

A Phase 1b Open-Label Study of the Novel DNA Replication Inhibitor SNS-595 in Refractory Acute Leukemia

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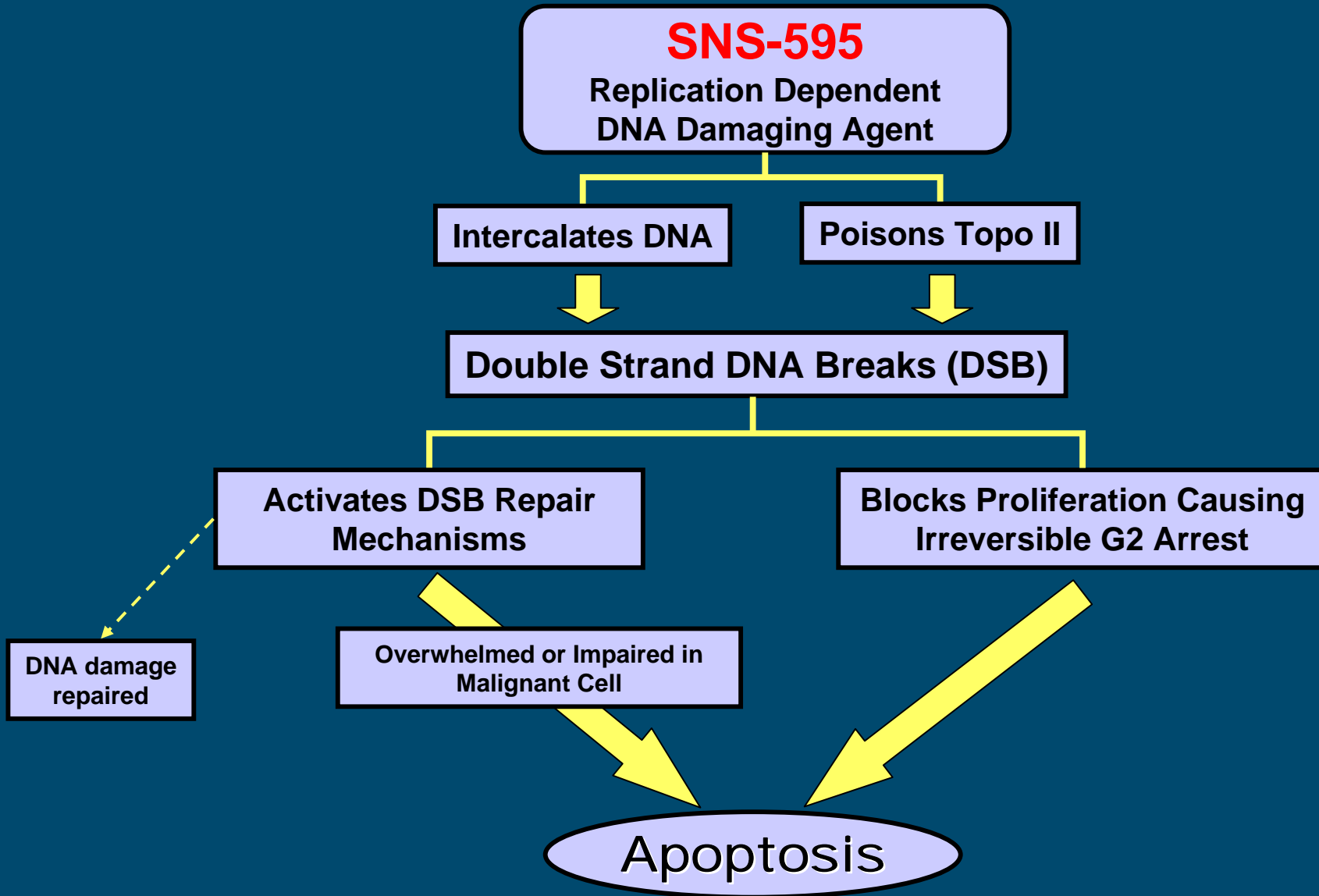
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SNS-595 Is A First-in-Class DNA Intercalator That Poisons Topoisomerase II



SNS-595 Has Favorable Pharmacological Properties

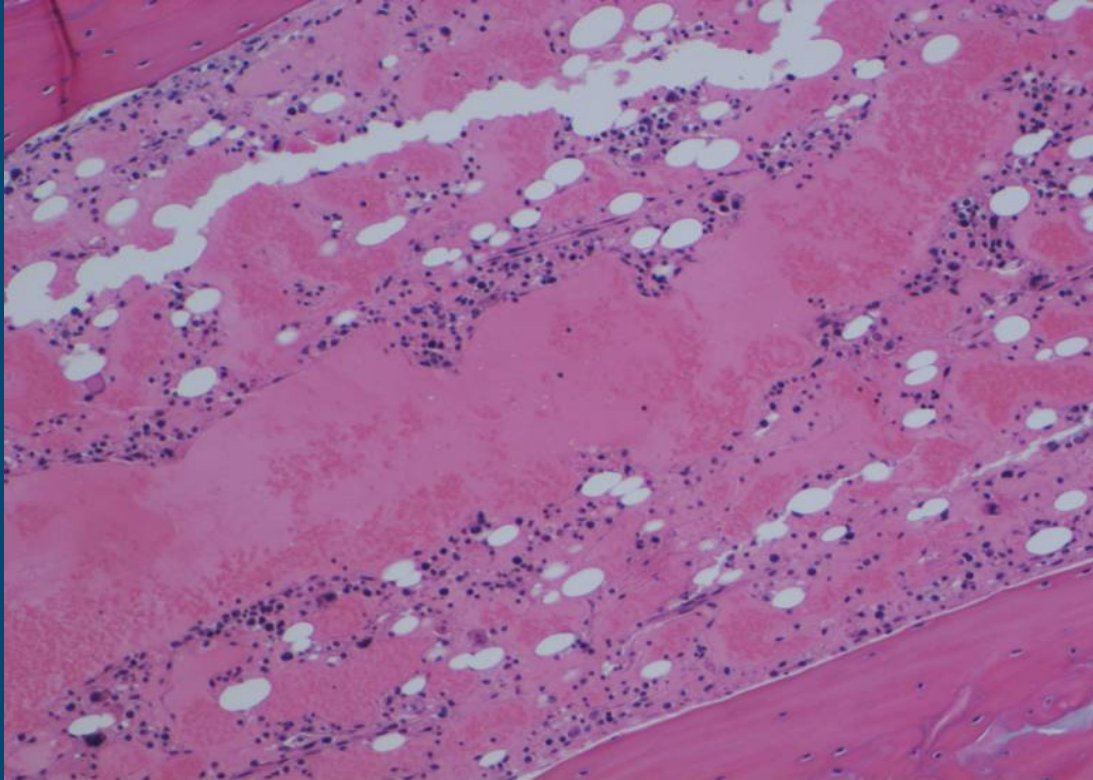
- **Not a P-glycoprotein substrate, evades common drug resistance mechanism- eg daunorubicin**
- **Low potential for CYP450-mediated drug-drug interactions**
- **Plasma protein binding low, between 50-75%**
- **Elimination ~85% intestinal; ~15% renal**
- **No evidence of QTc prolongation**
- **DLT in non-clinical models was myelosuppression and/or GI toxicity**

Preclinical Activity of SNS-595 Superior to Commonly Used Anti-Cancer Agents

Compound	Common Xenografts	Drug-Resistant	Syngeneic	Overall Activity*	%
SNS-595	8/10	3/3	3/3	14/16	87
Etoposide	0/10	0/3	0/2	0/15	0
CDDP	1/10	0/2	1/3	2/14	14
Taxol	7/8	0/3	0/3	0/6	50
CPT-11	7/10	0/2	0/3	0/5	47
Dox	2/10	0/3	1/3	1/6	19

* Activity determined by >60% inhibition of tumor growth at end of study

Preclinical Proof of Concept: SNS-595 More Potent Than Cytarabine and Activity Enhanced in Combination



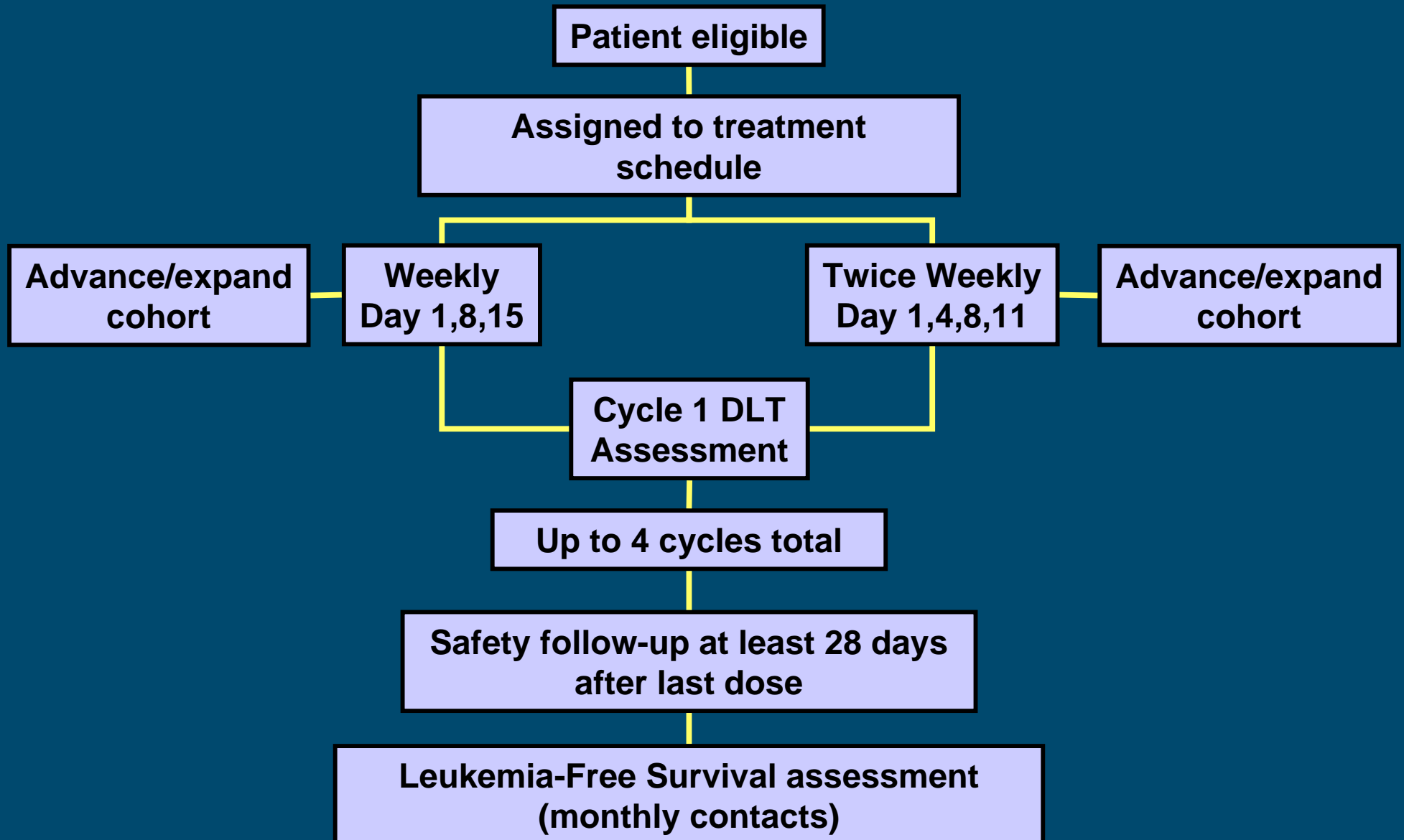
**SNS-595 10 mg/kg q4d x 2
+ Ara-C 20 mg/kg tid q4d x 2
93%↓ Cellularity**

Treatment	Decrease in Cellularity (%)
SNS-595 at MTD	82
Ara-C at MTD	42
SNS-595 at 50% MTD	44
Ara-C at 33% MTD	12
SNS-595 at 50% MTD Ara-C at 33% MTD	93

Study Objectives

- **Determine the MTD, safety and tolerability of escalating doses of SNS-595 given as a weekly or twice weekly injection**
- **Assess the pharmacokinetic (PK) profile of SNS-595 with advanced hematologic malignancies**
- **Define a recommended dose regimen for future phase 2 studies**
- **A secondary objective is to obtain preliminary assessments of antitumor activity**

Study Schema and Methods



Dose Limiting Toxicity (DLT) Definitions

Hematologic:

- **Grade 4 neutropenia or thrombocytopenia persisting beyond study day 57 in the absence of viable leukemia**

Non-hematologic:

- **≥ Grade 3**
 - **EXCEPT alopecia, controlled nausea/vomiting, febrile neutropenia controlled by antibiotics, or ALT/AST lasting < 7 days**

Eligibility Criteria

- **Relapsed or refractory**
 - AML
 - ALL
 - CML – blast phase
 - MDS (IPSS \geq 1.5)
- **Received \leq 3 induction/reinduction regimens**
- **ECOG PS 0-2**
- **Written informed consent**
- **Age \geq 18 years**
- **Adequate renal and hepatic function**

Patient Demographics

		Weekly	Twice Weekly	Total
Number of Patients		40	27	67
Age (yrs)	median	65	65	65
	range	21 - 80	26 - 85	21 - 85
Sex (n, %)	male	26 (65%)	16 (59%)	42 (63%)
	female	14 (35%)	11 (41%)	25 (37%)

Baseline Patient Characteristics

		Weekly n=40	Twice Weekly n=27	Total n=67
ECOG Performance Status (%)	0-1	85%	96%	90%
	2	10%	4%	7%
	outstanding	5%	0%	3%
Diagnosis (%)	ALL	10%	7%	9%
	AML	83%	85%	84%
	Other	7%	7%	7%
Disease Status (%)	relapsed	20%	19%	19%
	refractory	75%	81%	78%
	other	5%	0%	3%

DLT Results for SNS-595

Predominant DLT was grade 3+ oral mucositis occurring after the last dose of SNS-595 and resolved with supportive care/dose reduction

	Weekly (D1,8,15)					Twice Weekly (D1,4,8,11)		
Dose (mg/m ²)	18-38	50	60	72 MTD	90	9-30	40 MTD	50
Patient (n)	12	8	4	12	6	17	11	3
DLTs	0	1	0	2	2	0	3	3
Grade 3+ Mucositis	0	0	0	1	2	0	2	3

Dose Limiting Toxicities Of SNS-595 By Dosing Schedule (DLTs)

Weekly (D1,8,15)		
Dose Level (mg/m²)	DLT	Outcome
50	G4 Prolonged myelosuppression	Progressive disease
60	None	None
72	Bowel obstruction	Death
	G3 oral mucositis	Resolved
90	G3 Oral mucositis	Reduced dose to 72mg/m ²

Twice Weekly (D1,4,8,11)		
Dose Level (mg/m²)	DLT	Outcome
40	G3 oral mucositis	Resolved
50	G3 oral mucositis	Reduced dose to 40mg/m ²
	G4 oral mucositis	Reduced dose to 40mg/m ²

- Oral mucositis occurred following last dose of SNS-595 on both schedules
- At the MTD and below only 1 patient required dose reduction

Study Drug-Related AEs Reported By At Least 5% Of Patients (All CTCAE Grades)

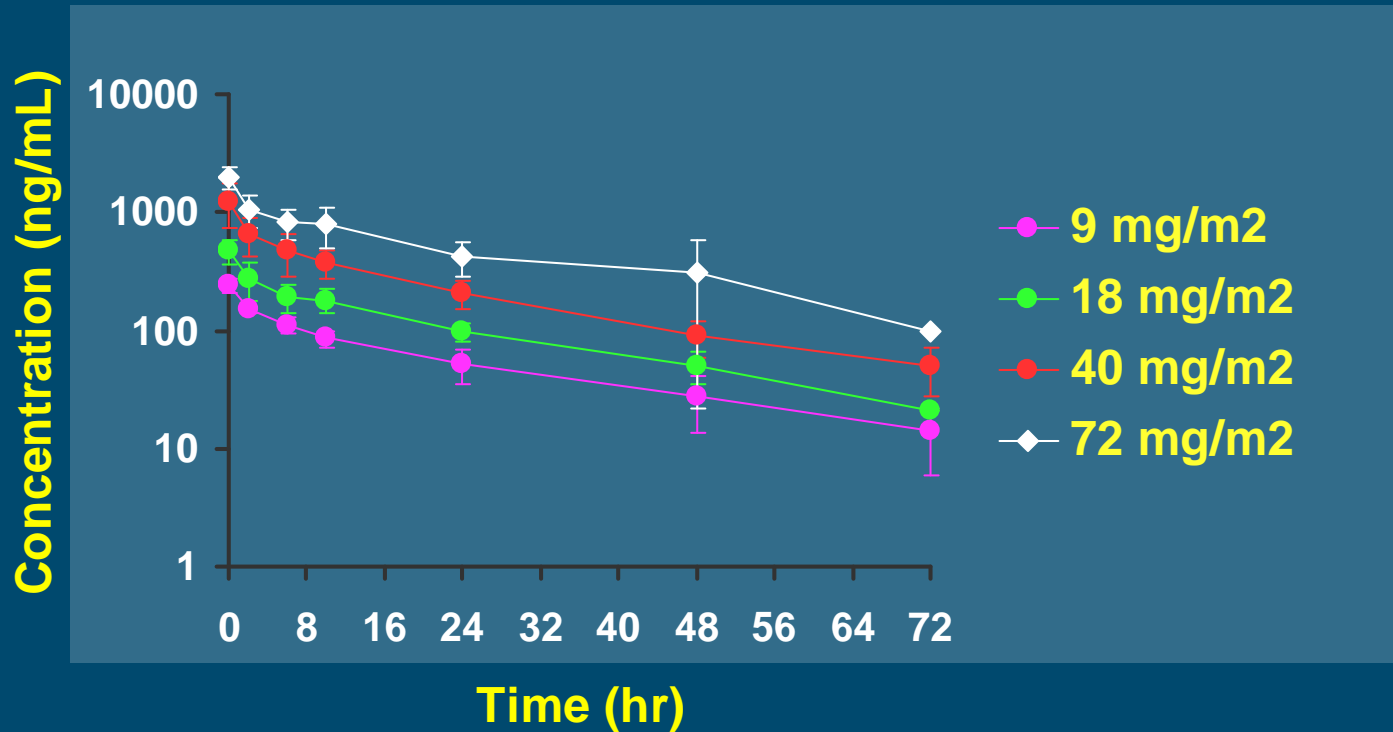
DLT on both schedules was Grade 3-4 stomatitis (oral mucositis)

CTCAE Category	CTCAE V3 Event	Weekly N=40		Twice Weekly N=27	
		1-2	3	1-2	3-4
Gastrointestinal	<i>Anorexia</i>	3		3	
	<i>Nausea</i>	7		8	
	<i>Stomatitis</i>	1	4	5	6
	<i>Diarrhea</i>	5		3	
	<i>Vomiting</i>	1		4	
	<i>Constipation</i>	1		2	
Constitutional Symptoms	<i>Fatigue</i>	3		2	
Dermatology/Skin	<i>Alopecia</i>	1		5	

- Multiple reports of the same AE in the same patient are counted only once
- 5 additional non-DLT G3/4 toxicities were observed including 1 febrile neutropenia, 1 diarrhea, and 1 renal failure.

SNS-595 Exhibits Predictable and Dose Linear Pharmacokinetics

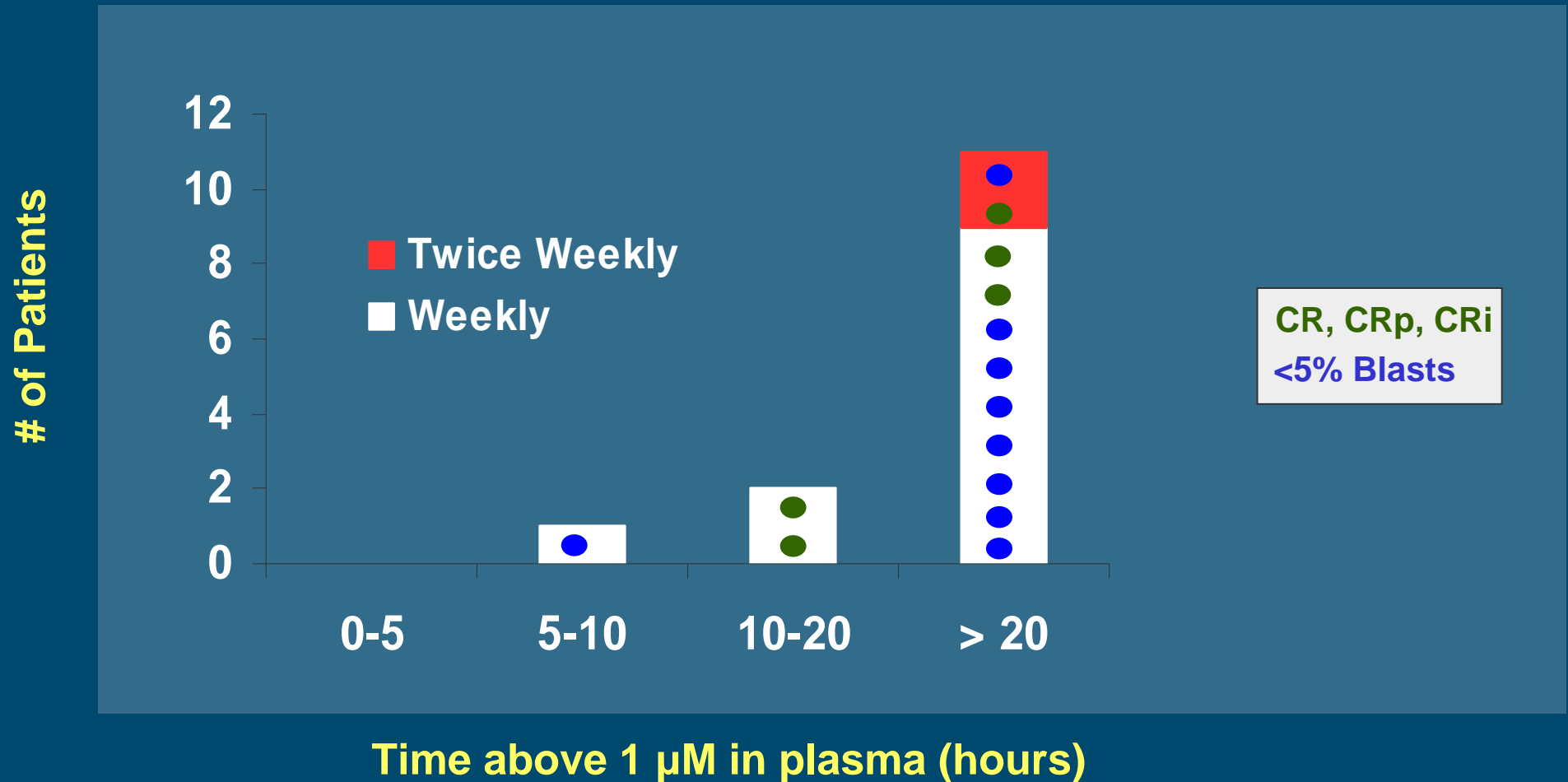
Day 1 Plasma Concentration-Time Profile



	N	Dose Range (mg/m ²)	C _{max} Range (µg/mL)	AUC Range (µg*hr/mL)	CL (L/hr/m ²)	V _{ss} (L/m ²)	T _{1/2} (hr)
Weekly	38	18 – 90	0.4 – 4.4	6 – 102	2.0±0.7	61±17	25±7
Twice Weekly	29	9 - 50	0.2 – 3.1	3 - 48	2.2±0.7	73±24	27±10

Anti-Leukemic Activity Correlated with Time Above Threshold SNS-595 Concentration

Time above 1 μ M SNS-595, in vitro IC90, correlated with activity



Overall Responses to Treatment with SNS-595 On Twice Weekly Schedule

	Twice Weekly (D1,4,8,11)		
Dose mg/m ²	9-30	40 MTD	50
Patient n	17	11	3
CR	0	1	0
Blasts <5% (without CR)	0	0	1

- CR relapsed after 6 months, was retreated and is now in CR
- MTD established at 40 mg/m²
- 2/14 (14%) patients experienced anti-leukemic activity at or above 40 mg/m²

Overall Responses to Treatment with SNS-595

On Weekly Schedule

*Broad therapeutic window with significant biologic activity
(50 mg/m² and above)*

	Weekly (D1,8,15)				
Dose (mg/m ²)	18- 38	50	60	72 MTD	90
Patient n	12	8	4	12	6
CR,CRp,CRI	0	1	1**	1	1
Blasts <5%	0	3	0	3*	2

- MTD established at 72 mg/m²
- 12/30 (40%) patients experienced anti-leukemic activity at or above 50 mg/m²
- All 4 CR patients had failed “7+3”
- Weekly schedule will be used for future single agent AML trials

*1 pt on-study, aplastic, waiting for recovery

** CRI – recovered trilineage hematopoiesis but died due to sepsis before full count recovery

AML Patients Achieving CR/CR_p

Pt #	Age	Dose level (mg/m ²)	Disease Status/ Prior Tx	Cytogenetics	CR Duration (months)
2021	66	50 qw	1st relapse ~ 14 m DNR/ Ara-C/VP-16	Intermediate 46XY	4
2028	41	72 qw	Refractory relapse DNR/Ara-C/VP-16, FLAM, HiDAC	Unfavorable 47XY, 9qh+, t(11;19)(q23pP13.1), +21	5+
2033	71	90/72 qw	Refractory to DNR/Ara-C	Unfavorable 46,XX,del(7);+(5;7) (p13,p11.2)/46XX	2+
2118	74	40 biw	Refractory relapse tipifarnib/VP-16	Intermediate 46XX	7

- Patients 2028 and 2033 remain in CR
- Patient 2118 was in CR for 7 months, retreated after relapse and is again in CR

SNS-595 Phase 1 in AML Conclusions and Future Directions

- **SNS-595 is a first-in-class naphthyridine analog that intercalates DNA and poisons Topo II causing selective DNA damage**
- **SNS-595 was generally well tolerated in patients with advanced leukemias**
- **MTD was 72 mg/m² weekly and 40 mg/m² twice weekly**
- **The dose limiting toxicity was oral mucositis on both schedules**

SNS-595 Phase 1 in AML Conclusions and Future Directions

- **Complete Remissions (4) as well as reductions in bone marrow leukemic blasts were observed in relapsed and/or refractory AML**
- **At biologically active doses, 40% (12/30) of patients dosed weekly and 14% (2/14) dosed twice weekly experienced anti-leukemic activity**
- **Schedule flexibility supports further single agent and combination studies**
- **A Phase 2 study of SNS-595 on the weekly schedule and a Phase 1b study of escalating doses of SNS-595 in combination with cytarabine are in progress**

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