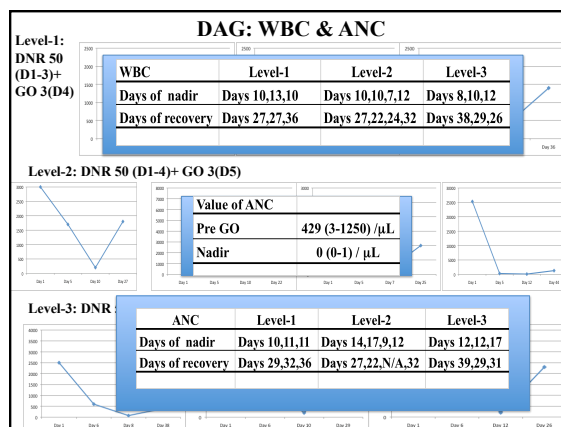


IAG: Non-Hematologic Toxicity

| | 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) | | | 1 |
| 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!

N. Usui, et al. JSMO 2010 001-012



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 |

N. Usui, et al. JSMO 2010 001-012

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

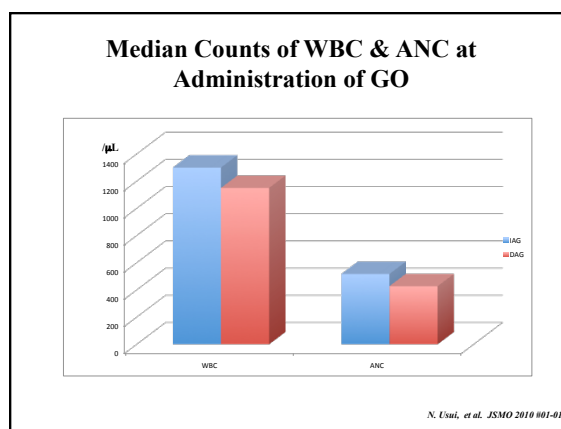
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Assessment of DLT

| | 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-2**
DAG-Level-4 will be MTD **Recommend Dose & Schedule:** **DAG-Level-3**

N. Usui, et al. JSMO 2010 001-012



| | IAG | | | DAG | | | Total (N=19) |
|----------------------|------------------|------------------|------------------|--------------------------|------------------|------------------|--------------|
| | Level-1 (N=3) | Level-2 (N=3) | Level-3 (N=3) | Level-1 (N=3) | Level-2 (N=4) | Level-3 (N=3) | |
| | (IDR 10/GO 3) | (IDR 12/GO 3) | (IDR 12/GO 5) | (DNR 30/GO 3 D4) | (DNR 40/GO 3 D5) | (DNR 50/GO 3 D6) | |
| CR | 1 | 2 | | ORR (CR+CRp) 10/19 (53%) | | | 1 |
| CRp | | | | REL | 8/14 (57%) | | 1 |
| PR | | | | REF | 2/5 (40%) | | 1 |
| NR (Blast Clearance) | 1 | | | Karyo | | | 1 |
| Resistant Disease | 1 | 1 | | CN | 4/10 (40%) | | 1 |
| | | | | CBF | 1/2 (50%) | | 3 |
| | | | | Comp/Others | 3/5 (60%) | | |

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

N. Usui, et al. JSMO 2010 001-012

| 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 |

N. Usui, et al. JSMO 2010 001-012

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| <p>All the Patients & their families participated in this study</p> <p style="text-align: right;"><i>N. Usui, et al. JSMO 2010 001-012</i></p> | |