Onconomics Plus RGCC ™

Results

Results Analysis Report

The sample that was sent to us for analysis was a sample of 10ml Blood that contains anti-coagulant, and packed with an ice pack.

Laboratory Process

Isolation of the malignant cells using flow cytometry and negative selection (isolated 4.8 cells/7.5 ml, SD +/- 0.3 cells). The isolated cells were expanded and they were split in two, from which, one part is going to viability assays and the other is going for transcriptomic micro-Arrays

Isolation of mRNA

Quality control of integrity of mRNA

Reversed transcription of mRNA to cDNA

Hybridisation of cDNA with micro-Arrays all genome transcriptomic micro-Arrays slide

Analysis of the data and detection of repeatable patterns

Normalization and assessment of clinical relevant probes

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RGCC

The following were defined	
Expression rates of the following clinical relevant genes	
Related with cell cycle regulation	p53, p21, p16, DHFR, TS, SHMT
Related with drug targets	Topo I & II, TS, DHFR, ribonucleotide reductase etc.
Related with signal transduction pathway	IGFr, EGFr, PDGFr, etc.
Related with epigenetic aberration	Dnmt1, DNA demethylase, etc.
Related with angiogenesis	VEGF-r, FGFr, PDGFr
Related with growth signal	c-erb-B1, c-erb-B2, bar-abl, etc.
Related with repair after physical application (radiation, hyperthermia)	HSP27, HSP70, HSP90, HIF1a, etc.

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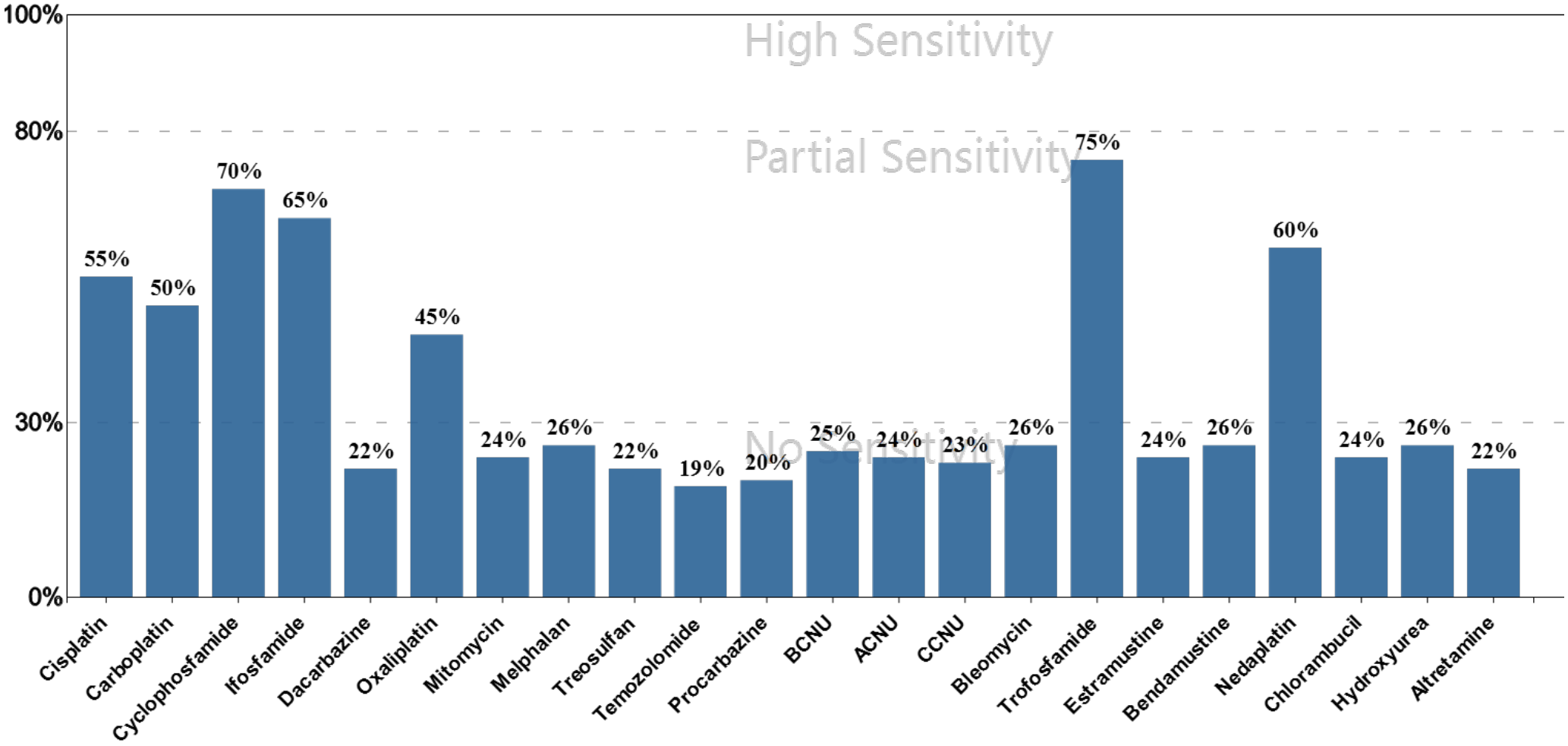
Alkylating Agents



High Sensitivity:

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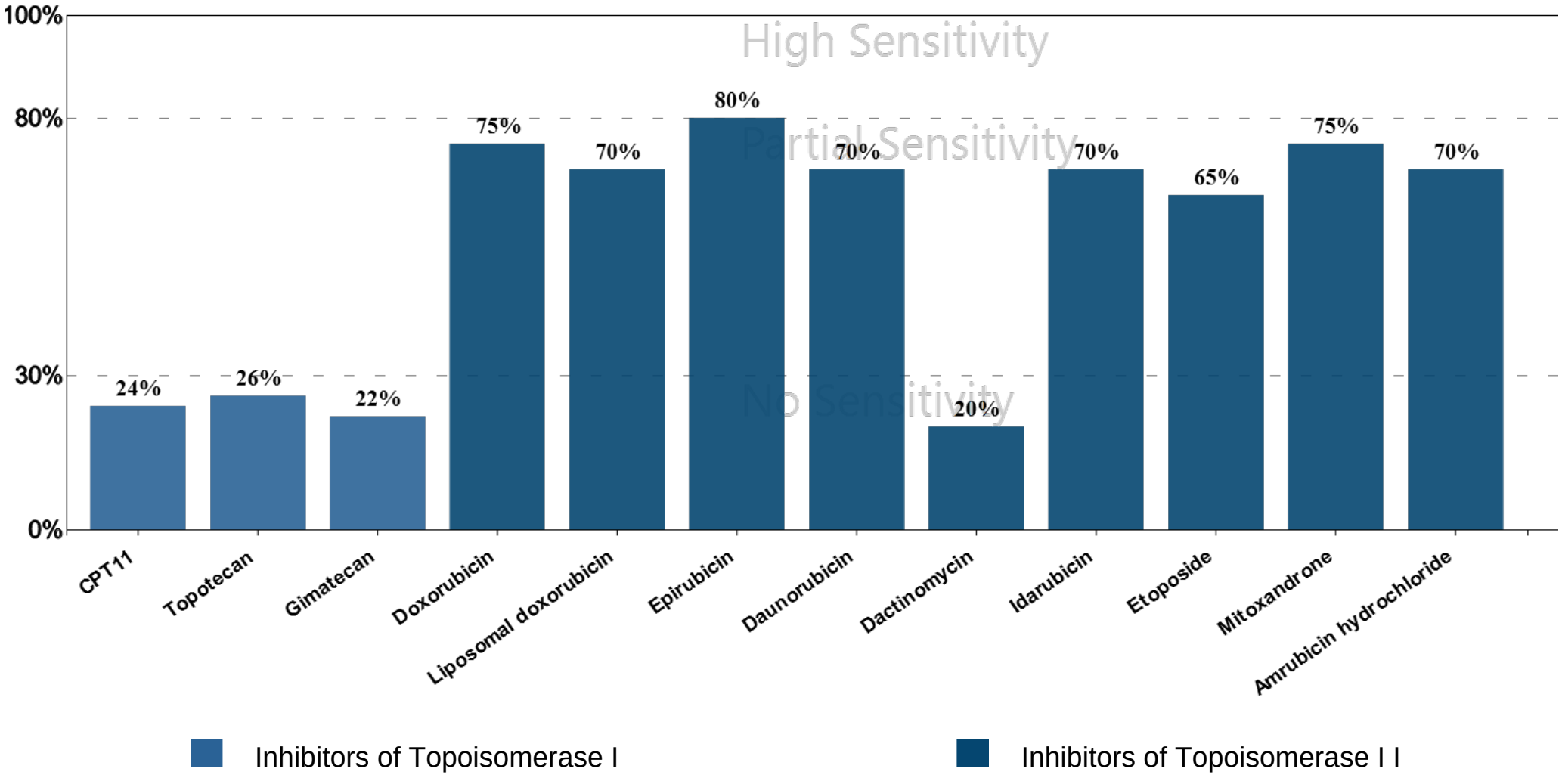
Inhibitors of Topoisomerase I & II



High Sensitivity: Epirubicin

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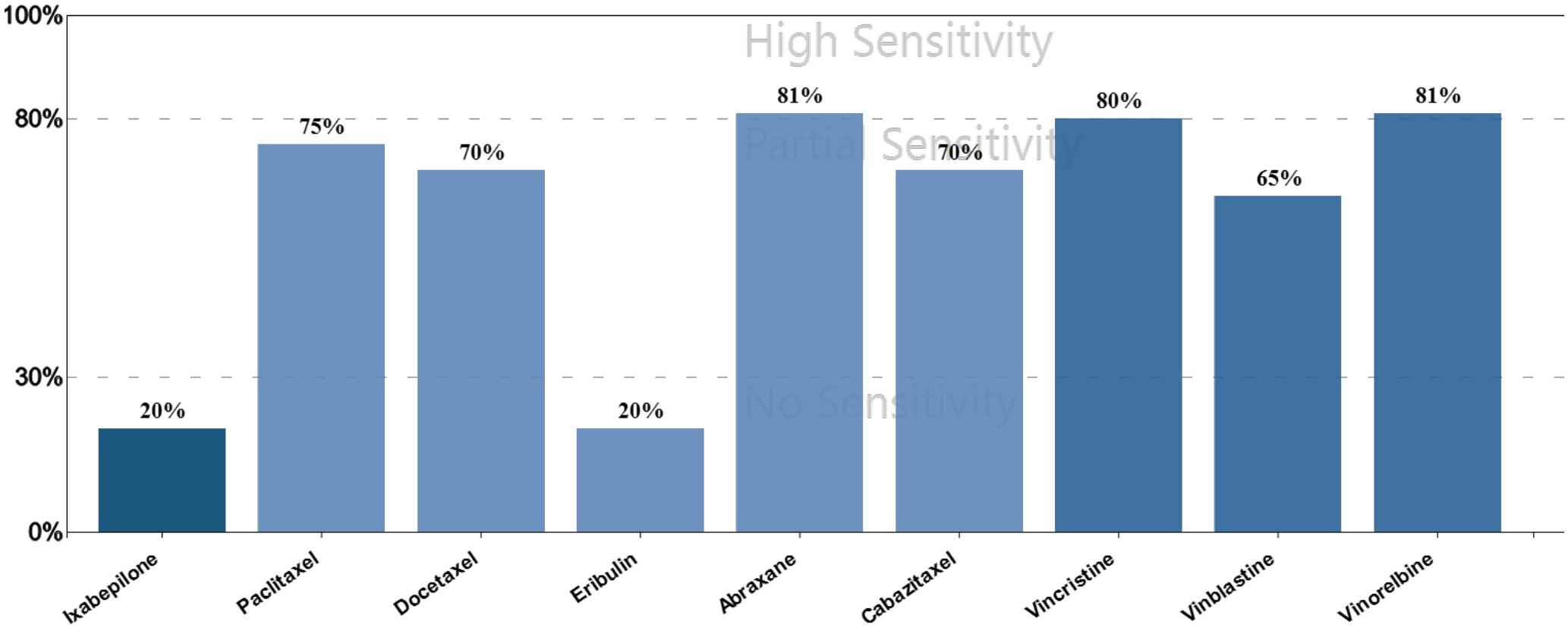
Epothilones & Nucleus Spindle Stabilizer I & II



High Sensitivity: Abraxane, Vincristine, Vinorelbine

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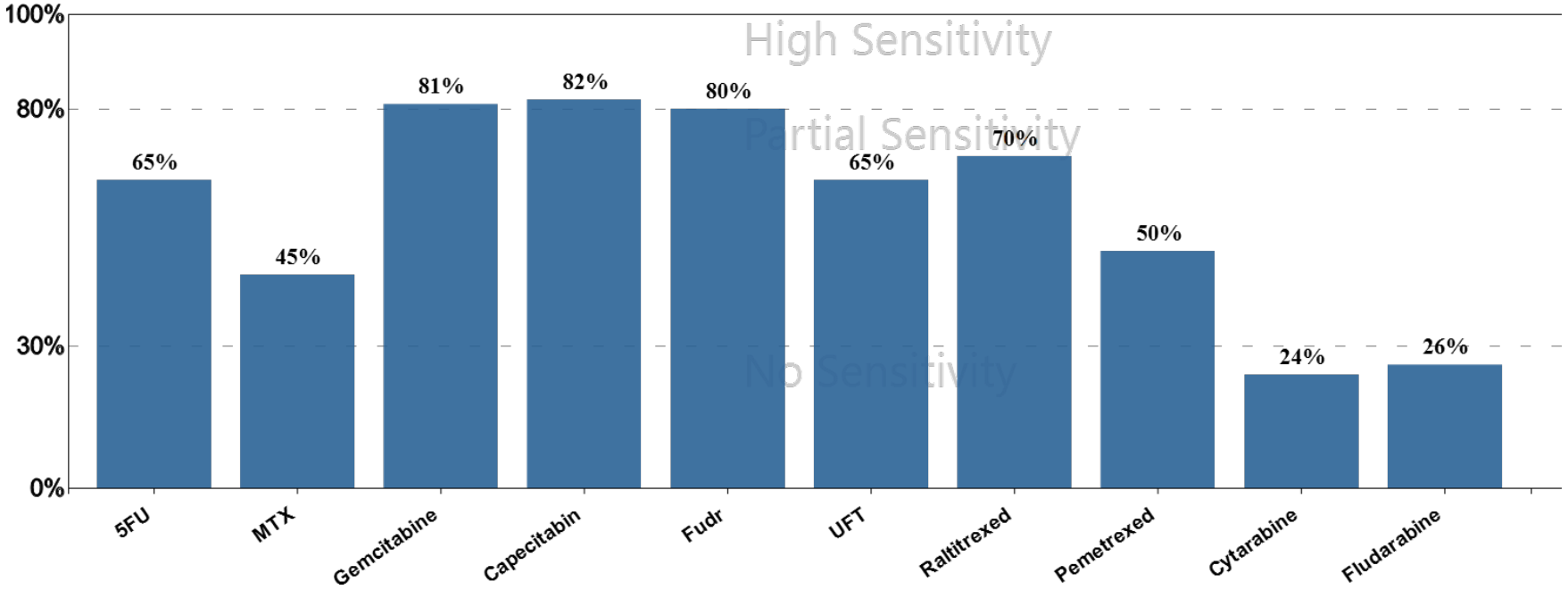
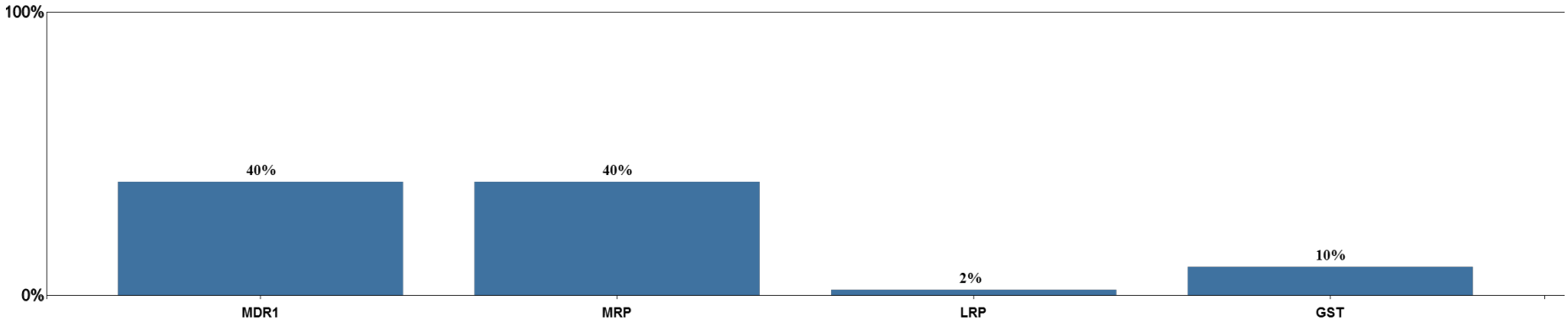
Nucleoside Analogues



High Sensitivity: Gemcitabine, Capecitabin, Fudr

Resistance Factors



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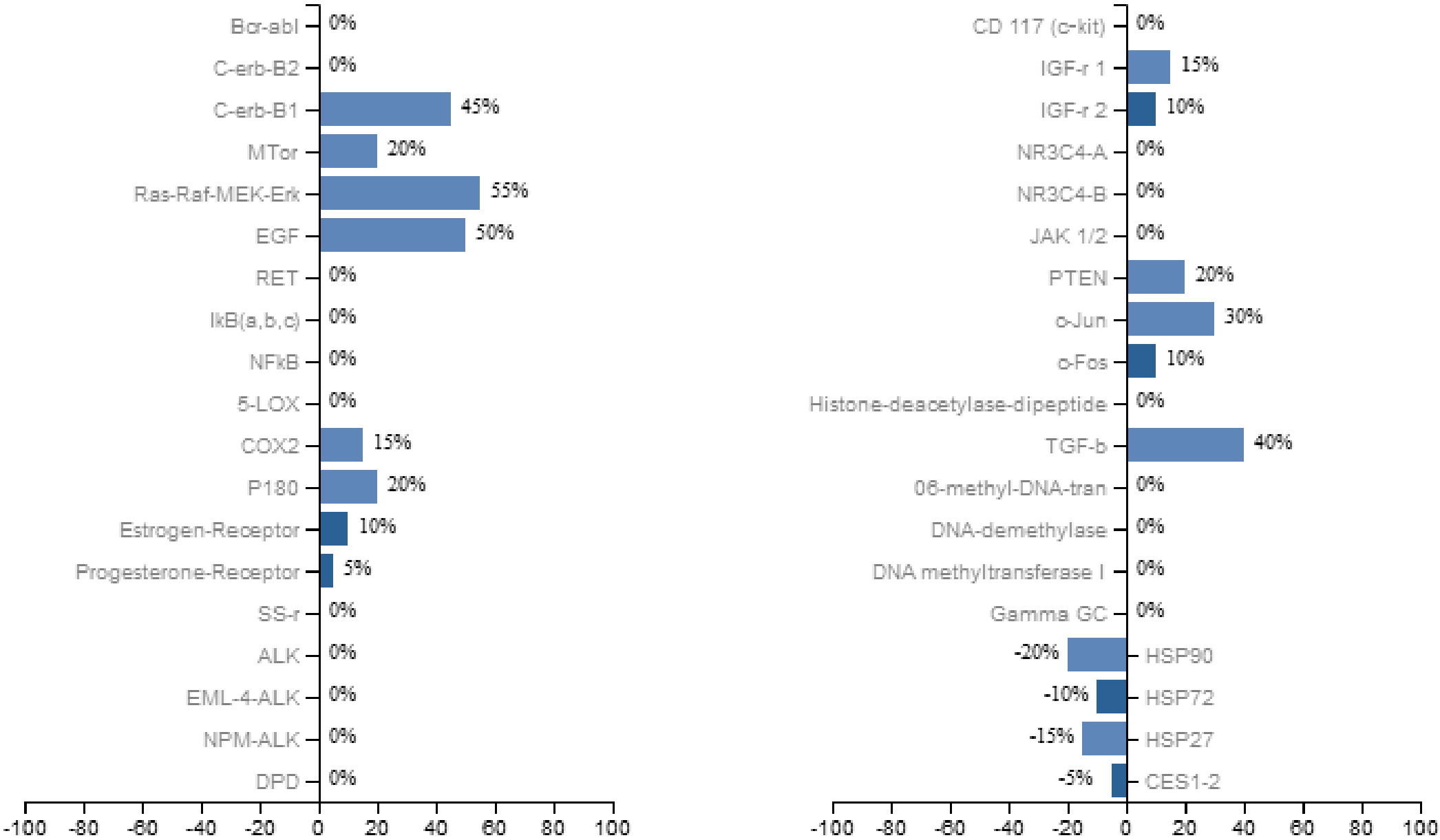
Tumor Related Genes I



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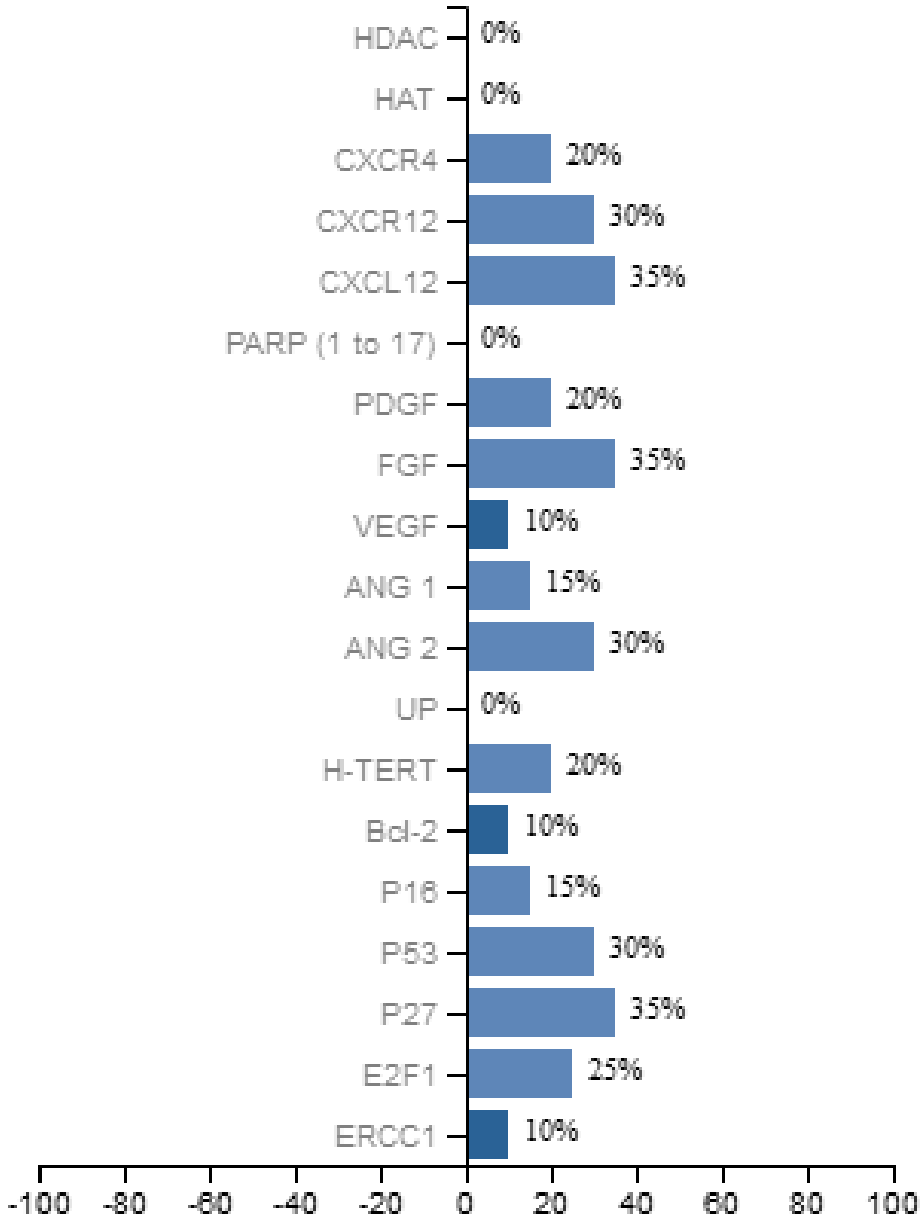
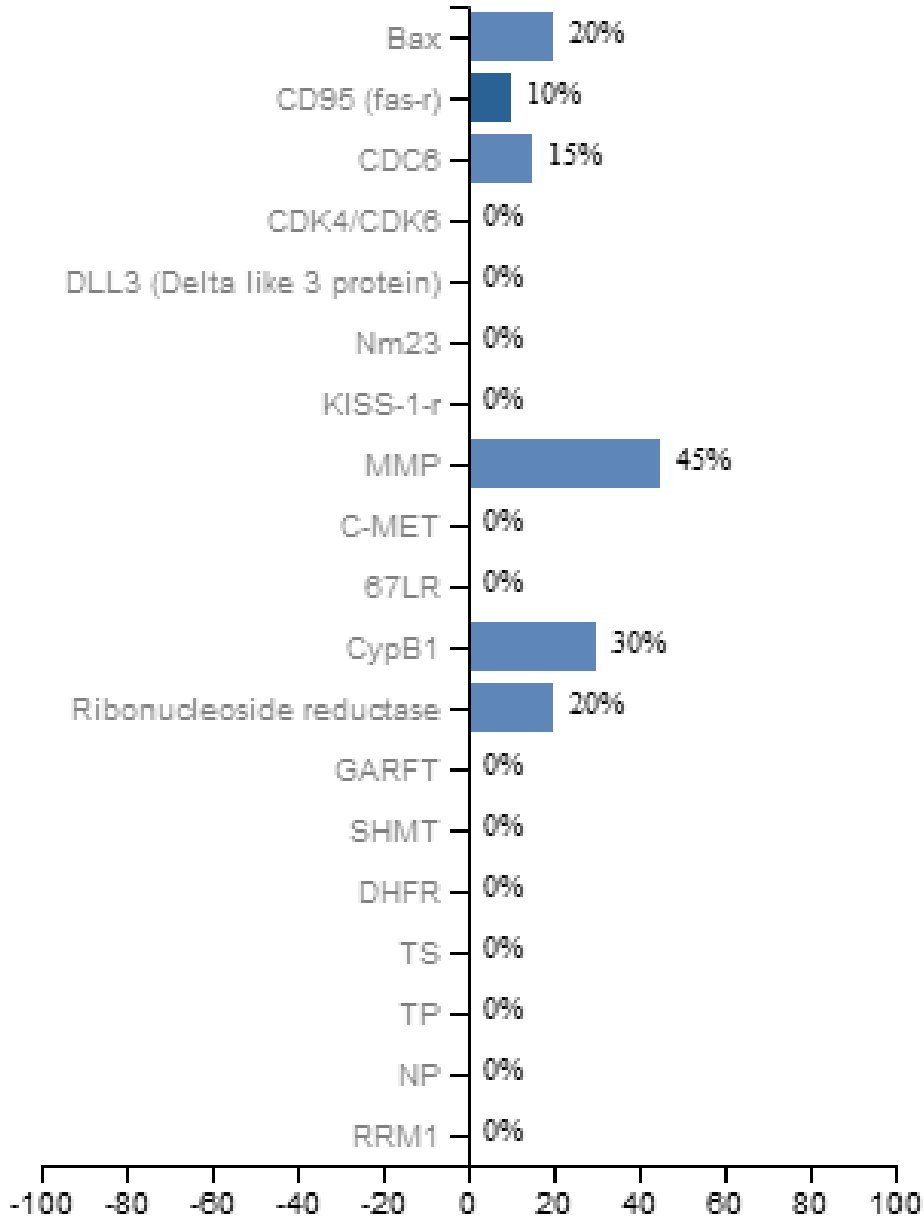
RGCC

Tumor Related Genes II





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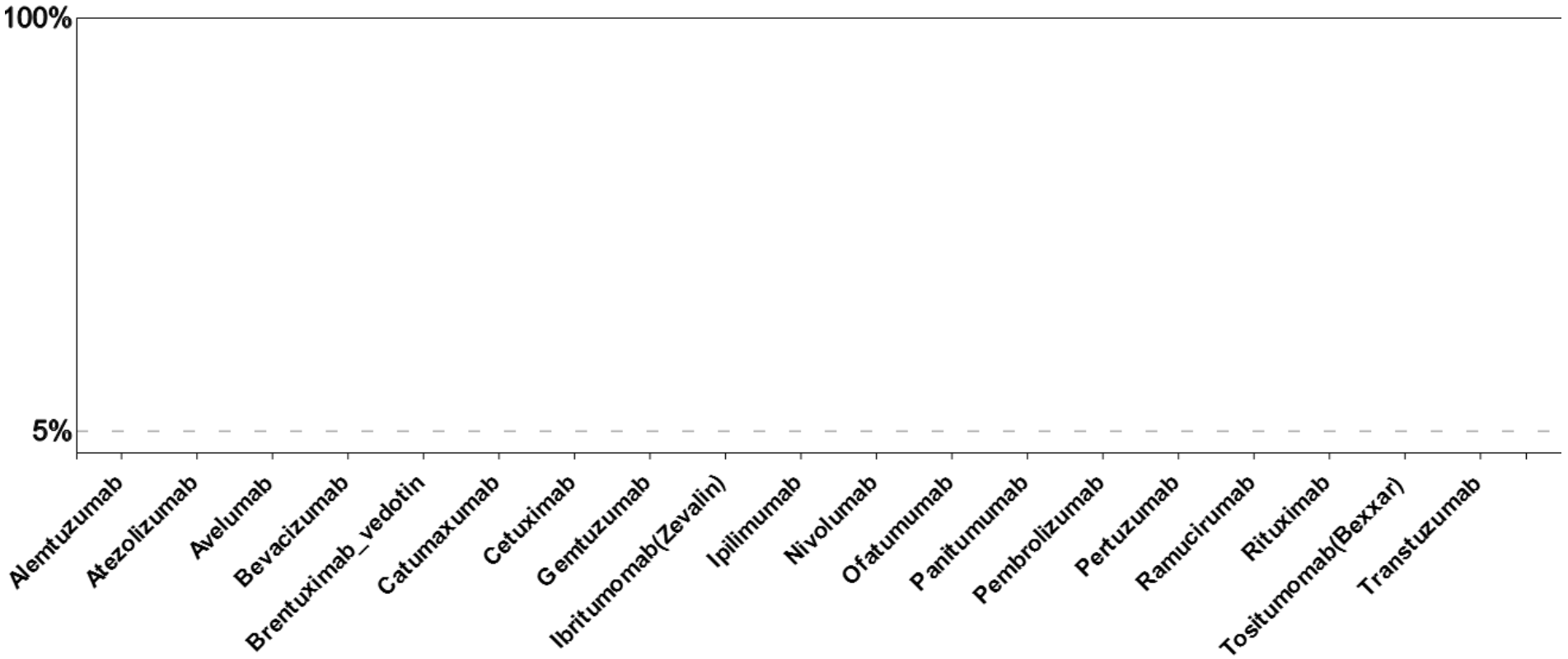
Moab -Monoclonal Antibodies



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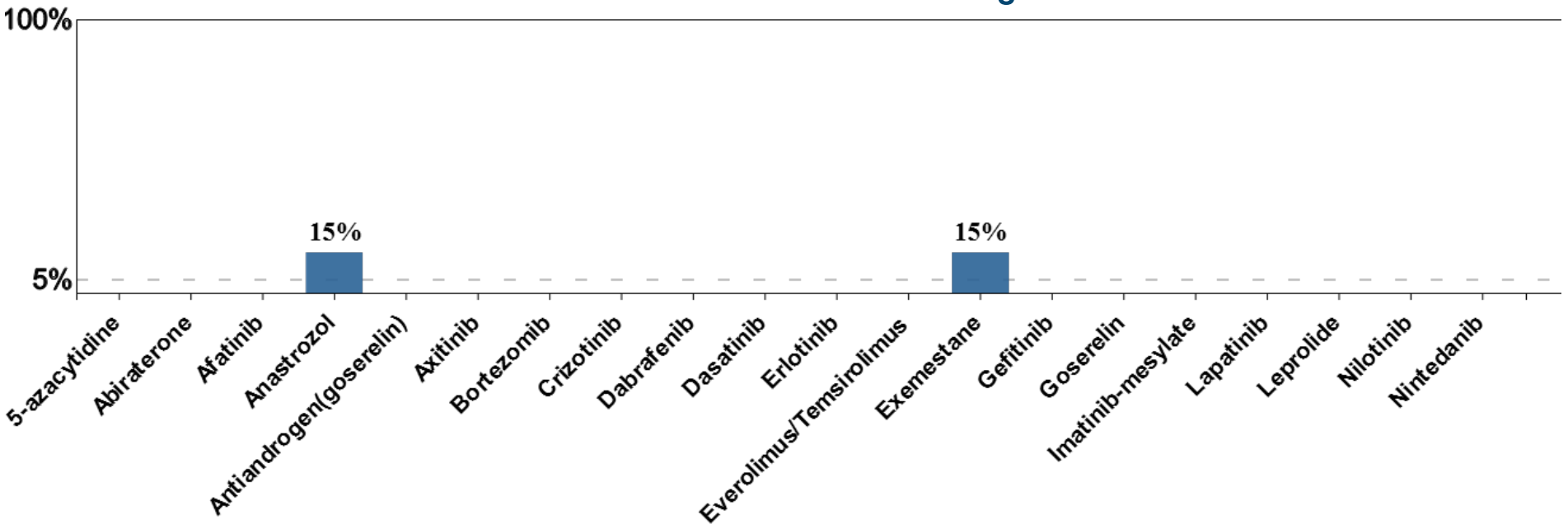
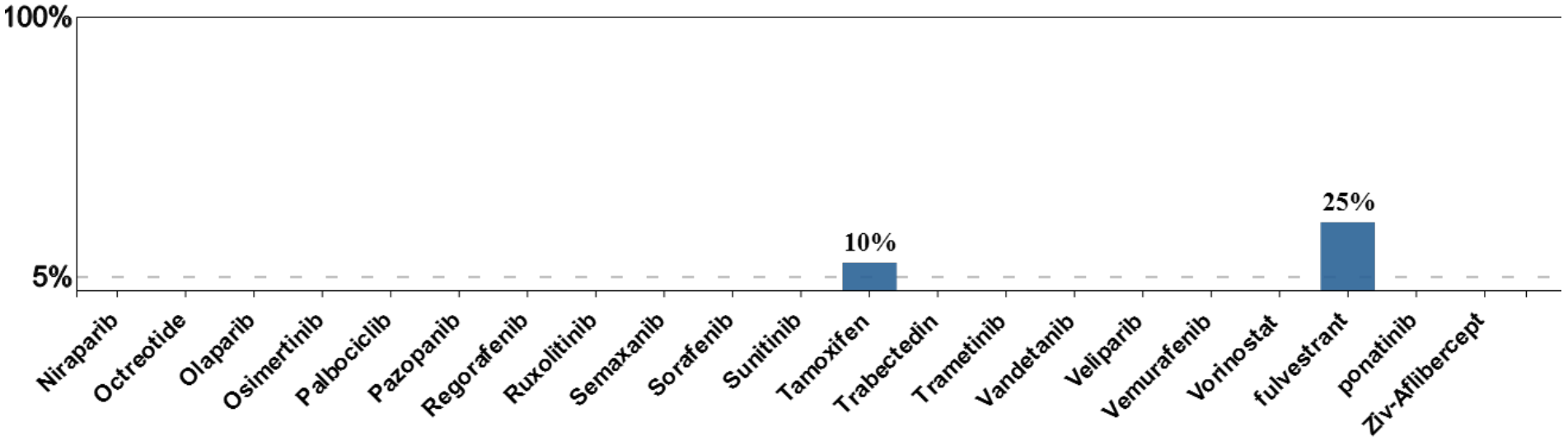
SMW - Small Molecular weight molecule



SMW - Small Molecular weight molecule



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GROWTH FACTORS PROLIFERATION STIMULI

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Preprotein for Cellular stress	HIGH RISK	p180	Tyrosin kinase growth f.	20	HIGH RISK
Fusion Protein	LOW RISK	Bcr-abl	Resist phenotype	Normal	LOW RISK
Repair Related Gene	HIGH RISK	PTEN	Tumor Suppressor Gene	20	HIGH RISK
Eicosanoid related protein	HIGH RISK	COX2	Tumour Growth	15	HIGH RISK
		5-LOX	Tumour Growth	Normal	LOW RISK
Proteasome inhibitors	LOW RISK	NFkB	Transcription fact	Normal	LOW RISK
		IkB(a,b,c)	Inhibitor of NFkB	Normal	LOW RISK
Proto-Oncogene	LOW RISK	ALK	Acute Leukemia kinase	Normal	LOW RISK
		EML-4-ALK	Fusion EML with ALK	Normal	LOW RISK
		NPM-ALK	Fusion NPM with ALK	Normal	LOW RISK
		RET	Proto-oncogene	Normal	LOW RISK

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GROWTH FACTORS PROLIFERATION STIMULI

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Growth Factor Receptor	HIGH RISK	SS-r	Somatostatin receptor	Normal	LOW RISK
		CD 117(c-kit)	Proliferate growth factor receptor	Normal	LOW RISK
		IGF-r 1	Insulin like growth factor receptor	15	HIGH RISK
		IGF-r-2	Insulin like growth factor receptor	10	HIGH RISK
		EGF	Tumour Growth	50	HIGH RISK
		c-erb-B1	Her1	45	HIGH RISK
		c-erb-B2	Her/neu2	Normal	LOW RISK
Signal transduction pathway	HIGH RISK	JAK 1/2	Single transduction pathway	Normal	LOW RISK
		c-Jun	Proto-Oncogene	30	HIGH RISK
		c-Fos	Proto-Oncogene	10	HIGH RISK
		Ras/Raf/MEK/Er k	Transduction pathway	55	HIGH RISK
		mTOR	Transduction pathway	20	HIGH RISK
Hormone Receptors	HIGH RISK	Progesterone Receptor	Growth Factor receptor	Normal	LOW RISK
		Estrogene Receptor	Growth Factor receptor	10	HIGH RISK
		NR3C4-A	Nucleous receptor group III Class 4 (androgen receptor A)	Normal	LOW RISK
		NR3C4-B	Nucleous receptor group III Class 4 (androgen receptor B)	Normal	LOW RISK

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SELF REPAIR - RESISTANCE

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Signal transduction	HIGH RISK	TGF-b	Tumour Growth	40	HIGH RISK
Radiotherapy / Hyperthermia sensitivity	SENSITIVE	HSP27	Heat Shock Protein	-15	SENSITIVE
		HSP72	Heat Shock Protein	-10	SENSITIVE
		HSP90	Heat Shock Protein	-20	SENSITIVE
Resistant Phenotype Markers	HIGH RISK	DNA methyltransferas eI	DNA methylation	Normal	LOW RISK
		DNA demethylase	DNA methylation	Normal	LOW RISK
		06-methyl-DNA- tran.	DNA methylation	Normal	LOW RISK
		Histonedeacetyla se-	DNA coiling (nucleosome)	Normal	LOW RISK
		HAT	Histone acetyl transferase	Normal	LOW RISK
		CXCR4	Resistant Phenotype	20	HIGH RISK
		CXCR12	Resistant Phenotype	30	HIGH RISK
		CXCL12	Resistant Phenotype	35	HIGH RISK
		Gamma GC	Resist to alkylating drug	Normal	LOW RISK
		HDAC	Histone deacetylase	Normal	LOW RISK

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ANGIOGENESIS

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Angiogenesis	HIGH RISK	VEGF	Angiogenesis	10	HIGH RISK
		FGF	Angiogenesis	35	HIGH RISK
		PDGF	Angiogenesis	20	HIGH RISK
		ANG 1	Angiogenin I	15	HIGH RISK
		ANG 2	Angiogenin II	30	HIGH RISK

CELL CYCLE REGULATION & IMMORTALIZATION / APOPTOSIS

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Increase protein Synthesis	HIGH RISK	E2F1	Transcr. Fact of TS & topo I	25	HIGH RISK
Rapid Cell Cycle	HIGH RISK	CDC6	Initiation of DNA replication	15	HIGH RISK
Immortalization	HIGH RISK	h-TERT	M2 crisis- aggressive phen.	20	HIGH RISK
Regulation of apoptosis	HIGH RISK	Bcl-2	Apoptosis	10	HIGH RISK
		Bax	Apoptosis	20	HIGH RISK
		CD95 (fas-r)	Apoptosis related receptor	10	HIGH RISK
Cell cycle Rate	HIGH RISK	p27	Cell arrest (G0)	35	HIGH RISK
		p53	Cell cycle regulator	30	HIGH RISK
		p16	Apoptosis	15	HIGH RISK

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ANGIOGENESIS - METASTASES

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Migration invasion	HIGH RISK	c-MET	Mesenchymal to epithelial transition	Normal	LOW RISK
		67LR	67 Laminin receptor	Normal	LOW RISK
		KISS-1-r	Metastases regulator	Normal	LOW RISK
		Nm23	Metastases regulator	Normal	LOW RISK
		MMP	Metastases	45	HIGH RISK

DRUG METABOLISMS & TARGETS

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Nucleoside Import transformation	HIGH RISK	DPD	Resist to 5FU	Normal	LOW RISK
		UP	Resist to 5FU	Normal	LOW RISK
		NP	Resist topyrim. Antagonist	Normal	LOW RISK
		TP	Resist to 5FU	Normal	LOW RISK
		TS	Rapid cell cycle (THFA)	Normal	LOW RISK
		DHFR	Rapid cell cycle (THFA)	Normal	LOW RISK
		SHMT	Rapid cell cycle (THFA)	Normal	LOW RISK
		GARFT	Rapid cell cycle(THFA)	Normal	LOW RISK
		Ribonucleosider eductase	DNA synthesis	20	HIGH RISK

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DRUG METABOLISMS & TARGETS

FUNCTION	CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
Activation of camptothecin	LOW RISK	CES1&2 (carboxyesterase)	Resist to camptothecin	Normal	LOW RISK
Xenobiotic	HIGH RISK	CypB1	Xenobiotic metabolism	30	HIGH RISK
DNA repair related gene	HIGH RISK	ERCC1	DNA repair mechanism	10	HIGH RISK
		RRM1	Nucleotide polymerizations	Normal	LOW RISK

MARKERS

CLINICAL RISK	NAME	RELATED	RESULTS	OUTCOME
LOW RISK	CD33	Myeloid cellorigin	Normal	LOW RISK
LOW RISK	CD52	Leukaemia marker	Normal	LOW RISK
LOW RISK	CD20	Lymphoma related antigen	Normal	LOW RISK
HIGH RISK	EpCAM (EpCAm+ve)	Epithelial marker	15 (3.9 cells/7.5 ml)	HIGH RISK
LOW RISK	PD-L1	Immunoregulatory factor	Normal	LOW RISK
LOW RISK	PD 1	Immunoregulatory factor	Normal	LOW RISK
LOW RISK	PD-L2	Immunoregulatory factor	Normal	LOW RISK

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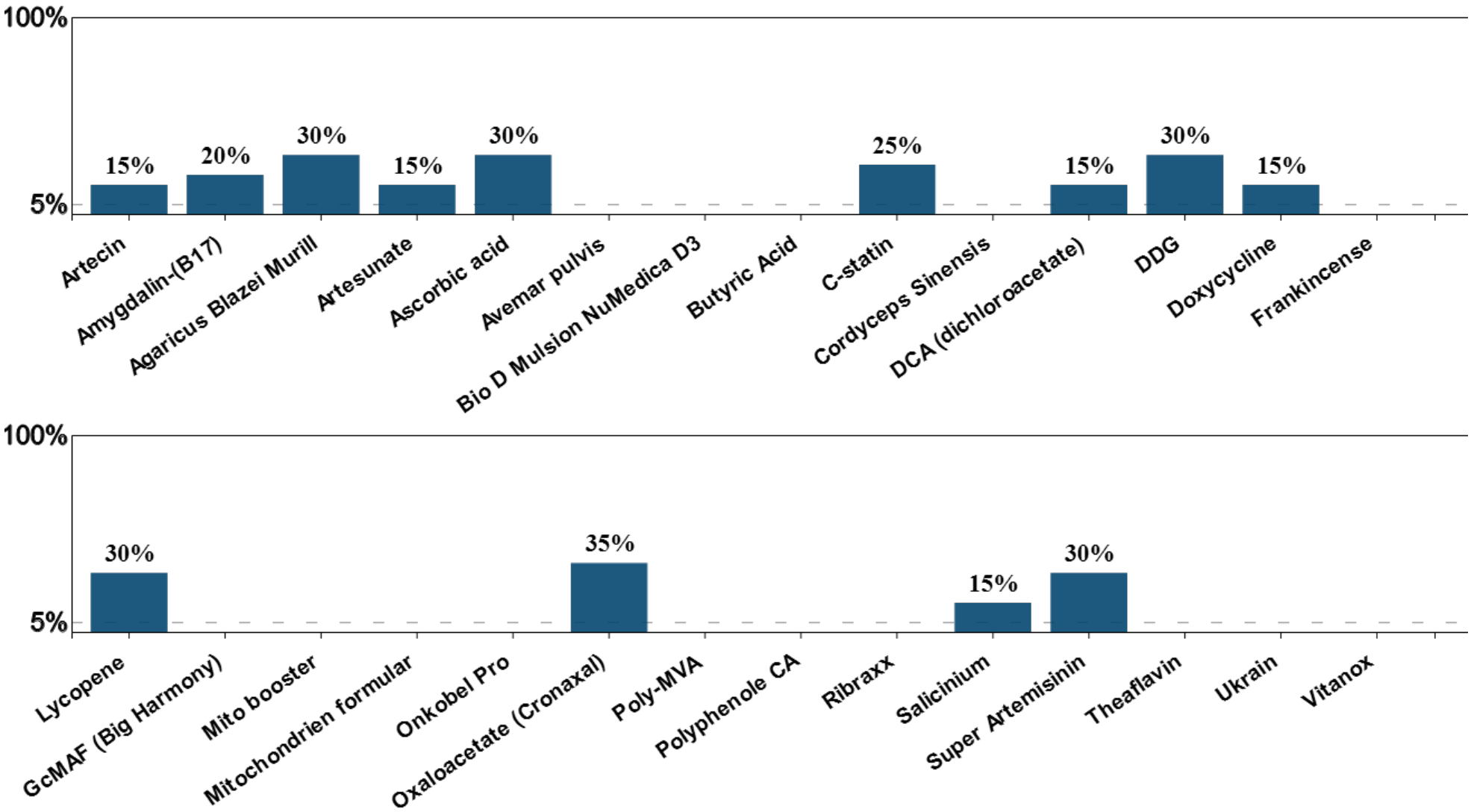
Class I (cytotoxic Agents)

Activation of Caspace (especially 3 and 9) and cytochrom C re



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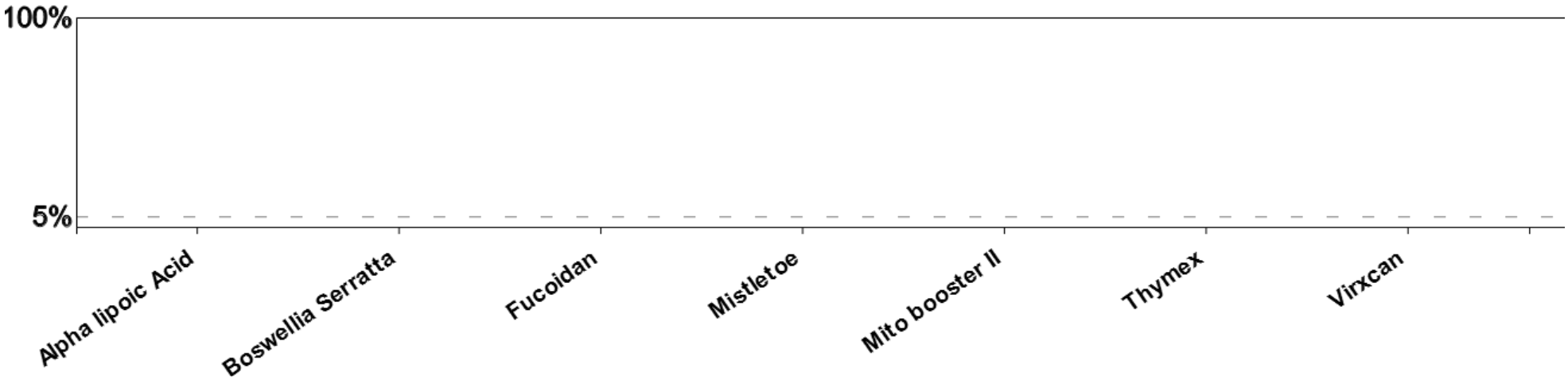
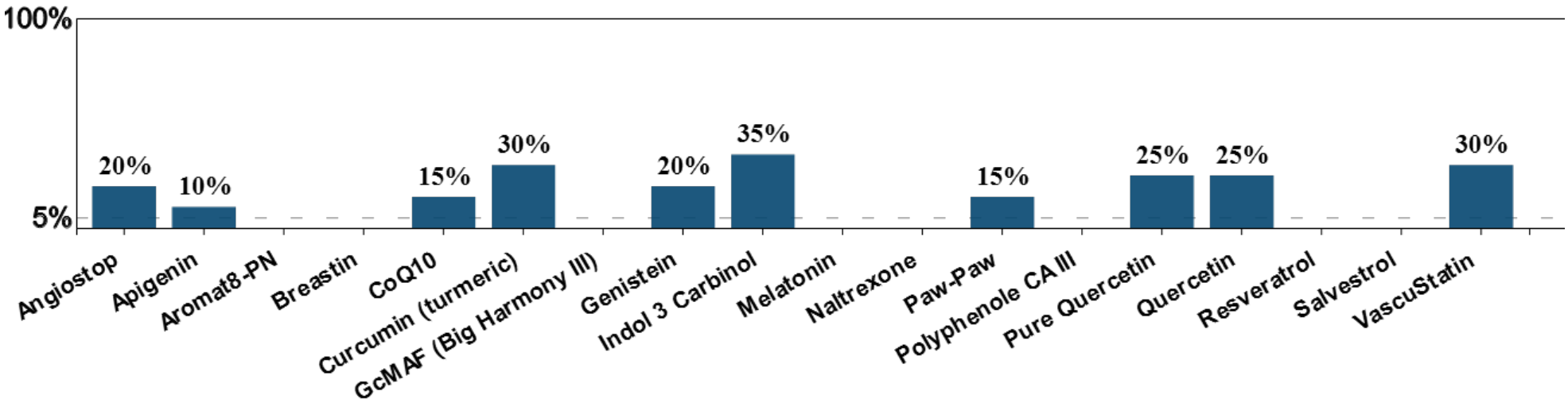
Class II (Immunostimulants/ immunomodulators)

Immunostimulants / immunomodulators release of Cytokins and increase of PBMC & NK



Class III (PK inhibitors)

Inhibitors of growth factors receptor inhibitors of EGFr, IGFr, VEGFr, PDGFr, FGFr signal transduction pathways



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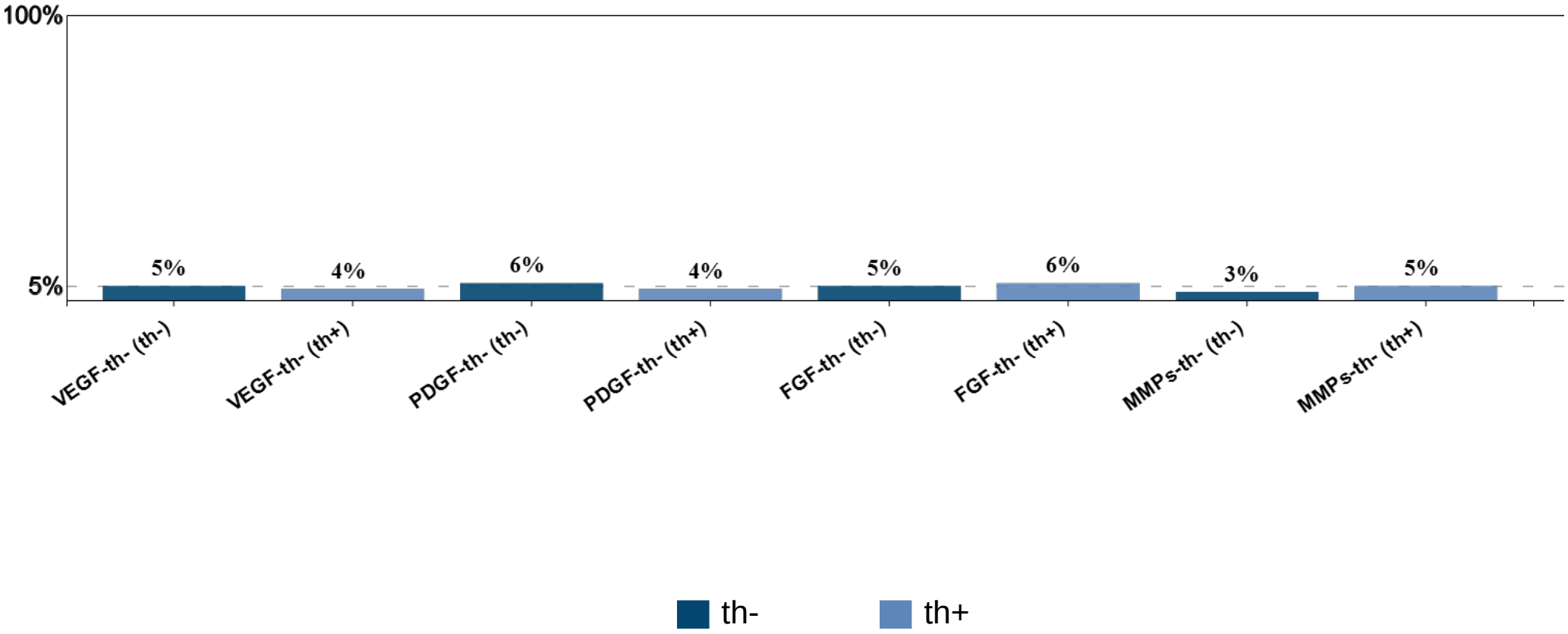
Malignant Cells - Thalidomide



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NATURAL SUBSTANCES

SUBSTANCE	W/O SUBSTANCE	WITH SUBSTANCE	EFFICACY
CBD Oil (Syringe) Class 1	12	15	Not Effective
DMSO Sodium Bicarbonate Class 1	14	11	Not Effective
Ganoderma Class 1	10	12	Not Effective
Hydrogen Peroxide Class 1	15	16	Not Effective
Astragalus Class 1	12	14	Not Effective

It seems that this specific population of malignant cells have greater sensitivity in

From Class I (cytotoxic Agents)

Agaricus Blazei Murill, Amygdalin-(B17), Artecin, Artesunate, Ascorbic acid, C-statin, DCA (dichloroacetate), DDG, Doxycycline, Lycopene, Oxaloacetate (Cronaxal), Salicinium, Super Artemisinin

From Class II (Immunostimulants/immunomodulators)

Nothing

From Class III (PK inhibitors)

Angiostop, Apigenin, CoQ10, Curcumin (turmeric), Genistein, Indol 3 Carbinol, Paw-Paw, Pure Quercetin, Quercetin, VascuStatin

*Disclaimer: The natural substances that are tested in our lab facilities are not bonded from restriction for medical use.

From the investigation above the following were concluded

From the whole neoplasmic population we have an expression of MDR1 in a percentage of 40% over control sample (positive in the check of resistance)	There is great overexpression of EGF, TGF-b There is normal expression of IkB(a,b,c), NFkB
The concentration of p180 is in high range.	It appears to have great sensitivity in the inhibitors of topoisomerase II a and II b.
Decreased sensitivity in alkylating factors.	There is no sensitivity in the inhibitors of Topoisomerase I
There is partial sensitivity in taxanes.	We notice great neoangiogenetic ability (overexpression of VEGF-R 10% over control sample).
There is great sensitivity in alkaloids of vinca.	We noticed down regulation of Heat Shock Protein HSP90 (-20%), HSP72 (-10%), HSP27 (-
There is no sensitivity in Eribulin.	There is no sensitivity in Epothilones.
There in no sensitivity in Cytarabine, Fludarabine There is partial sensitivity in 5FU, MTX, UFT, Raltitrexed, Pemetrexed There is great sensitivity in Gemcitabine, Capecitabin, Fudr	There is great over-expression of COX2 (15%), C-erb-B1 (45%), Estrogen-Receptor (10%) There is normal expression of 5-LOX, SS-r, C-erb-B2
There is over-expression of ANG 1 (15%), ANG 2 (30%), IGF-r 1 (15%), IGF-r 2 (10%) We noticed no down-regulation of ALK, EML-4-ALK, C-MET, NPM-ALK, CD 117 (ckit), HDAC, HAT, NR3C4-A, NR3C4-B	

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Conclusion

The neoplasmatic cells have the greatest sensitivity in Epirubicin, Abraxane, Vincristine, Vinorelbine, Gemcitabine, Capecitabin, Fudr

Also can be used Anastrozol, Exemestane, Tamoxifen, fulvestrant

The specific tumor appears to have resisting populations because of the MDR1 overexpression that can be reversed by the use of inhibitors of ABCG2 pumps

Sincerely,

Ioannis Papasotiriou MD., PhD Head of molecular medicine dpt. of R.G.C.C.-Research Genetic Cancer Centre International GmbH