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Phase I/II Study of gemtuzumab ozogamicin in combination chemotherapy for CD33+ refractory or relapsed AML: JALSG-AML206

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Background

- Current treatment results in young adults with non-APL-AML are improving (%CR >70%, 5Y-OS 40-50%), however, quite a few patients relapse or refractory to initial therapies.

STUDY	N	CR %	ED %	OS % (3-5 yr)
CALGB	474	72	9	34
GAMLCG	535	74	11	39
HOVON	253	77	7	38
ALFA	345	82	9	38
JALSG	1,064	78	4	51

Tallman M,2007

Study	N	%CR	OS	DFS
AML87	188	79.8	30.2	28.5
AML89	232	78.5	35.1	43.7
AML92	566	77.2	33.5	31.6
AML95	480	80.7	44.3	28
AML97	789	78.7	40.8	35.5
AML201*	1057	78	51	
IDR	532	78.6	53.1	41.8
DNR	525	77.5	49.1	42.2

* Ohtake S, et al. Blood 108:566a #2000,2006

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Background

- Patients with relapsed or refractory AML have a poor outcome (%CR<50%, 5Y-OS<30%).
- Gemtuzumab ozogamaicin(GO)is a humanized anti-CD33 MoAb conjugated with cytotoxic antitumor antibiotic, calicheamicin, that target CD33 Ag. More than 80% of AML cells have CD33 on their surface.
- GO induces CR+CRp in about 30% of relapsed/refractory AML
- Several studies tested the use of GO in combination chemotherapy, either at diagnosis or at time of relapse and most of them are more promising than monotherapy.

Name	No of patients	Age (years)	AML status	Dose of GO (mg/m2)	Schedule of GO	Combined Drugs	Dose & Schedule	CR(%)	CRp(%)	%Grade 3/4 hepatotoxicity	%VOD
MIA	14	34-74	Ref 4/Rel 10	6	Days 1 & 15	IDR Ara-C	9 mg/m2 D2-4 1.5g/m2 D1-5	3(21)	3(21)	29	14
MTA	17	23-78	Ref 9/Rel 8	9	Day 1	TOP Ara-C	1.25 mg/m2 D1-5 1g/m2 D1-5	2(1?		48	6
MFAC	32	18-78	Ref 11/Rel 21	4.5	Day 1	FLD Ara-C CSA	13mg/m2q12hrd D2-6 0.5 g/m2q12hrd D2-6 6mg/kg + 16 mg/kg D1-2			62	9
MDAC	11	16-67	Ref 1/Rel 10	6	Day 6	Ara-C DNX CSA	1 g/m2 D1-5 70 mg/m2 D 6-8 6mg/kg + 16 mg/kg D6-8			84	0
MHDAM	17	21-68	Ref 4/Rel 13	9	Day 4	Ara-C MIT	1g/m2 q12hr/D1-5 12 mg/m2 D1-2	12(70)	1(6)	24	7
MyHIDAC	44	59-69	Ref 7/Rel 37	9	Day 7	Ara-C	2g/m2 D1-5	7(19)	2(5)	24	0

ORR 76%

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AIMS and OBJECTIVES

- **AIMS**
  - In order to improve outcome of patients with AML, we investigate effective salvage therapies combining new agent (GO) with conventional chemotherapy (JALSG AML201 induction therapy regimen)
- **OBJECTIVES**
  - Determine: Maximum tolerated dose (MTD)
  - DLTs:
    - >Grade 4(CTCAE ver 3.0) of FN, Bleeding, Nausea & Vomiting, Infusion reaction, liver toxicity (hyperbilirubinemia, hypertransaminasis)
    - >Grade 3(CTCAE ver 3.0) or more of non hematologic toxicity not related to progression of AML
    - Prolongation of bone marrow suppression (ANC<500 μL, PLT<20,000/μL) over 6 weeks not related to AML
  - Toxicity profile (NCI-CTCAE ver3)
  - Response Rate (International Working Group Criteria)

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Eligibility

Inclusion Criteria

1. CD33+ de novo AML except APL ; refractory to the first remission induction therapy or first relapse (>6 months from CR1)
2. Age 20 – 64
3. ECOG performance status of PS 0 or 1
4. After 30 days or more from initial therapy and recovered to baseline from any toxicities of prior chemotherapy
5. Adequate hepatic, cardiac, renal, pulmonary function
6. Life expectancy ≥ 2 months

Exclusion Criteria

1. Previous MDS/MP
2. Secondary AML
3. CNS leukemia
4. Received Transplantation
5. Women who are pregnant or breastfeeding
6. Received therapy with anti-CD33 MoAb
7. Concurrent active malignant disease
8. Uncontrolled infection
9. HBV,HCV or HIV infection
10. Treated with investigational drugs
11. Previously received cumulative dose of >500 mg/m² of DNR(only for DAG arm)

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JALSG AML206-P1: Treatment Schedule

1. IDR arm (IAG)

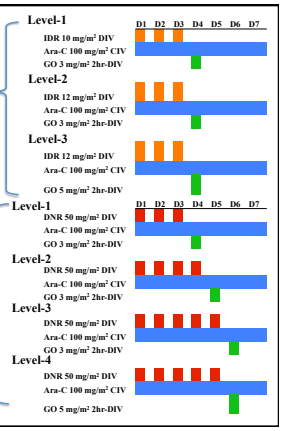
IDR+Ara-C+GOCombination

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ara-C 100mg/m²/day c.i.v.	↓	↓	↓	↓	↓	↓	↓
IDR 12or 10mg/m²/day d.i.v.	↓	↓	↓				
GO 3or 5mg/m²/day 2hr d.i.v.				↓			

2. DNR arm (DAG)

DNR+Ara-C+GO Combination

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ara-C 100mg/m²/day c.i.v.	↓	↓	↓	↓	↓	↓	↓
DNR 50mg/m²/day d.i.v.	↓	↓	↓	(↓)	(↓)		
GO 3 or 5mg/m²/day 2hr d.i.v.				↓	(↓)	(↓)	



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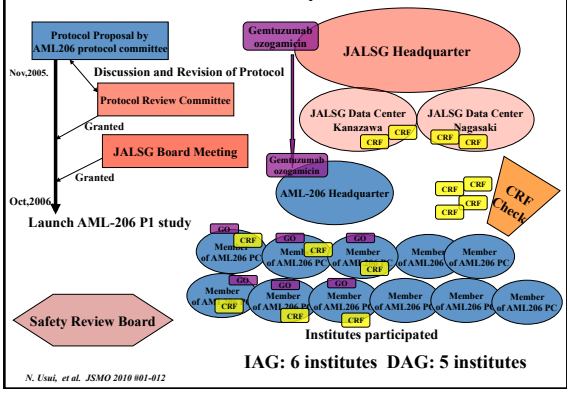
AML206 Study Schema



IAG: 6 institutes DAG: 5 institutes

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Patients Demographics

	Overall	IAG	DAG
N	19	9	10
M:F	9:10	4:5	5:5
Age			
Median	59	61	58
Range	33 - 64	38 - 64	33 - 62
Relapsed	14	7	6
Refractory	5	2	4
AML Subtypes			
M0	1		1
M1	1	2	1
M2	7	3	5
M4	6	3	3
M5	1	1	
Karytype			
CBF	2	1	1
CN	10	6	4
11q23	1	1	
t(6;9)	1		1
Complex	3	1	2
Others	2		2

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Patients Demographics-2

	Overall	IAG	DAG
Pre-treatment Status			
WBC ($x10^3/\mu L$)			
Median (Range)	3.0 (0.9-39.2)	3.7 (2.6-39.2)	2.1 (0.9-25.3)
Hb (g/dl)			
Median(Range)	10.9 (7.1-13.6)	12.5 (7.6-13.6)	10.6 (7.1-12.8)
PLT ($x10^4/\mu L$)			
Median (Range)	8.8 (2.6-44.3)	5.9 (2.6-20.7)	13.5 (3.4-44.3)
%Blasts			
Median (Range)	42.8 (7.9-96.8)	56.4 (17.3-88)	29.9 (7.9-96.8)
%CD33 Blasts			
Median (Range)	89.4 (39-100)	92.9 (62.8-100)	80.6 (39-96.9)

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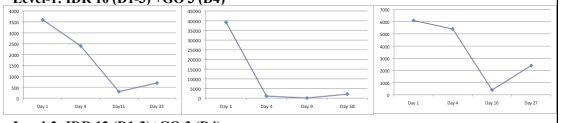
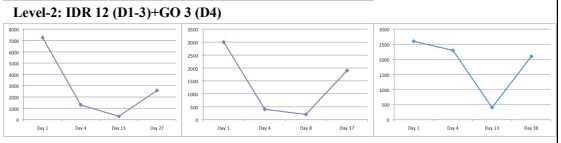
IAG: WBC & ANC

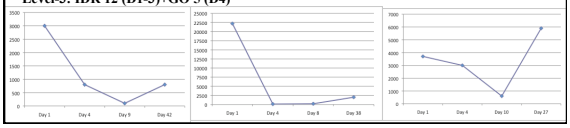
Level-1: IDR 10 (D1-3) +GO 3 (D4)



Level-2: IDR 12 (D1-3)+GO 3 (D4)

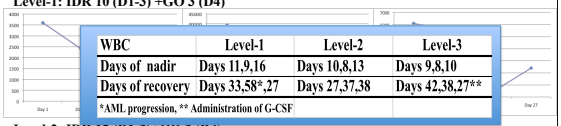


Level-3: IDR 12 (D1-3)+GO 5 (D4)



IAG: WBC & ANC

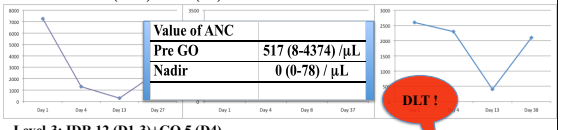
Level-1: IDR 10 (D1-3) +GO 3 (D4)



WBC	Level-1	Level-2	Level-3
Days of nadir	Days 11,9,16	Days 10,8,13	Days 9,8,10
Days of recovery	Days 33,58*,27	Days 27,37,38	Days 42,38,27**

*AML progression, ** Administration of G-CSF

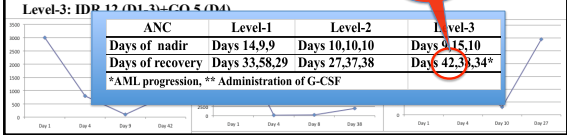
Level-2: IDR 12 (D1-3)+GO 3 (D4)



Value of ANC	
Pre GO	517 (8-4374) /μL
Nadir	0 (0-78) / μL

DLT !

Level-3: IDR 12 (D1-3)+GO 5 (D4)



ANC	Level-1	Level-2	Level-3
Days of nadir	Days 14,9,9	Days 10,10,10	Days 9,15,10
Days of recovery	Days 33,58,29	Days 27,37,38	Days 42,38,34*

*AML progression, ** Administration of G-CSF

IAG: Hematologic Toxicity

Hb	Level-1	Level-2	Level-3
Grade 0	0	0	1
Grade 1	1	1	1
Grade 2	2	1	1
Grade 3/4	0	0	0
Units of RBC-TF	4,4,12	4,6,2	8,16,4

Hb	Level-1	Level-2	Level-3
Days of nadir	Days 26,35,16	Days 18,27	Days 7,23
Days of recovery	Days none,39,35	Days 21,29	Days 30,27

Platelet	Level-1	Level-2	Level-3
Grade 3	3	2	3
Grade 4	0	1	0
Units of PLT-TF	90,130,100	130,130,50	70,220,70

DLT !

PLT	Level-1	Level-2	Level-3
Days of nadir	Days 11,11,17	Days 13,13,17	Days 14,8,17
Days of recovery	Days 33,none,none	Days none,46,38	Days 28,90,34

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IAG: Non-Hematologic Toxicity

	Level-1 (N=3)	Level-2 (N=3)	Level-3 (N=3)
Febrile Neutropenia			
Grade 3	3	2	2
Grade 4			1
Infection (Grade 4)			
Sepsis			1
Cerebral Abscess			1
Hepatic			
Grade 2	1	1	1
Grade 3			2
Anorexia, Nause/ Vomiting			
Grade 2			2
Edema			
Grade 1			2
Skin rash			
Grade 2			1
Diarrhea			
Grade 1			1
VOD/SOS	0	0	0

DLT !

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DAG: WBC & ANC

Level-1: DNR 50 (D1-3)+ GO 3(D4)

WBC	Level-1	Level-2	Level-3
Days of nadir	Days 10,13,10	Days 10,10,7,12	Days 8,10,12
Days of recovery	Days 27,27,36	Days 27,22,24,32	Days 38,29,26

Level-2: DNR 50 (D1-4)+ GO 3(D5)

Value of ANC	
Pre GO	429 (3-1250) /μL
Nadir	0 (0-1) / μL

Level-3: DNR

ANC	Level-1	Level-2	Level-3
Days of nadir	Days 10,11,11	Days 14,17,9,12	Days 12,12,17
Days of recovery	Days 29,32,36	Days 27,22,N/A,32	Days 39,29,31

DAG: Hematologic Toxicity

Hb	Level-1	Level-2	Level-3
Grade 0	0	2	0
Grade 1	3	1	1
Grade 2	0	1	2
Grade 3/4	0	0	0
Units of RBC-TF	18,0,6	0,6,10,10	6,6,8

Hb	Level-1	Level-2	Level-3
Days of nadir	Days 11,13,39	Days 13, 6	Days 22,14,21
Days of recovery	Days 20,15,36	Days 22,44	Days 28,25,26

Platelet	Level-1	Level-2	Level-3
Grade 3	2	4	3
Grade 4	1	0	0
Units of PLT-TF	150,60,90	50,70,110,170	170,60,40

PLT	Level-1	Level-2	Level-3
Days of nadir	Days 11,13,20	Days 13,10,11,12	Days 25,12,17
Days of recovery	Days 25,32,34	Days 36,24,N/A,46	Days 38,34,26

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DAG: Non-Hematologic Toxicity

	Level-1 (N=3)	Level-2 (N=4)	Level-3 (N=3)
Febrile Neutropenia			
Grade 3	1	3	2
Grade 4	2		
Hepatic			
Grade 2			2
Grade 3	1	1	
Anorexia, Nause/ Vomiting			
Grade 2	1		1
Colitis			
Grade 2	1		
Diarrhea			
Grade 2			1
Cardiac			
Grade 2		1	
Bleeding			
CNS		1*	
Laboratory			
Hypophosphatemia		1	
VOD/SOS	0	0	0

* Due to Disease Progression

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Assessment of DLT

	No of Pts	No of DLT	
IAG			
Level-1	3	0	
Level-2	3	0	
Level-3	3	3	Prolongation of neutropenia Prolongation of thrombocytopenia Grade 4 Infection (Brain Abscess)
DAG			
Level-1	3	0	
Level-2	4	0	
Level-3	3	0	
Level-4	SRB recommended not to proceed		

IAG-Level-3 is MTD
DAG-Level-4 will be MTD

Recommend Dose & Schedule: IAG-Level-2, DAG-Level-3

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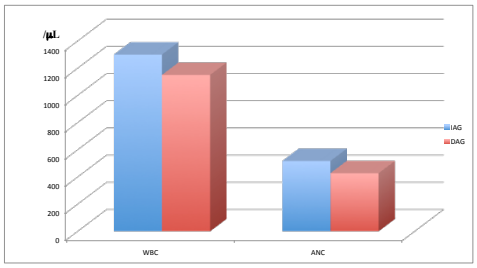
Median Counts of WBC & ANC at Administration of GO



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Response

	IAG			DAG			
	Level-1 (N=3) (IDR 10/GO 3)	Level-2 (N=3) (IDR 12/GO3)	Level-3 (N=3) (IDR 12/GO 5)	Level-1 (N=3) (DNR 36/GO3 D4)	Level-2 (N=4) (DNR 46/GO 3 D5)	Level-3 (N=3) (DNR 50/GO 3 D6)	Total (N=19)
CR	1	2	1			1	9
CRp			1				1
PR						1	2
NR (Blast Clearance)	1		1			1	4
Resistant Disease	1	1					3

ORR (CR+CRp)	10/19 (53%)
REL	8/14 (57%)
REF	2/5 (40%)
Karyo	
CN	4/10 (40%)
CBF	1/2 (50%)
Comp/Others	3/5 (60%)

Outcome:
Alive: 18 patients
Dead: 1 patient (DAG-level-2) died of CNS bleeding due to PD

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Conclusion

1. **Combination of GO with conventional(as JALSG) IDR+Ara-C or DNR-Ara-C is well tolerated and active in relapsed/ refractory AML**
2. **MTD of GO in the combination is considered 5 mg/m^2 (just after IDR or DNR administration)**
3. **Major toxicities are severe neutropenia, thrombocytopenia, febrile neutropenia**
4. **No VOD/SOS was observed**
5. **Both of IAG [IDR 12 mg/m^2 (D1-3)+Ara-C 100 mg/m^2 (D1-7)+GO 3 mg/m^2 (D4)] and DAG [DNR (50 mg/m^2 D1-5)+Ara-C 100 mg/m^2 (D1-7)+GO 3 mg/m^2 (D6)] therapies are recommend for phase II study to evaluate long term efficacy and safety**

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