on a suppressive antiviral prior to the initiation of cancer therapy. Patients with a history of hepatitis C should have completed or be receiving curative antiviral treatment with a viral load that is undetectable. For incurable cancers, active hepatitis C should be included if hepatitis C viral load is stable and the investigational agent is not suspected to exacerbate hepatitis.Recommendation: Broad, blanket statements on the exclusion of HIV and hepatitis without more specific criteria (as recommended per the FDA, ASCO-Friends) should be avoided.

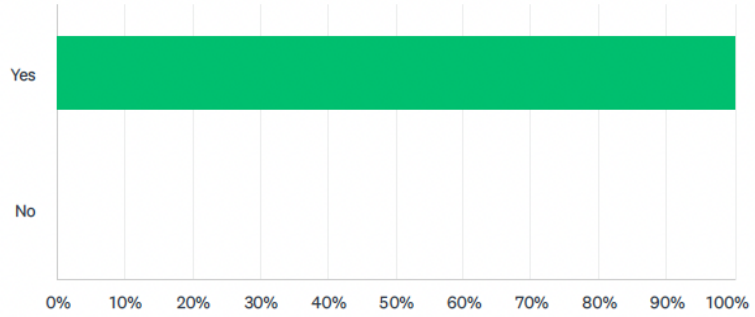
Answered: 22 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	100.00%	22
No	0.00%	0
TOTAL		22

Q15 Washout PeriodsBackground: This analysis showed a wide range of washout periods for the same therapeutic agents throughout MDS clinical trials. Generally, relevant clinical and laboratory parameters should be used preferentially in place of time-based washout periods to address safety considerations. This is particularly true for preceding cytotoxic chemotherapy or investigational agents with an unknown half-life. If time-based washout periods are included, pharmacological justification should be specified. Washout periods based on 5 half-lives may be appropriate for agents such as ESAs. For preceding immunotherapy, late occurring immune related adverse events (irAEs) can occur. However, in the absence of unresolved irAEs, it is recommended that the patient is eligible for trials with an understanding that late effects from prior immunotherapy may occur. An understanding of the common late occurring irAEs can be utilized to differentiate if effects are from prior or current therapy.Recommendation: Generally, relevant clinical and laboratory parameters should be used preferentially in place of time-based washout periods to address safety considerations.

Answered: 21 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	100.00%	21
No	0.00%	0
TOTAL		21

Table 4 (see manuscript)

ANSWER CHOICES	RESPONSES	
Yes	100.00%	21
No	0.00%	0
TOTAL		21