



Novel brain-penetrant BRAF paradox breaker HSK42360 demonstrates promising antitumor activity in patients with BRAF-mutant glioma

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I have the following relevant financial relationships to disclose:

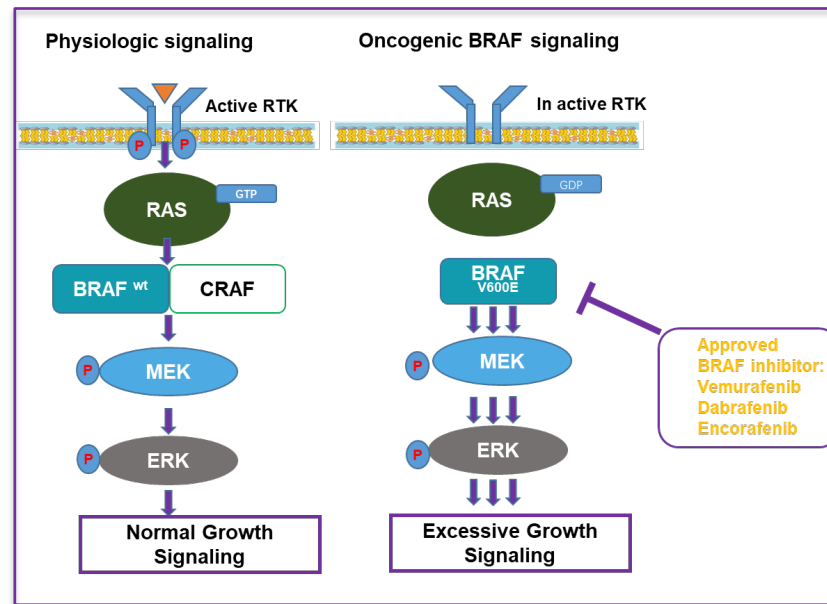
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BRAF V600 Mutations in Gliomas

- BRAF mutations cause constitutive activation of BRAF kinase, leading to dysregulated MAPK/MEK/ERK signaling and excessive cell growth and survival.
- BRAF V600 mutation is the most common mutation of the BRAF gene and occurs in various tumors, including melanoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC).
- BRAF V600 mutation is also present in both low-grade and high-grade gliomas in adults and children: the overall prevalence in adult malignant gliomas is approximately 3% ¹, around 17% in pediatric low-grade gliomas (pLGG) ², and 5–10% in pediatric high-grade gliomas (pHGG) ³.

Normal vs Oncogenic BRAF-MEK-ERK Signaling and Approved BRAF Inhibitors



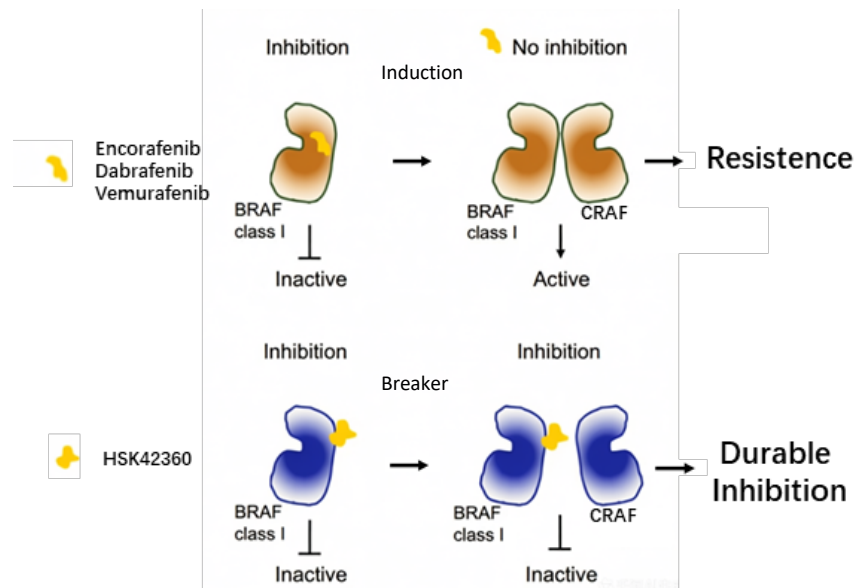
1. Cancers (Basel),2019,11(6):794; 2. Am Soc Clin Oncol Educ Book. 2024 Jun;44(3):e431450; 3. J Clin Oncol. 2023 Nov 20;41(33):5174-5183.

Paradoxical MAPK Activation

First-Gen BRAFi-Induced Paradoxical Activation Drives Drug Resistance and Cutaneous Toxicity

- ✓ The paradoxical activation occurs when a drug binds to one member of RAF homo-(CRAF/CRAF) or heterodimers (CRAF/BRAF), inhibiting one protomer while resulting in the transactivation of the drug-free protomer.
- ✓ First-generation BRAF inhibitor-induced paradoxical activation presents three major challenges: **acute intolerance**¹, **cutaneous toxicity**², and **paradox-driven resistance**³.
- ✓ Developing novel molecules that disrupt dimer formation is necessary to overcome this paradoxical activation.

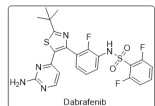
Mechanism of HSK42360: Dimer-Breaking BRAF Inhibition for Sustained Pathway Suppression



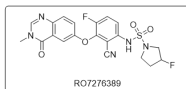
HSK42360 Demonstrates Best-in-Class Inhibition of Paradox Activation

Molecular dynamics (MD) study found :Compared to the Dabrafenib-bound BRAF kinase domain, HSK42360 induced a greater extent rotation of the α C-helix to prevent and disrupt the dimerization of BRAF.

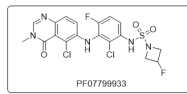
HSK42360 was experimentally proven to be free of paradoxical activation in HCT116 cells.



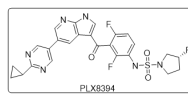
Paradox: 100%



23~50%



72%

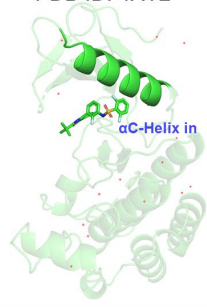


30%

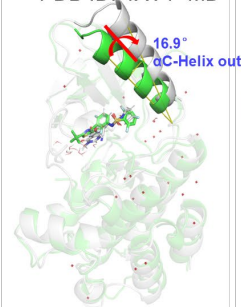
HSK42360

0%

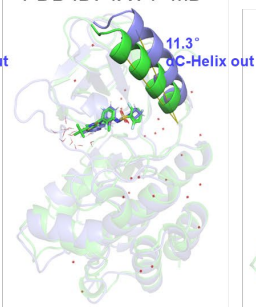
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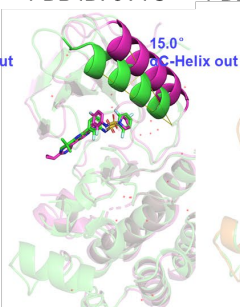
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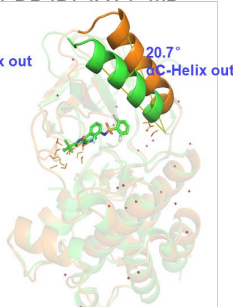
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PDB ID: 8VYS

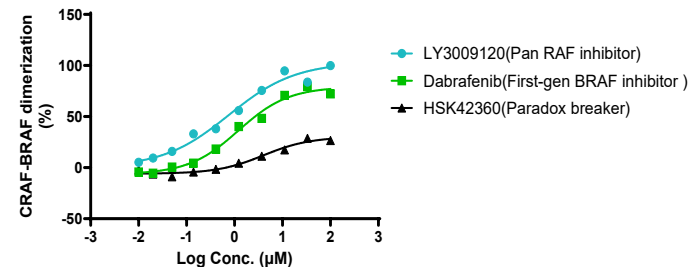


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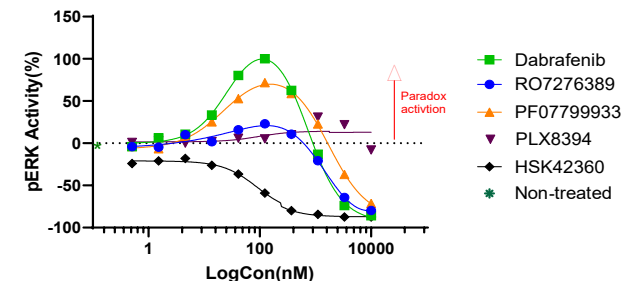


Disruption of BRAF-CRAF dimerization in HCT116 cells

HCT-116 (CRAF + BRAF)



Paradox activation in HCT116 cells



HSK42360 Exhibits strong potency in Non-V600 Mutant and Resistant

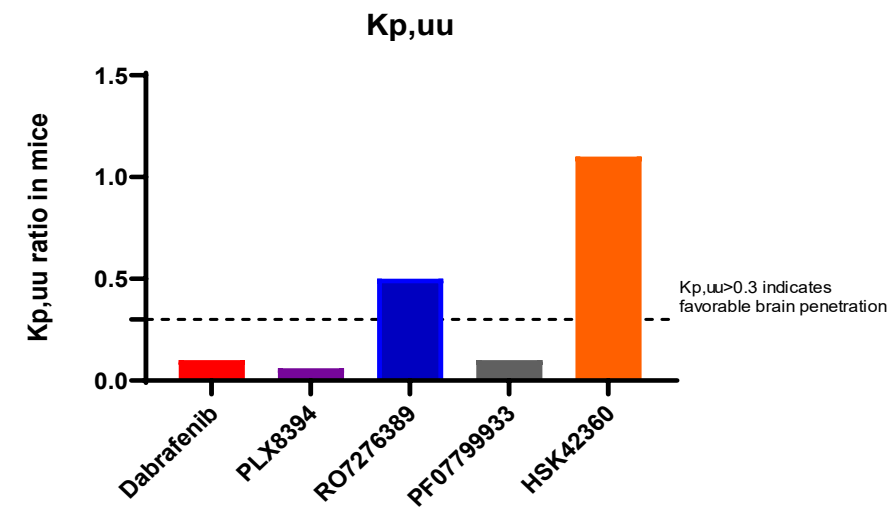
In Vitro Potency Comparison of BRAF Inhibitors

Assays	Genotypes /Species		Dabrafenib	PLX8394	RO7276389	PF07799933	HSK42360
Anti-proliferation potency (IC ₅₀ , nM)	Class I	BRAF-V600E/V600E (A375)	4.13	3.62	2.3-4.7	3.34	1.51-2.96
		BRAF-V600E/WT (COLO205)	3.75	2.53	7.6-8.4	ND	4.79
Anti-proliferation (or pERK inhibition) potency (IC ₅₀ , nM)	Class II	G469A (H1755)	515	ND	80	224	57.6
		G469A (H1395)	529	ND	99	467	101
	Class III	G466V (NCI-H1666)	446	ND	13	26	10
Anti-proliferation potency (IC ₅₀ , nM)	Resistant	NRAS mutant (A375)	547	135.2	330	1,807	48

ND, No test done

HSK42360 demonstrated the most robust brain penetration in mice

Kp,uu of BRAF Inhibitors in Mice: Implications for Brain Penetration



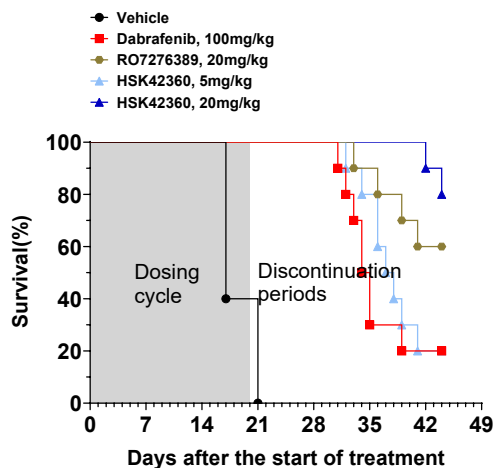
Comparison of Brain Penetration (Kp,uu) of Compounds in Mice

Assays	Species	Dabrafenib	PLX8394	RO7276389	PF07799933	HSK42360
Brain penetration (Kp,uu*)	Mouse	0.1	0.06	0.5	0.1	1.1

*Kp,uu = unbound brain-to-plasma concentration ratio (ub AUC_brain / ub AUC_plasma)

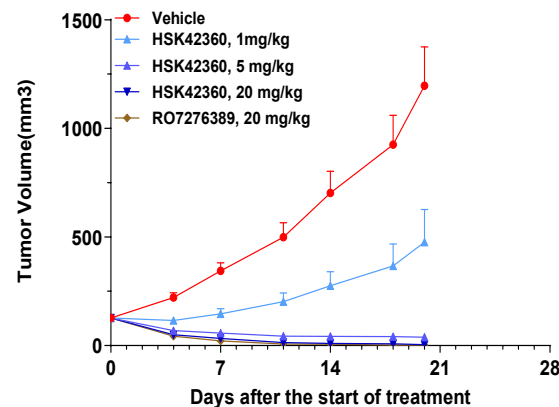
Significant Antitumor Activity in Intracranial CDX and Glioma PDX Models

Intracranial A375-Luc CDX(V600E)



HSK42360 Significantly Prolongs Survival in Intracranial A375 CDX Models

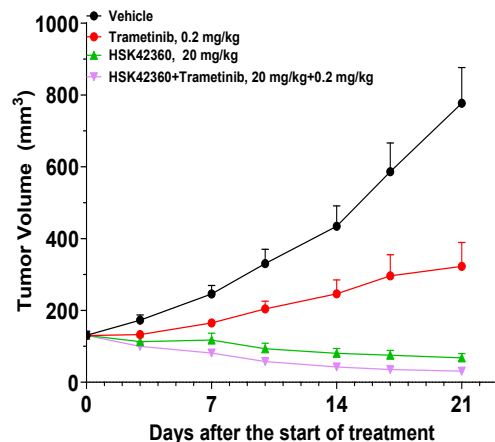
Glioma PDX BN2331(V600E)



HSK42360 Demonstrates Tumor Regression Potential in Glioma PDX Models

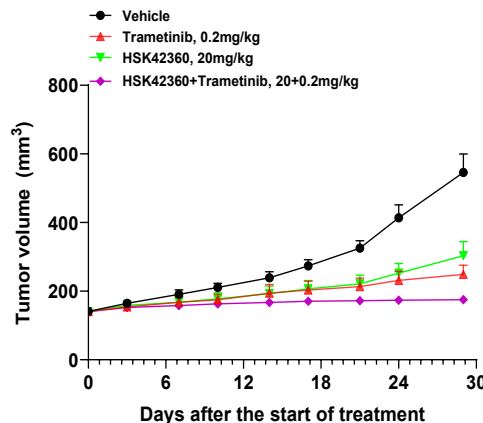
HSK42360 Shows Efficacy as Monotherapy and in Combination in BRAF Class II/III and Resistant Models

Melanoma PDX(Class II)



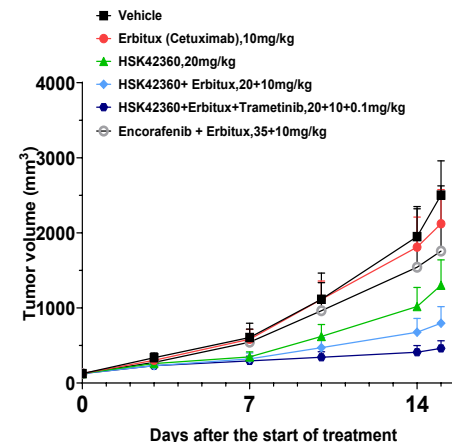
HSK42360 ± MEKi Inhibits Tumor Growth in BRAF G469A Mutant Melanoma PDX Models

NSCLC CDX H1666(Class III)



HSK42360 ± MEKi Shows Antitumor Activity in BRAF G466V Mutant NSCLC CDX Models

Resistant CRC PDX LD1-0012



HSK42360 Shows Efficacy in Cetuximab + Vemurafenib Resistant CRC PDX Models

HSK42360 Shows Promising Clinical Activity in Both Low-Grade and High-Grade Glioma

Overall (N=23)

Dosage

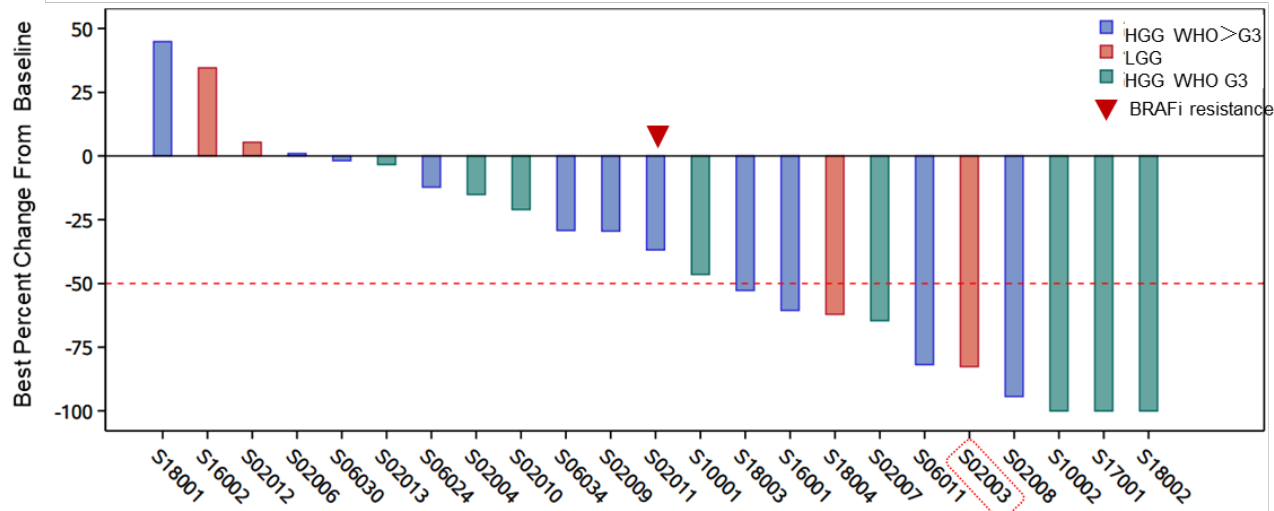
S02003	3600mg (1800mg BID)
Others	2400mg (1200mg BID)

WHO Grade

LGG	4 (17.4%)
Grade 3	8 (34.8%)
Grade 4	9 (39.1%)
Other(WHO Grade3-4)	2 (8.7%)

Anti-cancer Treatment History

Prior drug therapy	20 (87.0%)
TMZ	19 (82.6%)
Bev	6 (26.1%)
Prior radiotherapy	22 (95.7%)
Prior surgery	23 (100.0%)



*Tumor response was evaluated according to the RANO criteria

High-Grade Glioma (n=19):

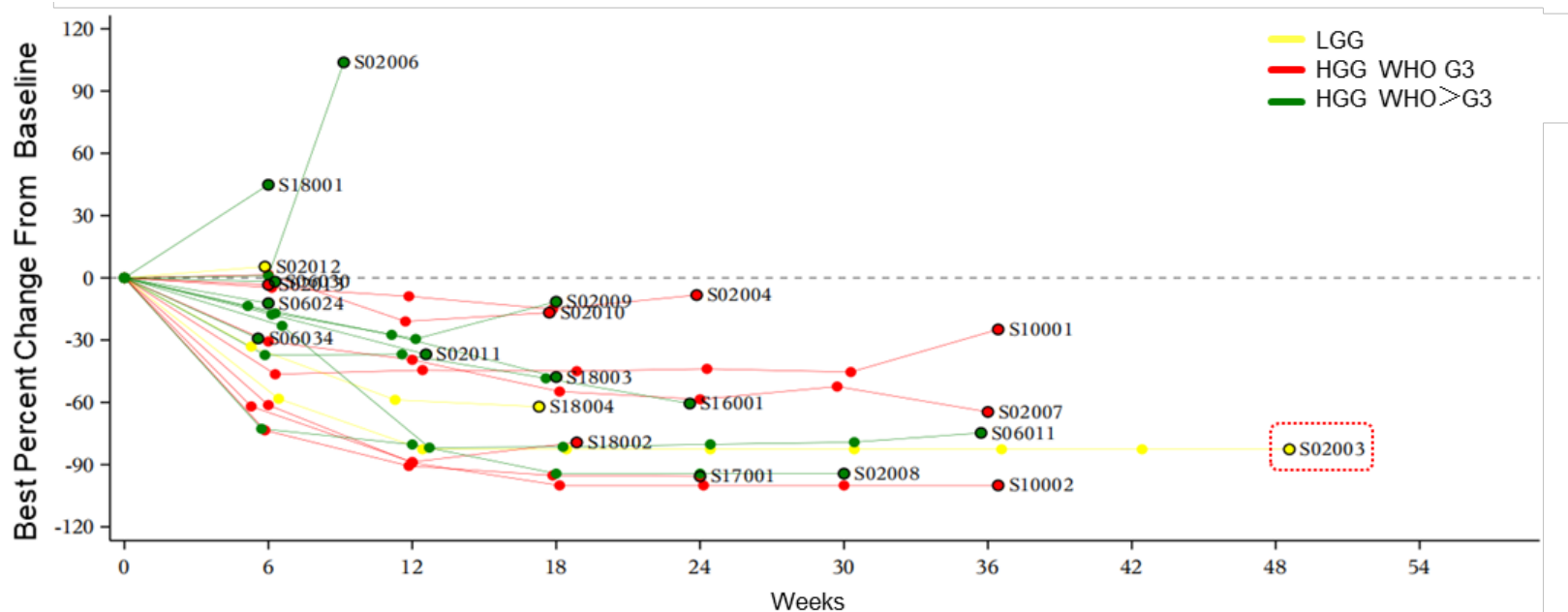
- **ORR:** 42.1% (8/19)
- **DCR:** 89.5% (17/19)
- **Deep Response** (>80% reduction): **62.5%** (5/8) of responders
- **DoR rate at 6 months:** 55.6%

Low-Grade Glioma (n=4):

- **ORR:** 50.0% (2/4)
- **DCR:** 75.0% (3/4)
- **Deep Response** (>80% reduction): 50.0% (1/2) of responders
- **DoR rate at 6 months:** 100%

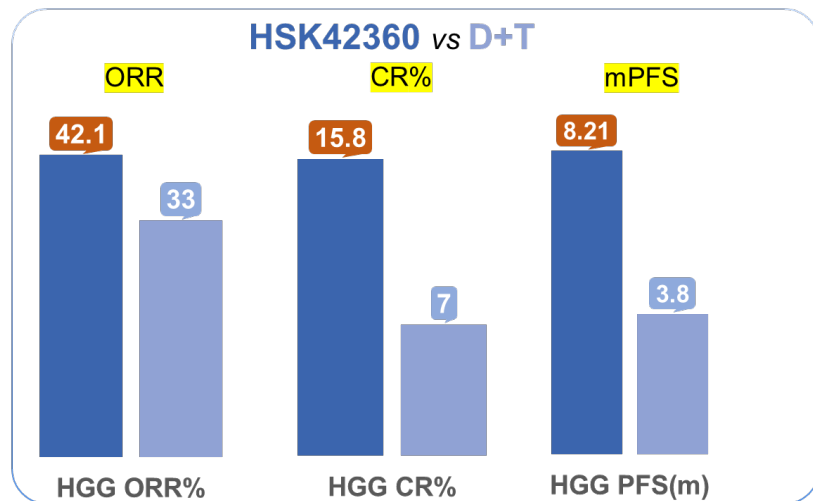
Sustained Clinical Responses with HSK42360 in Low- and High-Grade Glioma

- For most patients, the best response was achieved within 6–24 weeks after treatment initiation.
- Among patients with long-term follow-up (>36 weeks), LGG demonstrated superior durable response, while most patients in the HGG cohort also showed favorable durable response.



HSK42360: Superior Response and Prolonged PFS vs. Standard-of-Care in HGG Glioma

- Confirmed promising preclinical profile of **high brain-penetration**;
- Preliminary Confirmation of HSK42360 **Efficacy in Glioma** (both HGG & LGG);
- Demonstrated a significantly **longer mPFS** compared to D+T, suggesting the ability to **overcome BRAFi-resistance** by avoiding paradoxical activation.



D: Dabrafenib, T: Trametinib

	HSK42360	D+T (ROAR)*	Chemo*
Population	Recurrent Glioma (HGG/LGG)		
ORR			
HGG	42.1%(20-67)	33%(20-48)**	~5%
WHO 3 HGG	50%(16-84)	38%(14–68)	-
WHO 4 HGG	33.3%(7-70)	32%(17–51)	-
HGG CR	15.8%	7%	-
LGG	50%(7-93)	50%(23-77)**	-
mPFS			
HGG	8.21m (4.14-NA)	3.8m (1.8-9.2)	< 3m
LGG	NR (NA-NA)	NR (7.4-NA)	-

Abbreviations: NA, not applicable; NR, not reported

*Wen PY, et al. Lancet Oncol. 2022 Jan;23(1):53-64.

**TAFINLAR® (dabrafenib), HIGHLIGHTS OF PRESCRIBING INFORMATION.

HSK42360 Offers a Favorable Safety Profile by Reducing Classic BRAFi Toxicities

- ✓ HSK42360 shows markedly lower incidence and severity of classic BRAF inhibitor-associated TRAEs (e.g., **pyrexia, rash, myalgia**) than approved BRAF inhibitors.
- ✓ Its more frequent TRAEs (ALT/AST increased) occur at a **lower rate than with Dabrafenib + Trametinib**.

Type	Name	HSK42360 (N=69*)		Dabrafenib* (BREAK-3, MM, N=187)		Vemurafenib** (MM, N=132)		D+T* (ROAR, N=206)	
TRAE(%)		ALL	≥G3	ALL	≥G3	ALL	≥G3	ALL	≥G3
General	Pyrexia	5.8	0	28	3	20	2	55	4.9
Skin	Rash	1.4	0	17	0	55	8	40	2.4
	Hyperkeratosis	0	0	37	1	31	0	-	-
	Maculopapular rash	0	0	-	-	21	6	-	-
	PPE	0	0	20	2	11	2	-	-
	Skin papilloma	0	0	27	0	33	0	-	-
	csCC	0	0	7	4	26	26	-	-
	Keratocanthoma	0	0	-	-	5	5	-	-
Musculoskel etal tissue	Arthralgia	0	0	27	1	70	9	23	0.5
	Myalgia	1.4	0	11	0	27	2	24	0.5
	Back pain	0	0	12	3	13	<1	-	-
Chemistry	Increased GGT	11.6	1.4	-	-	17	7	-	-
	Increased ALP	7.2	1.4	19	0	-	-	51	5
	Increased AST	23.2	7.2	-	-	-	-	51	4.6
	Increased ALT	23.2	4.3	-	-	-	-	39	3

*TAFINLAR® (dabrafenib), HIGHLIGHTS OF PRESCRIBING INFORMATION;

**the label of ZELBORAF® (vemurafenib), Chinese vision.

#66 patients had reached the effective dose predicted by animal models.

- ◆ **No DLTs;**
- ◆ **No TRAEs led to discontinuation** (vs D+T=13.6%), **treatment termination, or death;**
- ◆ **Only 2 SUSARs reported:** increased CPK (G3) and pyrexia (G2), **both resolved;**
- ◆ **No Significant Skin, Ocular, or Cardiac Toxicity.**

HSK42360: A Brain-Optimized BRAF Paradox Breaker with Best-in-Class Penetration

- ❑ Potent RAF dimerization breaker, no paradoxical activation.
- ❑ Spares wild-type RAF, reduces classic BRAFi toxicities (dermatotoxicity, cSCC).
- ❑ Broad mutant coverage (Class I/II/III BRAF), drives robust tumor inhibition.
- ❑ Superior efficacy in HGG: higher ORR/CR, prolonged PFS vs. Dabrafenib + Trametinib.