Ex vivo drug sensitivity assay correlates with clinical response in pediatric AML

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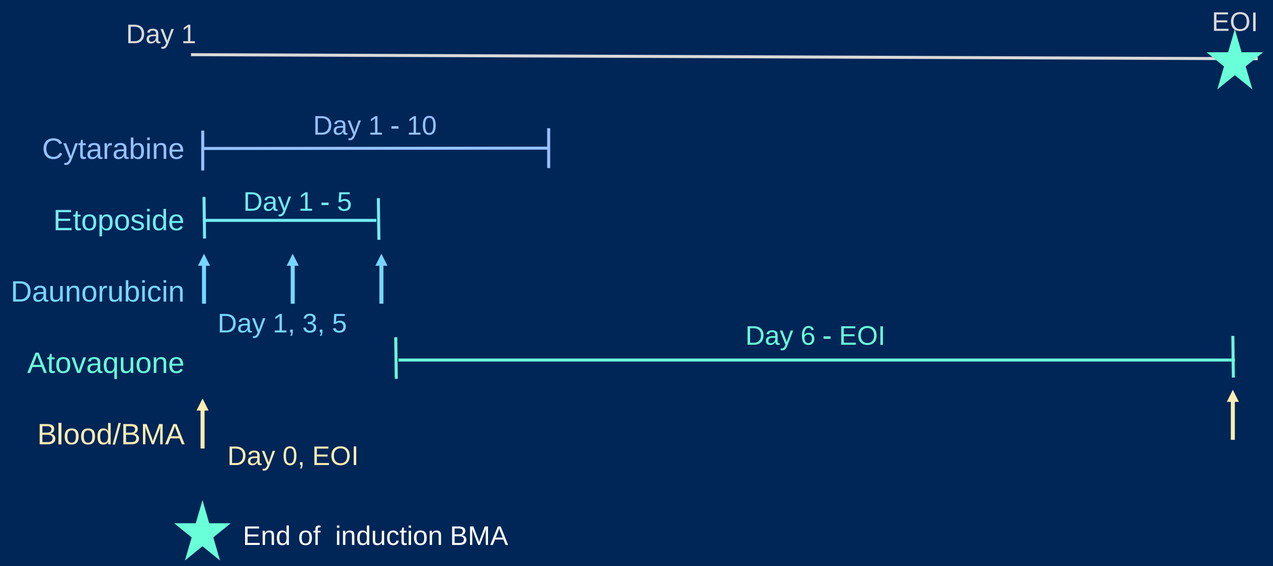
ATACC Trial – NCT03568994

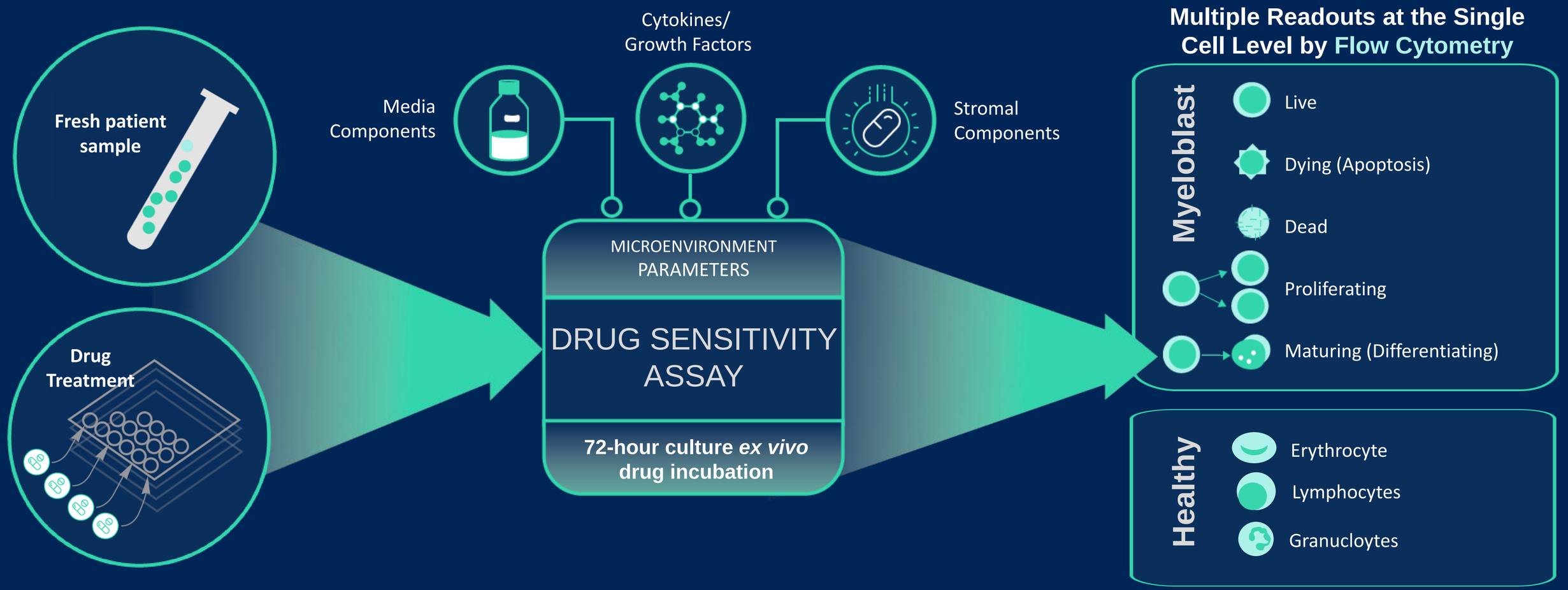
A Trial of Atovaquone Combined with Conventional Chemotherapy for De Novo AML in Children, Adolescents, and Young Adults



UPN	Age/Sex	Tissue Type	FAB	Cytogenetics	Mutations	MRD at EOI	Relapse	Clinical Outcome
pAML1	15/M	BM	M2	t(8;21)		9.7%	No	Alive
pAML2	16/F	BM	M2	11q23 dupl		0%	No	Alive
pAML3	16/M	BM	M5a	t(6;11), '+21		4.0%	Yes	DD
pAML4	7/M	PB	M4	+8	FLT3	0%	No	Alive
pAML5	13/M	BM	M2	t(8;21)		0%	No	Alive
pAML6	11/M	PB	M1	t(10;11)+ complex		50%	Yes	Alive
pAML7	19/F	PB	M1	NK	FLT3, NPM1	0.7%	No	TRM
pAML8	2/M	PB	M7	+10		0%	No	Alive
pAML9	16/F	BM	M1/M2	NK	CEBPa	0%	No	Alive
pAML10	16/F	BM	M4/M5	NK	NPM1	0%	No	Alive
pAML11	11/M	PB	M1/M2	NK	NPM1	0%	No	Alive
pAML12	12/M	PB	M1/M2	NK	FLT3, CEBPa	0%	No	Alive
pAML13	6/F	BM	M1/M2	t(1;11)not KMT2A; del(11q)	CEBPa	0%	No	Alive

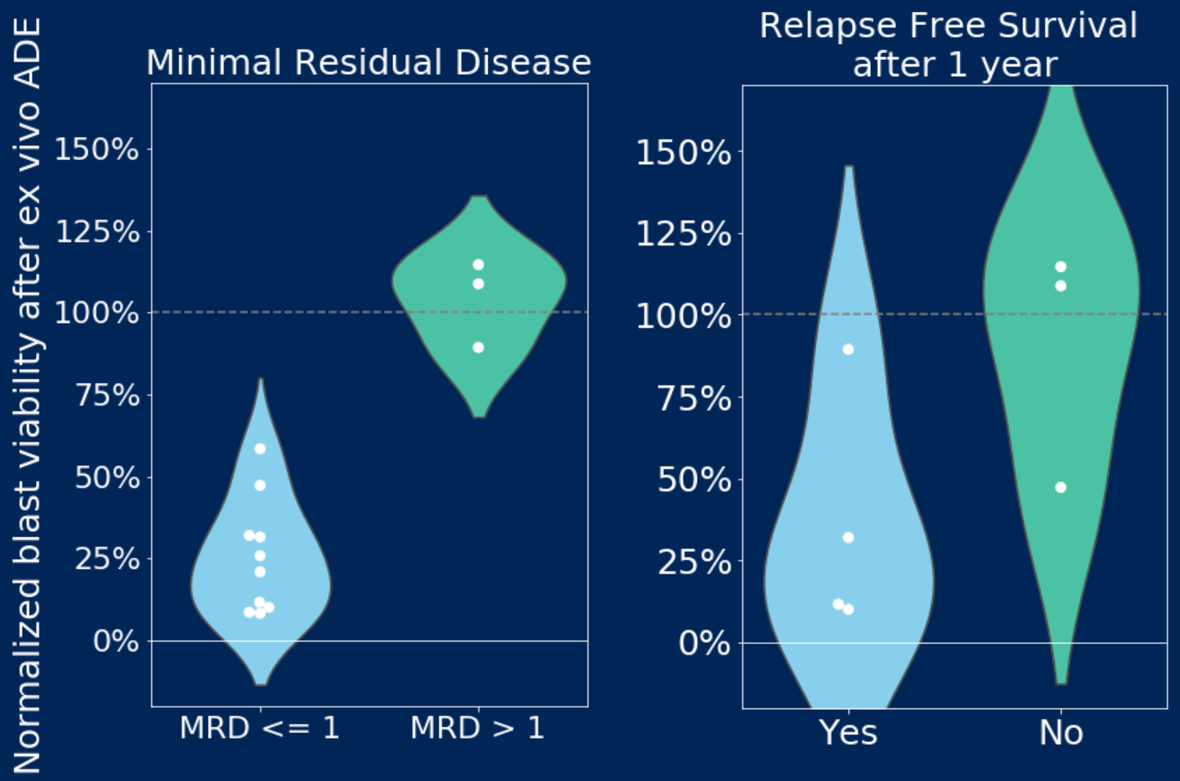
UPN: Unique Patient Number. Age: given in years at the time of initial diagnosis. M: Male, F: Female. BM: Bone Marrow; PB: Peripheral Blood. FAB: French-American-British morphologic classification. NK: Normal Karyotype. Mutations: FLT3, NPM1, CEBPa shown. MRD: Minimal Residual Disease by flow cytometry. EOI: End of Induction. Outcome column indicates status at last contact. DD: Death due to Disease; TRM: Treatment related mortality.

High Throughput Functional *Ex Vivo* Screening

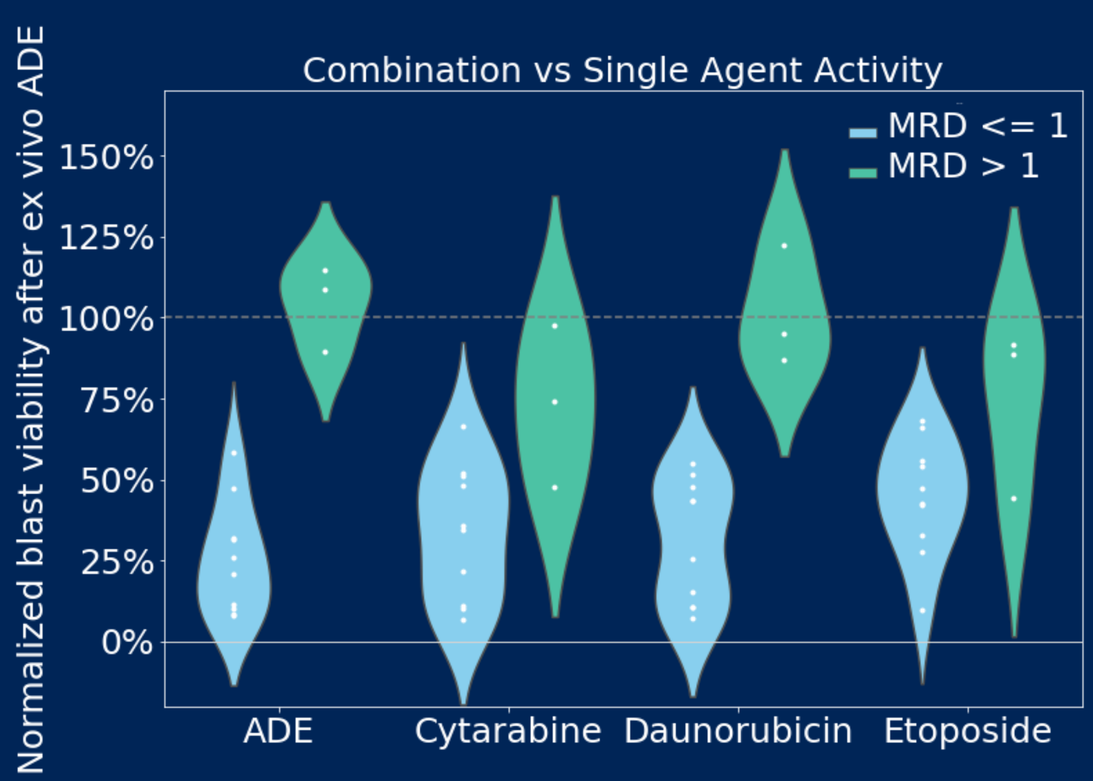


Spinner, M. et al. Blood Advances (2020)

Ex Vivo ADE (cytarabine, daunorubicin, etoposide) correlates with MRD and relapse free survival

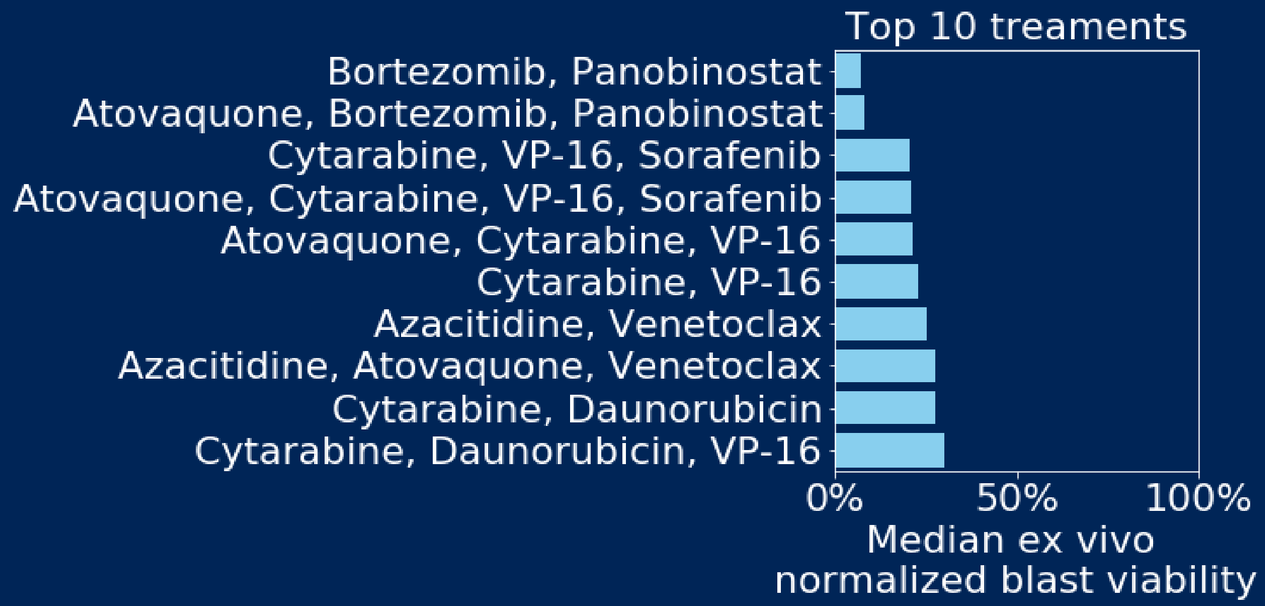


***Ex vivo* ADE treatment response correlates with clinical response**



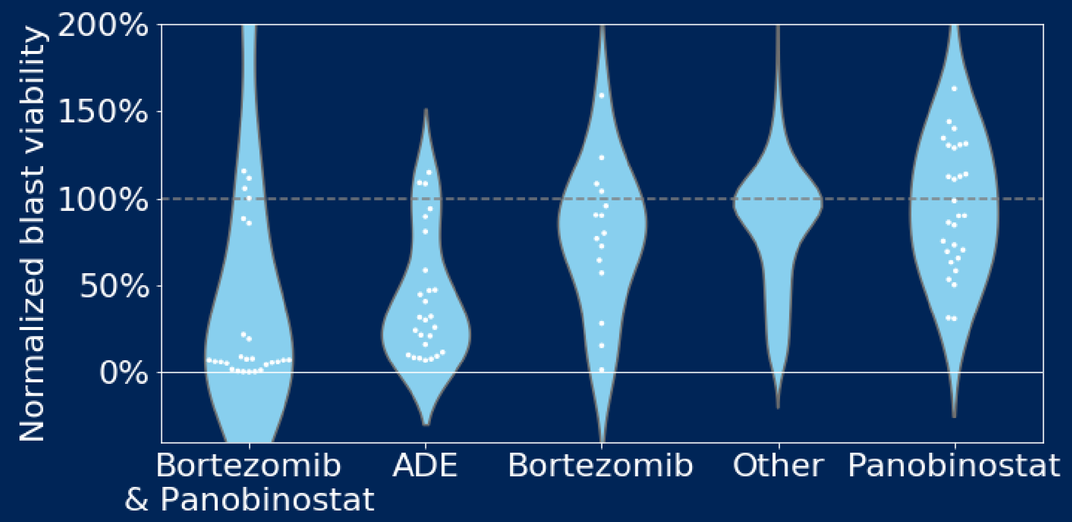
***Ex vivo* ADE treatment better correlates with MRD than single agents**

Ex vivo DSA response suggests Bortezomib/Panobinostat combination could be a novel treatment for pediatric AML



Compounds and ex vivo dosing (nM):
Atovaquone: 3000 nM; Bortezomib: 11 nM; Cytarabine: 300 nM; Daunorubicin: 70 nM; Etoposide (VP-16): 300 nM; Sorafenib: 40nM; Panobinostat: 5 nM; Venetoclax: 225 nM

Bortezomib + Panobinostat is the most potent treatment out of 169 conditions tested



Increased *ex vivo* efficacy with Bortezomib + Panobinostat combination

Next Steps - Validating *ex vivo* Bortezomib/Panobinostat results with *in vivo* and *in vitro* studies

In vitro

In vitro co-culture transwell assay exploring efficacy and relative activity to ADE

Vehicle	Panobinostat	Bortezomib	Panobinostat Bortezomib	ADE

Cryopreserved diagnostic PDX sample available for the following patients:

- pAML8 – Assay responder; RAM phenotype
- pAML3 – Assay non-responder; Induction failure

In vivo

In vivo efficacy studies evaluating the activity observed in the drug sensitivity assay

Cohort 1	Cohort 2	Cohort 3	Cohort 4
Vehicle	Panobinostat	Bortezomib	Panobinostat Bortezomib