Early Results of Phase 1 Study of JSP191, an Anti-CD117 Monoclonal Antibody, with Non-Myeloablative Conditioning in Older Adults with MRD-positive MDS/AML Undergoing Allogenic Hematopoietic Cell Transplantation

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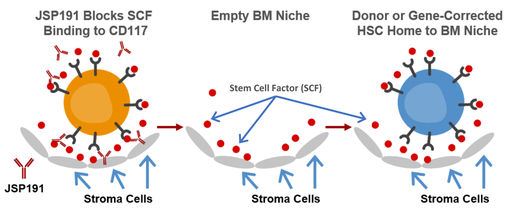
Background

Myeloablative allogeneic hematopoietic cell transplantation (AHCT) is potentially curative for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), but toxicities of conditioning limit its use in older or frail patients. Non-myeloablative (NMA) conditioning achieves better tolerability, at the expense of higher rates of relapse. We have developed a first-in-class monoclonal antibody (mAb), JSP191, which inhibits stem cell factor binding to CD117 (c-Kit), thereby depleting normal and MDS/AML disease-initiating hematopoietic stem cells (HSC). In pre-clinical models, anti-CD117 mAbs potently synergize with low dose total body radiation (TBI) to deplete HSC and facilitate donor cell engraftment. We reasoned that adding JSP191 to a standard NMA conditioning of fludarabine (Flu) and TBI (2 Gy) would be safe and result in depletion of measurable residual disease (MRD) in older adults with high-risk MDS/AML entering AHCT.

JSP191 Targets and Depletes MDS/AML Disease Initiating Cells and Normal HSCs



- JSP191 binds to CD117 (cKit or Stem Cell Factor receptor)
- SCF / CD117 interaction required for stem cell survival
- JSP191 blocks SCF signaling leading to patient stem cell depletion from the bone marrow
- Allows for healthy donor stem cell engraftment

Study Schema

Phase 1a: DOSE FINDING
JSP191 + Flu/TBI 2.0 Gy

- Cohort 1.2: JSP191 1.0 mg/kg
- ***Starting dose*** **Cohort 1.1**: JSP191 0.6 mg/kg
- Cohort 1.0: JSP191 0.3 mg/kg

Selection of RP2D: JSP191 0.6 mg/kg + Flu/ TBI 3.0 Gy

Phase 1b: DOSE EXPANSION
JSP191 0.6mg/kg + Flu/TBI 3.0 Gy

Subjects in morphologic CR

- **Group A**: AML morphologic CR (<5% blasts)
- **Group B**: MDS <5% blasts

Subjects with Active Disease

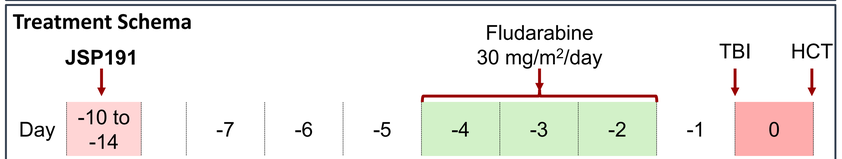
- **Group C**: MDS 5-10% blasts
- **Group D**: AML not in CR or MDS >10% blasts

ClinicalTrials.gov NCT04429191

Key Inclusion Criteria

- Patients with AML or MDS
- ≥ 60 years or with Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) ≥3
- Phase 1a (Dose Finding): Minimal Identifiable Disease (MID) or Measurable Residual Disease (MRD) detected by cytogenetics (cyto), difference from normal flow cytometry (flow), or next-generation sequencing (NGS)
- Opening enrollment May 2021: Phase 1b (Dose Expansion): AML (morphologic CR), MDS (<5% Blasts), MDS (>5% blasts), and AML (not in CR)
- HLA matched related or unrelated donor
- Patients with prior HCT were excluded

Treatment Schema



- Serial serum concentrations of JSP191 were obtained to predict the JSP191 concentration ≤ 2000 ng/mL, that day is designated Transplant Day -4
- Post-transplant immunosuppression consists of sirolimus, tacrolimus, and mycophenolate mofetil

Primary endpoints:
- Safety and tolerability of JSP191/TBI/Flu
- JSP191 pharmacokinetics (PK)

Secondary endpoints:
- Engraftment and donor chimerism
- MRD clearance, Non-relapse mortality, Event-free Survival and Overall Survival

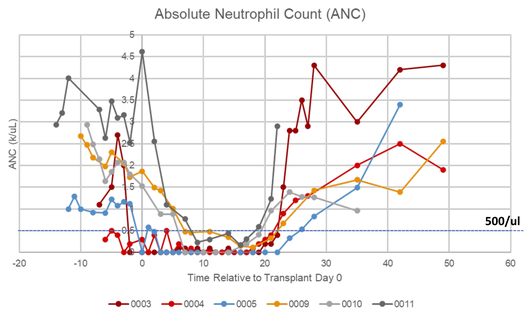
Phase 1a (Dose Finding) Subject Demographics

Subject Number	Age Sex	Diagnosis	Prior Therapy for MDS or AML	Donor
003	74F	AML	Azacitidine/ Venetoclax	Unrelated
004	70M	MDS	Erythropoietin	Related
005	68M	MDS	Azacitidine	Unrelated
009	74M	MDS	None	Unrelated
010	65M	AML	Cytarabine/Idarubicin (7+3) + Midostaurin; Azacitidine/ Venetoclax	Unrelated
011	69M	AML	Cytarabine/Daunorubicin (7+3) + myelotarg; Cytarabine/ Daunorubicin (5+2)	Related

JSP191 when added to TBI/Flu appears to be a safe and tolerable

- **No infusion reactions**
- **No treatment related toxicities**
- **Protocol allows for outpatient conditioning**
- **Subject 005 with grade 1 acute skin GVHD diagnosed TD+80 (resolved)**
- **No evidence of grade 2-4 acute GVHD**
- **Subject 003 cGVHD diagnosed TD+159**

Neutrophil engraftment observed



Subject Number	Days from HCT to ANC >500
003	23
004	22
005	26
009	23
010	22
011	19

JSP191 Conditioning Leads to Successful Transplant and Conversion to MRD-Negative/ MRD Reduction in First Five Evaluable Subjects

Subject Number	Screening	TD+28	TD+56	TD+90	TD+180
	NGS, Flow, or Cyto	NGS, Flow, or Cyto	NGS, Flow, or Cyto	NGS, Flow, or Cyto	NGS, Flow, or Cyto
003	DNMT3A (VAF: 4.7%)	DNMT3A (VAF: 0.3%)	DNMT3A (VAF: 0.4%)	**NEG**	**NEG**
	RUNX1 (VAF: 1.7%)	RUNX1 (VAF: 0.3%)	RUNX1 (VAF: 0.3%)	**NEG**	**NEG**
	PTPN11 (VAF: 0.7%)	**NEG**	**NEG**	**NEG**	**NEG**
004	ASXL1 (VAF: 0.3%)	**NEG**	ND	**NEG**	**NEG**
	PTPN11 (VAF: 0.4%)	**NEG**	ND	**NEG**	**NEG**
	Cyto: Del(20q)	**NEG**	ND	**NEG**	Cyto: Del(20q)†
005	DNMT3A (VAF: 25.2%)	**NEG**	ND	**NEG**	TBD
	SRSF2 (VAF: 0.3%)	**NEG**	ND	**NEG**	TBD
	Flow 3.1%	**NEG**	ND	**NEG**	TBD
	Cyto: Trisomy 8	**NEG**	ND	**NEG**	TBD
009*	Complex Cytogenetics	QNS	**NEG**	**NEG**	Off study
	Flow 0.7%	**NEG**	**NEG**	**NEG**	Off study
010	ASXL1 (VAF: 1.5%)	**NEG**	**NEG**	**NEG**	TBD
	KMT2A duplication	KMT2A duplication	**NEG**	**NEG**	TBD
			RUNX1 (0.3%)	**NEG**	TBD
011	SRSF2 (VAF: 14.6%)	SRSF2 (VAF: 0.69%)	SRSF2 (VAF: 1.0%)	SRSF2 (VAF: 1.9%)	TBD

VAF: Variable allele frequency
QNS: unable to obtain sufficient sample
ND: assays obtained on TD+56 only if TD+28 is positive
TBD: Sample not yet collected or analyzed

†Subject 004: Cytogenetic relapse at TD+180 converted to normal karyotype 1 month later following withdrawal of immune suppression; no evidence of clinical relapse
*Subject 009: secondary graft failure (no evidence of relapse) off study after TD+90

ClinicalTrials.gov NCT04429191 *JSP191 is an investigative drug and is not approved for any indication*

Phase 1a Donor Cell Chimerism Observed in Blood

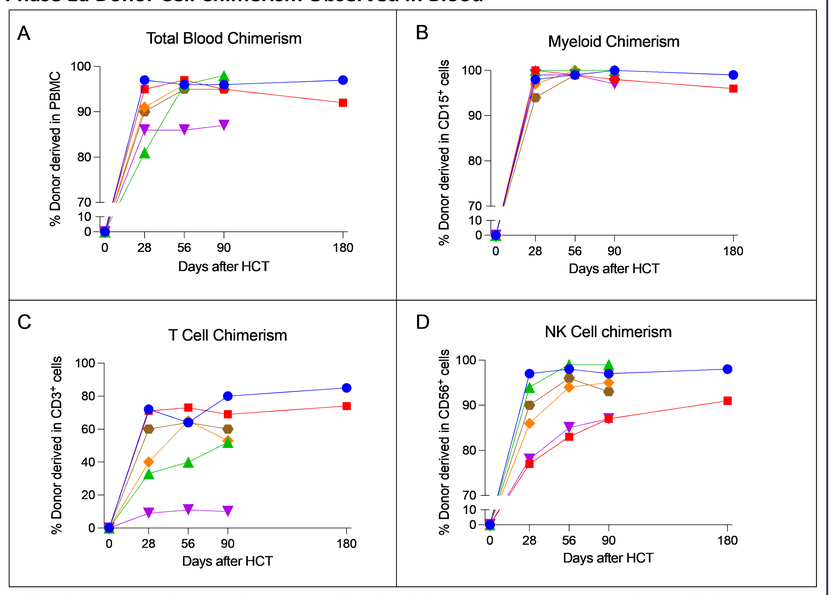


Table data reflected in graphs: A: Total blood cell chimerism, **B:** CD15+ Myeloid cell chimerism, **C:** CD3+ T cell chimerism, **D:** CD56+ NK cell chimerism.

Subject Number	Donor Chimerism															
	TD+28				TD+56				TD+90				TD+180			
	Total	CD15	CD3	CD56	Total	CD15	CD3	CD56	Total	CD15	CD3	CD56	Total	CD15	CD3	CD56
003	97%	98%	72%	97%	96%	99%	64%	98%	96%	100%	80%	97%	97%	99%	85%	98%
004	95%	100%	71%	77%	97%	99%	73%	83%	95%	98%	69%	87%	92%	96%	74%	91%
005	81%	100%	33%	94%	96%	100%	40%	99%	98%	100%	52%	99%	TBD			
*009	86%	99%	9%	78%	86%	99%	11%	85%	87%	97%	10%	87%	Off study			
010	91%	97%	40%	86%	96%	100%	65%	94%	96%	100%	53%	95%	TBD			
011	90%	94%	60%	90%	95%	99%	64%	96%	95%	98%	60%	93%	TBD			

*Subject 009: secondary graft failure (no evidence of relapse) at TD+90 TBD: Sample not yet collected or analyzed

Summary

- This study is the first to evaluate JSP191 given in combination with the non-myeloablative conditioning (NMA) regimen Flu/TBI 2Gy for older MDS/AML patients.
- JSP191 added to Flu/TBI 2Gy was well tolerated in the first 6 subjects
  - Protocol allows for subjects to receive conditioning regimen in outpatient setting
  - 3Gy of TBI will be evaluated in the Phase 1b dose expansion phase
- One subject (004) had cytogenetic relapse at TD+180 converted to normal karyotype 1 month later following withdrawal of immune suppression
- One subject (009) had secondary graft failure (without evidence of relapse) and went off study after TD+90
- In this Phase 1a cohort, 5 of 6 evaluable subjects achieved MRD-clearance by TD+90
- One subject with a therapy related AML (Subject 003) has maintained full chimerism and remained MRD-negative beyond TD+180
- This trial is currently enrolling in the Phase 1b dose expansion phase

Acknowledgements

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