PHASE II STUDY INCORPORATING A NOVEL BH3-PROFILING BIOMARKER APPROACH OF ALVOCIDIB FOLLOWED BY CYTARABINE AND MITOXANTRONE IN RELAPSED/ REFRACTORY ACUTE MYELOID LEUKEMIA (AML)

The Zella 201 Trial

TOLERO PHARMACEUTICALS
Sumitomo Dainippon Pharma Global Oncology

PF 243

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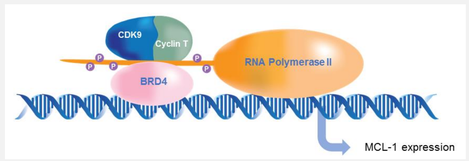
I. Introduction

- Serial studies have shown that alvocidib, followed by cytarabine and mitoxantrone (ACM), is active in newly diagnosed and relapsed/refractory (R/R) AML.
- Alvocidib's primary mechanism of action appears to be predominantly through inhibition of the transcriptional regulator, CDK9, resulting in suppression of CDK9-regulated genes, such as the BCL-2 family member, MCL-1.
- Retrospective correlative analyses showed that leukemic cells dependent on MCL-1 have heightened sensitivity to alvocidib-containing regimens[1,2].

Figure 1: CDK9 Regulates Expression of MCL-1



The MCL-1 gene is under the control of a superenhancer element, which is regulated by the activity of CDK9. Inhibition of CDK9, through the action of alvocidib, leads to a reduction in MCL-1 expression, resulting in sensitivity to apoptotic signals and tumor cell death

Figure 2: Regulation of BCL-2 Family Members by BH3 Peptides

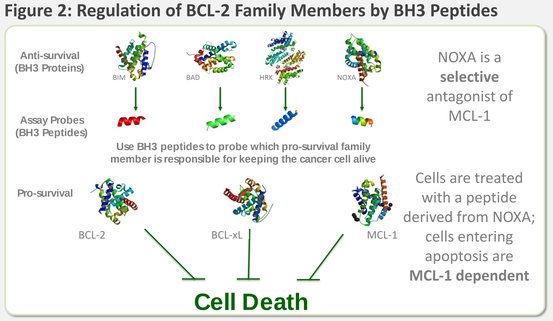
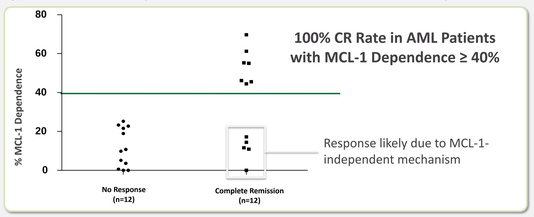
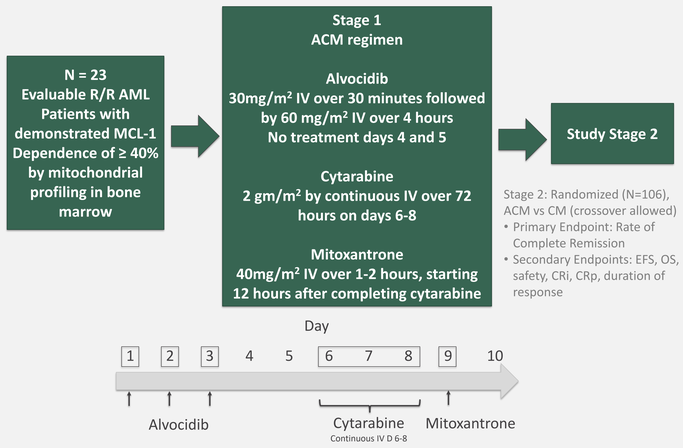


Figure 3: MCL-1 Dependence as a Biomarker for ACM Response[1,2]



Viably frozen bone marrow from pre-treatment newly-diagnosed AML patients was tested for MCL-1 dependence by mitochondrial BH3 profiling. Patients were treated with ACM and classified according to response (CR vs NR). All patients with MCL-1 dependence ≥40% achieved a CR. MCL-1 dependence did not predict response in patients treated with 7+3

II. Study Design



III. Results (Cutoff Date: 5/10/18)

Figure 4: Zella 201 MCL-1 Dependence Assay Disposition – R/R AML

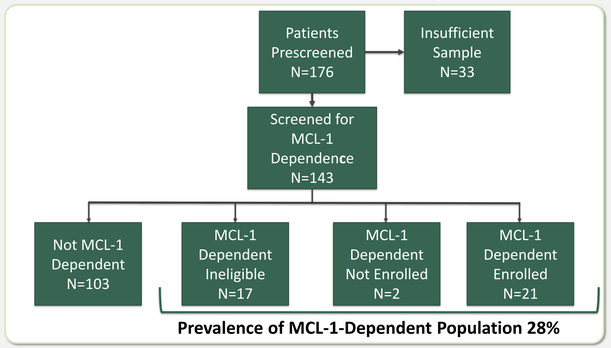
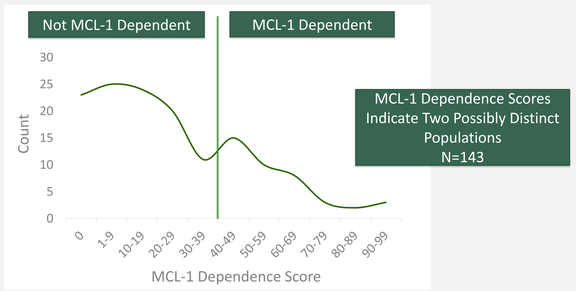


Figure 5: Zella 201 MCL-1 Dependence Score Distribution - R/R AML



III. Results (Cutoff Date: 5/10/18)

Table 1: Zella 201 Patient Characteristics, N=21

Response to Frontline Therapy	Number of Patients (%)	Median MCL-1 Score	Median Age	Median Bone Marrow Blast % at Baseline	Prior SCT	Secondary AML
Refractory	11/21 (52%)	53 (43-91)	57 (27-65)	41 (7-92)	1/11 (9%)	6/11 (55%)
Late Relapse	4/21 (19%)	55 (41-98)	55 (26-65)	36 (9-89)	2/4 (50%)	1/4 (25%)
Early Relapse	6/21 (29%)	62 (51-95)	49 (41-62)	51 (15-84)	2/6 (33%)	1/6 (17%)
Total / Overall	21/21 (100%)	61 (41-98)	54 (26-65)	46 (7-92)	5/21 (24%)	8/21 (38%)

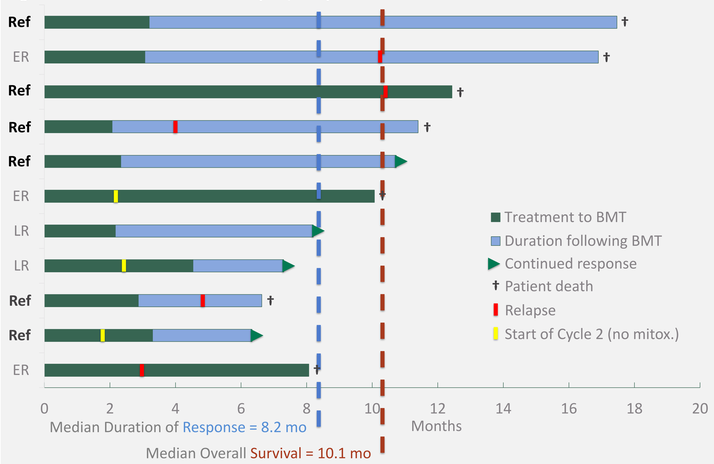
Early Relapse: CR duration 90 days to 1 year, Late Relapse: CR duration ≥ 1 year but ≤ 24 months, Refractory: persistent disease or CR duration ≤ 90 days

Table 2: Zella 201 Clinical Activity in Evaluable Patients

Response to Frontline Therapy	# of Patients Evaluable for Response, N=18 (%)	CR/CRi (%)	CR/CRi (excl. early deaths) (%)	ORR (CR / CRi / PR) (%)	Post-Study SCT	Pending Evaluation (%)
Refractory	8/18 (44%)	6/8 (75%)	6/8 (75%)	7/8 (88%)	5/8 (63%)	3/21 (14%)
Early Relapse	6/18 (33%)	3/6 (50%)	3/4 (75%)	3/6 (50%)	1/6 (17%)	0/21 (0%)
Late Relapse	4/18 (22%)	2/4 (50%)	2/3 (67%)	2/4 (50%)	2/4 (50%)	0/21 (0%)
Total / Overall	18/18 (100%)	11/18 (61%)	11/15 (73%)	12/18 (67%)	8/18 (44%)	3/21 (14%)

One Early Relapse patient was assessed as NR following Cycle 1; now awaiting assessment following Cycle 2.

Figure 6: Duration of Remission (CR / CRi) and Survival



Duration of ACM response and survival, defined as the time from first exposure to relapse, patient death, or cutoff, in patients exhibiting CR or CRi
AML History: ER - Early Relapse, LR - Late Relapse, Ref - Refractory

Table 3: Zella 201 Ongoing Safety Data

Non-Hematologic Treatment-Emergent Adverse Events Grade ≥ 3 in ≥ 3 Patients (N=21)	
MedDRA Preferred Term	N (%)
Tumor Lysis Syndrome	Gr.3: 4/21 (19%) Gr. 4: 2/21 (10%)
Aspartate Aminotransferase Elevated	Gr.3: 3/21 (14%)
Sepsis	Gr. 4: 1/21 (5%) Gr. 5: 2/21 (10%)
Diarrhea	Gr. 3: 3/21 (14%)

Grade 5 Toxicities: one patient with sepsis (assessed by investigator as being possibly alvocidib related); one patient MVR with CHF (assessed by investigator as being probably alvocidib related) were both later assessed by DSMB to be non-alvocidib related; one patient attempted suicide (assessed by investigator as non-alvocidib related), which resulted in death by infection of central line, and died on-study prior to assessment
Median time to onset in days: TLS 1, AST 10, Sepsis 18, Diarrhea 2

Table 4: Zella 201 Causes of On-Study Death

Mortality on Study (N=3)		
MedDRA Preferred Term	30 Day Mortality	Study Day
Sepsis / Acute Respiratory Distress	1	18
Sepsis / Acute Kidney Injury	1	22
Mitral Valve Regurgitation	1	27

IV. Conclusions

- Early data from Stage 1 of the Zella 201 study indicates a response rate of 11/18 (61%) in a relapsed / refractory AML population with MCL-1 Dependency.
  - 52% (11/21) of the patients enrolled in Zella 201 to date were refractory to frontline treatment, and of these patients 55% (6/11) had secondary AML.
  - Five out of eight (83%) previously refractory patients achieving CR / CRi went on to receive SCT.
- Patients attaining a complete response (CR / CRi) following ACM treatment experienced clinical benefit as represented by a median duration of response of 8.2 months (including transplant), a median overall survival of 10.1 months, as well as 44% (8/18) receiving a stem cell transplant.
- Grade 3 or greater adverse events included TLS, sepsis, diarrhea, and elevated AST, and were consistent with previous clinical studies.
- Mitochondrial profiling for MCL-1 dependence may be an effective tool for identifying patients with MCL-1 dependent relapsed or refractory AML who are more likely to respond to the alvocidib-containing regimen, ACM.
- A phase Ib study of alvocidib followed by 7+3 induction in newly diagnosed AML is ongoing (Zella 101). Future directions include a randomized phase II expansion comparing cytarabine and mitoxantrone with or without preceding timed sequential alvocidib, and prospective BH3 profiling of AML patients enrolled in both studies.

V. References

[1] J Clin Oncol 33, 2015 (suppl; abstr 7062)
[2] Blood 2015 126:3799

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