SUCCESSFUL TREATMENT WITH BORTEZOMIB, PANOBINOSTAT, AND DEXAMETHASONE OF ACUTE MYELOID LEUKEMIA (AML) IN 2ND RELAPSE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (SCT): THERAPY SELECTED BASED UPON RESULTS OF A PERSONALIZED FLOW CYTOMETRIC SCREEN FOR DRUG SENSITIVITY

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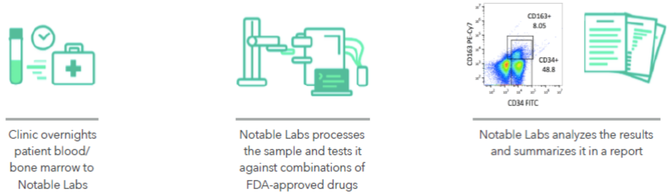
BACKGROUND

- The prognosis for patients with AML who relapse after allogeneic stem cell transplantation (SCT) remains grim.
- The risk of relapse depends on many factors:
  - Preparative regimen
  - Stem cell source
  - AML subtype
  - Cytogenetic and molecular markers
  - MRD status pre-SCT
- Donor lymphocyte infusion (DLI) can induce responses in a significant proportion of patients with relapsed CML post-SCT, but AML patients who relapse post-SCT are less likely to respond to DLI.
- For a small percentage of patients with good performance status who achieve remission after relapsing post-SCT, a second SCT may be considered as a curative option.
- Notable Labs uses a flow cytometric-based assay to test a panel of FDA-approved chemotherapy and targeted agents—singly and in combinations using a custom robotic platform—to determine anti-cancer effect against individual patient's tumor cells.
- This personalized test is an attractive strategy for screening to find novel agents and/or drug combinations to treat AML patients who have failed previous therapies, including SCT.

NOTABLE LABS PROCESSS OVERVIEW



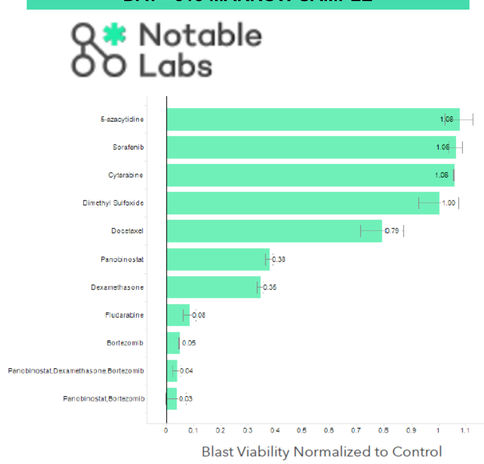
CASE REPORT

- A 15-year-old male was diagnosed with M4-AML. Molecular studies revealed NPM1 gene mutation and no FLT3-ITD.
- He was treated with the standard risk arm of COG trial AAML1031.
- Eight months after completion of initial scheduled chemotherapy, he had an isolated bone marrow relapse.
- His leukemia at relapse was FLT3-ITD positive.
- He achieved a second remission by MRD and morphology with fludarabine, cytarabine, and sorafenib; and underwent MSD-BMT after conditioning with busulfan and cyclophosphamide.
- He developed grade 2 VOD and had grade I acute GVHD, but no chronic GVHD. Immunosuppressive therapy was discontinued on day +98.
- BMA performed on day +180 was MRD positive (0.13%).
- Repeat BMA done on day +204 showed 5.7% MRD.
- He started sorafenib 300 mg po q 12h on day +212.
- He received donor lymphocyte infusion (DLI)#1 with 64x10e6 CD3+cells/kg on day +246.
- He then received 2 cycles of azacitadine (AZA) 100 mg/m2/dose daily x 5 followed by DLI (100x10e6 CD3+cells/kg). Cycle 1 began day +264; cycle 2, with 80% AZA dosing due to myelosuppression, on day +291.
- On day +264, sorafenib dose was decreased to 300 mg po daily due to concomitant voriconazole.
- Treatment was complicated by the following:
  - Varicella meningitis diagnosed day +258
  - Grade I aGVHD of skin diagnosed day +290
  - Febrile neutropenia and C. difficile colitis diagnosed day +299
  - Respiratory infection secondary to metapneumovirus diagnosed day +333.
- Despite extremely low levels of leukemia in the samples, Notable Lab testing performed on the patient's leukemia cells from marrow collected on days +313 and +343 revealed leukemia cell sensitivity to a combination of bortezomib, panobinostat, and dexamethasone.
- Because of prolonged cytopenias, multiple infectious complications, and increasing MRD, he discontinued sorafenib and started bortezomib, panobinostat, and dexamethasone on day +368 according to JF San-Miguel et al [Lancet Oncol 15 (11):1195–1206] as follows:
  - BORTEZOMIB 1.3 mg/m2 IV on days 1, 4, 8, and 9
  - DEXAMETHASONE 20 mg po on days 1, 2, 4, 5, 8, 9, 11, and 12
  - PANOBINOSTAT 20 mg po on days 1, 3, 5, 8, 10, 12.
  - Chemotherapy cycles repeated every 21 days.
- He received his last scheduled chemotherapy on day +407.
- He tolerated treatment without side effects and with resolution of rash and cytopenias.
- He achieved full donor chimerism and complete remission by morphology and flow cytometry after two cycles.

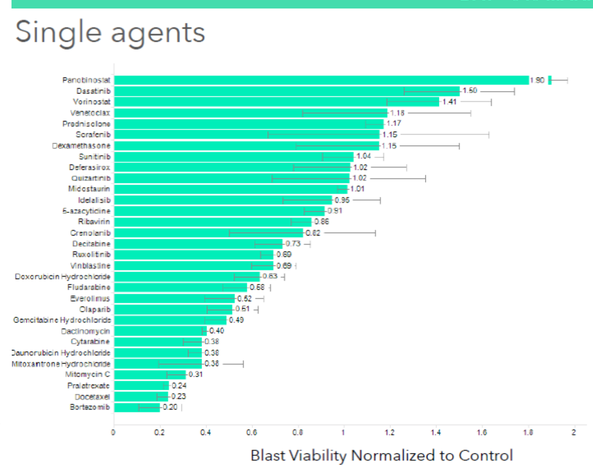
RESULTS

FIGURES. NOTABLE LAB TESTING RESULTS

DAY +313 MARROW SAMPLE



DAY +343 MARROW SAMPLE



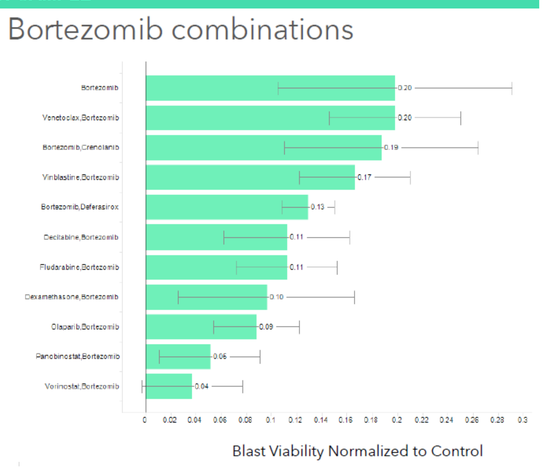


TABLE. TREATMENT AND DISEASE RESPONSE

PRECEDING TREATMENT	DAYS POST-SCT	MARROW MORPHOLOGY	MARROW MRD BY FLOW	MARROW FLT3-ITD (ALLELIC RATIO)	MARROW CHIMERISM
Fludarabine, ARA-C, Sorafenib	-30	No evidence of malignancy	Negative (<0.01%)	Not detected	Not applicable
Busulfan, Cytoxan, MSD-BMT	+30	No evidence of malignancy	Negative (<0.01%)	Not detected	99.8% donor
None	+60	No evidence of malignancy	Negative (<0.01%)	Not detected	100% donor
None	+100	No evidence of malignancy	Negative (<0.01)	Not detected	98.8% donor
None	+180	No evidence of malignancy	Positive (0.13%)	Not detected	98% donor
None	+204	No evidence of malignancy	Positive (5.7%)	Positive (0.02)	94% donor
Sorafenib	+230	19% blasts	Positive (16%)	Positive (0.09)	77% donor
Sorafenib, DLI	+265	63% blast	Positive (15.7%)	Positive (0.49)	23% donor
Sorafenib, AZA, DLI	+313	Hypocellular, no evidence of malignancy	Small abnormal myeloid population (<0.1%+)	Positive (0.03)	92% donor
Sorafenib, AZA, DLI	+343	Hypocellular, no evidence of malignancy	0.16% residual leukemia	Positive (<0.02)	94% donor
Bortezomib, panobinostat, dexamethasone	+382	No evidence of malignancy	Negative (<0.01%)	Negative	98% donor
Bortezomib, panobinostat, dexamethasone	+412	No evidence of malignancy	Negative (<0.01%)	Negative	100% donor

CONCLUSIONS

- Notable Lab testing is a powerful tool for evaluating the sensitivity of small populations of leukemic blasts (MRD <0.01%) to novel drug therapy.
- Results from Notable Lab testing may serve as a useful guide for treatment selection after failure of standard AML therapy.
- BORTEZOMIB, PANOBINOSTAT, and DEXAMETHASONE—a regimen shown by Notable Lab testing to cause in vitro killing of leukemic blasts from this AML patient in second relapse—successfully induced morphologic and MRD remission and full donor chimerism post-SCT.

DISCLOSURES

NONE OF THE AUTHORS HAVE ANY RELEVANT CONFLICTS OF INTEREST TO REPORT