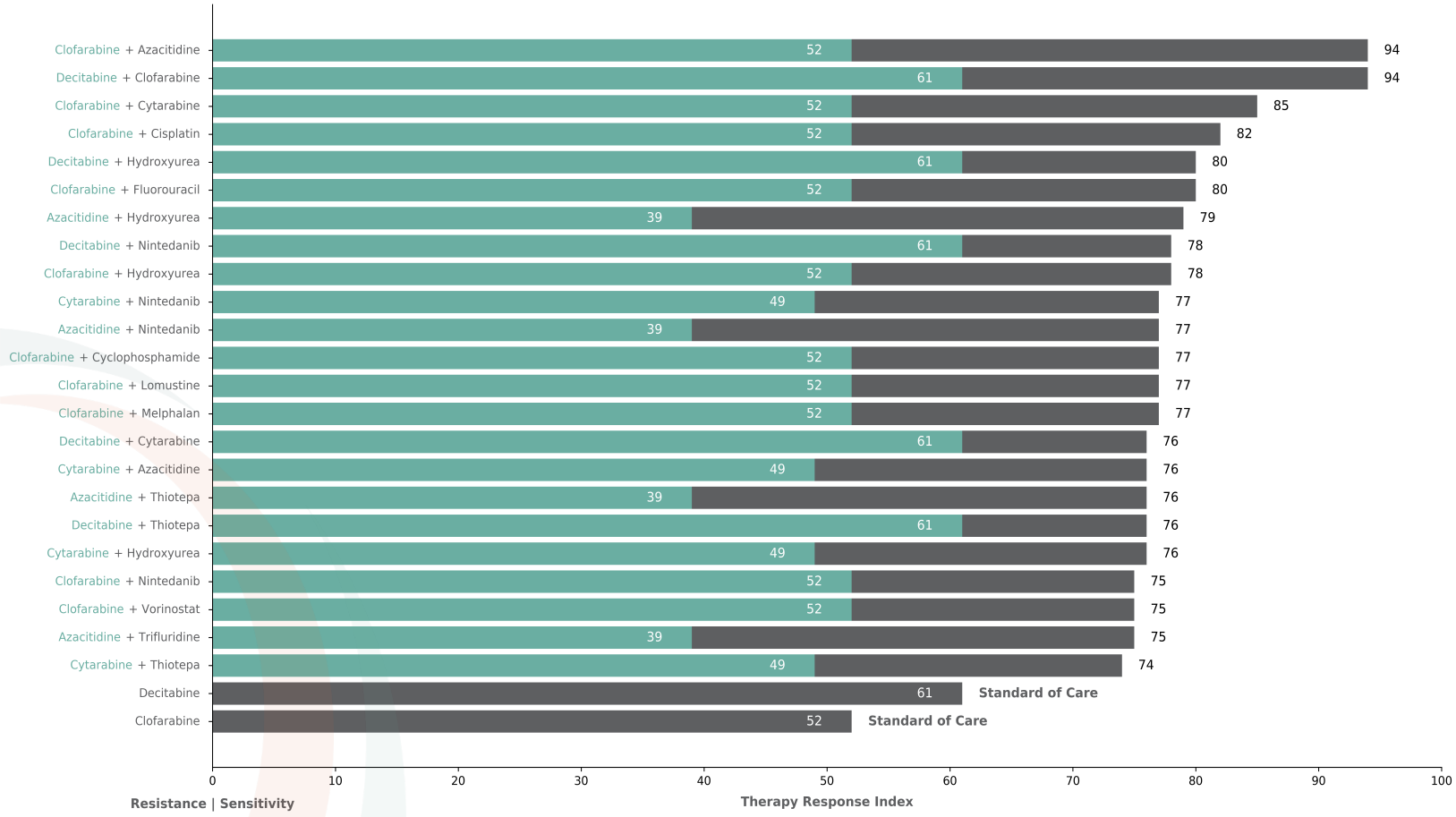
Order ID :	123456
Clinical ID :	ABC123
Indication :	Acute Myeloid Leukemia (AML) - NOS
Physician :	Dr. Smith
Patient Age :	65
Patient Gender :	Male
Patient Status :	Refractory
Biopsy Date :	Nov 01, 2021
Sample Type :	Bone Marrow
Genomic Input :	NGS Report
Additional Input :	NA

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

1. Top Biosimulation Treatments

The top 25 TRI treatments are listed below. The total score of the treatment is listed as a dark grey bar. For combination therapies, the light green section represents the strongest monotherapy component of the combination. The Standard Care treatments are labeled. See Section 4.2 for a complete list of Standard care treatments



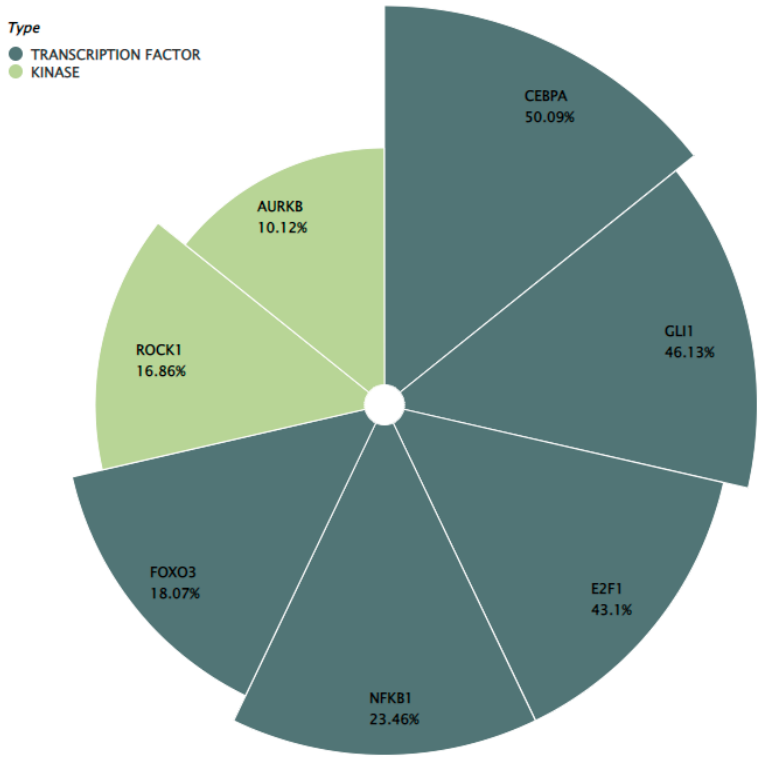
Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

2. Master Regulators

The master regulators are uniquely selected for each patient. The Biosimulation process uses the master regulators to identify the targetable pathways for maximum phenotype impact. Up to 10 master regulators are shown her. See Section 7 for detailed illustrations of Specific Master Regulators and their impact on the patient's disease profile.

2.1 Master Regulator Impact Weight



2.2 Treatment Impact on Master Regulators

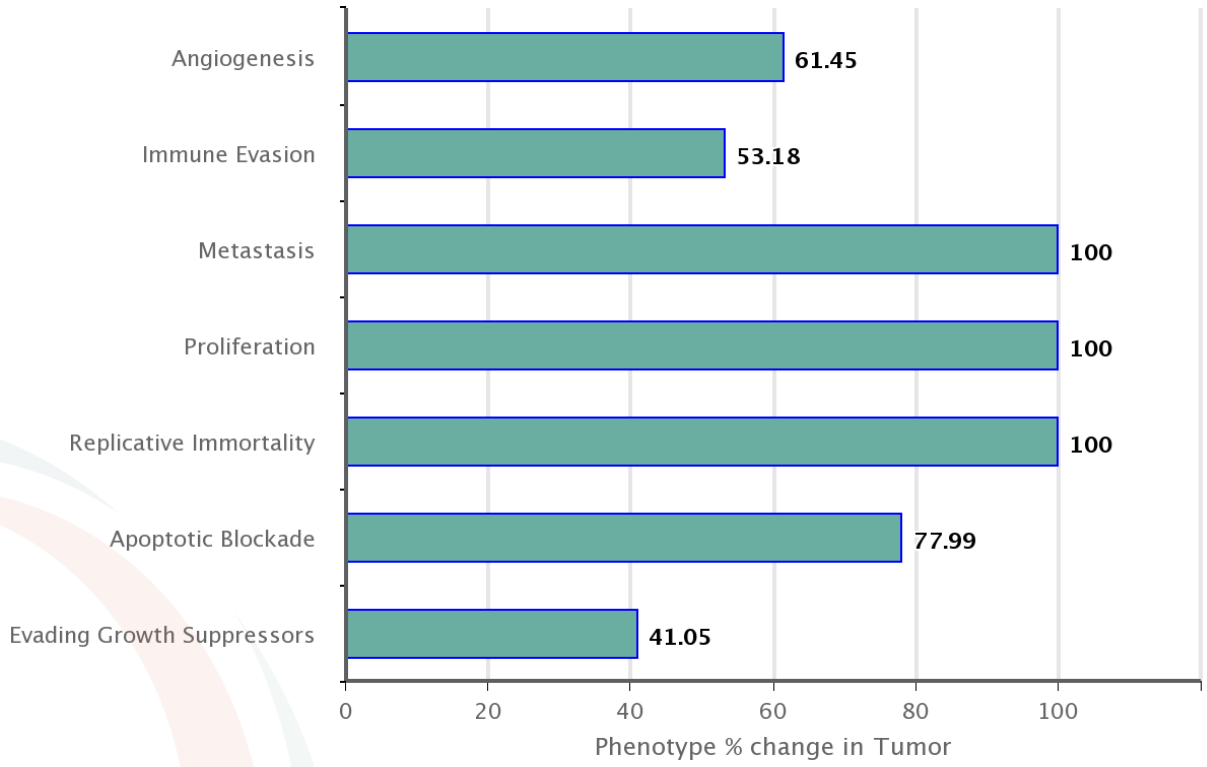
The marks indicate whether each treatment has a meaningful impact on each of the master regulators. It is not required for each responder treatment to impact every master regulator since phenotype response can be driven by more than one pathway. Typically however, treatments that successful impact several master regulators tend to have the best outcomes.

Therapies of Interest	Master Regulators									
	CDKN1A	H2AFX	PARP1	FOXO3	ROCK1	NFKB1	E2F1	AURKB	GLI1	CEBPA
Azacitidine + Clofarabine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clofarabine + Decitabine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clofarabine + Cytarabine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

3. Phenotype Index Values



Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

4. Clinical Trials

Clinical Trial Id	Trial Title	Trial Sponser	Treatment	Cellworks Prediction
NCT04002115	Clofarabine Pre-conditioning Followed by Stem Cell Transplant for Non-remission AML	Milton S. Hershey Medical Center	Clofarabine	Favorable Outcome
NCT03096782	Umbilical Cord Blood Transplant With Added Sugar and Chemotherapy and Radiation Therapy in Treating Patients With Leukemia or Lymphoma	M.D. Anderson Cancer Center	Clofarabine	Favorable Outcome
NCT03164057	A Trial of Epigenetic Priming in Patients With Newly Diagnosed Acute Myeloid Leukemia	St. Jude Children's Research Hospital	Decitabine	Favorable Outcome
NCT01515527	Cladribine Plus Low Dose Cytarabine (LDAC) Alternating With Decitabine in Patients With Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS)	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome
NCT04817241	Testing Oral Decitabine and Cedazuridine (ASTX727) in Combination With Venetoclax for Higher-Risk Acute Myeloid Leukemia Patients	National Cancer Institute (NCI)	Decitabine	Favorable Outcome
NCT04657081	Pharmacokinetics, Safety, and Efficacy of ASTX727 in Combination With Venetoclax in Acute Myeloid Leukemia (AML)	Astex Pharmaceuticals, Inc.	Decitabine	Favorable Outcome

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Clinical Trial Id	Trial Title	Trial Sponser	Treatment	Cellworks Prediction
NCT03306264	Study of ASTX727 vs IV Decitabine in MDS, CMML, and AML	Astex Pharmaceuticals, Inc.	Decitabine	Favorable Outcome
NCT04746235	Venetoclax and ASTX727 for the Treatment of Relapsed, Refractory, or Newly Diagnosed Acute Myeloid Leukemia	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome
NCT04055844	Multi-Ctr PII Cmb.Modality Tx Ruxolitinib, Decitabine, and DLI for Post HSCT in AML/MDS	Masonic Cancer Center, University of Minnesota	Decitabine	Favorable Outcome
NCT03404193	Venetoclax and Decitabine in Treating Participants With Relapsed/Refractory Acute Myeloid Leukemia or Relapsed High-Risk Myelodysplastic Syndrome	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome
NCT05010122	ASTX727, Venetoclax, and Gilteritinib for the Treatment of Newly Diagnosed, Relapsed or Refractory FLT3-Mutated Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome
NCT03661307	Quizartinib, Decitabine, and Venetoclax in Treating Participants With Untreated or Relapsed Acute Myeloid Leukemia or High Risk Myelodysplastic Syndrome	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome
NCT04774393	Decitabine/Cedazuridine and Venetoclax in Combination With Ivosidenib or Enasidenib for the Treatment of Relapsed or Refractory Acute Myeloid Leukemia	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Clinical Trial Id	Trial Title	Trial Sponser	Treatment	Cellworks Prediction
NCT04282187	Decitabine With Ruxolitinib or Fedratinib for the Treatment of Accelerated/Blast Phase Myeloproliferative Neoplasms	University of Washington	Decitabine	Favorable Outcome
NCT04188405	Decitabine, Venetoclax, and Ponatinib for the Treatment of Philadelphia Chromosome-Positive Acute Myeloid Leukemia or Myeloid Blast Phase or Accelerated Phase Chronic Myelogenous Leukemia	M.D. Anderson Cancer Center	Decitabine	Favorable Outcome
NCT04730258	A Study of CFI-400945 With or Without Azacitidine or Decitabine in Patients With AML, MDS or CMML	Treadwell Therapeutics, Inc	Decitabine	Favorable Outcome
NCT04644016	Cord Blood Transplant in Children and Young Adults With Blood Cancers and Non-malignant Disorders	Memorial Sloan Kettering Cancer Center	Clofarabine	Favorable Outcome

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

5. Patient Profile

5.1 Summary of Patient Genomic Profile

The table below includes all of the patient genomic and lab results used as input when generating this report.

Input Data Type	Mutations and CNV
Genetic Mutation(s)	29
Copy Number Variation(s)	407
Gene(s) Methylated	0

5.2 Detailed Information of Genomic Aberration(s) Modeled

The table below lists all of the gene mutations and copy number variations in chromosomal order.

5.2.1 Gene Mutation(s) with Gain of Function

ESRRA R377_A378delinsP	MUC4 A4166_D4213del
MUC4 S3736_A3737insSSTGQATPLPVTSTSSVSTGHVTPLHVTSPSS	MUC4 T3823_T3854del
MUC4 V3305_S3320del	PSPH G90S

5.2.2 Gene Mutation(s) with Loss of Function

ACO2 G463W	CDK12 D235del
CLSPN G328R	CMA1 splice_donor_variant
DDX3X splice_acceptor_variant	DDX3X splice_acceptor_variant_NMD_transcript_variant
FANCD2 splice_donor_variant	GALE R169W
HLAB Q94Hfs*4	KIR2DL1 K176Sfs*8
KIR2DL1 V177Afs*72	LIN28A R192*
MKI67 splice_acceptor_variant	MUC4 D3261Hfs*16
MUC4 P3478Ffs*23	MUC4 S3477Nfs*783
PPARA T71Sfs*11	PSPH splice_donor_variant
SDHA L649Efs*4	TP53 L383*
TTK S108T	ZDHHC11 W98*

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

5.2.3 Gene Mutations(s) with Switch of Function

IDH2 R140Q

5.2.4 Gene(s) with Increase in Copy Number Variation [CNV]

ANGPT1	ANGPT2	ASAH1	ASH2L	ATP6V1H	BAALC	BAG4	BLK
CCAR2	CCNE2	CEBPD	CLU	CNOT7	COPS5	CSGALNACT1	CTSB
CYP7A1	DEPTOR	DERL1	DGAT1	DKK4	DLC1	DPYS	E2F5
EGR3	EIF3E	EIF3H	EIF4EBP1	ELP3	EPHX2	ESRP1	EXT1
EYA1	FABP5	FBXO32	FBXO43	FDFT1	FGFR1	FNTA	GATA4
GFRA2	GGH	GPT	GSR	HAS2	HEY1	HSF1	IDO1
IDO2	IKBKB	IL7	KAT6A	KLF10	LOXL2	LPL	LY96
LYN	LYPLA1	MCM4	MIR30D	MMP16	MTDH	MTUS1	MYC
NAPRT	NBN	NCOA2	NDRG1	NEIL2	NRG1	NSD3	NSMAF
NUDT18	OPLAH	PAG1	PBK	PDLIM2	PDP1	PIP4P2	PLAT
POLB	PPP2R2A	PREX2	PRKDC	PTDSS1	PTK2	PTK2B	PTP4A3
RAB2A	RAD21	RAD54B	RB1CC1	RECQL4	RIPK2	RRM2B	RSPO2
RUNX1T1	SCRIB	SDC2	SFRP1	SFTPC	SGK3	SLC25A32	SNAI2
SOX17	SQLE	ST3GAL1	STK3	TCEA1	TERF1	TNFRSF10A	TNFRSF10B
TNFRSF10C	TNFRSF10D	TNFRSF11B	TNKS	TPD52	UBE2V2	UBR5	WRN
WWP1	XKR4	XKR9	YWHAZ	ZDHHC2	ZFPM2	ZNF703	

5.2.5 Gene(s) with Decrease in Copy Number Variation [CNV]

ABCB1	ABCB5	ACTB	ADA	ADCY1	ADCYAP1R1	ADRM1	AHR
AICDA	AKAP9	AKR1B10	ALG10	ANO6	ARID2	ARPC1A	ASB4
ASL	ASNS	ATG9B	AURKA	B4GALT5	BCL7B	BHLHA15	BHLHE41
BLVRA	BRAF	C1R	C1S	CAMK2B	CARD11	CASP2	CAV1
CCL26	CCND2	CD27	CD36	CD4	CD40	CDK5	CDK6
CDKN1B	CEBPB	CHD4	CHN2	CLDN4	CLEC2A	CLEC2B	CLEC2D

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

CLEC7A	CNOT4	COL1A2	COPS6	COPS7A	CREB3L2	CSE1L	CTCFL
CUL1	CUX1	CYCS	CYP24A1	CYP3A4	CYP51A1	DAGLB	DBF4
DDC	DGKB	DGKI	DMTF1	DNAJB6	DNAJB9	DOCK4	DPPA3
DUSP16	EGFR	EIF3B	ELMO1	ELMO2	ENO2	EPHA1	EPHB4
EPHB6	EPO	EPS8	ERC1	ETV1	ETV6	EXOC4	EZH2
FBXL13	FOXM1	FSCN1	FZD9	GABARAPL1	GAPDH	GGCT	GLI3
GNA12	GNAS	GRB10	GRIN2B	GSTK1	GTF2I	HBP1	HDAC9
HGF	HIPK2	HNF4A	HNRNPA2B1	HOXA1	HOXA10	HOXA11	HOXA13
HOXA2	HOXA3	HOXA5	HOXA7	HOXA9	HSPB1	HTR5A	HUS1
IGFBP1	IGFBP3	IKZF1	IL6	IMPDH1	ING4	INHBA	INSIG1
IRAK4	ITGB8	ITPR2	KDM5A	KDM7A	KLRB1	KLRC1	KLRC2
KLRF1	KLRF2	KLRG1	KLRG2	KLRK1	KMT2C	KMT2E	KRAS
L3MBTL1	LAG3	LAMA5	LAMB1	LDHB	LEP	LIMK1	LRP6
LRRK2	LTBR	MAD1L1	MAFK	MAGI2	MCM7	MDH2	MET
MGP	MGST1	MIOS	MIR182	MIR200C	MIR25	MIR29A	MIR29B1
MIR550A1	MLXIPL	MMP9	MNX1	MYBL2	NAMPT	NANOG	NCF1
NCOA3	NFATC2	NOS3	NRF1	NTF3	NUDT1	NUP205	OGDH
PAXIP1	PCK1	PDE3A	PDGFA	PDIA4	PDK4	PIK3CG	PMS2
PODXL	POLD2	POLM	POT1	PPP1R3A	PREX1	PRICKLE1	PRSS1
PSMA2	PSMA7	PSMC2	PSMG3	PTGIS	PTHLH	PTK6	PTN
PTPN1	PTPN6	PTPRO	PTPRT	PTPRZ1	RAC1	RAD52	RAE1
RALA	RASA4	RBM38	RFC2	RGS19	RHEB	RPA3	SALL4
SDC4	SEC61G	SEMA3A	SEMA3E	SERPINE1	SFRP4	SH2B2	SHH
SLC29A4	SLC2A3	SLC2A4RG	SLCO1A2	SLCO1B1	SLCO1B3	SLPI	SMO
SMURF1	SNAI1	SNX13	SPSB2	SRPK2	SRSF6	ST8SIA1	STEAP1
STEAP4	STK4	STX1A	TAPBPL	TAX1BP1	TBXAS1	TEAD4	TFPI2
TIGAR	TNFRSF1A	TPI1	TRIM24	TRRAP	TUBB1	TWIST1	UBE2C
UBE2V1	UBE3C	UPP1	USP42	USP5	VIPR2	WASL	WEE2

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

WIPI2	WNK1	XRCC2	YBX3	YWHAB	ZC3HC1	ZDHHC4	ZNF217

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

6. Therapy Rationale(s)

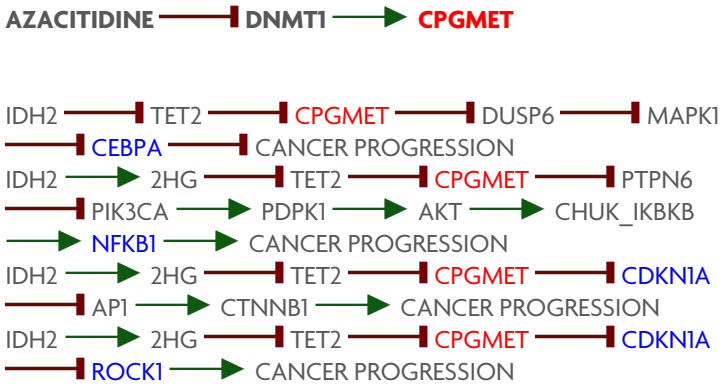
Rationales provided in this section highlight the pathways connected to drug sensitivity and resistance and include references to supporting published literature.

Species in red denote drug impact points. Species highlighted in blue are the Master Regulators.

Azacitidine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
EZH2	CNV Knockdown	Resistant Pathway	**AZACITIDINE** ⊣ **DNMT1** → **CPGMET** EZH2 → PRC2 COMPLEX → CPGMET ⊣ ZEB1 → CANCER PROGRESSION	23671287 16357870 20601954 18360650

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Azacitidine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
IDH2	Switch of Function	Sensitive Pathway		19194470 28193779 33043739 25398940 12046058 12119358 21130701 23671287 12383256 22569363 25224413 26498513 10488096 19609947 26779436 11304577 18650261 28646232 21355845 28054552 22461507 24890832 17164422 24978161 21858223 23250430 12592393 16039586 12579297 19259613 26516376 23979523 21071137 15824892 26833217 19417127 24510345 16357870 12154409 29554906 22343901 25886188 24875481 24216483 11278353 24688109 9261115 14563837

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Azacitidine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
KAT6A	CNV Overexpression	Sensitive Pathway	**AZACITIDINE** ⊣ **DNMT1** → **CPGMET** KAT6A → EZH2 → PRC2_COMPLEX → CPGMET ⊣ CDKN1A ⊣ ROCK1 → CANCER PROGRESSION KAT6A → EZH2 → PRC2 COMPLEX → CPGMET ⊣ DUSP6 ⊣ MAPK3 → GLI1 → CANCER PROGRESSION KAT6A → EZH2 → PRC2_Complex → CPGMET ⊣ PPARG ⊣ NFKB1 → CANCER PROGRESSION KAT6A → EZH2 → PRC2 COMPLEX → CPGMET ⊣ CDKN1A ⊣ CDK2_CCNA2 → FOXM1 → CANCER PROGRESSION	23671287 25772242 16357870 18360650 16850502 7626805 18285455 12154409 12579297 18806826 28869966 15824892 24222120 19142899 26292171 15793220 30121333
GGH	CNV Overexpression	Resistant Pathway	**AZACITIDINE** ⊣ **DNMT1** → **CPGMET** GGH ⊣ S ADENOSYL METHIONINE → CPGMET ⊣ PPARG ⊣ NFKB1 → CANCER PROGRESSION	25886188 12154409 12383256 23671287 23647960 25502219 25224413
L3MBTL1	CNV Knockdown	Sensitive Pathway	**AZACITIDINE** ⊣ **DNMT1** → **CPGMET** L3MBTL1 ⊣ E2F1 → EZH2 → DNMT1 → CPGMET ⊣ CDKN1A ⊣ CDK2_CCNA2 → FOXM1 → CANCER PROGRESSION	7626805 16850502 18285455 11895758 17540172 23671287 16357870 21149733
PIK3CG	CNV Knockdown	Resistant Pathway	**AZACITIDINE** ⊣ **DNMT1** → **CPGMET** PIK3CG → PI45P2 → PTK2 ⊣ GSK3B ⊣ DNMT1 → CPGMET ⊣ ZEB1 → CANCER PROGRESSION	17317726 27405758 12496760 32094334 15547111

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Clofarabine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
PMS2	CNV Knockdown	Sensitive Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** PMS2 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	23663976 20544529 23361057 11292842 19793570
KMT2C	CNV Knockdown	Sensitive Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** KMT2C → H3K4 METHYLATION → MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	23663976 20544529 24403070 15475387 24081332 25135975 25043185 23361057
MYC	CNV Overexpression	Resistant Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** MYC → MYC_MAX → DHODH → dCTP ⊣ DCK → CAFdAMP → CAFdADP → CAFdATP → DNA DAMAGE	23663976 20544529 27641501 18628958 3871794 25127121
CLSPN	Loss of Function	Sensitive Pathway	**CLOFARABINE** → **CAFdADP** ⊣ **RRM1/2** → **dNTP** ⊣ **REPLICATION STRESS** CLSPN → CHEK1 ⊣ REPLICATION STRESS → APOPTOSIS	19500427 20544529
RRM2B	CNV Overexpression	Resistant Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** RRM2B → dNTP ⊣ DCK → CAFdAMP → CAFdADP → CAFdATP → DNA DAMAGE	23663976 20544529 24024897 3484676 19842938 16918309
HUS1	CNV Knockdown	Sensitive Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** HUS1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	23663976 20544529 20188637 15314187 23361057
IDH2	Switch of Function	Sensitive Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** IDH2 → 2HG ⊣ TET2 ⊣ CPGMET ⊣ MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	1707752 22395470 24403070 10072435 25886910 25398940 15475387

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Clofarabine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
EZH2	CNV Knockdown	Resistant Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** EZH2 → PRC2 COMPLEX → H3K27 METHYLATION ⊣ HOXA5 → MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	23663976 20544529 26472914 16756717 15475387 10072435 25043185 22211105 24987060
KDM5A	CNV Knockdown	Resistant Pathway	**CLOFARABINE** → **CAFdATP** → **DNA DAMAGE** KDM5A ⊣ H3K4 METHYLATION → MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	15475387 2311169 25043185 25190814 24403070 23361057
CUX1	CNV Knockdown	Sensitive Pathway	**CLOFARABINE** → **CAFdADP** ⊣ **RRM1/2** → **dNTP** ⊣ **REPLICATION STRESS** CUX1 → ATR → CHEK1 ⊣ REPLICATION STRESS → APOPTOSIS	21628579 28442502 32316968 24038068 32187883 22319212

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Cytarabine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
EZH2	CNV Knockdown	Resistant Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** EZH2 → PRC2 COMPLEX → H3K27 METHYLATION ⊣ HOXA5 → MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	26472914 16756717 15475387 10072435 25043185 22211105 24987060 2311169
HUS1	CNV Knockdown	Sensitive Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** HUS1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	23361057 20188637 15314187 2311169
IDH2	Switch of Function	Sensitive Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** IDH2 → 2HG ⊣ TET2 ⊣ CPGMET ⊣ MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	22395470 24403070 15475387 25886910 25398940 10072435 2311169
KDM5A	CNV Knockdown	Resistant Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** KDM5A ⊣ H3K4 METHYLATION → MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	15475387 24403070 25043185 23361057 2311169 25190814
KMT2C	CNV Knockdown	Sensitive Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** KMT2C → H3K4 METHYLATION → MLH1 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	24403070 15475387 24081332 25135975 25043185 23361057 2311169
MYC	CNV Overexpression	Resistant Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** MYC → MYC_MAX → DHODH → dCTP ⊣ DCK → AraCMP → AraCTP → DNA DAMAGE	27641501 3871794 18628958 25127121 2311169
PMS2	CNV Knockdown	Sensitive Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** PMS2 → DNA REPAIR (MMR) ⊣ DNA DAMAGE	23361057 11292842 19793570 2311169

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Cytarabine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
RRM2B	CNV Overexpression	Resistant Pathway	**CYTARABINE** → **AraCTP** → **DNA DAMAGE** RRM2B → dCTP ⊣ DCK → AraCMP → AraCTP → DNA DAMAGE	24024897 19842938 16918309 2311169
CLSPN	Loss of Function	Sensitive Pathway	**CYTARABINE** → **AraCTP** → **REPLICATION STRESS** CLSPN → CHEK1 ⊣ REPLICATION STRESS → APOPTOSIS	16126823 12766152 27625304 2311169
CUX1	CNV Knockdown	Sensitive Pathway	**CYTARABINE** → **AraCTP** → **REPLICATION STRESS** CUX1 → ATR → CHEK1 ⊣ REPLICATION STRESS → APOPTOSIS	22319212 28176818 22869869 29789314 27625304 25795119 2311169

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Decitabine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
IDH2	Switch of Function	Sensitive Pathway	**DECITABINE** ⊣ **DNMT1** → **CPGMET** IDH2 → 2HG ⊣ TET2 ⊣ CPGMET ⊣ PTPN6 ⊣ SRC → PIK3CA → AKT → CHUK_IKBKB → NFKB1 → CANCER PROGRESSION IDH2 → 2HG ⊣ TET2 ⊣ CPGMET ⊣ CDKN1A ⊣ AP1 → CTNNB1 → CANCER PROGRESSION	21130701 23671287 12383256 22569363 25224413 25398940 15824892 24510345 26833217 29554906
KAT6A	CNV Overexpression	Sensitive Pathway	**DECITABINE** ⊣ **DNMT1** → **CPGMET** KAT6A → EZH2 → PRC2_COMPLEX → CPGMET ⊣ CDKN1A ⊣ ROCK1 → CANCER PROGRESSION KAT6A → EZH2 → PRC2 COMPLEX → CPGMET ⊣ DUSP6 ⊣ MAPK3 → GLI1 → CANCER PROGRESSION KAT6A → EZH2 → PRC2_COMPLEX → CPGMET ⊣ PPARG ⊣ NFKB1 → CANCER PROGRESSION KAT6A → EZH2 → PRC2 COMPLEX → CPGMET ⊣ CDKN1A ⊣ CDK2_CCNA2 → FOXM1 → CANCER PROGRESSION	23671287 25772242 16357870 18360650 16850502 7626805 18285455 20126405 25886188 12154409 23647960 12579297 18806826 28869966 15824892 24222120 19142899 26292171 15547111
EZH2	CNV Knockdown	Resistant Pathway	**DECITABINE** ⊣ **DNMT1** → **CPGMET** EZH2 → PRC2 COMPLEX → CPGMET ⊣ ZEB1 → CANCER PROGRESSION	23671287 20126405 16357870 20601954 24688109 18360650
GGH	CNV Overexpression	Resistant Pathway	**DECITABINE** ⊣ **DNMT1** → **CPGMET** GGH ⊣ SAM → CPGMET ⊣ PPARG ⊣ NFKB1 → CANCER PROGRESSION	19417127 25502219 8647346 28122515
L3MBTL1	CNV Knockdown	Sensitive Pathway	**DECITABINE** ⊣ **DNMT1** → **CPGMET** L3MBTL1 ⊣ E2F1 → EZH2 → DNMT1 → CPGMET ⊣ CDKN1A ⊣ CDK2_CCNA2 → FOXM1 → CANCER PROGRESSION	7626805 16850502 20126405 18285455 11895758 17540172 16357870 21149733

Acute Myeloid Leukemia (AML) - NOS

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Decitabine				
Gene	Status	Type	Gene Status Drug Action Pathway(s)	Supporting PMID(s)
PIK3CG	CNV Knockdown	Resistant Pathway	**DECITABINE** ⊣ **DNMT1** → **CPGMET** PIK3CG → PI45P2 → PTK2 ⊣ GSK3B ⊣ DNMT1 → CPGMET ⊣ ZEB1 → CANCER PROGRESSION	17317726 27405758 12496760 32094334 20126405

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Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

7. Genomic Aberration to Master Regulator Pathway(s)

This section provides a snapshot of paths connecting the most significant gene aberrations with patient master regulators and references to published research supporting these pathways.

RED: Gain of Function/Switch of Function Mutation(s) or Amplified Gene(s) BLUE: Loss of Function Mutation(s) or Deleted Gene(s)

TRANSCRIPTION FACTORS:

Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
NFKB1	COPS5 → CUL4A → CUL4A_DDB1 ⊣ ULK1 → FBP1 ⊣ NPM1 → NFKB1	21258367
	ZNF703 → CUL4A_DDB1 ⊣ ULK1 → FBP1 ⊣ NPM1 → NFKB1	21258367
	TP53 ⊣ NFKB1	17567906
	HUS1 → HUS1_RAD1 → TOPBP1 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → PRDX1 → NFKB1	11395493 12773567 17575048 20029092 8428596
	MYC → PCNA → DNMT1 → CPGMET ⊣ CDKN1A ⊣ CCNB1_CDK1 → PRDX1 → NFKB1	12145218 12408820 12711675 15616584 16474839 17576694 9989826
	PRKDC → AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → PRDX1 → NFKB1	12517798 15710331 23748345 8428596
	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → PRDX1 → NFKB1	8428596
NFKB1	IKBKB → NFKB1	10356400 10747026 17298882 18571841
	RIPK2 → BCL10 → MALT1 → PRKCE → AKT ⊣ CHEK1 → WEE1 ⊣ CCNB1_CDK1 → PRDX1 → NFKB1	12517798 14638696 15125833 15710331 20516126 23690623 23748345 8428596

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Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
E2F1	EIF3H → EIF3E → CUL3_KLHL18 → AURKA → E2F1	20300951 23213400
	ZNF703 → CUL4A_DDB1 ⊣ ULK1 → FBP1 ⊣ NPM1 → AURKA → E2F1	20300951 21258367 9418871
	ESRP1 → FGFR2 → PTPN11 → KRAS → TIAM1 → RAC1 → PAK1 → AURKA → E2F1	11438654 14988728 20300951 22247021
	TP53 → PRKAA1 → ULK1 → FBP1 ⊣ NPM1 → AURKA → E2F1	12198151 14627987 17409411 19610065 20300951
	LYN → DOCK1 → CDC42 → PAK1 → AURKA → E2F1	19182796 20300951 22323579
	MYC → PCNA → DNMT1 ⊣ FBP1 ⊣ NPM1 → AURKA → E2F1	17576694 20300951
	PTP4A3 → ITGA1_ITGB1 → ILK → PTK2 → DNM2 → RAC1 → PAK1 → AURKA → E2F1	12782622 15673687 19118217 19889638 20300951 21102636 21474670 25501815 8538749 8649427 9736715
	CTSB → PLAU → PLAUR → PTPN11 → KRAS → TIAM1 → RAC1 → PAK1 → AURKA → E2F1	11438654 14988728 15677342 1900515 19133257 20300951 22247021
	EIF3E → CUL3_KLHL18 → AURKA → E2F1	20300951 23213400
	PRKDC → AKT ⊣ STK11 → PRKAA1 → ULK1 → FBP1 ⊣ NPM1 → AURKA → E2F1	14985505 15231735 16027121 20300951 20412774 21159649 22611470 23518498
E2F1	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → CDK1 → DNM2 → RAC1 → PAK1 → AURKA → E2F1	20300951 8428596

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Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
CEBPA	FNTA → NRAS → RAF1 → XIAP → AKT → DNMT1 ⊣ CEBPA	16964381 21151116 23640046
	YWHAZ → RAF1 → XIAP → AKT → DNMT1 ⊣ CEBPA	16964381 21151116 23640046
	ZNF703 → CUL4A_DDB1 → GRB10 → AKT → DNMT1 ⊣ CEBPA	15718470 16221682 16226444 19995915 21151116 21659605
	ESRP1 → FGFR2 → PLCG1 → PRKCE → AKT → DNMT1 ⊣ CEBPA	21151116
	LYN → PLCG2 → PRKCE → AKT → DNMT1 ⊣ CEBPA	21151116 8395016
	MYC → PCNA → DNMT1 ⊣ CEBPA	17576694
	PTP4A3 → ITGA1_ITGB1 → FLT4 → PIK3CA → PDPK1 → AKT → DNMT1 ⊣ CEBPA	10698680 11553610 21151116 8662748
	PTPN6 ⊣ PIK3CA → PDPK1 → AKT → DNMT1 ⊣ CEBPA	10698680 11406619 12105209 12616480 12874320 18064631 19289601 21151116
	PRKDC → AKT → DNMT1 ⊣ CEBPA	21151116
	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → XIAP → AKT → DNMT1 ⊣ CEBPA	17991895 21151116 23640046 27927753 8428596
CEBPA	RIPK2 → BCL10 → MALT1 → PRKCE → AKT → DNMT1 ⊣ CEBPA	14638696 15125833 20516126 21151116 23690623
	STK4 → LATS1 ⊣ YAP1 → BIRC5 → AKT → DNMT1 ⊣ CEBPA	15688006 17379520 19962312 21151116 21199877 23245941 27847303

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Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
FOXO3	FNTA → NRAS → RAF1 → XIAP → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 16027121 16964381 20412774 21159649 22611470 23640046
	YWHAZ → RAF1 → XIAP → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 16027121 16964381 20412774 21159649 22611470 23640046
	ZNF703 → CUL4A_DDB1 → GRB10 → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 15718470 16027121 16221682 16226444 18692468 19995915 20412774 21159649 21460630 21659605
	ESRP1 → FGFR2 → PLCG1 → PRKCE → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 16027121 20412774 21159649 22611470
	TP53 → PRKAA1 → SIRT2 → FOXO3	17409411
	LYN → PLCG2 → PRKCE → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 16027121 20412774 21159649 22611470 8395016
	PTP4A3 → ITGA1_ITGB1 → FLT4 → PIK3CA → PDPK1 → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	10698680 11553610 14985505 15231735 16027121 20412774 21159649 21775285 22611470 8662748
	PTPN6 ⊣ PIK3CA → PDPK1 → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	10698680 11406619 12105209 12616480 12874320 14985505 15125833 15231735 16027121 18064631 19289601 20412774
	CDK12 → BRCA1 → CDKN1A ⊣ CSNK2A1 → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	11255227 14985505 15231735 16027121 20412774 21159649 22611470
	PRKDC → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 16027121 20412774 21159649 22611470

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Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
FOXO3	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → XIAP → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 16027121 20412774 21159649 22611470 23640046 27927753 8428596
	RIPK2 → BCL10 → MALT1 → PRKCE → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14638696 14985505 15125833 15231735 16027121 20412774 20516126 21159649 22611470 23690623
	STK4 → LATS1 ⊣ YAP1 → BIRC5 → AKT ⊣ STK11 → PRKAA1 → SIRT2 → FOXO3	14985505 15231735 15688006 16027121 17379520 19962312 20412774 21159649 21199877 22611470 23245941 27847303

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Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
GLI1	FNTA → NRAS → RAF1 → PLK1 → NEK2 → GLI1	
	YWHAZ → RAF1 → PLK1 → NEK2 → GLI1	
	EIF3H → EIF3E → CUL3_KLHL18 → AURKA → PLK1 → NEK2 → GLI1	23213400
	ZNF703 → CUL4A_DDB1 → EED → CPGMET ⊣ BRCA1 ⊣ PLK1 → NEK2 → GLI1	16357870 17041588 24067368
	ESRP1 → FGFR2 → PTPN11 → KRAS → RAF1 → PLK1 → NEK2 → GLI1	
	TP53 ⊣ BCL2 ⊣ BRCA1 ⊣ PLK1 → NEK2 → GLI1	10406804 17567906 17823980 19128456 21444675 22295238 24067368 8898082
	HUS1 → HUS1_RAD1 → TOPBP1 → ATRIP → BRCA1 ⊣ PLK1 → NEK2 → GLI1	11395493 12773567 16530042 17575048 20029092 23582259 24067368
	LYN → CSF3R_LYN → PTPN11 → KRAS → RAF1 → PLK1 → NEK2 → GLI1	9824671
	MYC → PCNA → DNMT1 ⊣ BRCA1 ⊣ PLK1 → NEK2 → GLI1	17576694 24067368 24771642 24944674
	WIPI2 → MAP1LC3B ⊣ TRAF6 → PIK3CA → PDPK1 → RPS6KA3 → NEK2 → GLI1	11406619 11923207 12105209 12616480 12874320 18064631 19289601 9445476

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Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

Master Regulator(s)	Molecular Pathway Rationale for Master Regulator(s)	Reference PMID(s)
GLI1	PTP4A3 → ITGA1_ITGB1 → FLT4 → PIK3CA → PDPK1 → RPS6KA3 → NEK2 → GLI1	11553610 11923207 8662748 9445476
	PTPN6 ⊣ PIK3CA → PDPK1 → RPS6KA3 → NEK2 → GLI1	11406619 11923207 12105209 12616480 12874320 18064631 19289601 9445476
	CDK12 → BRCA1 ⊣ PLK1 → NEK2 → GLI1	24067368
	CTSB → PLAU → PLAUR → PTPN11 → KRAS → RAF1 → PLK1 → NEK2 → GLI1	15677342 1900515 19133257
	EIF3E → CUL3_KLHL18 → AURKA → PLK1 → NEK2 → GLI1	23213400
	PRKDC → AKT ⊣ BAD ⊣ BCL2 ⊣ BRCA1 ⊣ PLK1 → NEK2 → GLI1	10880354 11050396 11707444 12897128 14641020 15694340 15990872 16873482 17322918 18951090 19667065 21444675
	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → BORA → PLK1 → NEK2 → GLI1	18566290 24067368 8428596

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KINASE**:

Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
AURKB	FNTA → NRAS → RALGDS → RALA → CCNB1_CDK1 → BIRC5 → AURKB	11322487 15208305 19158485 20118982 20200357
	YWHAZ → RAF1 → PLK1 → CDC25C → CCNB1_CDK1 → BIRC5 → AURKB	19158485
	EIF3H → EIF3E → CUL3_KLHL18 → AURKA → RALA → CCNB1_CDK1 → BIRC5 → AURKB	15208305 19158485 23213400
	ESRP1 → FGFR2 → PTPN11 → KRAS → RALGDS → RALA → CCNB1_CDK1 → BIRC5 → AURKB	11322487 15208305 19158485
	TP53 ⊣ BIRC5 → AURKB	16595680 18027854 21920899
	HUS1 → HUS1_RAD1 → TOPBP1 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → BIRC5 → AURKB	11395493 12773567 17575048 19158485 20029092 8428596
	LYN → CSF3R_LYN → PTPN11 → KRAS → RALGDS → RALA → CCNB1_CDK1 → BIRC5 → AURKB	11322487 15208305 19158485 9824671
	MYC → PCNA → DNMT1 → CPGMET ⊣ CDKN1A ⊣ CCNB1_CDK1 → BIRC5 → AURKB	12145218 12408820 12711675 15616584 16474839 17576694 19158485 9989826
	PTP4A3 → ITGA1_ITGB1 → FLT4 → PIK3CA → PDPK1 → AKT ⊣ STK11 ⊣ YAP1 → BIRC5 → AURKB	10698680 11553610 12535517 22611470 23027127 23245941 8662748
	PTPN6 ⊣ PIK3CA → PDPK1 → AKT ⊣ STK11 ⊣ YAP1 → BIRC5 → AURKB	10698680 11406619 12105209 12535517 12616480 12874320 18064631 19289601 22611470 23027127 23245941

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
AURKB	CTSB → PLAU → PLAUR → PTPN11 → KRAS → RALGDS → RALA → CCNB1_CDK1 → BIRC5 → AURKB	11322487 15208305 15677342 1900515 19133257 19158485
	EIF3E → CUL3_KLHL18 → AURKA → RALA → CCNB1_CDK1 → BIRC5 → AURKB	15208305 19158485 23213400
	PRKDC → AKT ⊣ STK11 ⊣ YAP1 → BIRC5 → AURKB	12535517 22611470 23027127 23245941
	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → BIRC5 → AURKB	19158485 8428596
	RIPK2 → BCL10 → MALT1 → PRKCE → AKT ⊣ STK11 ⊣ YAP1 → BIRC5 → AURKB	12535517 14638696 15125833 20516126 22611470 23027127 23245941 23690623
	STK4 → LATS1 ⊣ YAP1 → BIRC5 → AURKB	15688006 17379520 19962312 21199877 23245941 27847303

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
ROCK1	FNTA → NRAS → RAF1 → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 16964381
	YWHAZ → RAF1 → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 16964381
	EIF3H → EIF3E → CUL3_KLHL18 → AURKA → PTK2 → DNM2 → RAC1 → RHOA → ROCK1	12782622 16187236 23213400 25501815
	ZNF703 → CUL4A_DDB1 → GRB10 → AKT → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 14645242 15718470 16221682 16226444 19995915 21659605 22984590 8810315
	ESRP1 → FGFR2 → PLCG1 → PRKCE → RHOA → ROCK1	
	TP53 ⊣ PTK2 → DNM2 → RAC1 → RHOA → ROCK1	12782622 15157737 16187236 17725966
	LYN → PTK2 → DNM2 → RAC1 → RHOA → ROCK1	12782622 16187236
	MYC → PCNA → DNMT1 → CPGMET ⊣ CDKN1A ⊣ CCNB1_CDK1 → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 12145218 12408820 12711675 15616584 16474839 17576694 27927753 9989826
	PTP4A3 → ITGA1_ITGB1 → ILK → PTK2 → DNM2 → RAC1 → RHOA → ROCK1	12782622 16187236 19118217 19889638 21102636 8538749 8649427 9736715
	PTPN6 ⊣ BTK → PLCG2 → PRKCE → RHOA → ROCK1	11507089 11788586 12093870 12724322 15184383 23836557 8691147

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Key Biomarker(s)	Molecular Pathway Rationale for Biomarker(s)	Reference PMID(s)
ROCK1	CTSB → PLAU → PLAUR → PTPN11 → KRAS → TIAM1 → RAC1 → RHOA → ROCK1	10893266 14988728 15677342 1900515 19133257 22247021
	EIF3E → CUL3_KLHL18 → AURKA → PTK2 → DNM2 → RAC1 → RHOA → ROCK1	12782622 16187236 23213400 25501815
	PRKDC → AKT → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 14645242 22984590 23640046 8810315
	PMS2 → CHEK1 → WEE1 ⊣ CCNB1_CDK1 → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 27927753 8428596
	RIPK2 → BCL10 → MALT1 → PRKCE → RHOA → ROCK1	14638696 15125833 20516126 23690623
	STK4 → LATS1 ⊣ YAP1 → BIRC5 → AKT → XIAP → TGFBR1_TGFBR2 → RHOA → ROCK1	11356828 14645242 15688006 17379520 19962312 21199877 22984590 23245941 23640046 27847303 8810315

** Assayable key kinase biomarkers identified for this patient.

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8. Ventura™ Assessment sections: How to Read the Report

Cellworks Precision Medicine Reports equip oncologists with the knowledge of how an individual patient will respond to all standard care drugs (Singula™) and novel combination therapies (Ventura™) prior to treatment. The biosimulation analyzes mutational interactions of 4,000+ networked genes to predict and rank phenotype responses to millions of drug combinations.

The Ventura™ report predicts and ranks the patient's response to combinations of FDA-approved drugs, including off-label and non-oncology drugs.

Please Note:

The current assessment assumes that the drugs are faithfully delivered to the site of action. Cellworks considers all molecular interactions once the therapy is delivered to the site of action (Pharmacodynamics of the drug compound). Cellworks does not account for absorption, distribution, metabolism & excretion (ADME) properties of the drug that determine how the drug is delivered to the site of action. Any toxicity in the delivery process, or pharmacokinetics, is not considered.

Cellworks does not provide recommendations on drug dosage. However, it is highly recommended to follow the dosage instructions in the drug FDA labels and standard guidelines.

1. Top Biosimulation Predictions

The 'Top Biosimulation Predictions' table lists the top three Therapy Response Index treatments (monotherapy or combinations) predicted to be effective in treating the patient's cancer. These top three treatments can be Standard Care monotherapies or combinations, or combinations including off-label and non-oncology drugs.

Digital drug models of all the drugs in the Cellworks Drug Library are simulated individually on the personalized disease model of the patient. Next we iterate through various combinations of drugs to identify the best treatments based on the patient's personalized disease network. The NCT number for ongoing trials (if any), utilizing combinations recommended are listed against the recommended combination. Similarly, PMID references to publications supporting the use of a recommended combination are printed against the recommended combination.

A detailed rationale explaining why each selected treatment is efficacious is provided in the 'Therapy Rationale' section (Section 6).

2. Patient Specific Master Regulators

Cellworks multi-omics biosimulation determines master regulators in the patient's disease network. They are points of convergence of the pathways impacted by the aberrations in the patient's genomic profile. These master regulators are tumor promoter/suppressor genes that a drug needs to impact for the patient to respond to treatment.

Detailed illustrations showing molecular biochemical pathways from genomic aberrations in the patient profile to the master regulators are provided in the Genomic Aberration to Master Regulator Pathway Section (Section 6).

3. Treatment Impact on Master Regulators

Cellworks multi-omics biosimulation classifies a patient as a responder or a non-responder to a drug based on the impact the drug has on the

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phenotype of the patient's cancer as well as the impact on the master regulators identified in the patient's disease network.

If the drug successfully impacts a master regulator to a significant extent, it is represented by a check symbol ('✓'). Absence of a check symbol implies that the drug does not sufficiently impact the master regulator.

4 Biosimulation of Therapy Response Index (TRI)

Therapy Response Index: This index represents the patient specific biosimulation score for each treatment or combination Cellworks evaluates. The score is determined by the impact on master regulators and phenotype responses in the patient disease model.

4.1 Top Biosimulation Treatments

The top overall list represents the highest scoring TRI prediction treatments. The histogram ranks Standard Care drug treatments and monotherapies, and combinations including off-label and non-oncology drugs on the Y-axis in decreasing order of efficacy. The number on the X-axis is the Therapy Response Index which reflects the predicted effectiveness of the drug treatments.

The histogram also indicates the efficacy of individual treatments in a combination. The total score of the treatment is listed as a dark grey bar. For combination therapies, the light green section represents the strongest monotherapy component of the combination. The Standard Care treatments are labelled.

4.2 Standard Care Predicted Responders

This table lists all the Standard Care treatments to which the patient is predicted to respond.

The "Therapy Response Index" column shows the TRI score for each of these treatments. Top scoring Standard Care treatments will be found in the top 25 treatments shown in the histogram, Section 4.

4.3 Standard Care Predicted Non-Responders

This table lists all the Standard Care treatments to which the patient is predicted to not respond.

5.1 Summary of Patient Genomic Profile

This section provides a summary of the patient genomics used for therapy assessment. It shows the type of input received from the next generation sequencing data (NGS) with the number of genetic mutations, copy number variations (CNVs) and any epigenetic data that is reported. Some indications also require additional lab tests as input to the biosimulation process.

5.2 Aberrations by Chromosome Location

The plot contains the CNVs from the patient profile as determined by NGS, showing gain and loss values. The values are plotted in chromosomal order for ease of understanding. The genomic mutations are plotted at the bottom of the chart colored to illustrate gain of function (blue dot), loss of function (red dot), or switch of function (purple dot).

5.3 Detailed Information of Genomic Aberration(s) Modeled

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Aberrations of oncogenic significance found in the patient's genomic profile are used to create the disease model of the patient and are listed in this section. Based on the type of mutation and original functionality of a gene, aberrations are categorized into 5 major groups -

I. Gene Mutation(s) with Gain of Function
II. Gene Mutation(s) with Loss of Function
III. Gene Mutation(s) with Switch of Function
IV. Gene(s) with Increase in Copy Number Variation [CNV]
V. Gene(s) with Decrease in Copy Number Variation [CNV]

This information forms the patient-specific input on which a Cellworks assessment is based.

6. Therapy Rationales

Each therapy recommendation made in a Cellworks report is accompanied by a clear rationale explaining the reason behind the recommendation.

A therapy rationale illustrates the role of key aberrations in causing sensitivity or resistance to drugs. A drug will have a therapy rationale for every aberration that contributes significantly to its sensitivity or resistance.

The first illustration in the rationale defines the mechanism of action of the drug.

The second illustration articulates the signaling or metabolic pathway by which the aberration of interest contributes to drug sensitivity or resistance including the point of intersection with the drug's mechanism of action.

The pathway can be read as a dependent relationship (represented by an arrow) where an increase in one gene increases the next, or a block or inverse relationship (represented by a line with a bar) where an increase in one gene decreases the next. The description is accompanied by relevant PMID references that support the drug mechanism of action and rationale for drug sensitivity or resistance.

7. Genomic Aberration to Key Biomarker Pathway(s)

This section illustrates molecular biochemical pathways from a genomic aberration in the patient profile to critical master regulators identified by Cellworks' multi-omics biosimulation. These illustrations explain why the master regulators listed in Section 2 are important to the patient's disease network. The illustration is accompanied by relevant PMID references that were used to determine the interaction.

Acute Myeloid Leukemia (AML) - NOS

Clinical ID: ABC123 **Cellworks ID:** 123456 **Ref Physician:** Dr. Smith

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