DBPR216

A Novel Multi-targeted Kinase Inhibitor for the Treatment of Gastrointestinal Stromal Tumor and Acute Myeloid Leukemia

多重激酶抑制劑治療胃腸道基質瘤與急性骨髓性白血病

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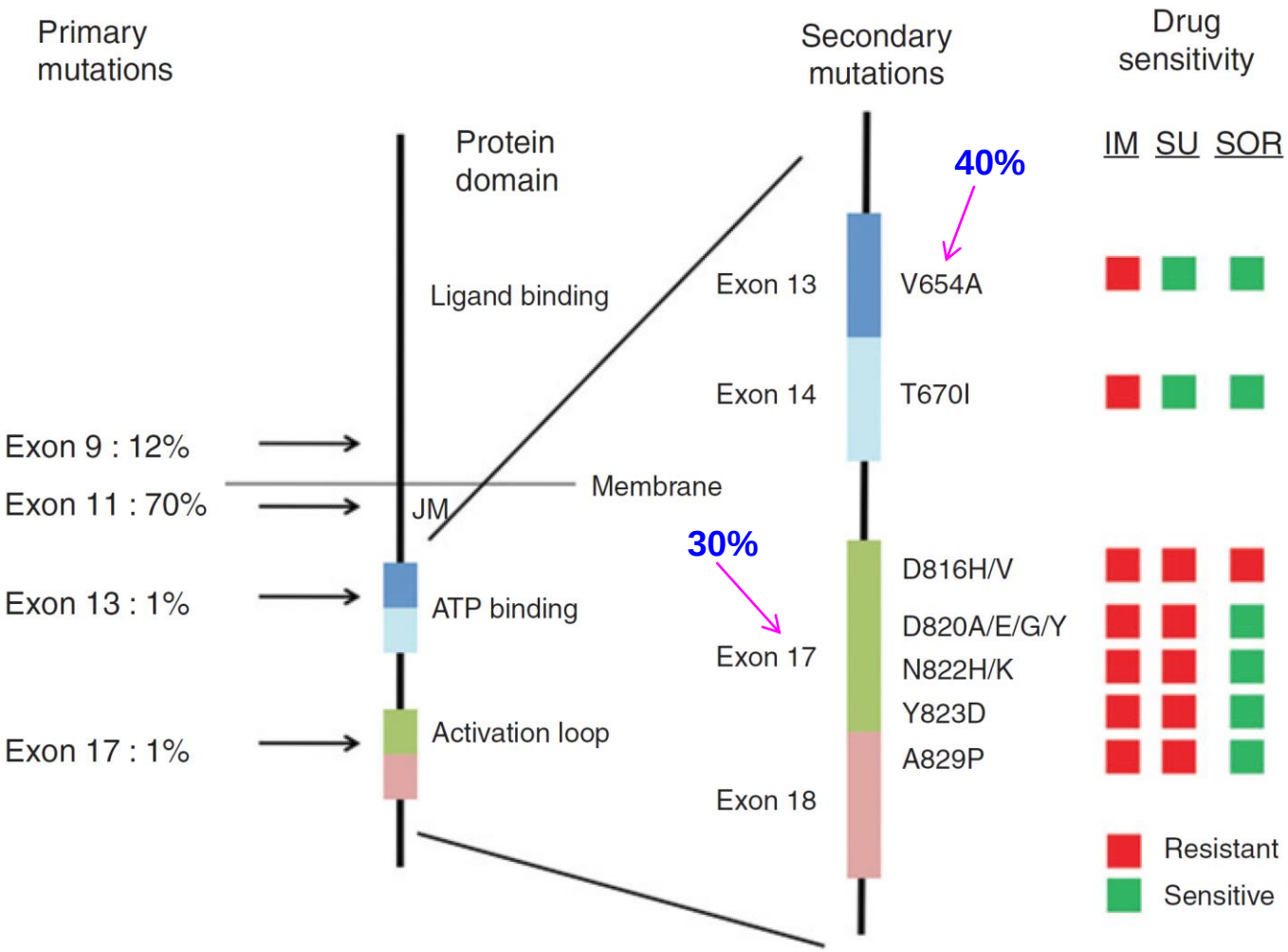
Gastrointestinal Stromal Tumor (GIST)

- **Gastrointestinal stromal tumors (GIST) are the most common gastrointestinal mesenchymal tumors (sarcoma), originate from interstitial cells of Cajal.**
- **Median age of occurring is 60-65 years.**
- **Worldwide incidence of 10-20 per one million people.**
- **In the US, the incidence of GIST is estimated to range from about 4,000 to 5,000 cases each year, while in the EU, the incidence of GIST is estimated to be more than 5,000 cases each year.**
- **Approximately 80% of GIST have mutations in the proto-oncogene KIT which encodes a tyrosine kinase receptor. About 8% of GIST are associated with mutations in the gene for platelet-derived growth factor receptor alpha (PDGFRα).**
- **Other rare mutations: succinate dehydrogenase complex, BRAF, RAS family gene.**
- **About 60% of GIST are cured by surgery.**
- **Conventional chemotherapy and radiation therapy are not responsive to unresectable and/or metastatic GIST.**

Joensuu et al. Lancet 2013;382:973-983
Wu L et al. Drug Design, Development and Therapy 2014;8:2061–2067
Corless CL et al. Nat Rev Cancer 2011;11:865-878

Graphical Comparison of Potency of IM, SU and SOR for IM-resistant KIT Mutations



- **Drug sensitivity (cellular IC_{50}): Sunitinib < 200 nM; Sorafenib < 1,000 nM**

Mol Cancer Ther 2012;11:1770-1780

Inhibitory Activity of DBPR216 against Mutant Forms of c-KIT Assay

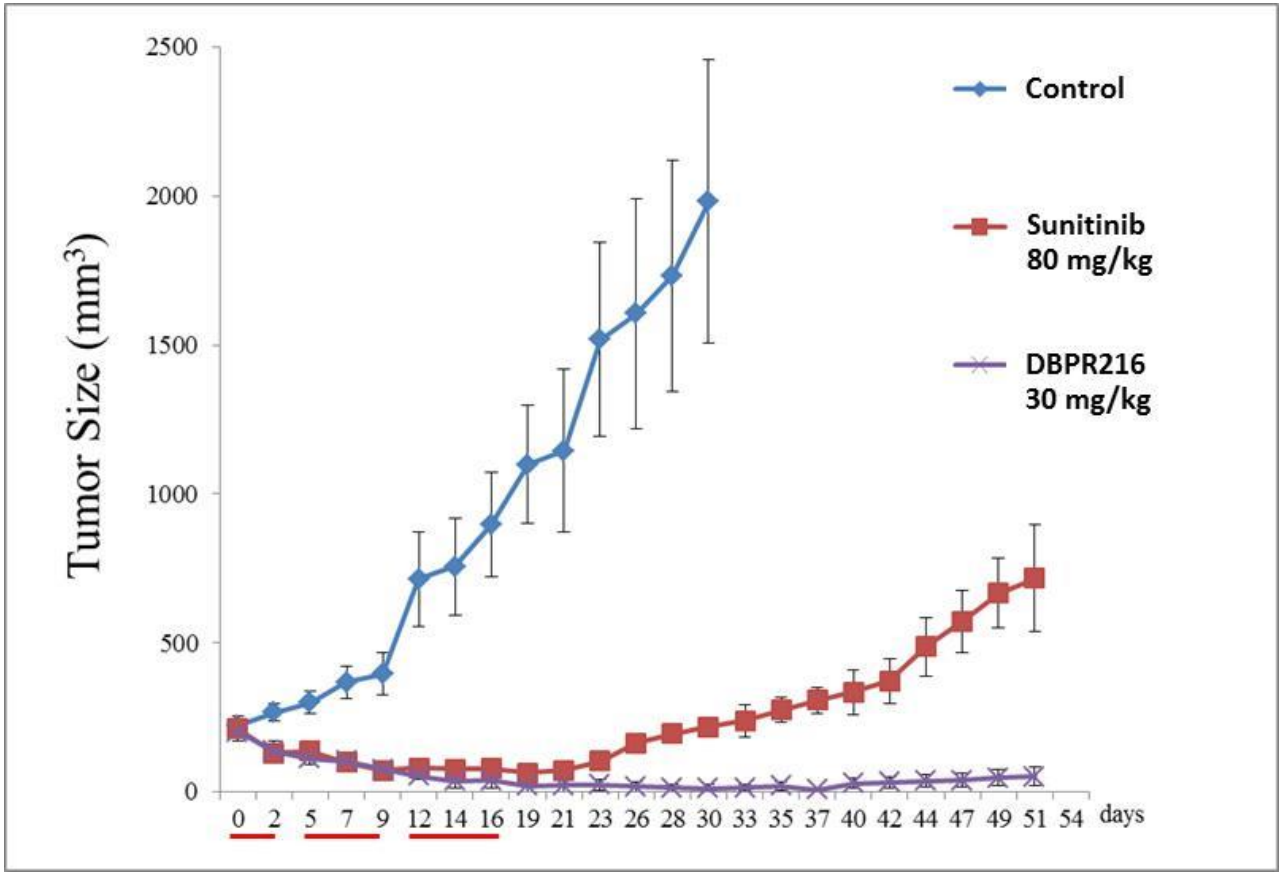
Mutant forms of c-KIT		% Enzyme Activity Inhibition at 100 nM or 10 nM					
		DBPR216		Sunitinib		Regorafenib	
		100 nM	10 nM	100 nM	10 nM	100 nM	10 nM
Exon 11	V560G	93	56	41	8	67	24
Exon 13	V654A	74	49	73	48	14	3
Exon 13	K642E	94	77	80	60	52	16
Exon 14	T670I	89	42	93	43	50	9
Exon 17	D816H	90	47	56	12	9	0
Exon 17	D816V	92	49	47	5	10	5
Exon 17	D820E	98	53	65	16	65	13
Exon 17	D820Y	99	90	81	36	80	25
Exon 17	Y823D	99	93	85	28	88	27
Exon 18	A829P	95	61	43	6	44	4
Exon 11/13	V559D/V654A	54	12	82	32	1	0
Exon 11/17	V560G/D816V	92	54	52	9	0	0
Exon 11/17	V560G/N822K	95	61	51	7	50	7

DBPR216 against GIST Cell Lines

GI_{50} (nM)	Imatinib	Sunitinib	Regorafenib	DBPR216
GIST430	1,000	44	702	3.8
GIST48	625	2,000	>1,000	19
GIST882	253	118	—	12
GIST-T1	28	13	102	6.6

Cell line	Primary KIT mutation	Secondary KIT mutation	Resistance pharmacology
GIST430	Exon 11; p.V560_L576del	Exon 13; p.V654A	Imatinib-resistant
GIST48	Exon 11; p.V560D	Exon 17; p.D820A	Imatinib/sunitinib-resistant
GIST882	Exon 13; p.K642E		imatinib sensitive
GIST-T1	Exon 11; a heterozygous deletion		imatinib sensitive

Sunitinib and DBPR216 GIST430 Tumor Xenograft Model



Day51			
	Control	Sunitinib 80mg/kg	DBPR216 30mg/kg
Tumor size (mm^3)	sacrificed	718 ± 180	52 ± 31
Mouse number		4/4	4/5

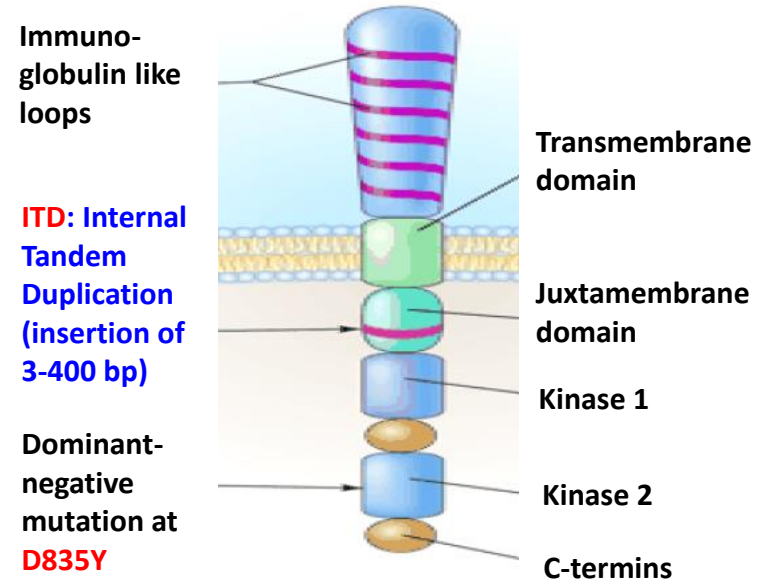
An Overview of FLT3/c-KIT TKIs in AML

FLT3 (Fms-like tyrosine kinase 3), a receptor tyrosine kinase, is important for the normal development of hematopoietic stem cells.

Genetic mutations, such as *FLT3* and *c-KIT* play their role in the stepwise leukemogenesis. The most frequent mutations among acute myeloid leukemia (AML) are FLT3 mutations, which account for approximately 30% of genetic mutations and are predictive markers of poor prognosis. C-KIT mutations account for approximately 6% of known mutations among AML and predicted a higher relapse rate and a shorter overall survival.

At present, the most promising FL3-ITD inhibitor appears to be AC220, which appears to completely suppress FLT3-ITD autophosphorylation in some studies. Clinically relevant AC220 resistance–conferring mutations have thus far been restricted to 2 residues in the FLT3 KD, the "gatekeeper" residue F691 (F691L), and the activation loop (AL) residue D835 (D835V/Y/F).

FLT3 structure

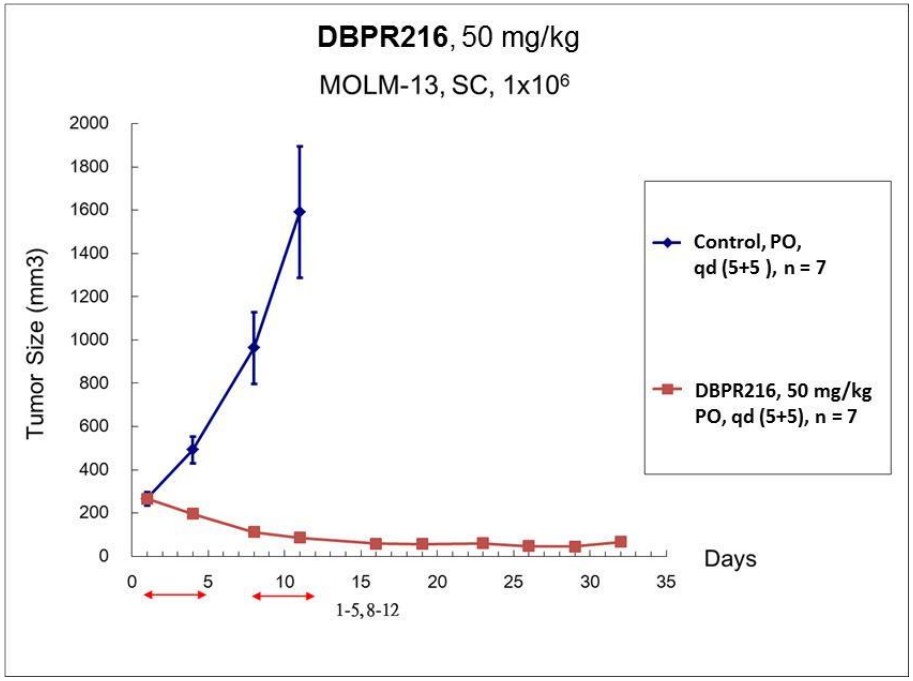


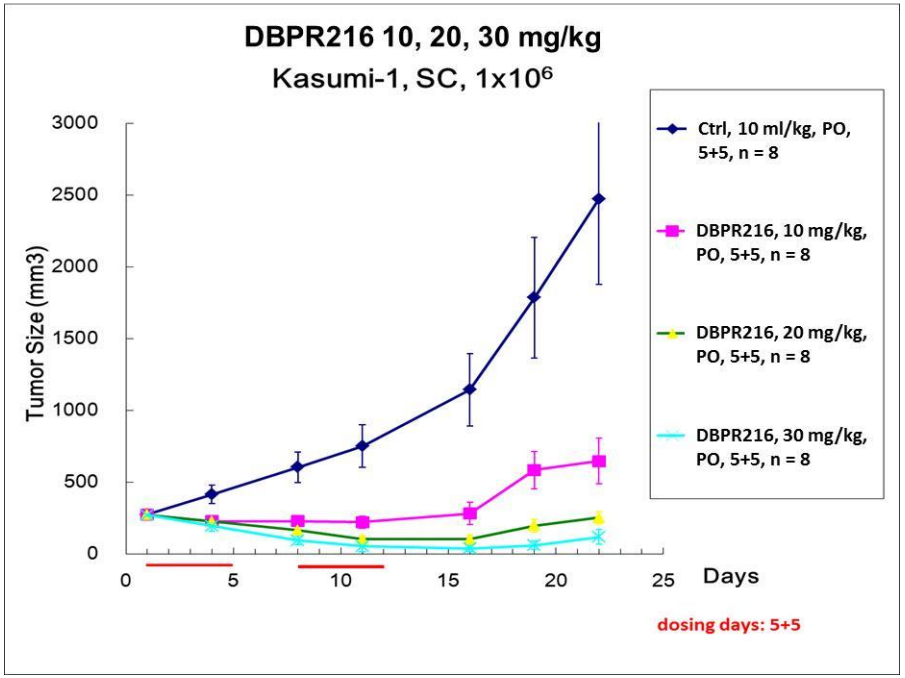
Tyrosine kinase inhibitors (TKI) targeting c-KIT, such as imatinib, has been used successfully to treat c-KIT driven GISTs. However, the effect of TKI on c-KIT-driven leukemia, including CBF-AML and systemic mastocytosis (SM), has not been satisfactory.

DBPR216 against FLT3-ITD and c-KIT Mutant AML Cell Lines

Cell lines	Characterization	DBPR216	AC220	PKC412
		Proliferation GI_{50}, nM		
MOLM-13	AML-FLT3-ITD (heterozygous)	14.6 ± 8.8	4.2 ± 1.8	55 ± 18
MV4;11	AML-FLT3-ITD (homozygous)	20.7± 6.6	2.9 ± 1.4	38 ± 12
Kasumi-1	AML-N822K c-kit mutation	37	41	268 ± 72

*KasumiI-1 GI_{50}: IM= 207 nM; SU = 186 nM; REG = 253 nM.





Kinase Profile of DBPR216 assayed by Reaction Biology Corporation

Enzymes	% Inhibition @ 100 nM
ABL1	97
ALK2/ACVR1	45
c-Kit	85
c-Src	94
CDK7/cyclin H	20
CK2a2	95
CLK1	80
DDR1	97
DDR2	89
DRAK1/STK17A	58
FLT1/VEGFR1	72
FLT3	99
FLT3 (D835Y)	99
FLT3 (ITD)	99
FMS	93
HIPK1	73
HIPK2	41
HIPK4	60
IRAK4	91

Enzymes	% Inhibition @ 100 nM
KDR/VEGFR2	51
LCK	94
MEK5	46
MLCK/MYLK	10
MNK1	52
MNK2	47
MUSK	33
PDGFRα	75
PDGFRα (D842V)	55
PDGFRα (T674I)	98
PDGFRα (V561D)	75
PDGFRβ	88
RIPK2	27
TAK1	35
TRKA	90
TRKB	93
TYK2	36
YSK4/MAP3K19	6
ZAK/MLTK	92

The advantages of DBPR216 over other FLT3/c-KIT inhibitors

1. **DBPR216 has very good inhibitory effect on mutant c-KIT kinase and exhibits excellent growth inhibition against imatinib-resistant GIST cell lines, GIST430 and GIST48; the GI_{50} values are at least 10-fold more potent than second-line Sunitinib and third-line Regorafenib.**

2. **DBPR216 exhibits very potent in vivo efficacy against c-KIT driven GIST430 xenografts when compared to second-line Sunitinib.**

3. **DBPR216 exhibits excellent anti-tumor response to c-KIT mutant kasium-1 xenografts and FLT-ITD mutant MOLM-13 xenografts, and partial regression is observed in both the animal models.**

4. **DBPR216, an inhibitor with multi-targeted kinase inhibition, might be applied to the management of solid tumors.**