MBT-C101, a First-in-class, Selective, and Potent HSP90 Chaperone-Mediated Degrader of PI3Kα

PB031

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MagicBullet Therapeutics

Abstract

PIK3CA, which encodes PI3K p110α (PI3Kα), is one of the most commonly mutated oncogenes across cancers especially 40% incidence in HR+, HER2- breast cancers. PI3Kα-selective Inhibitor alpelisib combination with fulvestrant is only approved drug for targeting PIK3CA. However, alpelisib had clinical limitations due to on-target adverse effects including hyperglycemia. Although ATP-competitive or allosteric inhibitors are in clinical settings to overcome the limitation, new drug modalities for PI3Kα inhibition, including in excellent selectivity and durable efficacy are still on demand.

Scientific Rationale to Develop mtPI3Kα Selective Degrader

alpelisib
- ✓ Approved for PIK3CA-mutant HR+, HER2- metastatic breast cancer (30% prevalent among of 70% of HR+, HER2- patient)
- ✓ Still dose limited toxicity (460 mg) & grade 3 toxicity : hyperglycemia and diarrhea
- ✓ Poor degradation effect

inavolisib
- ✓ Efficacy is better than alpelisib due to inhibitory activity and degradation effect
- ✓ Dose limited toxicity & grade 3 hyperglycemia and diarrhea
- ✓ Breast cancer subtype dependent partial degrader

CM-Degrader

PI3Kα HSP90

MBT-C101
- ✓ mtPI3Kα isoform selective degrader
- ✓ Orally available selective mtPI3Kα degrader
- ✓ No hyperglycemia effect observed
- ✓ Broad spectrum of degradation effect in HER2+ and HER2-
- ✓ Good activity and degradation in mtPI3K/mtKRAS double mutant

MBT Platform: Chaperone-Mediated Degrader (CM-Degrader)

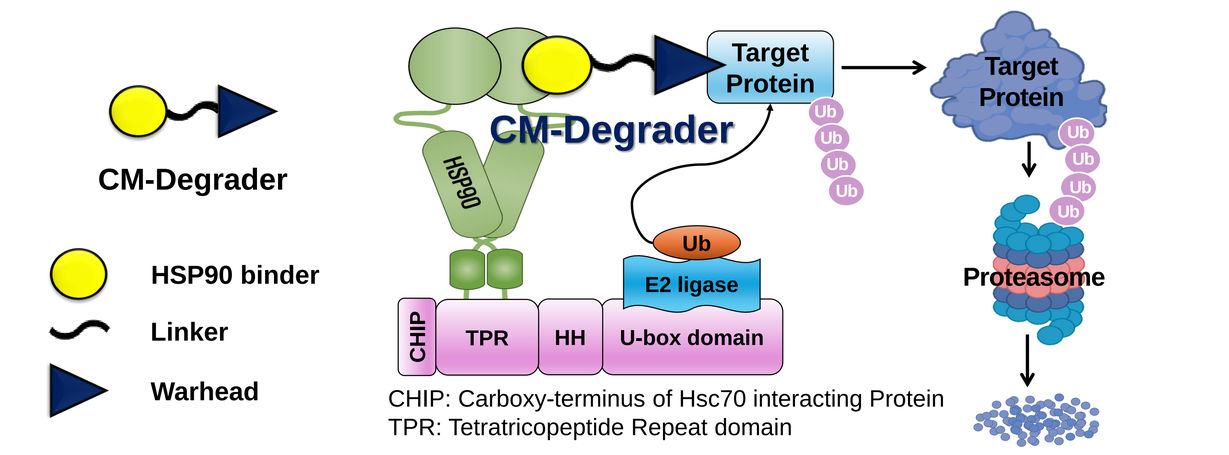


Figure 1. Mechanism of chaperone-mediated degrader (CM-Degrader)

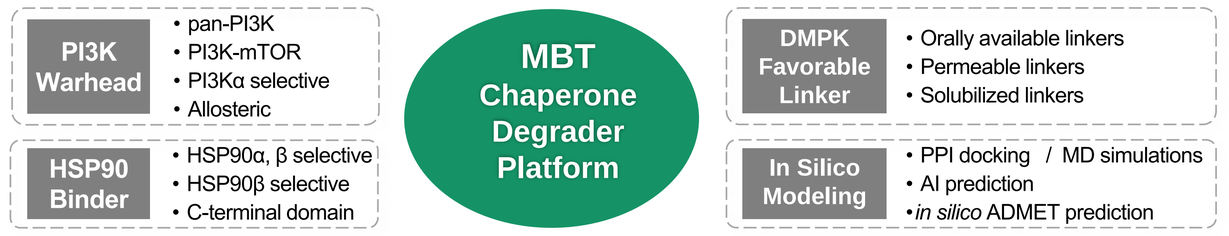


Figure 2. MagicBullet Therapeutics chaperone-mediated degrader platform.

Mechanism of Action over mtPI3Kα CM-Degrader

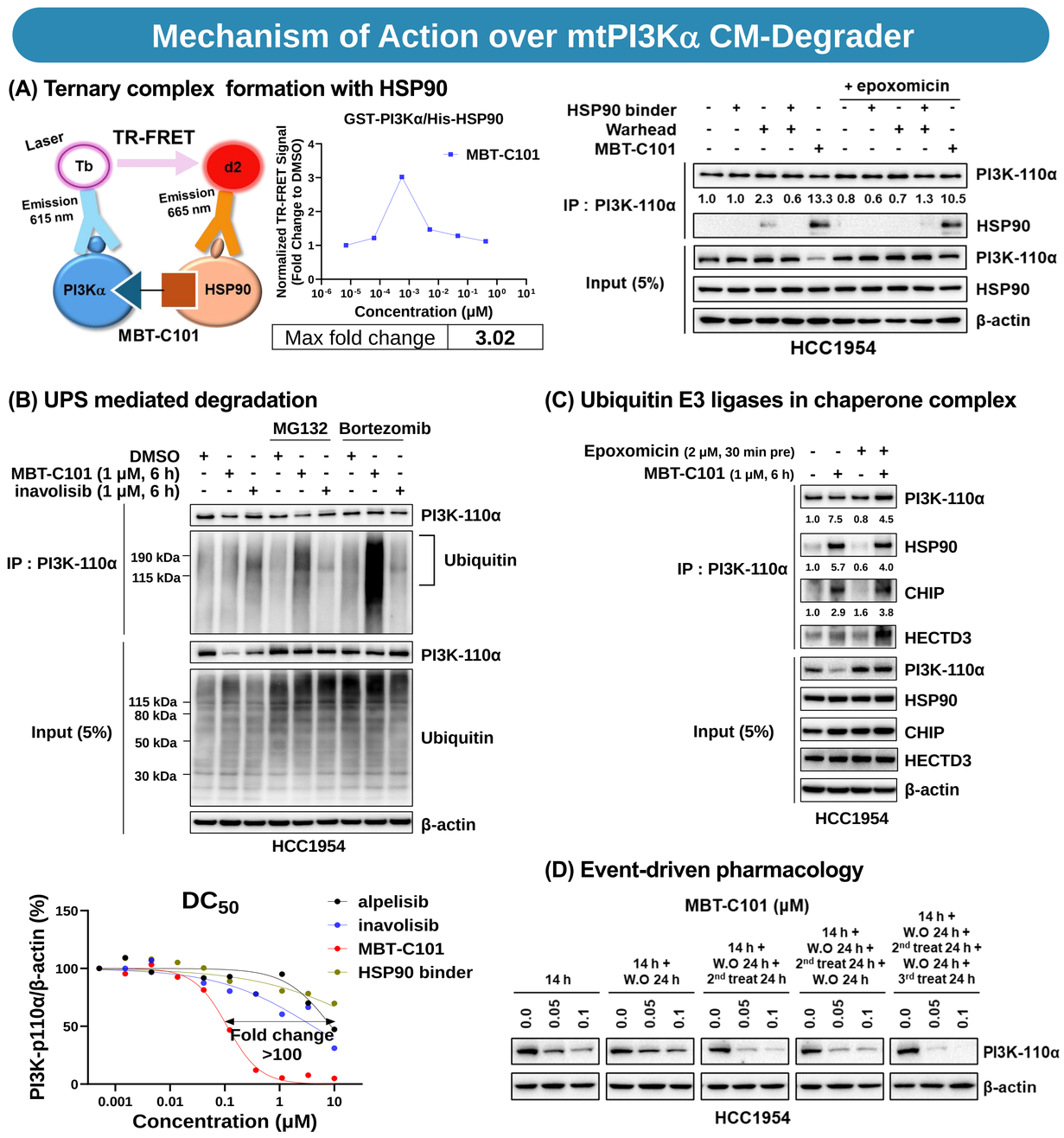


Figure 3. Degradation mechanism of PI3Kα by MBT-C101. (A) MBT-C101 forms a ternary complex with HSP90 (B) MBT-C101 induces PI3Kα degradation via the ubiquitin-proteasome system. (C) Multi-E3 ligases were involved in ternary complex by MBT-C101. (D) Longer duration of degradation effect of MBT-C101 following the wash-out and intermittent treatment.

In vitro Activity & Selectivity

IC_{50} (nM)	alpelisib	inavolisib	MBT-C101
PI3K isoforms (α, β, γ, δ)	1.4 / 1343 / 53 / 51	0.6 / 298 / 31 / 27	**1.0** / 256 / 27 / 134
PI3Kα-H1047R	1.7	< 0.5	**< 0.5**
PI3Kα-E542K	1.2	< 0.5	**0.6**
PI3Kα-E545K	1.4	< 0.5	**< 0.5**
HSP90α	>10,000	>10,000	**18.3**

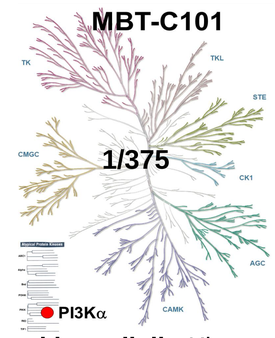
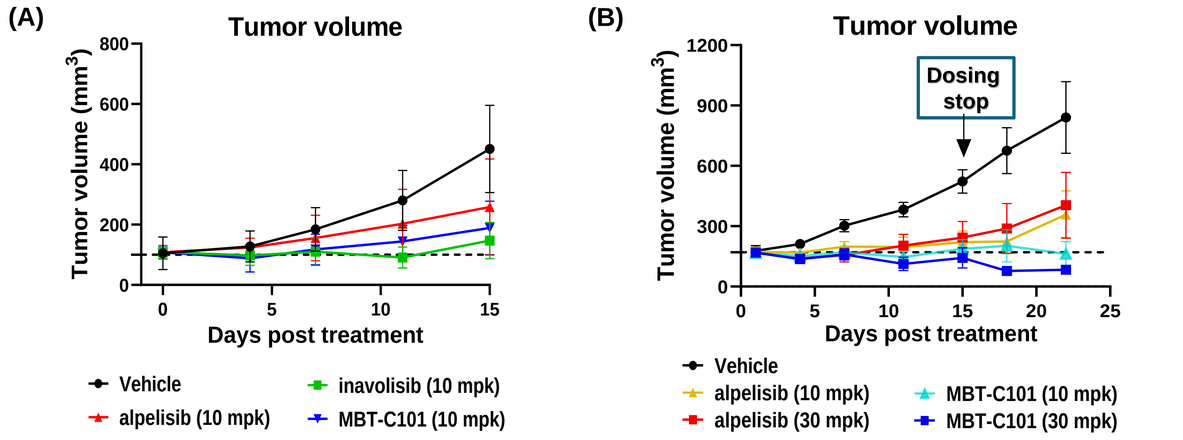


Table 1. *In vitro* activity and selectivity comparison of MBT-C101 to alpelisib and inavolisib. Kinases showing >90% inhibition by 0.1 μM MBT-C101 are clustered on the kinome tree.

In vivo Efficacy HCC1954 Xenograft Model (PO, QD)



Compounds	TGI (%)
alpelisib (10 mpk)	76.6
inavolisib (10 mpk)	96.6
MBT-C101 (10 mpk)	90.4

Compounds	TGI (%, 2 week)		TGI (%, 3 week)	
	10 mpk	30 mpk	10 mpk	30 mpk
alpelisib	96.6	90.1	80.0	73.6
MBT-C101	97.2	120.9	104.1	122.1

Figure 4. MBT-C101 potently suppresses of tumor growth in the HCC1954 xenograft mouse model. Compounds/vehicle was orally administrated to mice, once a day for 2 weeks.

Differential Advantages to Comparator Inavolisib

① Excellent chaperone-induced degradation activity

Breast Cancer Cells	Mutant	Type			alpelisib		inavolisib		MBT-C101	
	PI3Kα	HER2	ER	PR	GI_{50}	DC_{50}	GI_{50}	DC_{50}	GI_{50}	DC_{50}
HCC1954	H1047R	+	-	-	314	>5,000	**52**	961	20	**75**
T47D	H1047R	-	+	-	578	>10,000	**55**	1,774	19	**21**
MCF-7	E545K	-	+	+	490	>10,000	**86**	>10,000	18	**110**
MDA-MB-453	H1047R	-	-	-	363	5,300	**61**	3,047	32	**44**
BT-20	H1047R	-	-	-	1,503	>10,000	**199**	>10,000	26	**39**

Table 2. Broad mtPI3Kα degradation effect of MBT-C101 compare to alpelisib and inavolisib

② No glucose level changed

Hyperglycemia

inavolisib + fulvestrant
Ph1b, Arm D[1] (N = 60)
40% | 22%

alpelisib + fulvestrant
BYLieve[2] (N = 127)
30% | 29%

Grade1-2 Grade3+

1.SABCS 2021, #P5-17-05;
2.Rugo 2021 Lancet Oncol 22;489;

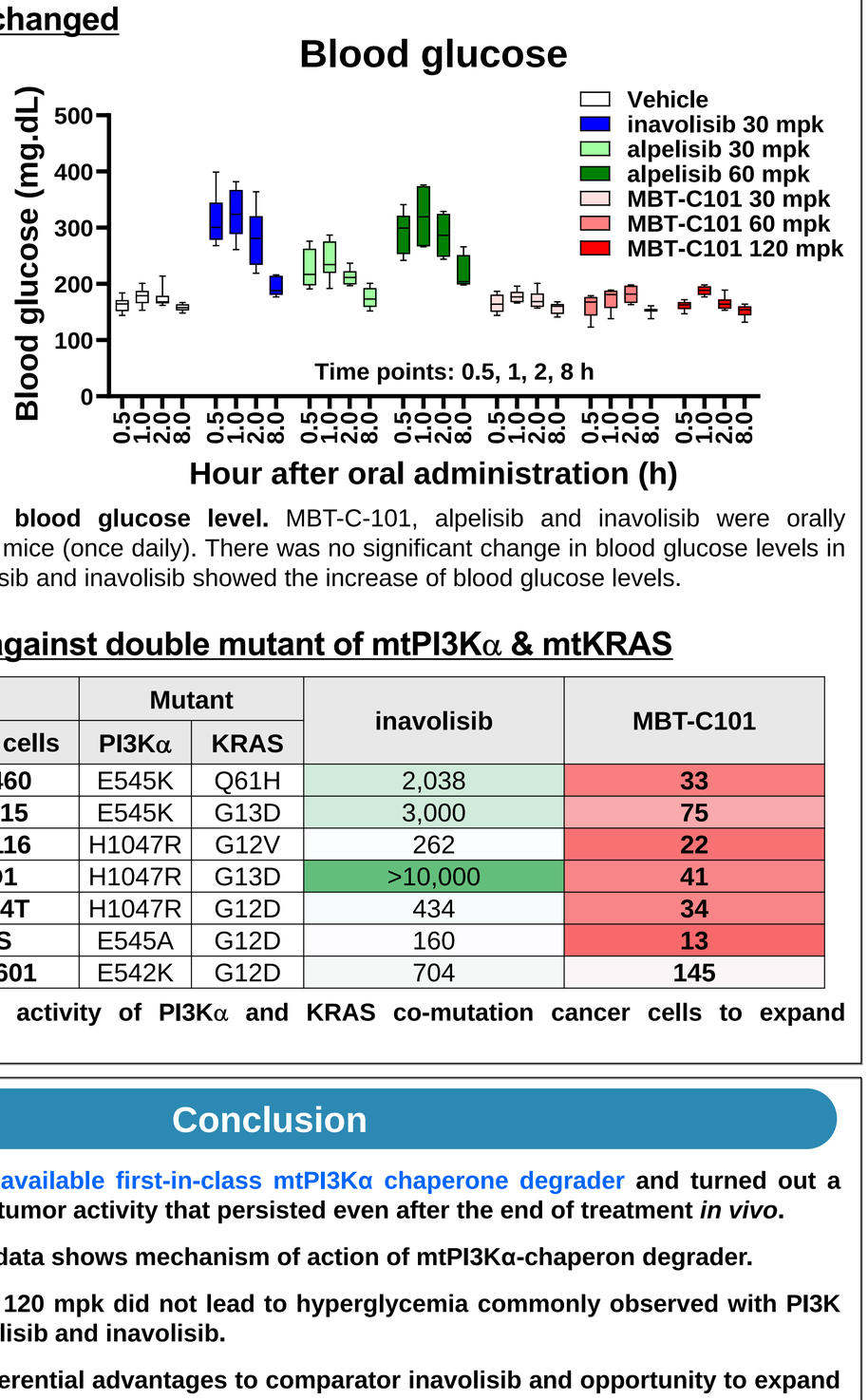


Figure 5. Comparison of blood glucose level. MBT-C-101, alpelisib and inavolisib were orally administrated for 2 weeks in mice (once daily). There was no significant change in blood glucose levels in MBT-C101 groups, but alpelisib and inavolisib showed the increase of blood glucose levels.

③ Superior activity against double mutant of mtPI3Kα & mtKRAS

GI_{50} (nM)		Mutant		inavolisib	MBT-C101
Cancer	Cancer cells	PI3Kα	KRAS		
Lung cancer	NCI-460	E545K	Q61H	2,038	**33**
Colon cancer	HCT-15	E545K	G13D	3,000	**75**
	HCT116	H1047R	G12V	262	**22**
	DLD1	H1047R	G13D	>10,000	**41**
	LS174T	H1047R	G12D	434	**34**
Gastric cancer	AGS	E545A	G12D	160	**13**
	SNU-601	E542K	G12D	704	**145**

Table 3. Anti-proliferative activity of PI3Kα and KRAS co-mutation cancer cells to expand therapeutic indications.

Conclusion

- **MBT-C101 is the orally available first-in-class mtPI3Kα chaperone degrader and turned out a robust and durable anti-tumor activity that persisted even after the end of treatment *in vivo*.**
- **We present preliminary data shows mechanism of action of mtPI3Kα-chaperon degrader.**
- **MBT-C101 dosing up to 120 mpk did not lead to hyperglycemia commonly observed with PI3K inhibitors including alpelisib and inavolisib.**
- **MBT-C101 has three differential advantages to comparator inavolisib and opportunity to expand therapeutic indications.**

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