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Phase 1 Study of JSP191, an Anti-CD117 Monoclonal Antibody, with Low Dose Irradiation and Fludarabine in Older Adults with MRD-Positive AML/MDS Undergoing Allogeneic HCT

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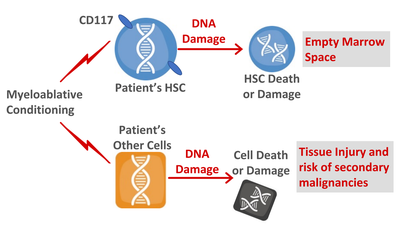
Background

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are hematologic malignancies primarily affecting older adults. Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for MDS/AML, but intensive conditioning limits its application in older or frail patients. Non-myeloablative (NMA) or reduced intensity conditioning (RIC) achieves tolerability at the expense of heightened disease relapse; thus, innovative strategies to reduce relapse while maintaining low toxicity are needed. We are developing a first-in-class monoclonal antibody (mAb), JSP191, which targets and depletes normal and MDS/AML disease-initiating hematopoietic stem cells (HSC). JSP191 acts by inhibiting stem cell factor (SCF) binding to CD117 (c-Kit) present on HSC. We and others showed in pre-clinical models that HSC depletion and donor cell engraftment can be enhanced by combining anti-CD117 mAb with low dose total body radiation (TBI). Based on these data, we hypothesized that the addition of JSP191 prior to NMA HCT conditioning of 200 cGy TBI and fludarabine (Flu) would result in clearance of disease, lower toxicity, and reduced relapse in older patients with MDS/AML and measurable residual disease (MRD). This Phase 1 trial evaluates this clinical hypothesis (NCT#04429191).

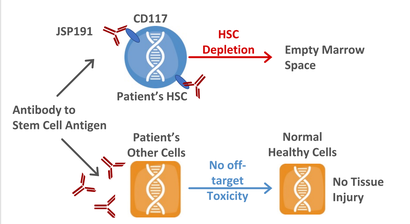
Toxic Conditioning Regimens is an Obstacle for Transplant: JSP191 is a targeted approach

Current Myeloablative Conditioning Removes HSCs Through Highly Toxic Regimens



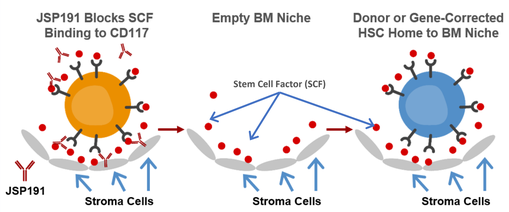
Myeloablative conditioning is not considered appropriate for older MDS / AML patients

JSP191 Selectively Targets HSCs: An Alternative to Toxic Conditioning Regimens



Using an antibody to stem cell antigen will limit extramedullary tissue damage and may enhance NMA conditioning

JSP191 Binds to CD117 on HSCs and Depletes HSCs

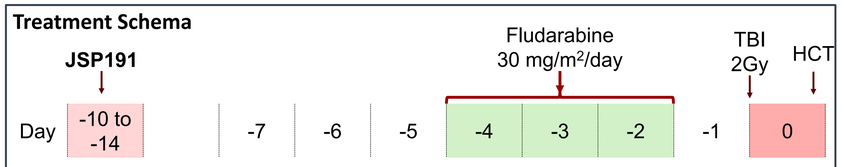


- Stem Cell Factor (SCF) / Stem Cell Factor Receptor (CD117) interaction required for stem cell survival
- JSP191 blocks SCF signaling leading to patient stem cell depletion from the bone marrow
- Allows for healthy donor stem cell engraftment

Key Inclusion Criteria

- Patients with AML or MDS
- ≥ 60 years or with HCT-CI ≥3
- Minimal Identifiable Disease (MID) or Measurable Residual Disease (MRD) detected by cytogenetics (cyto), difference from normal flow cytometry (flow), or next-generation sequencing (NGS)
- HLA matched related or unrelated donor
- Patients with prior HCT were excluded

Treatment Schema



Serial serum concentrations of JSP191 were obtained to predict the a JSP191 concentration ≤ 2000 ng/mL, that day is designated Transplant Day -4

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

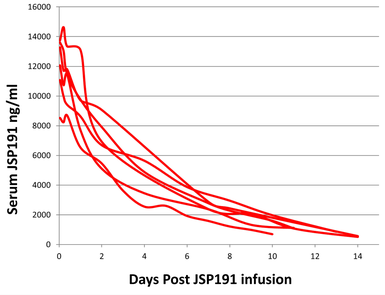
Subject Demographics

Subject Number	Age Sex	Diagnosis	Prior Therapy for MDS or AML	Donor
003	74F	AML	Azacitidine/ Venetoclax	Matched unrelated
004	70M	MDS	Erythropoietin	Matched related
005	68M	MDS	Azacitidine	Matched unrelated
009	74M	MDS	None	Matched unrelated
010	65M	AML	Cytarabine/Idarubicin (7+3) +Midostaurin Azacitidine/ Venetoclax	Matched unrelated
011	69M	AML	Cytarabine/ Daunorubicin (7+3) Cytarabine/ Daunorubicin (5+2)	Matched 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**
- **All subjects are still on study**

JSP191 PK at 0.6 mg/kg was observed to be consistent among subjects (n = 6)



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	MRD at Screening NGS, Flow, or Cyto	MRD at TD+28 NGS, Flow, or Cyto	MRD at TD+56 NGS, Flow, or Cyto	MRD at TD+90 NGS, Flow, or Cyto
003	DNMT3A (VAF: 4.7%)	DNMT3A (VAF: 0.3%)	DNMT3A (VAF: 0.4%)	*Subject still on study – assessments TBD*
	RUNX1 (VAF: 1.7%)	RUNX1 (VAF: 0.3%)	RUNX1 (VAF: 0.3%)	
	PTPN11 (VAF: 0.7%)	**NEG**	**NEG**	
004	ASXL1 (VAF: 0.3%)	**NEG**	ND	**NEG**
	PTPN11 (VAF: 0.4%)	**NEG**	ND	**NEG**
	Del(20q)	**NEG**	ND	**NEG**
005	DNMT3A (VAF: 25.2%)	**NEG**	ND	*Subject still on study – assessments TBD*
	SRSF2 (VAF: 0.3%)	**NEG**	ND	
	Flow 3.1%	**NEG**	ND	
009	Complex Cytogenetics	QNS	*Subject still on study – assessments TBD*	
	Flow 0.7%	**NEG**		
010	ASXL1 (VAF: 1.5%)	**NEG**	*Subject still on study – assessments TBD*	
	KMT2A duplication	KMT2A duplication		
011	SRSF2 (VAF: 14.6%)	*Subject still on study – assessments TBD*		

VAF: Variable allele frequency
QNS: unable to obtain sufficient sample, will be repeated at TD+56
ND: MRD assays obtained on TD+56 only if TD+28 is positive

Mutation clearance after transplantation for MDS is associated with an improved Progression-Free Survival (Duncavage et al, NEJM 2018; 379:1028-41).

Chimerism observed

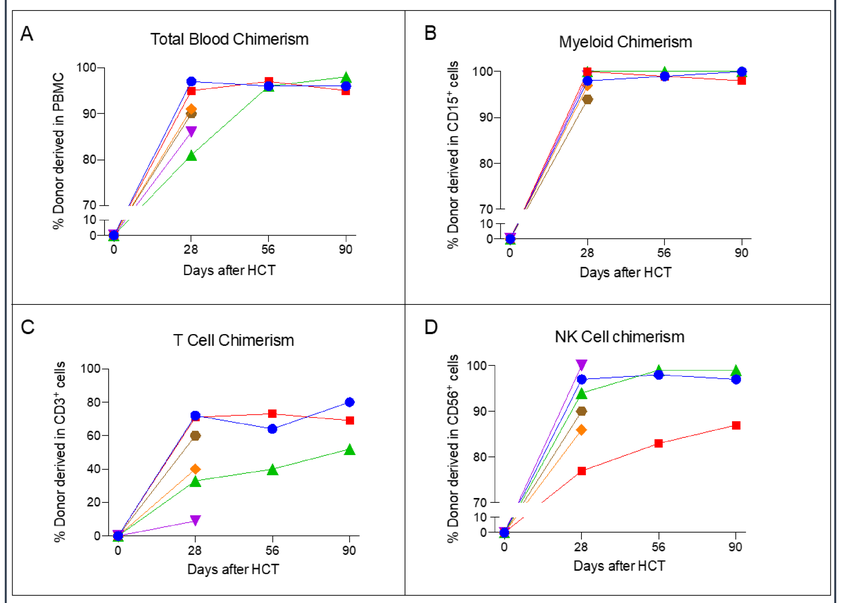


Table data reflected in graphs: A: Total blood cell chimerism, **B:** CD15+ Myeloid cell chimerism, **C:** CD3+ T cell chimerism, **D:** CD56+ NK cell chimerism.

Subject Number	Donor Chimerism TD+28 Total	CD15	CD3	CD56	TD+56 Total	CD15	CD3	CD56	TD+90 Total	CD15	CD3	CD56
003	97%	98%	72%	97%	96%	99%	64%	98%	96%	100%	80%	97%
004	95%	100%	71%	77%	97%	99%	73%	83%	95%	98%	69%	87%
005	81%	100%	33%	94%	96%	100%	40%	99%	98%	100%	52%	99%
009	86%	99%	9%	100%	*Subject still on study – assessments TBD*							
010	91%	97%	40%	86%	*Subject still on study – assessments TBD*							
011	90%	94%	60%	90%	*Subject still on study – assessments TBD*							

Summary

- This study is the first to evaluate JSP191 given in combination with non-myeloablative conditioning (NMA) Flu/TBI 2Gy for older MDS/AML patients.
- JSP191 added to TBI/Flu was well tolerated in the first 6 subjects; protocol allows for subjects to receive conditioning regimen in an outpatient setting
- JSP191 PK (at 0.6 mg/kg) was observed to be consistent between subjects
- MRD was undetected or reduced in all five evaluable subjects at TD+28 and are all still on study
- This trial is currently enrolling (NCT#04429191)

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