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GFH375治疗KRAS G12D突变型晚期胰腺癌临床开发进展

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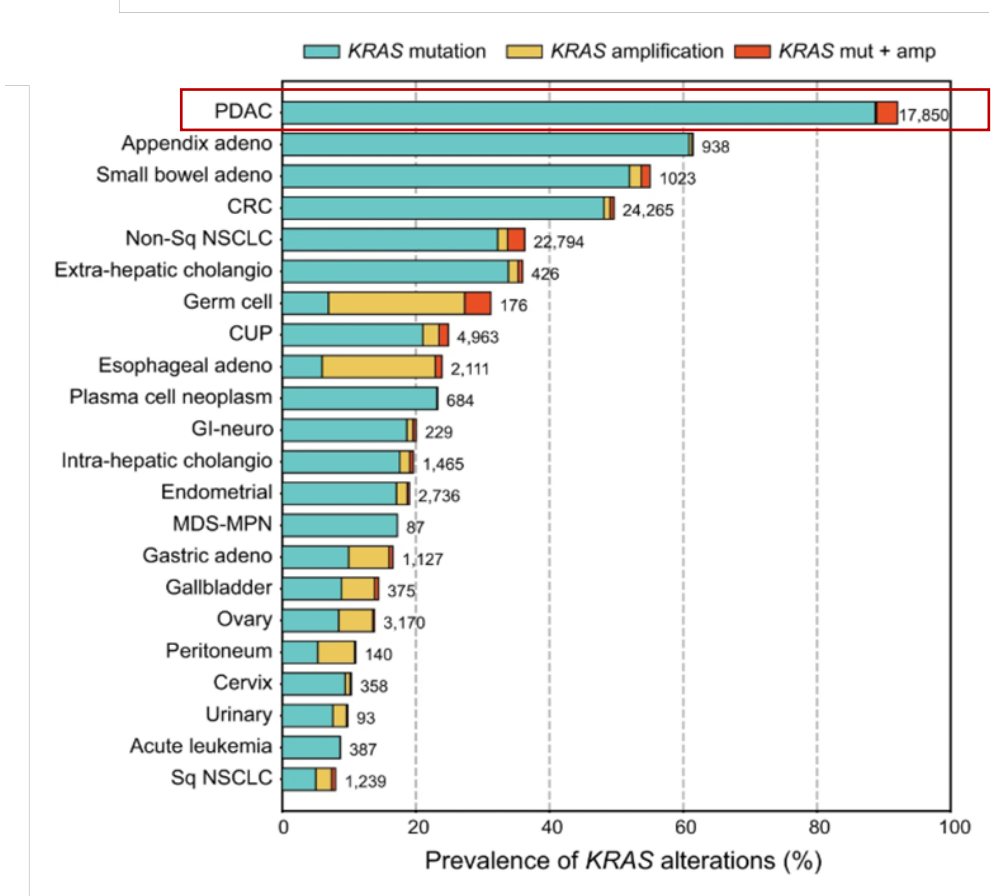
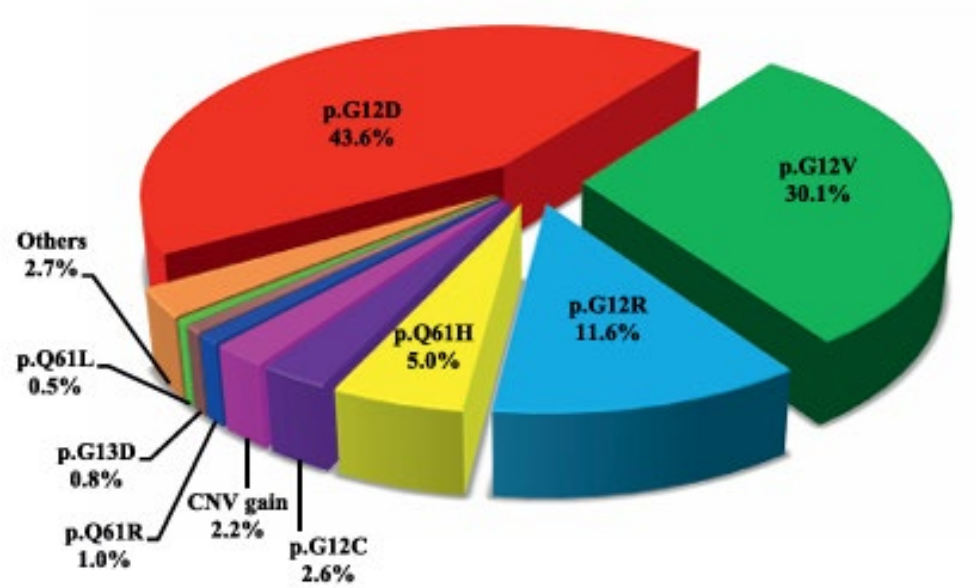
KRAS突变型晚期实体瘤

- KRAS 突变是多种实体瘤的常见致癌驱动因子，它会持续激活细胞生长信号，导致肿瘤增殖
- 胰腺癌KRAS突变频率约80-90%，其中最常见的亚型为G12D，占所有KRAS突变胰腺癌的43.6%



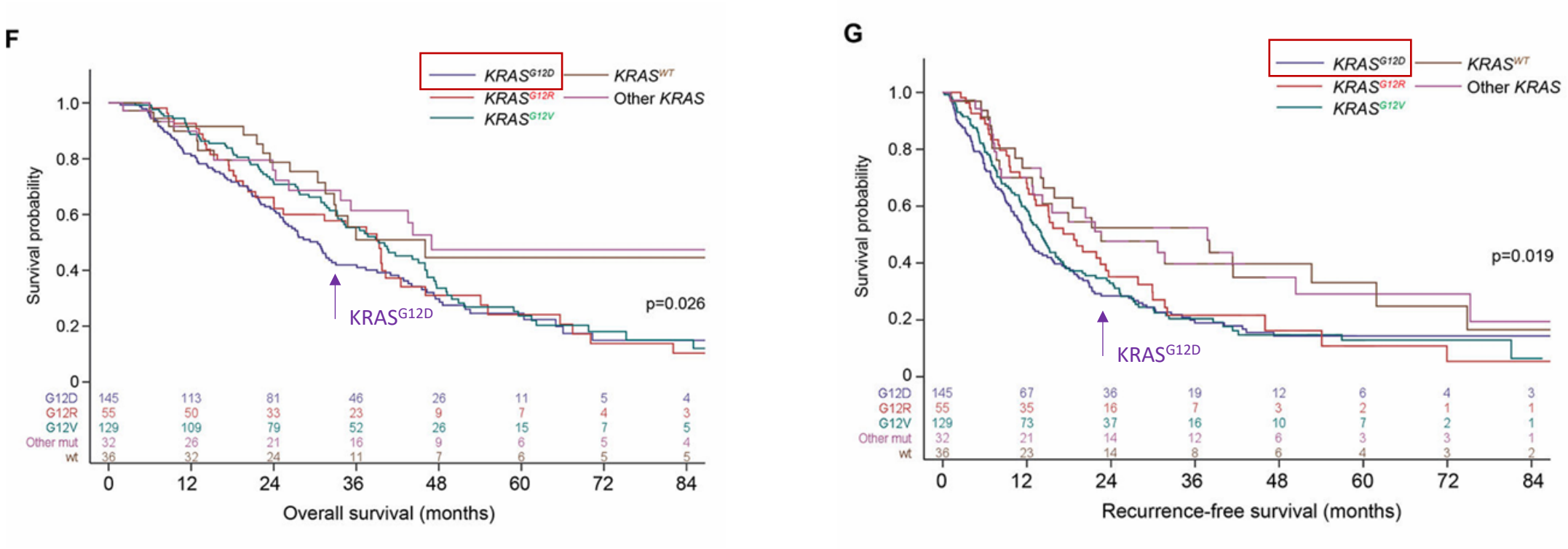


胰腺癌KRAS亚型的比例

Source: 1. Lee, J.K., Sivakumar, S., Schrock, A.B. et al. npj Precis. Onc. 6, 91 (2022). 2. Zhang X, Mao T, Zhang B, et al. EBioMedicine. 2022 Mar;77:103897.

KRAS G12D突变是胰腺癌的独立预后不良标志物

- 携带KRAS G12D突变的胰腺癌患者中位OS及中位RFS最短
  - 中位OS：**KRAS G12D 30个月** vs. KRAS野生型46个月， KRAS G12R 39个月，KRAS G12V39个月，其他KRAS亚型 47个月
  - 中位RFS: **KRAS G12D 12个月** vs. KRAS野生型23个月， KRAS G12R 19个月，KRAS G12V14个月，其他KRAS亚型 38个月



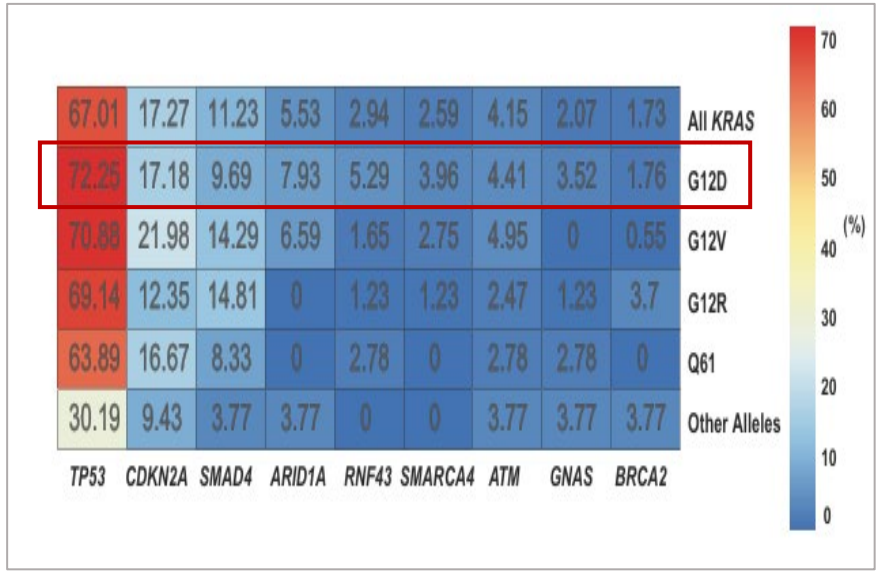
1360例胰腺癌术后患者，不同突变亚型的OS及RFS

Source: McIntyre CA, Grimont A, Park J, et al. Cancer Cell. 2024 Sep 9;42(9):1614-1629.e5.

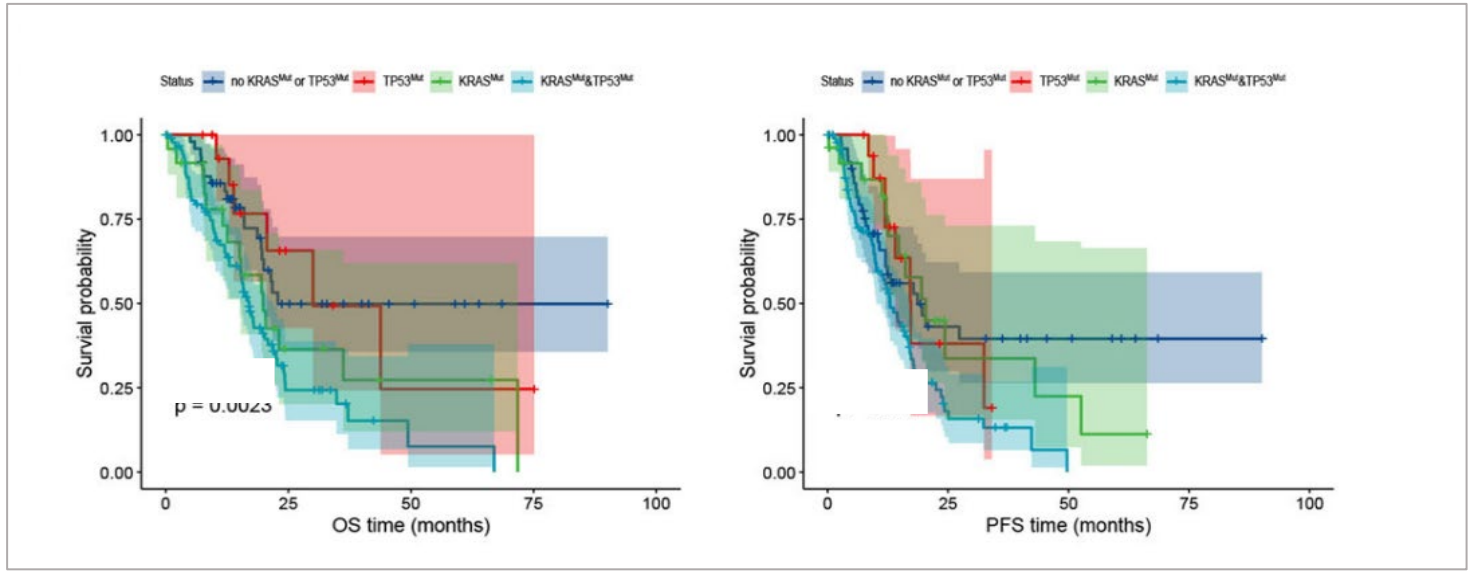
KRAS突变型胰腺癌常见共突变基因

KRAS 突变型胰腺导管腺癌（PDAC）最常见的共突变基因为肿瘤抑制基因，其中以 TP53 最为常见，其次依次为 CDKN2A、SMAD4 及 ARID1A

- 对于同时携带 KRAS 及 TP53 突变的 PDAC 患者，其总生存期（OS）及无进展生存期（PFS）明显短于未携带该两种突变或仅携带其中一种突变的患者



不同KRAS突变亚型的共突变基因及频率



KRAS^{mt}/TP53^{mt}患者PFS及OS差

Source: 1. Yousef, A., Yousef, M., Chowdhury, S. et al. npj Precis. Onc. 8, 27 (2024). 2. Jiang Y, Mai G, Zhao X, et al. NPJ Precis Oncol. 2025 Aug 22;9(1):299.

晚期胰腺癌的治疗现状

- 化疗治疗晚期胰腺癌疗效极为有限，5年生存率仍低于10%
  - 一线（AG、FOLFIRINOX方案）：ORR 23 ~ 32%；mPFS 5.5 ~ 6.4个月；mOS 8.5-11.1个月
  - 二线（脂质体伊立替康联合方案）：ORR 12.8 ~ 17%；mPFS 2.9 ~ 5.2个月；mOS 5.9 ~ 9.2个月
  - 三线及以上（CSCO等国内指南和NCCN均无推荐）：mPFS约2个月，mOS约5.5个月

Source: 1. Lancet Gastroenterol Hepatol. 2019 Dec;4 (12):934-947. 2. N Engl J Med. 2011 May 12;364 (19):1817-25. 3. N Engl J Med. 2013 Oct 31;369 (18):1691-703. 4. Lancet. 2016 Feb 6;387 (10018):545-557. 5. Eur J Cancer. 2019 Feb;108:78-87. 6. J Clin Oncol. 2014 Aug 10;32 (23):2423-9. 7. Eur J Cancer. 2021 Nov;157:21-30. 8. J Clin Oncol. 2016 Nov 10;34 (32):3914-3920. 9. Signal Transduct Target Ther. 2024 Sep 19;9 (1):248. ; 10. Gueiderikh et al. BMC Cancer (2024) 24:272； 11. Stoop, Thomas F et al. The Lancet, Volume 405, Issue 10485, 1182 - 1202

KRAS G12D抑制剂在胰腺癌中的临床开发进展

尚无覆盖面较广的胰腺癌靶向药获批上市

靶点	占比	代表药物
KRAS^{wt}	10-17%	尼妥珠单抗
dMMR	2%	帕博利珠单抗
BRCA1/2突变	3-5%	奥拉帕利
NTRK融合	1-3%	拉罗替尼
NRG1融合	1%	泽妥珠单抗

Source: 1. 胰腺癌精准检测与分子诊断中国专家共识（2025版）
2. Home | ClinicalTrials.gov

在研新药的临床研究

靶点/机制	占比	代表药物	最高临床阶段
KRAS G12D突变	40%	GFH375（口服单药） HRS-4642（注射、联用）	III
RAS突变	~90%	Daraxonrasib	III
KRAS突变	~90%	JAB-23E73	I
Claudin 18.2	50~70%	IBI343	III
FGFR-dependent	6%	Pemigatinib	II
TF	~80%	MRG004A	III
TP53突变	50-80%	JAB-30355	I
肿瘤微环境	~	TQB2868 (PD-L1/TGF-β)， Motixafortide (CXCR4)	III
免疫	~	伊沃西单抗	III

RAS靶向疗法在胰腺癌中的临床开发进展

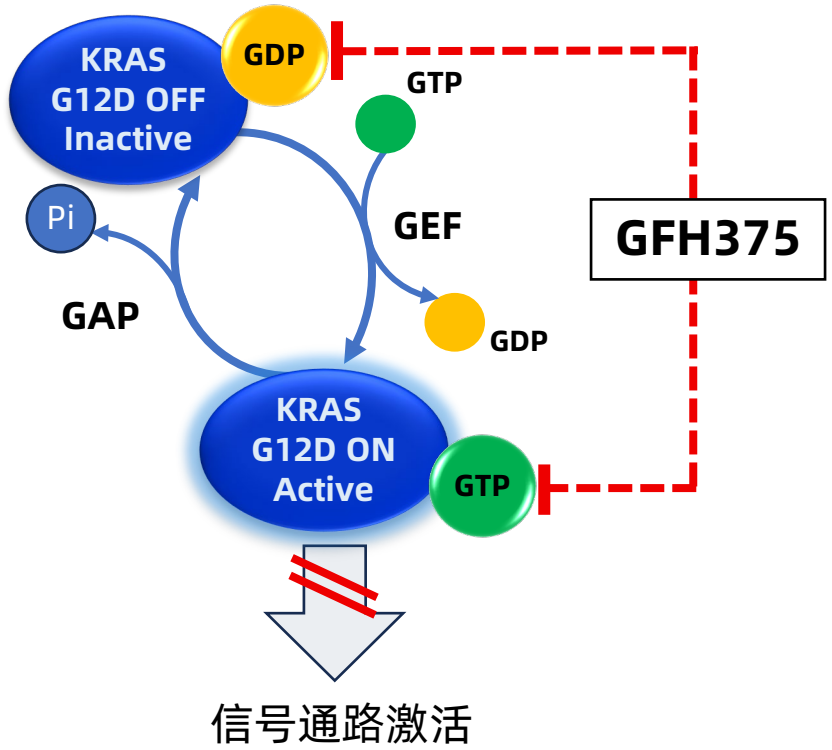
- GFH375 是全球范围内研发进展最快的口服 KRAS G12D抑制剂，目前已进入III期确证性试验阶段。

药物	人群	治疗方案	1期	2期	3期
GFH375 $KRAS^{G12D}$ (ON & OFF) 抑制剂，口服	2L+ 转移性胰腺癌	单药			
	1L 晚期胰腺癌	联合AG			
	2L+ 晚期胰腺癌	联合西妥昔单抗			
HRS-4642 $KRAS^{G12D}$ 抑制剂，静脉	1L 晚期胰腺癌	联合AG			
	2L+ 晚期胰腺癌	单药			
Zoldonrasib $KRAS^{G12D}$(ON)抑制剂，口服	2L+ 晚期胰腺癌	单药/联合			
INCB161734 $KRAS^{G12D}$ (ON & OFF) 抑制剂，口服	2L+ 晚期胰腺癌	单药/联合			
ASP3082 $KRAS^{G12D}$蛋白降解剂，静脉	2L+ 晚期胰腺癌	单药/联合			
TSN1611 $KRAS^{G12D}$ (ON & OFF) 抑制剂，口服	2L+ 晚期胰腺癌	单药			
QTX3034 泛RAS (ON)抑制剂，口服	2L+ 晚期胰腺癌	单药/联合			
Daraxonrasib 泛RAS (ON)抑制剂，口服	2L 转移性胰腺癌	单药			
	1L 转移性胰腺癌	单药/联合AG			
	局部可切除胰腺癌	单药			

上表未纳入研究者发起的研究。 Source: 1. Home | ClinicalTrials.gov. 2. https://www.revmed.com/

GFH375 – 产品介绍

GFH375为高选择性、强效KRAS G12D（ON&OFF）双重作用机制的抑制剂



- 临床前细胞学和动物模型中显示了显著的抑瘤效果，临床前细胞学药效学指标p-ERK IC_{90}水平为11 ng/ml（*AsPC-1*）
- 在所用剂量范围下，实验动物对GFH375的耐受性良好，对 hERG 钾通道电流抑制作用的 IC_{50} 为9.65 μM
- GFH375 无遗传毒性
- GFH375单药获得FDA授予快速通道资格（FTD）认定，用于$KRAS^{G12D}$突变局部晚期或转移性胰腺导管腺癌的一线及后线治疗

GFH375 - 晚期胰腺癌患者中的有效性（ESMO 2025）

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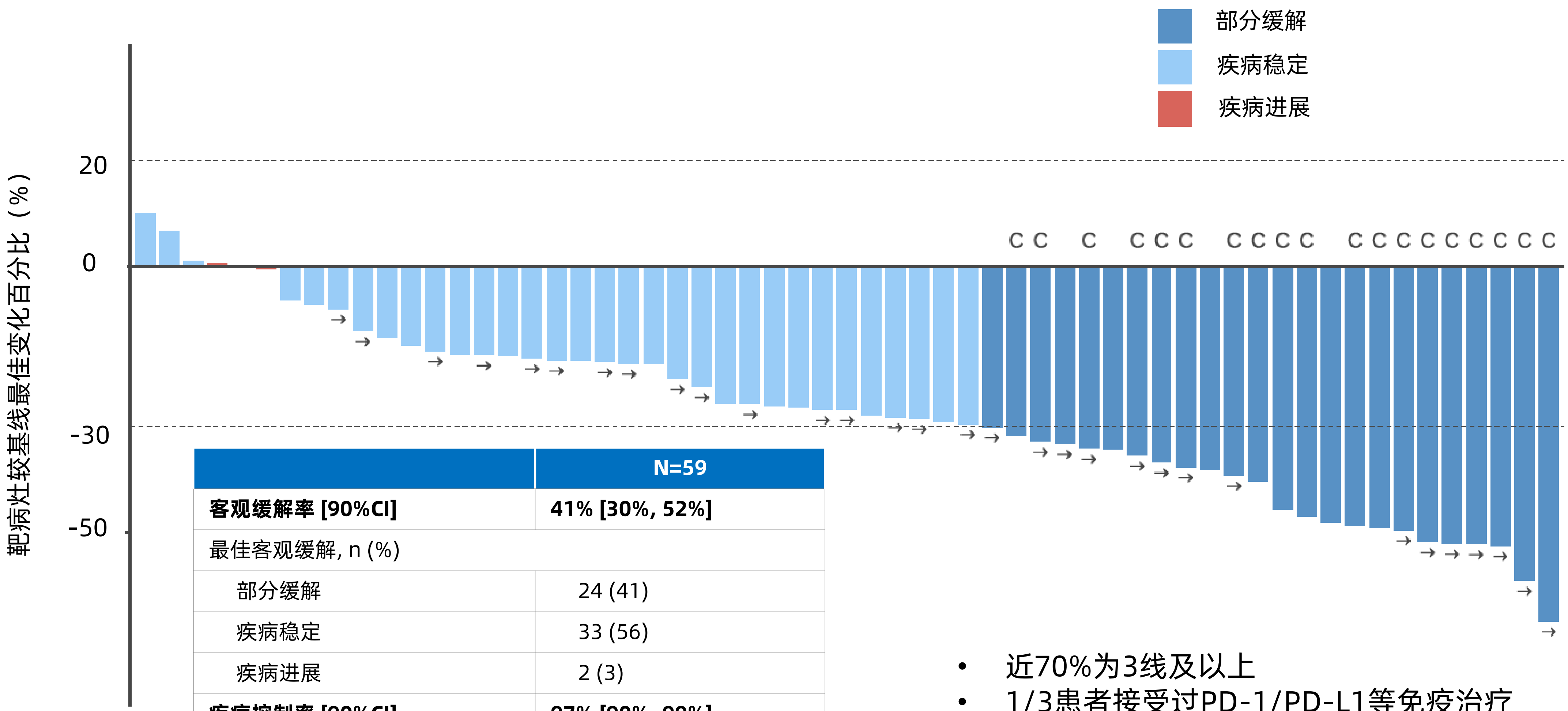


	N=59
客观缓解率 [90%CI]	**41% [30%, 52%]**
最佳客观缓解, n (%)	
部分缓解	24 (41)
疾病稳定	33 (56)
疾病进展	2 (3)
疾病控制率 [90%CI]	**97% [90%, 99%]**

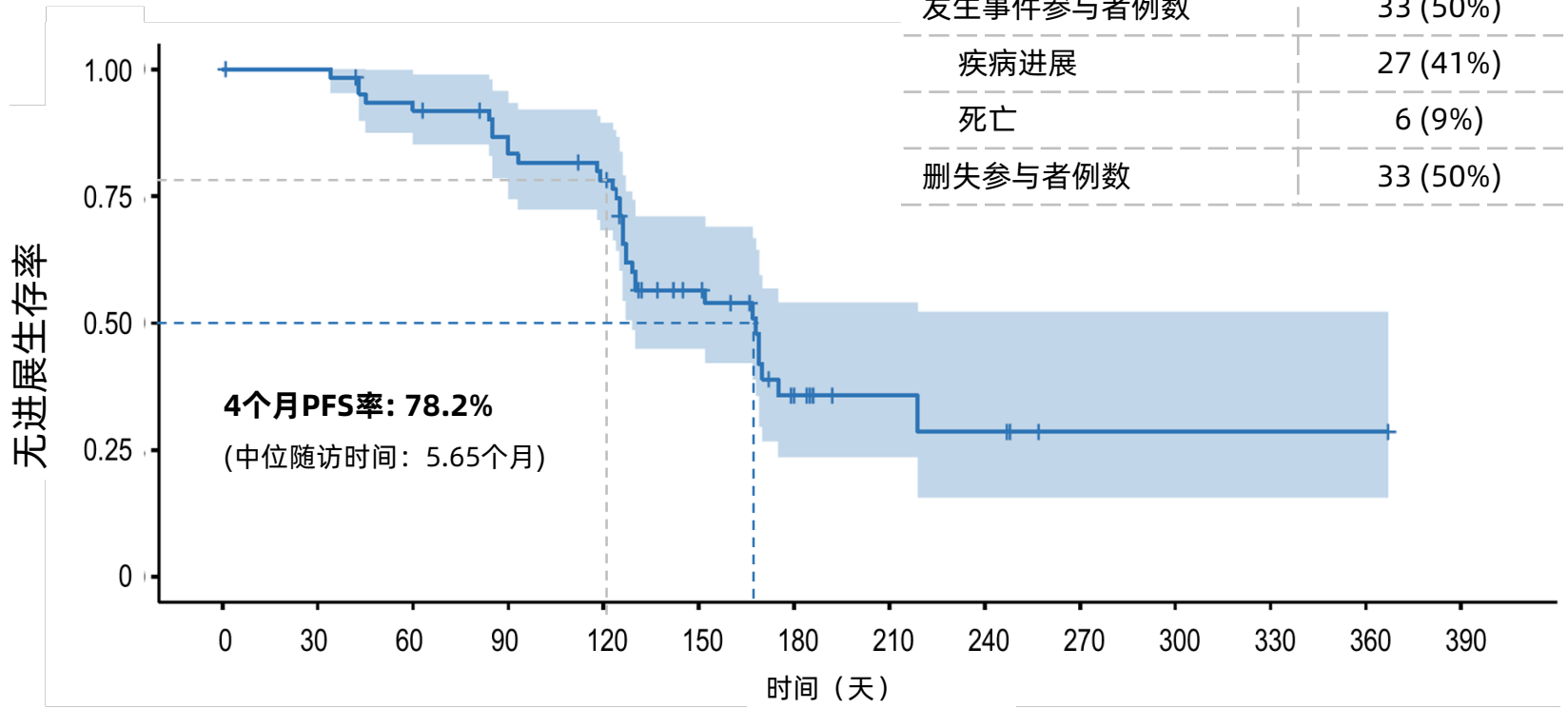
- 近70%为3线及以上
- 1/3患者接受过PD-1/PD-L1等免疫治疗

Source: ESMO 2025; C代表确认的部分缓解；箭头代表继续治疗。

GFH375 - 胰腺癌患者中的有效性（续ESMO 2025）

- 当中位随访5.65个月（90%CI: 4.96, 6.08）时，中位无进展生存期为 **5.52个月**（90%CI: 4.27, 7.20）
- 4个月PFS率为**78.2%** （90%CI: 69.8%, 87.5%）

	N=66, n (%)
发生事件参与者例数	33 (50%)
疾病进展	27 (41%)
死亡	6 (9%)
删失参与者例数	33 (50%)



风险参与者例数	66	62	57	51	45	23	10	5	4	1	1	1	1	0

Source: ESMO 2025

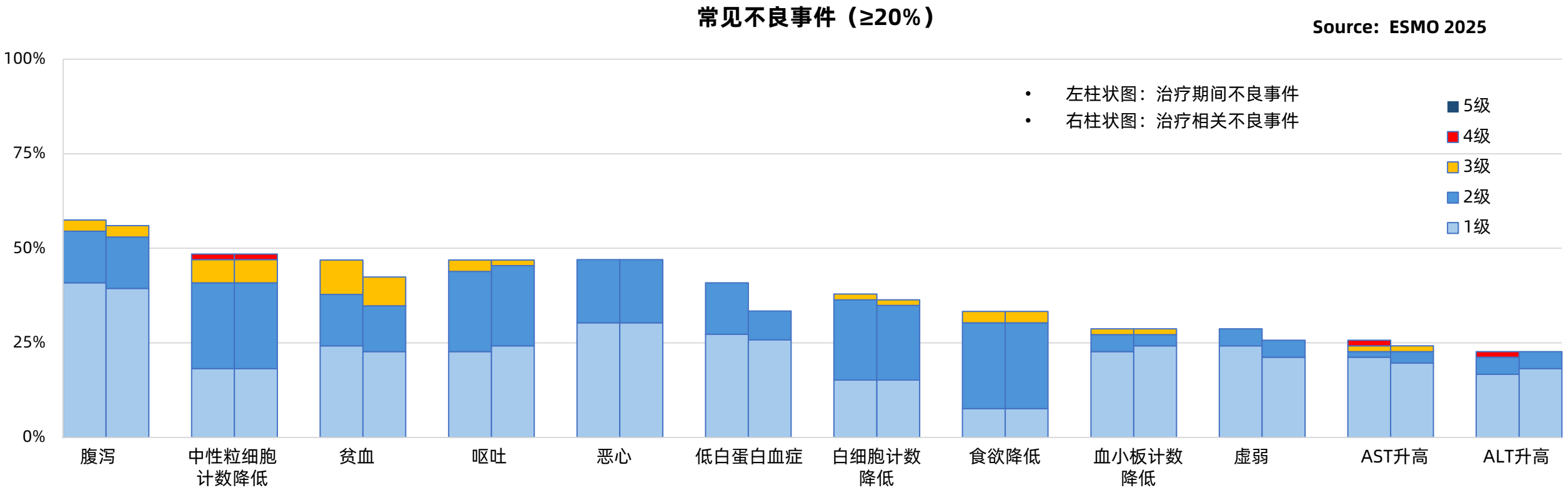
GFH375 - 临床安全性（cross-trial比较）

- GFH375总体安全性可控，耐受性良好

	GFH375 600mg QD[1]	Daraxonrasib 300mg daily[2]	
	2L+ PDAC, N=66	2L+ PDAC, N=83	1L PDAC, N=40
TRAE	100%	96%	95%
G3 or above	**31.8%**	34%	35%
Leading to discontinuation	**3.0%**	0	10%
Leading to reduction	**6.1%**	30%	33%
Leading to interruption	**27.3%**	43%	53%
Mean dose intensity*	**93%**	86%	85%

GFH375 - 临床安全性（续）

- GFH375总体安全性可控
  - 常见治疗相关不良事件为消化系统反应及血液系统毒性，多为1-2级，多数予对症治疗后即可恢复
  - 1例G4 AST/ALT升高为疾病进展导致下端胆道梗阻所致，研究者判断不相关



GFH375 – 针对2线及以上转移性胰腺癌的III期关键性试验

- GFH375 是全球范围内研发进展最快的口服 KRAS G12D抑制剂，目前已进入III期关键性试验阶段。
- 针对2L+患者标准化疗组对照（允许对照组转组）

关键入排

- 经组织学或细胞学确认的**转移性胰腺癌**
- **既往至少接受过1种系统性治疗**（须包括氟尿嘧啶类或吉西他滨的联合治疗），并发生疾病进展，且经末次治疗后进展或不耐受
- 经中心实验室确认携带KRAS G12D突变
- ECOG PS 0 ~ 1

分层因素：

- ECOG PS以及既往抗肿瘤治疗

随机比：1：1

试验组 – GFH375

GFH375
600 mg QD

直至BICR评估的疾病进展或出现不可耐受的毒性等

安全性及生存随访

对照组 – 研究者选择化疗

AG方案、脂质体伊立替康+5-FU/LV、替吉奥

直至BICR评估的疾病进展或出现不可耐受的毒性等

若不转组

GFH375
600 mg QD

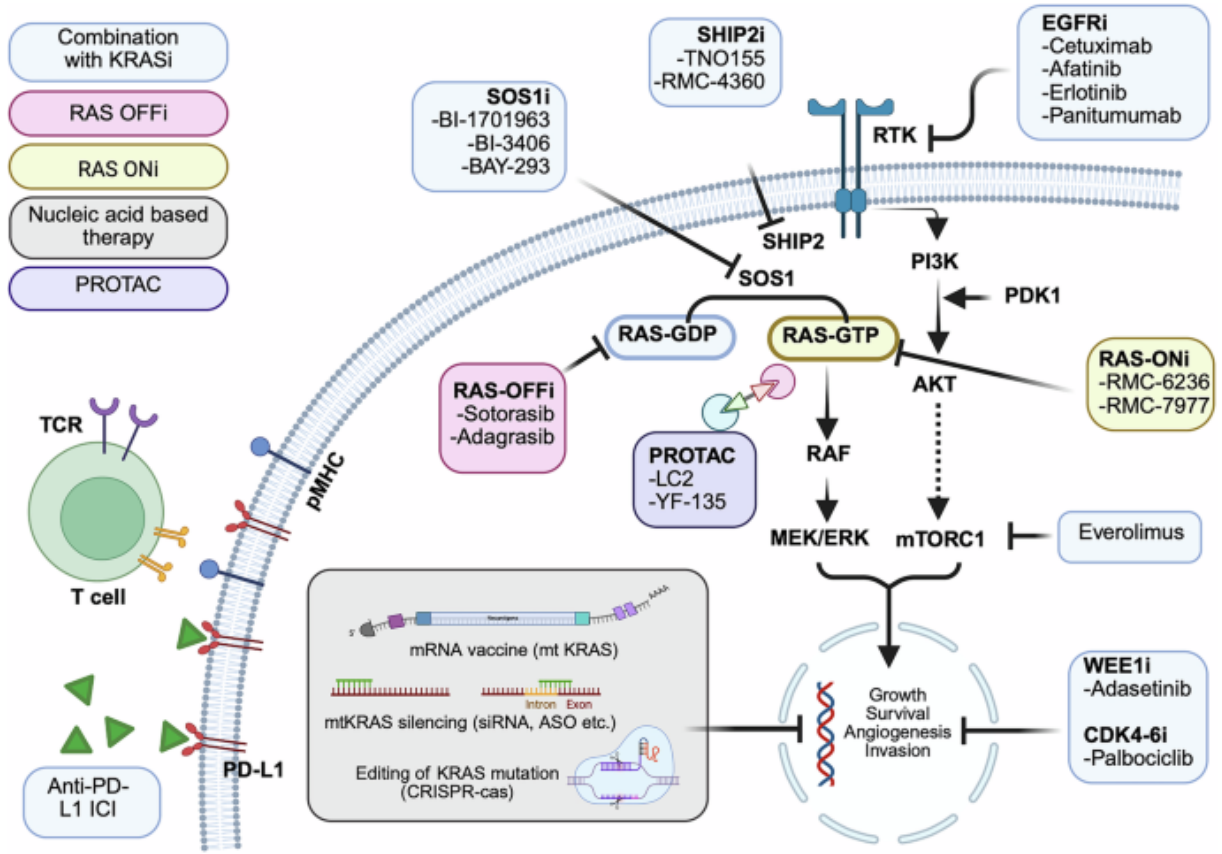
直至疾病进展或出现不可耐受的毒性

转组

✓ 主要终点指标：PFS、OS

✓ 次要终点指标：ORR、DCR、DoR；安全性；患者报告结局

KRAS G12D靶向药的未来临床开发方向



- **联合治疗**
  - 联合标准化疗（AG、FOLFIRINOX等）
  - 联合上、下游抑制剂（如EGFR等）
  - 联合免疫治疗
- **新型模式药物**
  - 蛋白降解剂（PROTAC）
  - siRNA（如iExoKrasG12D）
  - 肿瘤疫苗
  - 细胞治疗

Source: Choucair, K., Imtiaz, H., Uddin, M.H. et al. Sig Transduct Target Ther 10, 385 (2025).

GFH375联合治疗在晚期胰腺癌患者中的探索

Ib期 — 剂量递增阶段

方案 A：KRAS G12D突变的晚期实体瘤参与者

- GFH375，口服，600 mg QD+ 西妥昔单抗
- GFH375，口服，400 mg QD+ 西妥昔单抗

方案B：适合接受AG的KRAS G12D突变的PDAC参与者

- GFH375，口服，600 mg QD + AG方案
- GFH375，口服，400 mg QD + AG方案

RP2D

RP2D

II期 — 扩展阶段

方案A：

KRAS G12D突变的经标准治疗方案后进展或不适合标准治疗方案的：

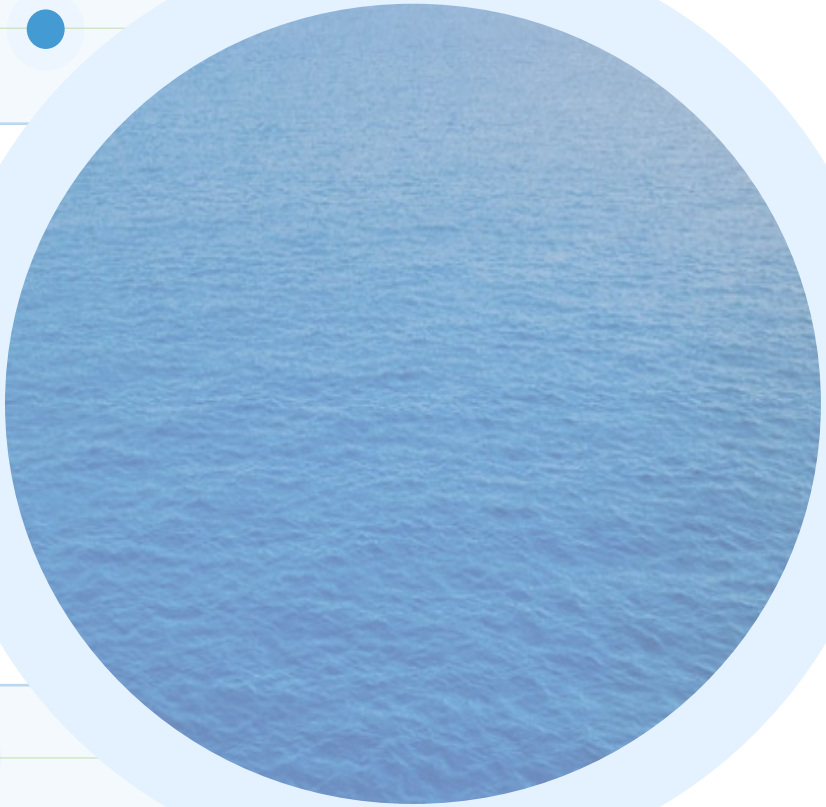
- 队列1：PDAC
- 队列 2：CRC

方案B：

未接受过系统治疗且携带KRAS G12D突变的PDAC参与者

总结

- KRAS G12D 突变在胰腺癌中占比大，预后不良，临床需求巨大
- 目前乏缺针对KRAS G12D突变靶向治疗：
  高选择性（ON/OFF）抑制剂、Pan KRAS (SWII pocket inhibitor)、Pan RAS（分子胶）等多种作用机制的药物在研
- GFH375在目前全球口服KRAS G12D抑制剂中进展最快，安全性可控、疗效好，目前国内首个进入到关键临床III期，值得期待
- 后续的临床开发需要结合药物特性，联合标准治疗或西妥昔单抗在胰腺癌一线进行探索开发




風飛浪勁·据義履方

GFS202A（GDF15/IL-6双抗）治疗肿瘤恶病质的临床开发进展

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恶病质

恶病质是一种与慢性疾病相关的代谢失调综合征，涉及全身多个系统/器官，以持续性骨骼肌丢失（伴或不伴脂肪丢失）、体重减轻、炎症状态和/或厌食为特征，常规营养治疗不能完全缓解。

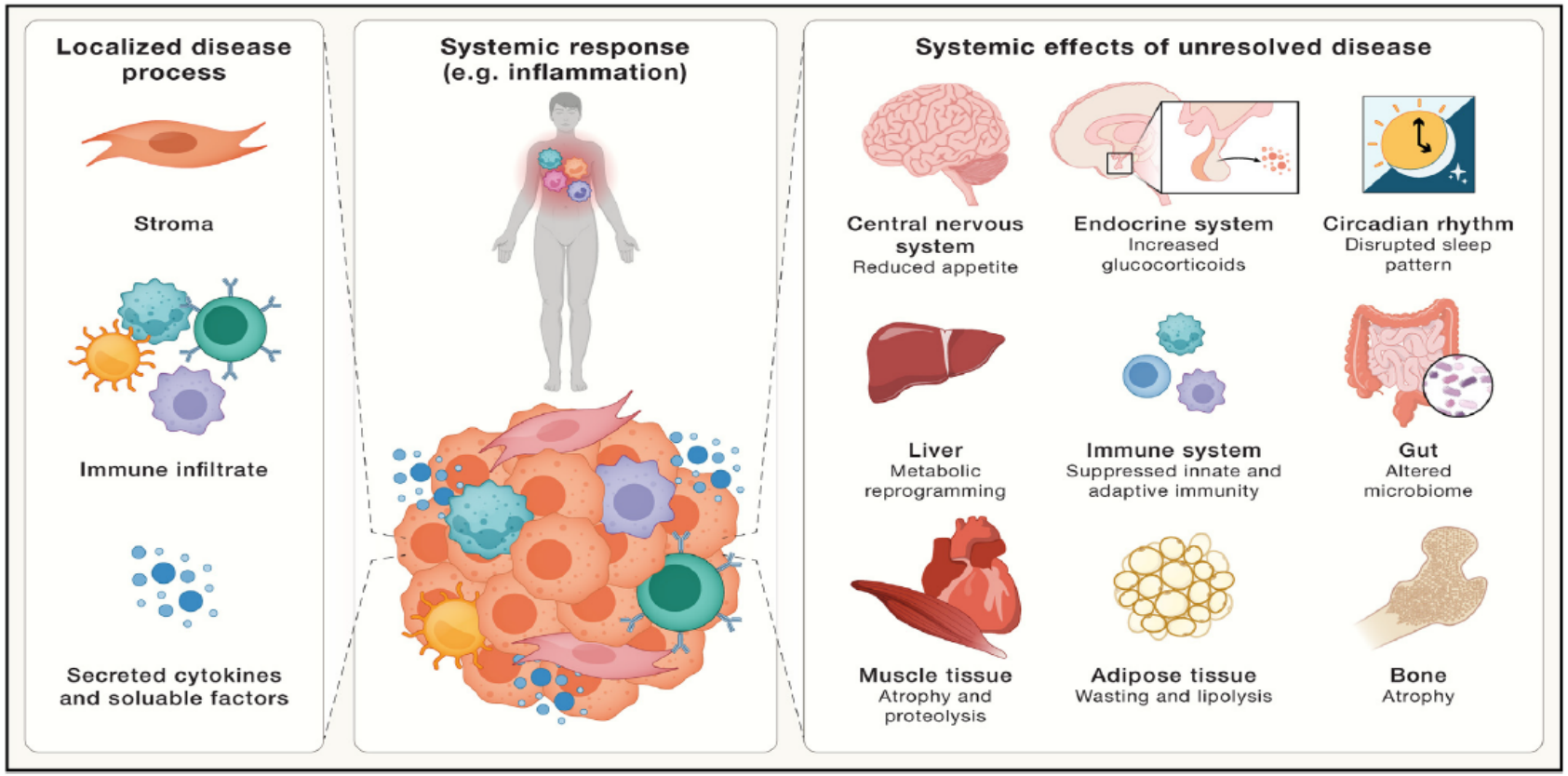


Figure 1. Interconnected causes and consequences of disease- or cancer-associated cachexia at organ level
Examples of host cell contributors to and organ level consequences of cachexia inducing inflammatory and non-inflammatory processes are illustrated.

1.Ferrer, Miriam et al. Cell vol. 186,9 (2023): 1824-1845.

恶病质（Cachexia）不是饥饿（Starvation）

Starvation	Cancer Anorexia/ Weight Loss
Loss of fat	Loss of fat and lean tissue
Hunger	No hunger
Drop in resting energy expenditure	Resting energy expenditure sometimes increased
Specific mediators not as well implicated	Specific mediators have been implicated (eg, TNF-α)

Fearon K, et al. *Lancet Oncol.* 2011;12:489-495[1]; National Comprehensive Cancer Network. *NCCN Guidelines. Palliative Care.* v.2.2013.[9]

恶病质流行病学

- 恶病质常见于肿瘤、心力衰竭、慢性肾脏病、COPD、类风湿关节炎等恶性肿瘤及慢性非恶性疾病。
- 其中肿瘤恶病质最为常见，60－80%的肿瘤患者合并恶病质，恶病质是20%肿瘤患者的直接死因。

Table 1 Estimates for the prevalence of cachexia in several chronic illnesses in Europe, the USA, and Japan

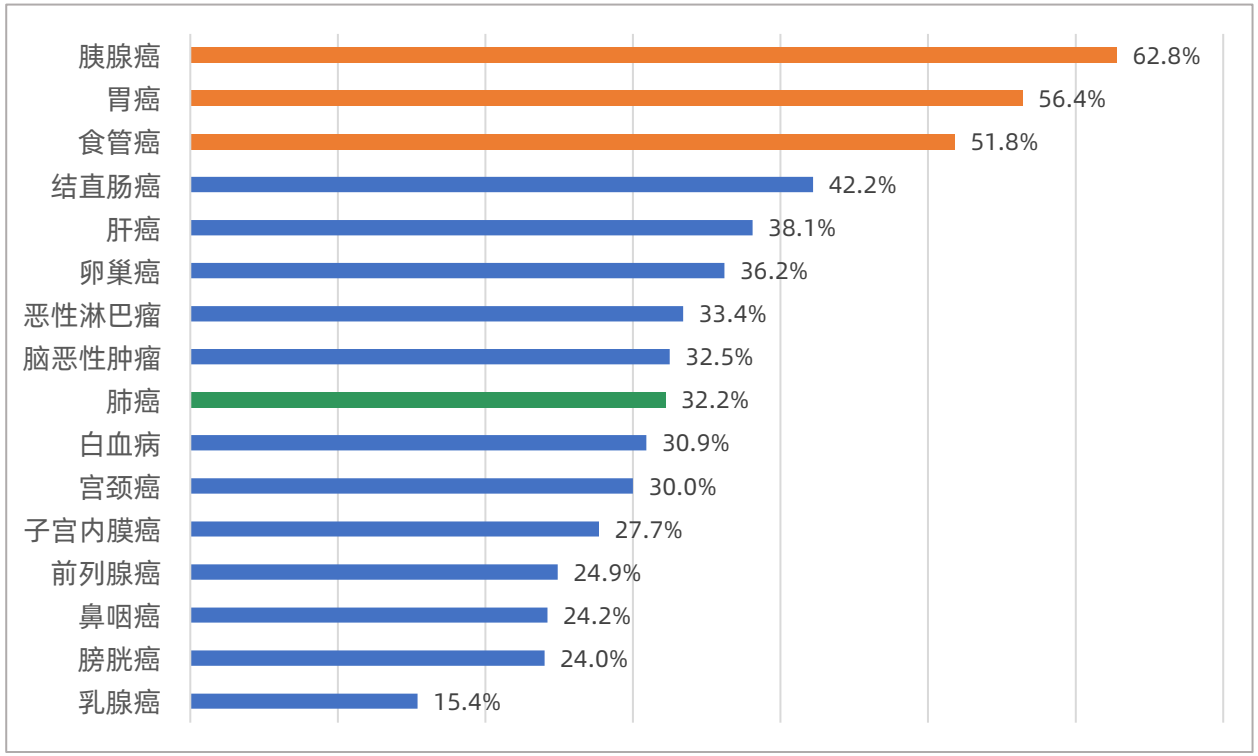
	Prevalence in population (%)	Patients at risk (%)	Prevalence in patients at risk (%)	Patients in Europe	Patients in the USA	Patients in Japan	1-Year mortality (%)
COPD (moderate severity)	3.5	15	35	1 400 000	600 000	230 000	15–25
CHF (NYHA II-IV)	2.0	80	10	1 200 000	510 000	200 000	20–40
Cancer	0.5	90	30 (all types)	1 000 000	430 000	170 000	20–80
Rheumatoid arthritis (severe form)	0.8	20	10 (cachexia)	120 000	50 000	20 000	5
CKD	0.1	50	50	190 000	80 000	30 000	20

Population assumptions (2013/14): Europe—742 million, the USA—319 million, and Japan—127 million.

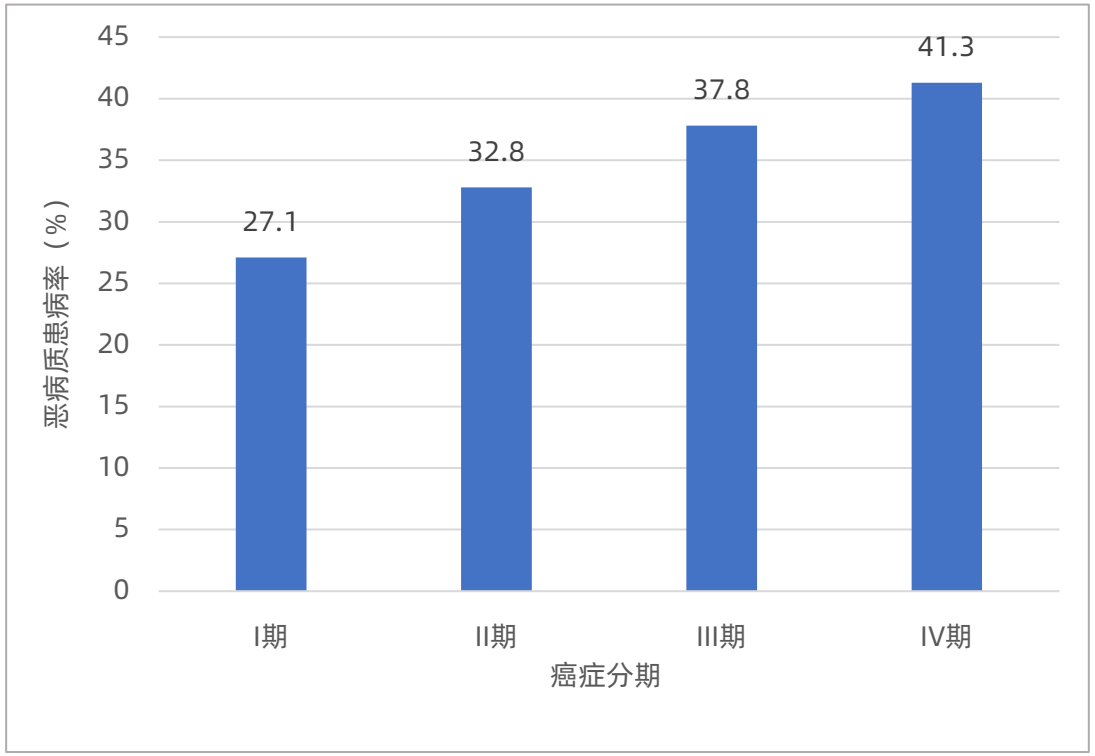
Stephan von Haehling S, et al. J Cachexia Sarcopenia Muscle. 2016;7(5):507-509.

肿瘤恶病质流行病学

- 肿瘤恶病质的总患病率达37.0%，肿瘤部位是肿瘤恶病质患病率重要决定因素之一。
- 胰腺癌(62.8%)、胃癌(56.4%)、食管癌(51.8%)是与肿瘤恶病质患病关联最密切的三种肿瘤。
- 肺癌是中国恶性肿瘤中发病率和死亡率均最高的恶性肿瘤，肿瘤恶病质在肺癌患者中占比约32.2%。



中国肿瘤恶病质在不同瘤种中的患病率

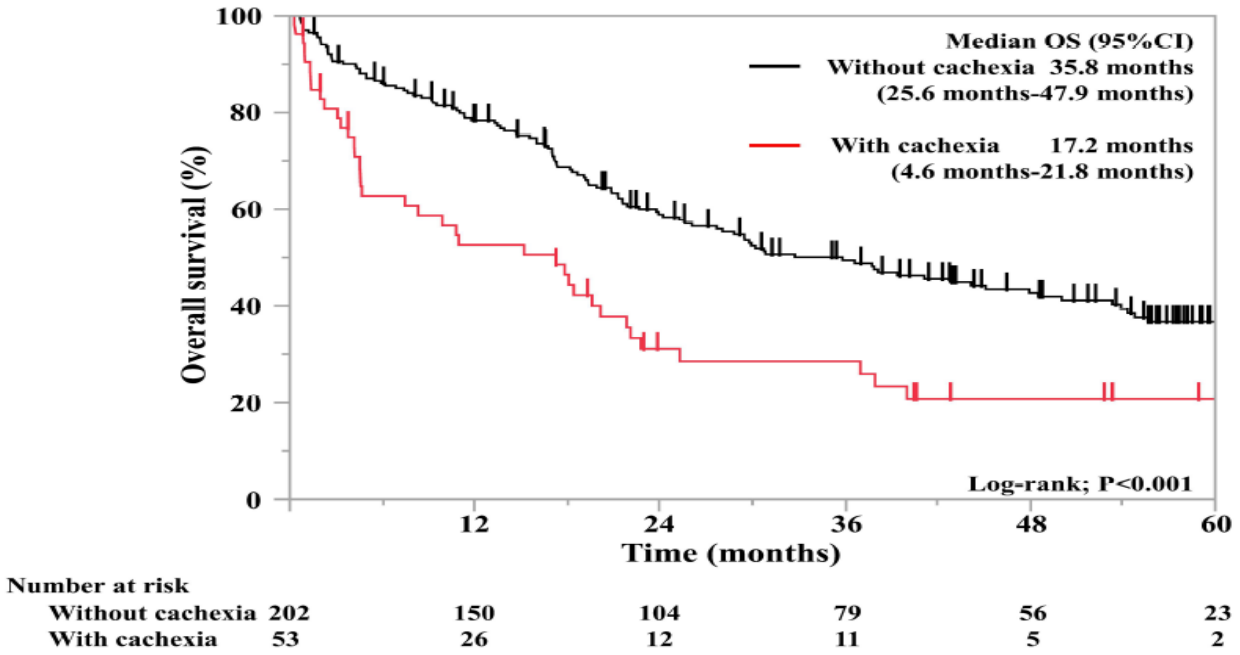


不同癌症分期的肿瘤恶病质患病率

1. Li, Xiangrui, et al.. Precision Nutrition 1(1):10.1097/PN9.0000000000000008, June 2022. 2. Han B, et al. 2024;4(1):47-53. 2024 Feb 2.

肿瘤恶病质影响肿瘤患者的预后

- 患者一般状况和炎性状态常常不合适使用免疫治疗，也存在超进展的风险
- IV期或术后复发NSCLC肿瘤恶病质期患者接受帕博利珠单抗单药治疗后mOS相较于非恶病质期患者显著缩短。



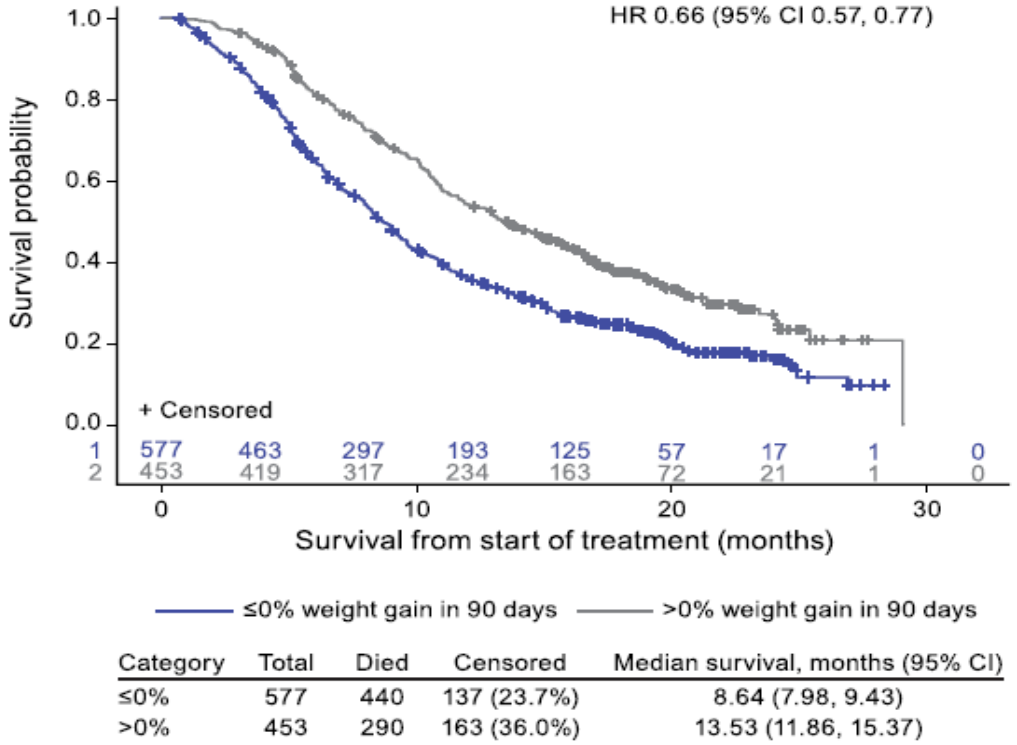
*一项在日本开展的回顾性(2017.3-2020.12)、多中心队列研究，纳入441例PD-L1（TPS）≥50% IV期或术后复发NSCLC患者，分为帕博丽珠单抗组(n=255)与帕博丽珠单抗联合化疗组(n=156)，在帕博丽珠单抗单药组中肿瘤恶病质53例，非肿瘤恶病质202例。

恶病质期及非恶病质期NSCLC患者接受帕博利珠单抗单药治疗的OS Kaplan-Meier生存曲线

Gastric Cancer (2019) 22:793–802；*Kawachi H, et al. Oncoimmunology. 2025;14(1):2442116.*

抗肿瘤治疗期间的体重增加可以显著改善OS

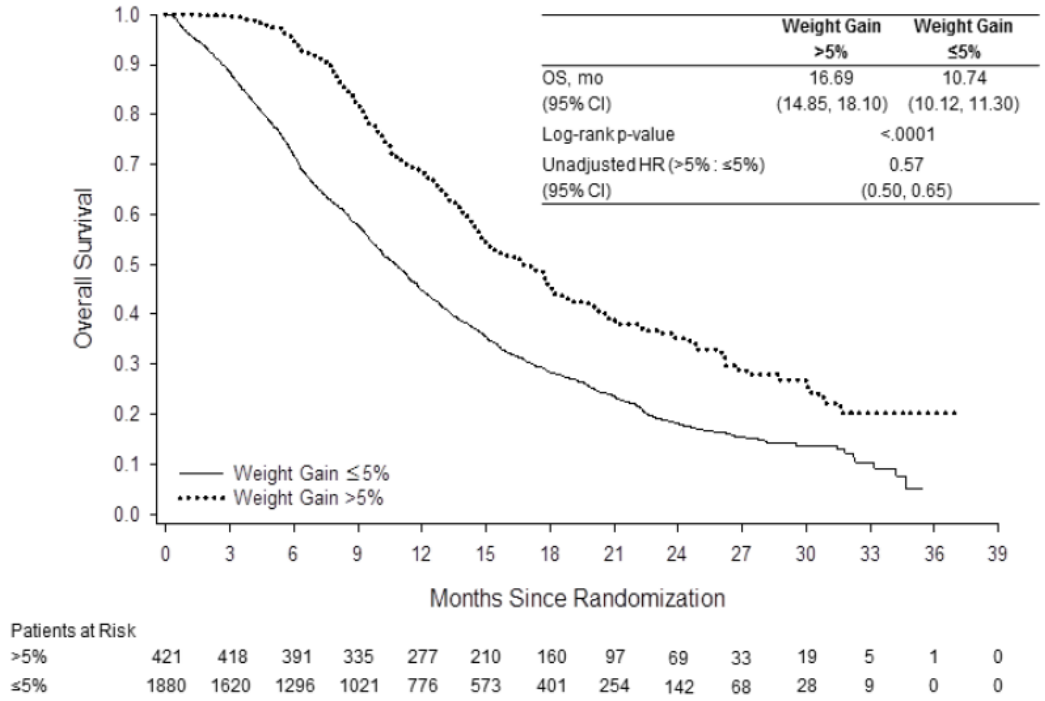
体重增加相较于体重不变/降低，死亡风险下降34%[1]



Category	Total	Died	Censored	Median survival, months (95% CI)
≤0%	577	440	137 (23.7%)	8.64 (7.98, 9.43)
>0%	453	290	163 (36.0%)	13.53 (11.86, 15.37)

图1. 接受抗肿瘤治疗90天内体重增加或体重不变/降低的OS Kaplan-Meier生存曲线

体重增加>5%相较于≤5%，死亡风险下降43%[2]



	Weight Gain >5%	Weight Gain ≤5%
OS, mo	16.69	10.74
(95% CI)	(14.85, 18.10)	(10.12, 11.30)
Log-rank p-value	<.0001	
Unadjusted HR (>5% : ≤5%)	0.57	
(95% CI)	(0.50, 0.65)	

Patients at Risk

>5%	421	418	391	335	277	210	160	97	69	33	19	5	1	0
≤5%	1880	1620	1296	1021	776	573	401	254	142	68	28	9	0	0

图2. 接受抗肿瘤治疗期间或研究结束30天内体重增加>5%或≤5%的OS Kaplan-Meier生存曲线

1. Miyawaki T, et al. Support Care Cancer. 2022;30(2):1633-1641 2.Patel JD, et al. Ann Oncol. 2016;27(8):1612-1619.

肿瘤恶病质分期和分期标准

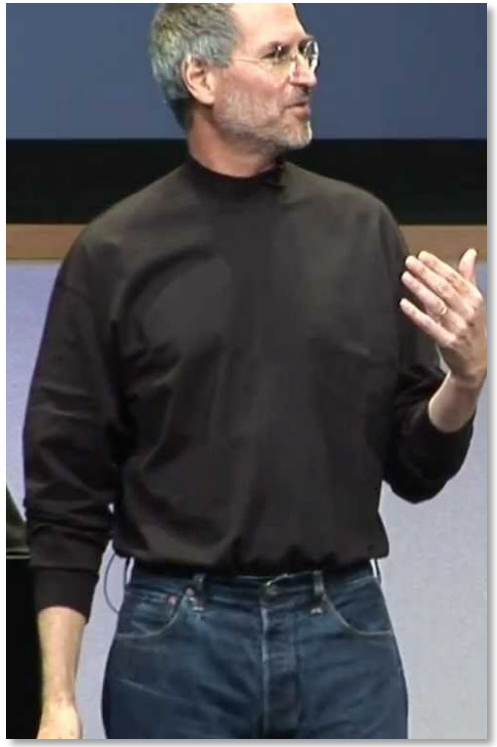
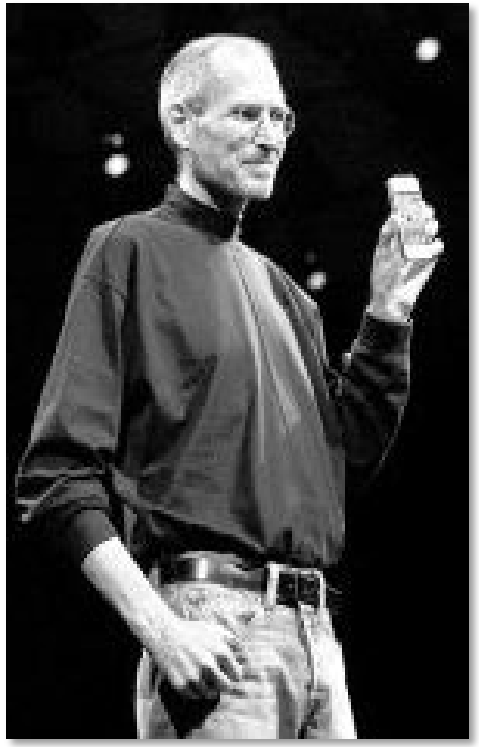
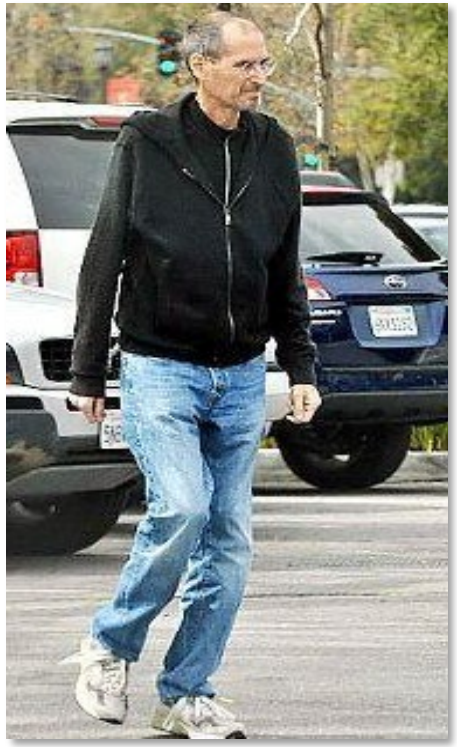
恶病质前期	恶病质期	恶病质难治期
• 非自主体重下降≤5%伴代谢改变（如厌食、糖耐量异常） [证据级别:1A类]	以下任一症状，同时合并食欲减退或系统性炎症 • 近6个月非自主体重下降＞5% • BMI<18.5时体重下降>2% • 肌肉量减少时体重下降>2% *系统性炎症（CRP＞5mg/L）	对抗肿瘤治疗无反应 • 分解活跃，体重下降无法纠正 • WHO体力评分3或4分 • 预期生存期小于3月

恶病质前期	恶病质期	难治期/顽固性恶病质期
• 表现为厌食和代谢改变 • 6个月内无意识体质量减轻≤5%	• 6个月内无意识体质量减轻>5%（排除单纯饥饿）； • 或BMI<20kg/m2（中国人为BMI<18.5kg/m2），6个月内体质量减轻>2%； • 或四肢骨骼肌指数符合肌肉减少症诊断标准（男性<7.26kg/m²；女性<5.45kg/m²）同时体质量减轻>2%； • 常有摄食减少或系统性炎症	• 肿瘤持续进展，对治疗无反应 • 分解代谢活跃，体质量持续减轻无法纠正 *必须指出，在此分期中，对难治性恶液质的诊断标准尚无共识

1. 中国临床肿瘤学会 肿瘤厌食-恶病质综合征诊疗指南 2025 2.肿瘤恶液质临床诊断与治疗指南（2020版）

肿瘤恶病质分期和分期标准

恶病质前期 | 恶病质期 | 难治期/顽固性恶病质期


1. 中国临床肿瘤学会 肿瘤厌食-恶病质综合征诊疗指南 2025 2.肿瘤恶液质临床诊断与治疗指南（2020版）

肿瘤恶病质治疗现状及研发方向

- 国内尚无针对肿瘤恶病质的药物治疗获批上市。
- 仅阿拉莫林（ghrelin受体激动剂）在日本获批上市，
  适应症：NSCLC、胃癌、胰腺癌、结直肠癌恶病质

CSCO2025 肿瘤厌食-恶病质综合征诊疗指南

用于改善肿瘤厌食-恶病质综合征相关症状的药物

	I级推荐	II级推荐	III级推荐
刺激食欲	孕酮类[1A类]	糖皮质激素[1B类]	n-3多不饱和脂肪酸或鱼油补充剂[2B类]
		精神科药物：奥氮平、米氮平[2A类]	阿拉莫林[2A类]
改善早饱		促胃肠动力药[2A类]	

局限性

孕酮类：血栓栓塞事件、外周水肿、女性突发阴道出血等风险增加

糖皮质激素：水钠潴留、代谢紊乱、低钾血症、骨质疏松、蛋白分解等

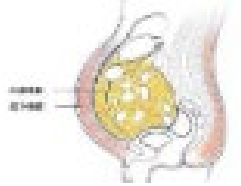
精神科药物：代谢、心血管毒性等

促胃肠动力药：甲氧氯普胺的中枢系统不良反应（如锥体外系），多潘立酮的心脏不良反应，存在机械性消化道梗阻的患者禁用

N-3多不饱和脂肪酸：中富含EPA不建议与伊布替尼联用，以免增加出血的风险

阿拉莫林：未显著改善患者握力、6分钟步行距离，对身体功能直接提升有限。

研发方向



促进合成代谢类药物
（无上市品种）

阻断肌肉萎缩类药物
（无上市品种）

阻断单一炎症因子
（无上市产品）

促进食欲类药物
（Anamorelin，2021年日本获批上市）

1. 中国临床肿瘤学会 肿瘤厌食-恶病质综合征诊疗指南 2025

肿瘤恶病质机制研究进展

- 肿瘤恶病质是由宿主或肿瘤来源的肿瘤恶病质诱导因子引起的伴有系统性炎症的消耗性代谢紊乱综合征。
- **GDF15与IL-6**是宿主及肿瘤共同分泌的重要且高水平的肿瘤恶病质驱动因子，两者之间相对独立。

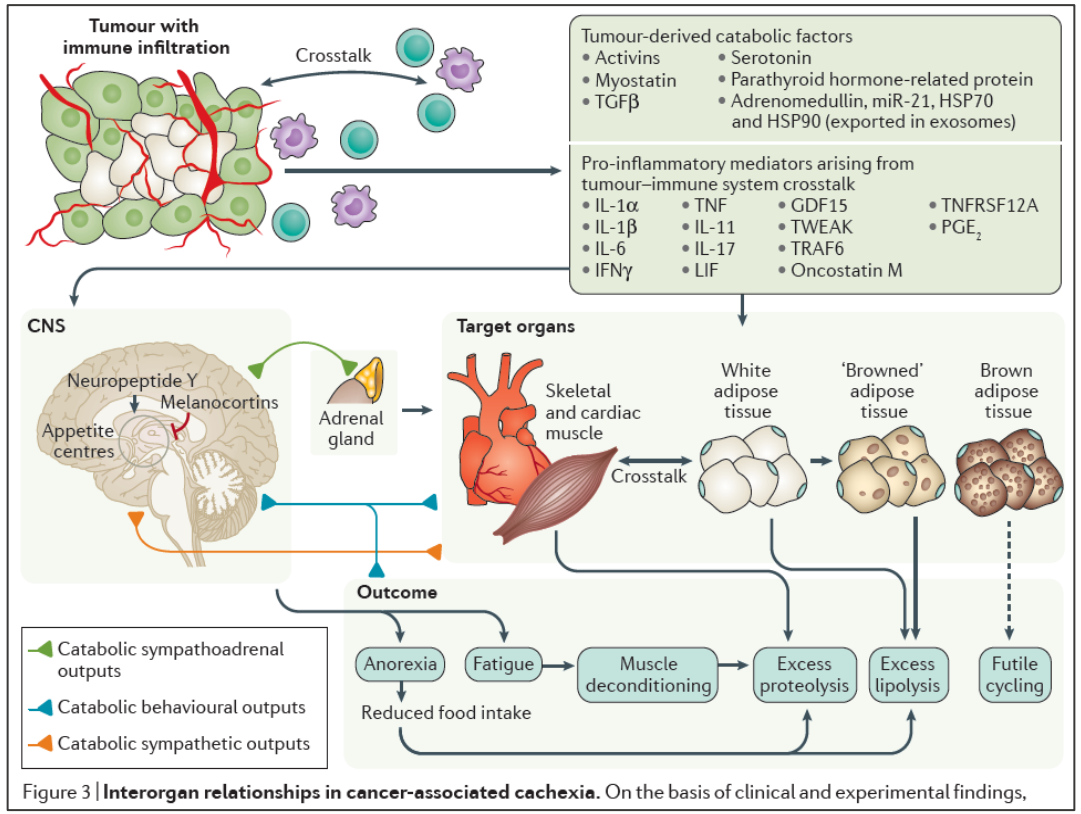


Figure 3 | **Interorgan relationships in cancer-associated cachexia.** On the basis of clinical and experimental findings,

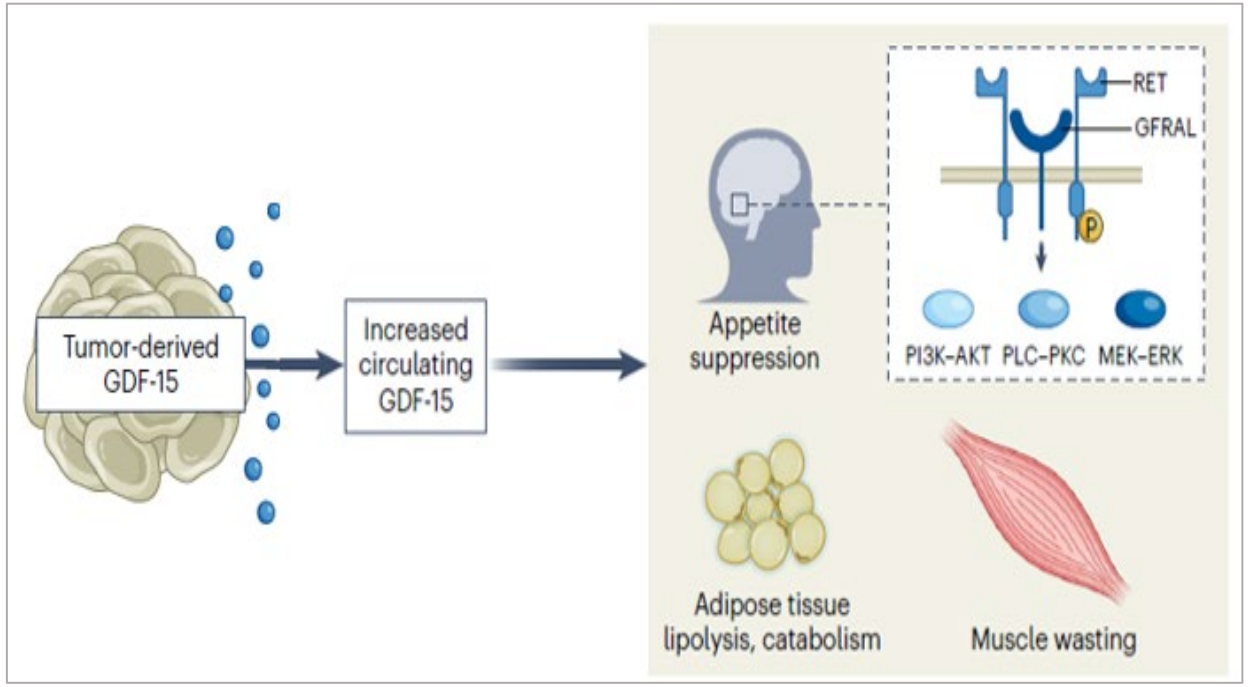
图1. 恶病质诱导因子在癌症恶病质发生发展中的多重作用

1.Baracos VE,et al. Nat Rev Dis Primers. 2018;4:17105. 2.Ferrer M, et al. Cell. 2023;186(9):1824-1845.

GDF15

- GDF15属于转化生长因子（TGF-β）超家族，在多种晚期肿瘤及肿瘤恶病质患者中过度表达。
- 肿瘤细胞分泌的**GDF15**结合位于脑干后区及极后区部位的**GFRAL受体**，诱导RET共受体的激活与磷酸化，从而激活下游PI3K/MAPK通路，已证实该通路与肿瘤恶病质的发生发展有关，GDF15的浓度与体重、脂肪量、肌肉和食欲呈负相关。

	循环GDF15浓度
健康人（按年龄，中位数）	
20-<30	429 pg/ml
30-<40	500 pg/ml
40-<50	614 pg/ml
50-<60	757 pg/ml
60-<70	866 pg/ml
≥70	1060 pg/ml
晚期肿瘤患者	可达10,000 - 100,000 pg/ml
肿瘤NSCLC、CRC、PANC恶病质患者	健康人循环GDF15浓度的4-5倍



Cheng LY, et al. Nat Med. 2025;31(4):1069-1070

图1 GDF15在肿瘤恶病质中的作用机制

靶向GDF15/GFRAL通路的肿瘤恶病质药物研发竞争格局

- 目前临床阶段在研治疗肿瘤恶病质的药物均为单靶向GDF15或GFRAL。
- **GFS202A是全球首个GDF15/IL-6双抗产品及恶病质双靶向疗法（First-in-class）。**

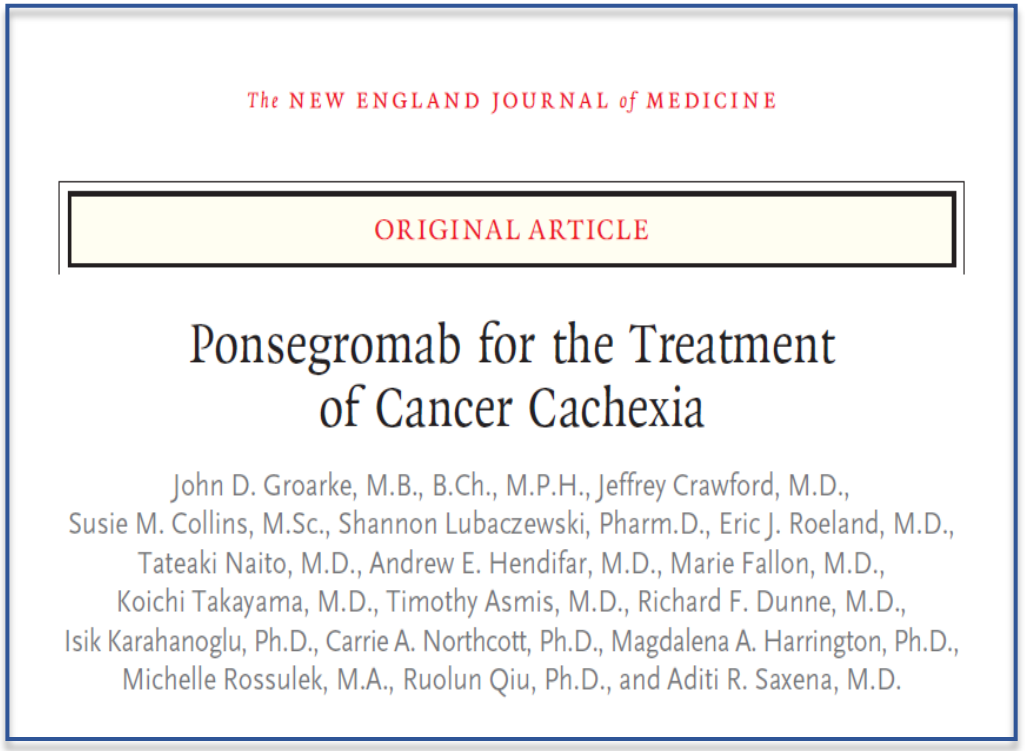
研发公司	化合物	靶点	开发阶段
Pfizer	Ponsegromab	GDF15mAb	IIb/III期
CATALYM	Visugromab	GDF15mAb	II/III期
AVEO ONCOLOGY	AV-380	GDF15mAb	Ib期
Kexing Biopharm 科兴制药	GB18	GDF-15纳米抗体	I期
NGMBio	NGM120	GFRAL	II期
JMT-BIO	JMT-203	GFRAL	I/II期
劲方医药 GENFLEET	GFS202A	GDF15mAb+IL6mAb	I期

1. https://www.clinicaltrials.gov/ 2.药物临床试验登记与信息公示平台

辉瑞GDF15单抗ponsegromab可显著增加肿瘤恶病质期患者体重

II 期，随机，双盲PROACC研究

- 在12周时，与安慰剂组相比，所有剂量水平的活性药物组均观察到体重的增加，且具有剂量依赖性。



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ponsegromab for the Treatment of Cancer Cachexia

John D. Groarke, M.B., B.Ch., M.P.H., Jeffrey Crawford, M.D., Susie M. Collins, M.Sc., Shannon Lubaczewski, Pharm.D., Eric J. Roeland, M.D., Tateaki Naito, M.D., Andrew E. Hendifar, M.D., Marie Fallon, M.D., Koichi Takayama, M.D., Timothy Asmis, M.D., Richard F. Dunne, M.D., Isik Karahanoglu, Ph.D., Carrie A. Northcott, Ph.D., Magdalena A. Harrington, Ph.D., Michelle Rossulek, M.A., Ruolun Qiu, Ph.D., and Aditi R. Saxena, M.D.

Groarke, John D et al. The New England journal of medicine vol. 391,24 (2024): 2291-2303.

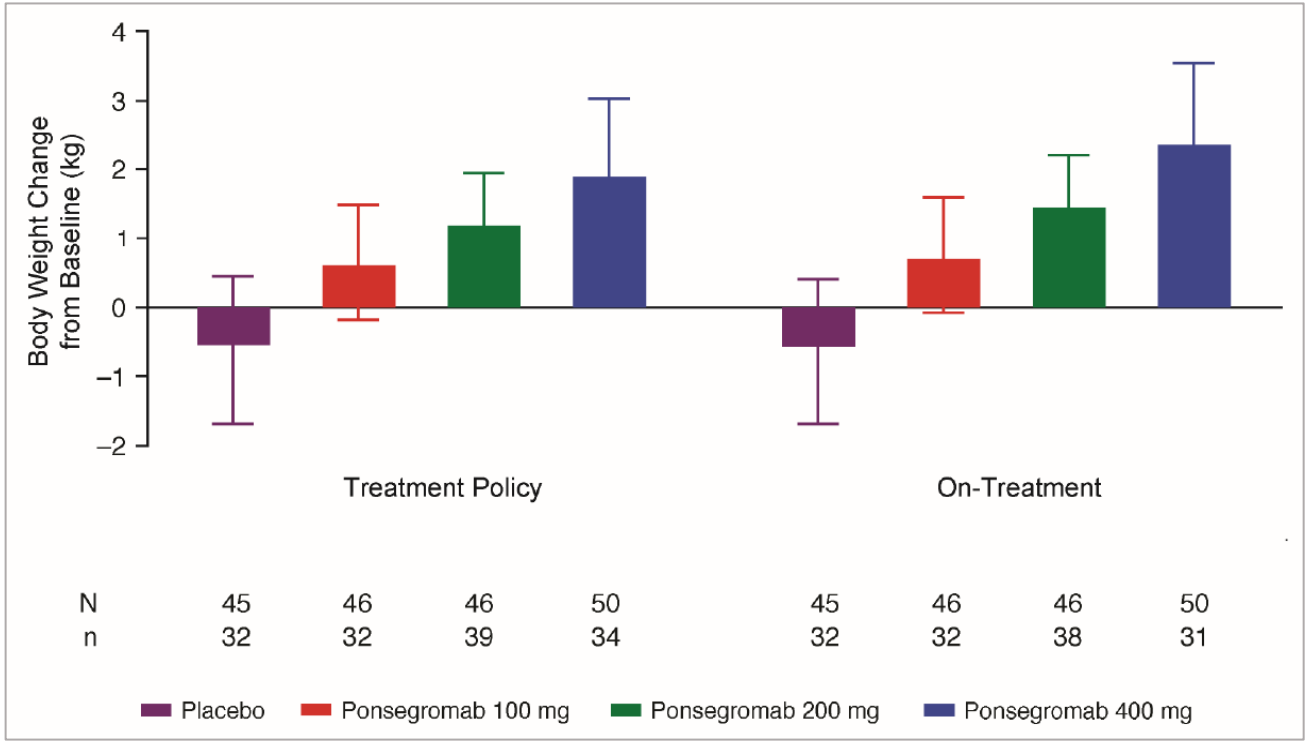


图1. 恶病质期肿瘤患者接受ponsegromab 100mg、200mg、400mg及安慰剂 Q4W 治疗12周后较基线的体重变化

GDF15单抗ponsegromab可显著改善肿瘤恶病质期患者食欲

II 期，随机，双盲PROACC研究

- 在12周时，与安慰剂组相比，100mg及400mg剂量组均观察到FAACT-ACS*、FACCT-5IASS*评分较基线显著增加。

表1 接受ponsegromab 100mg、200mg、400mg及安慰剂 Q4W 治疗12周后较基线的FAACT-ACS及FACCT-5IASS评分变化(恶病质期肿瘤患者)

End Point	Baseline			Change from Baseline at Week 12		
	N1†	Observed Mean	N2†	Observed Mean	Modeled Mean (95% Credible Interval)	Modeled Mean Difference from Placebo (95% Credible Interval)
Patient-reported outcome						
FAACT–Anorexia and Cachexia Subscale‡						
Placebo	42	27.5±7.9	30	0.5±8.3	0.57 (–1.64 to 2.79)	NA
Ponsegromab, 100 mg	43	27.3±7.8	27	5.5±7.2	4.68 (2.25 to 7.11)	4.12 (0.86 to 7.34)
Ponsegromab, 200 mg	41	28.4±9.2	33	1.2±10.1	1.30 (–1.02 to 3.49)	0.73 (–2.40 to 3.91)
Ponsegromab, 400 mg	47	27.0±9.3	30	4.2±5.8	5.07 (2.71 to 7.52)	4.50 (1.29 to 7.77)
FAACT–5-Item Anorexia Symptom Scale§						
Placebo	42	11.9±4.2	30	–0.2±4.5	0.22 (–1.02 to 1.45)	NA
Ponsegromab, 100 mg	43	11.0±3.9	27	3.1±4.2	2.43 (1.15 to 3.63)	2.20 (0.36 to 3.99)
Ponsegromab, 200 mg	41	12.2±5.2	33	–0.2±5.4	0.20 (–0.99 to 1.42)	–0.02 (–1.73 to 1.72)
Ponsegromab, 400 mg	47	11.0±4.8	30	2.5±3.7	2.62 (1.37 to 3.87)	2.39 (0.61 to 4.15)

*FAACT-ACS:厌食症恶病质量表,得分范围为0～48分，得分越高，厌食症和恶病质症状负担越轻; FAACT-5IASS:厌食症状量表, 得分范围为 0 至 20 分，得分越高表明厌食症状负担越低。

Groarke, et al. The New England journal of medicine vol. 391,24 (2024): 2291-2303.

IL-6

- 相较于健康成年人，肿瘤恶病质患者体内IL-6水平明显增高。
- IL-6与IL-6Rα/gp130或者sIL-6Rα结合后，在**外周**通过激活萎缩相关基因和抑制mTOR通路促进肌肉萎缩，激活JAK/STAT3信号通路促进脂肪组织分解；在**中枢**影响下丘脑神经元抑制食欲，与瘦素呈相反作用。

表1 肿瘤恶病质患者生物标志物分析

Marker	Reference ranges	Patients mean (±SD)	Controls mean (±SD)	*p*-value for Significance (Patients versus Controls)	*p*-value for Significance (Patients versus Reference Constant)
Albumin (g/L)	35–50	39.66 (±6.41)	46.99 (±2.21)	$p<0.01$	
WBC × 10^9/L	4.0–12.0	7.89 (±6.34)	7.07 (±1.87)	$p=0.42$	
Neutrophils × 10^9/L	2.0–7.5	5.43 (±5.60)	4.40 (±1.65)	$p=0.27$	
Lymphocytes × 10^9/L	1.0–4.0	1.45 (±0.73)	2.04 (±0.60)	$p<0.01$	
Platelets × 10^9/L	150–450	300.34 (±155.32)	231.00 (±55.15)	$p<0.01$	
Haemoglobin (g/dL)	13.8–18.8	12.38 (±2.04)	15.13 (±0.92)	$p<0.01$	
NLR	2.73[a]	4.85 (±6.59)	2.31 (±1.10)	$p=0.02$	$p=0.008$
PLR	148.82[a]	232.90 (±119.70)	119.18 (±34.63)	$p<0.01$	$p<0.001$
SII	791.96[a]	1387.35 (1866.47)	543.54 (±301.74)	$p<0.01$	$p=0.051$
CRP (mg/L)	2.775	31.65 (±56.54)	2.78 (±6.72)	$p<0.01$	$p=0.002$
TNFα (pg/mL)	20.745	43.52 (±52.77)	15.69 (±13.51)	$p<0.01$	$p=0.009$
IL-6 (pg/mL)	4.39	41.13 (±6.87)	35.64 (±69.07)	$p=0.04$	$p<0.001$
IL-8 (pg/mL)	9.175	33.08 (±59.90)	29.85 (±81.53)	$p=0.02$	$p=0.023$
CXCL5 (pg/mL)	42.28	91.37(±140.30)	61.74 (±59.01)	$p=0.22$	$p=0.033$
H3Cit (ng/mL)	1.295	2.38(±2.88)	2.38 (±6.72)	$p=0.99$	$p=0.023$

Agca S, Kir S. FEBS J. 2024;291(18):4009-4023.

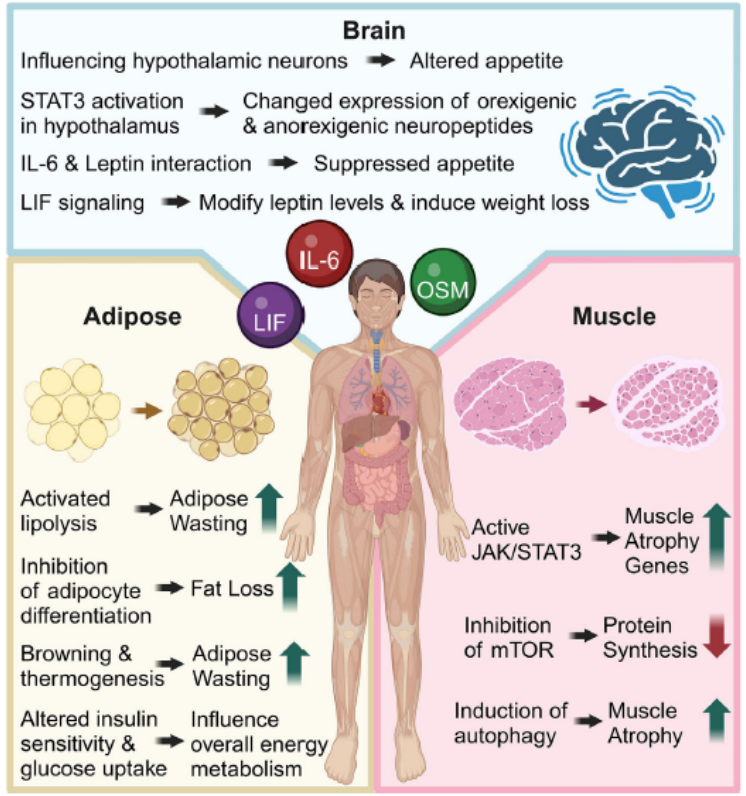


图2 IL-6调控肿瘤恶病质的机制

IL-6受体抑制剂可显著改善NSCLC恶病质期患者的整体状况

单中心、回顾性队列研究

- 托珠单抗联合标准抗肿瘤治疗组的OS相较于标准抗肿瘤组显著延长。
- 治疗12周时，托珠单抗联合标准抗肿瘤治疗组中存活且mGPS较基线改善的患者比例显著高于标准抗肿瘤治疗组。
- 治疗12周时，托珠单抗联合标准抗肿瘤组较基线的体重增幅及食欲的改善率等综合指标显著优于标准抗肿瘤组。

	Combination of tocilizumab and antitumour therapy ($n=26$)	Antitumour therapy alone ($n=23$)	p
Primary endpoint[a]			
Overall survival (months)	15.1 (9.1–30.4)	3.2 (1.3–4.5)	<0.001
Survival with mGPS improvement at Week 12	23 (88.5%)	0 (0)	<0.001
Secondary endpoints[b]			
Body weight (kg)	5.15 ± 0.53	−5.69 ± 0.76	0.041
Albumin (g/dL)	5.89 ± 0.70	−2.97 ± 0.71	<0.001
CRP (mg/L)	−91.50 ± 7.15	9.47 ± 13.69	<0.001
mGPS	−1.61 ± 0.15	0.03 ± 0.08	<0.001
Exploratory analysis endpoints[c]			
Appetite improvement	26 (100.0%)	6 (26.1%)	<0.001
Fatigue improvement	26 (100.0%)	3 (13.0%)	<0.001

Abbreviations: CRP, C-reactive protein; mGPS, modified Glasgow Prognostic Score.
[a]For primary endpoints, data are presented as median (95% CI) or n of patients with an event (%).
[b]Secondary endpoints were changes from baseline over 12 weeks in body weight, mGPS, CRP and albumin. Least-squares means, standard errors and p values were obtained from a mixed-effects repeated measures model.
[c]For exploratory analysis endpoints, data are presented as n of patients with an event (%).

Du, Yang et al. Journal of cachexia, sarcopenia and muscle vol. 15,6 (2024): 2815-2825.

IL-6受体抑制剂可改善晚期胰腺癌患者肌肉萎缩与远期生存获益

- 接受Toc/Gem/Nab治疗4个月后SKM较基线增加0.704%，显著优于Gem/Nab组。
- 仅在Toc/Gem/Nab组中观察到，治疗4个月时SKM变化率与患者OS存在显著正相关。
- Toc/Gem/Nab相较于Gem/Nab显著延长晚期胰腺癌18个月OS（27.1% vs 7.0%, P=0.001）。

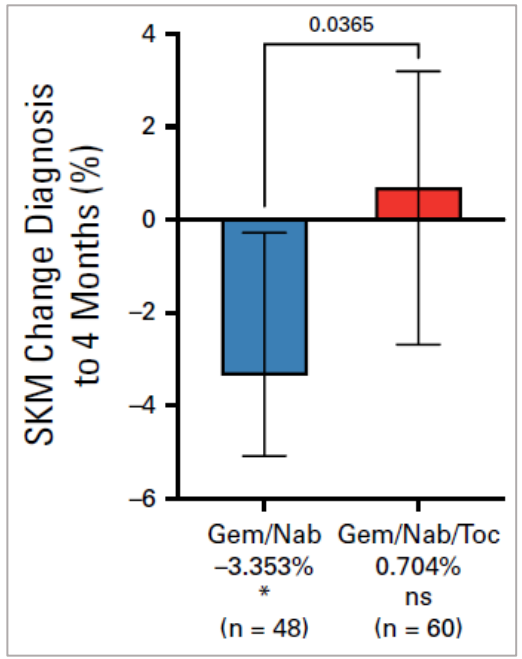


图1. 晚期胰腺癌患者接受Gem/Nab/Toc 或Gem/Nab治疗4个月后骨骼肌较基线变化情况

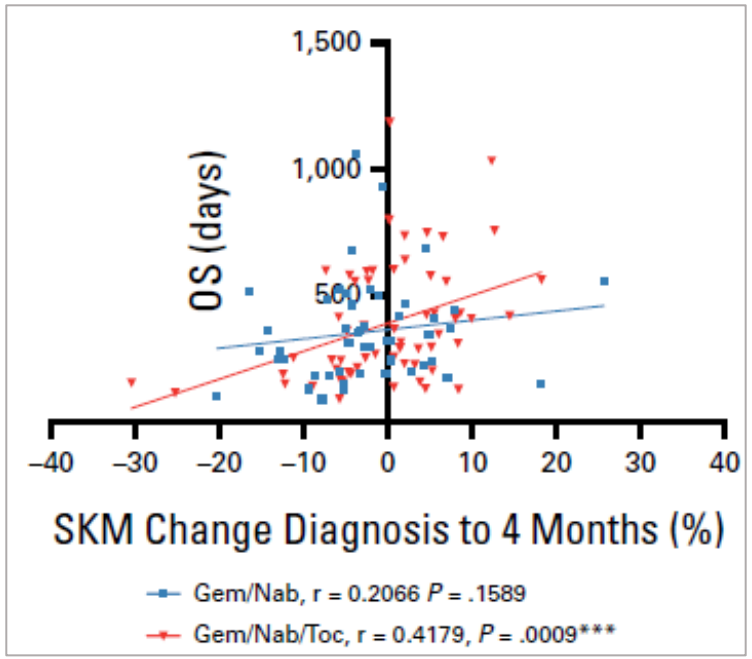


图2. 晚期胰腺癌患者接受Gem/Nab/Toc 或Gem/Nab治疗4个月时骨骼肌变化与OS的相关性

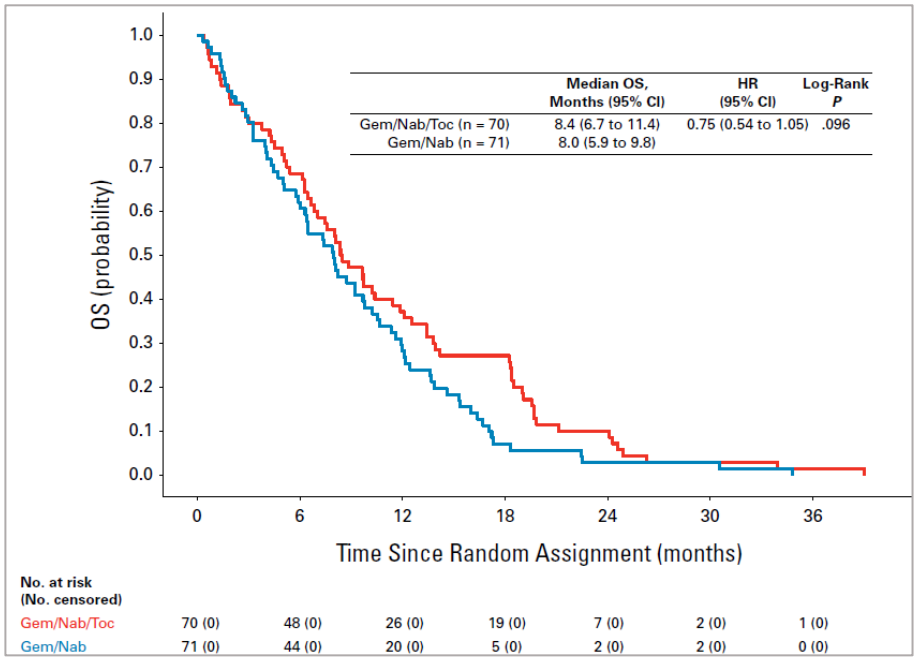


图3.晚期胰腺癌患者接受Gem/Nab/Toc 或Gem/Nab治疗后的OS Kaplan-Meier生存曲线

Chen IM, et al. J Clin Oncol. 2025;43(18):2107-2118.

劲方GFS202A：高选择性、靶向GDF15/IL-6的双特异性抗体

- GFS202A可以同时靶向GDF15及IL-6，与GDF15及IL-6具有高亲和力。
- GFS202A特异性结合GDF15，且不与TGF家族其他成员结合，如TGF-β、GDF8、BMP3。
- GFS202A预期可增加肿瘤恶病质患者体重、改善食欲及其他恶病质相关症状/体征。

Source：2025 AACR

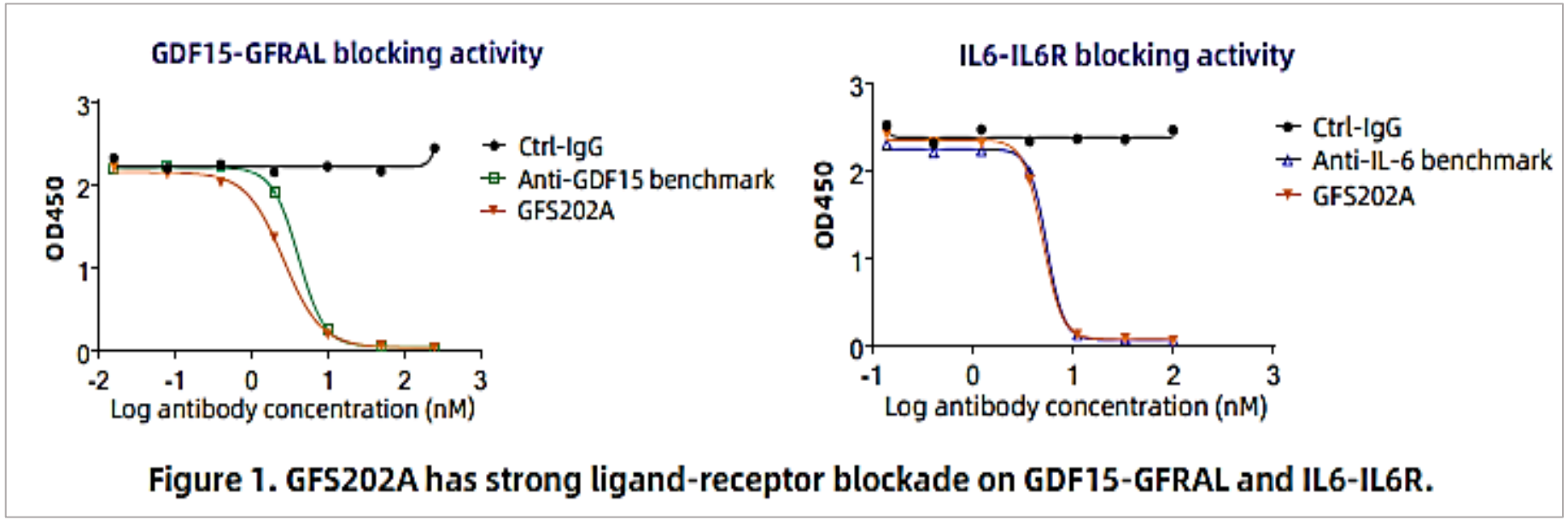


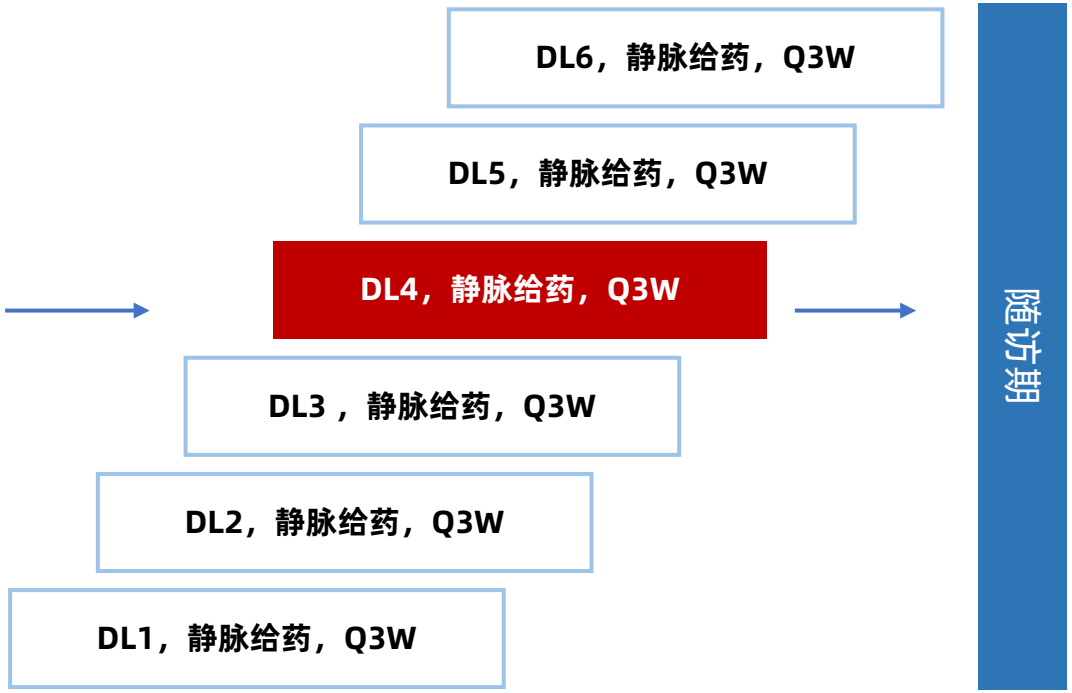
Figure 1. GFS202A has strong ligand-receptor blockade on GDF15-GFRAL and IL6-IL6R.

GFS202A I 期临床研究设计（ NCT06898255）

GFS202A 的首次人体试验正在国内开展，目前正处于第四个剂量组的入组阶段。

关键入排标准：

1. 经组织学或细胞学确诊的晚期实体瘤患者
2. 首次研究给药前6个月内有体重下降，或基线BMI < 21 kg/m^2 。
3. 合并肿瘤导致的食欲降低
4. ECOG PS ≤ 2且预期生存 ≥ 3月



主要研究终点：

① 安全性/耐受性

② 最大耐受剂量（MTD）/为未来研究推荐剂量

次要研究终点：

① PK及ADA

② GDF-15、CRP的变化

③ 体重、LSMI较基线的变化

④ 食欲、生活质量较基线的变化

缩写：ADA，抗药抗体；DL，剂量水平；Q3W，每三周给药一次；PK，药代动力学；CRP，超敏C反应蛋白；L3SMI，第三腰椎骨骼肌指数；ECOG，东部肿瘤协作组体能状态评分

GFS202A – 晚期肿瘤恶病质患者中的初步临床数据

安全性：GFS202A单药在前四个剂量组整体安全性优异

- ✓ 无DLT事件、治疗相关严重不良事件及特别关注不良事件
- ✓ 未观察到3级及以上治疗相关不良事件

初步有效性

- ✓ **已在多个剂量组观察到参与者给药后体重增加且食欲改善**

药代动力学

- ✓ GFS202A的暴露（C_{max}和AUC）随剂量增加而增加

药效动力学

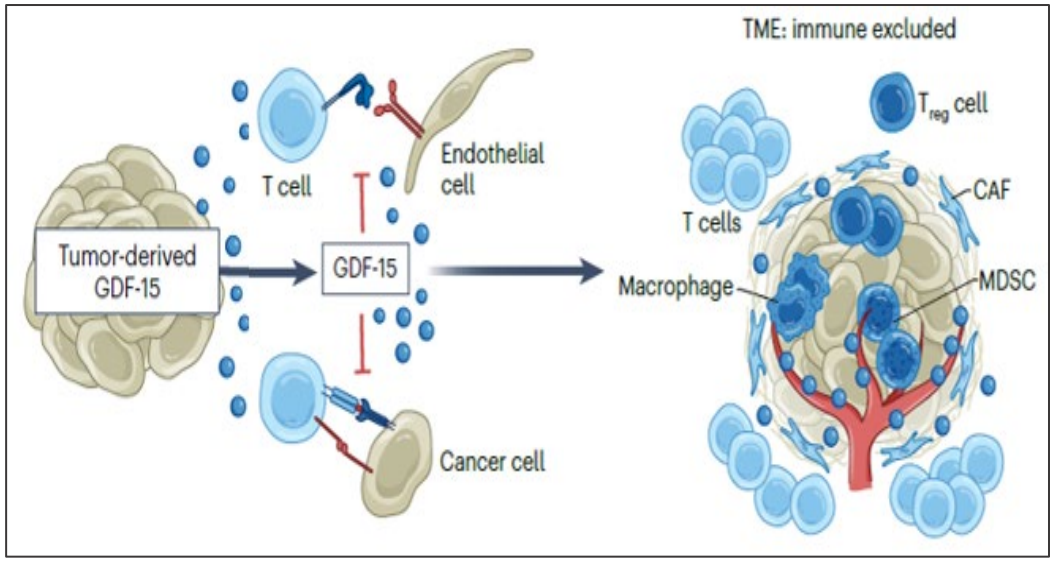
- ✓ GDF15 在 GFS202A 给药后迅速降至检测下限并维持
- ✓ CRP水平在给药后明显降低

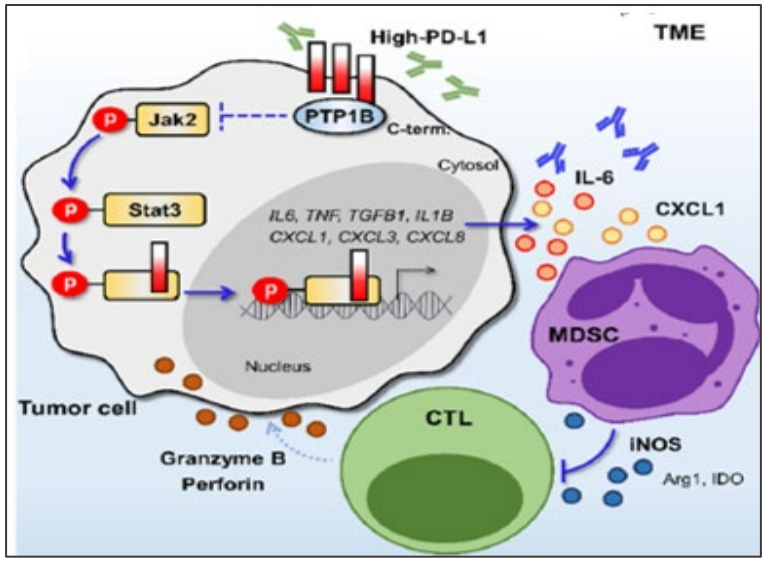
GFS202A的未来临床开发方向：I/O增效

GDF15与IL-6共同构建免疫抑制性肿瘤微环境，介导PD-(L)1抑制剂耐药

GDF15通过LFA1-ICAM1途径，阻止T细胞与血管内皮细胞结合进入肿瘤微环境中，造成免疫抑制性肿瘤微环境

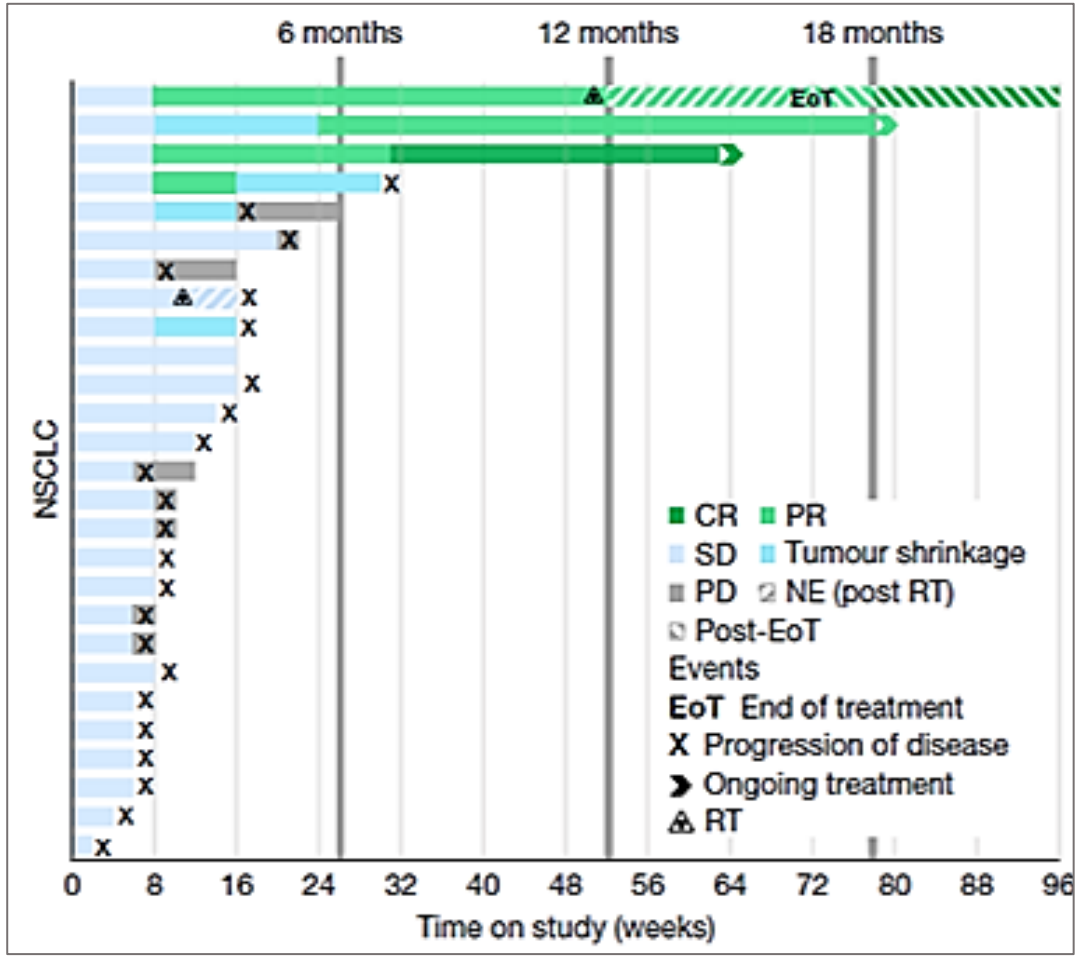
- IL-6与肿瘤细胞或免疫细胞表面的受体结合后激活JAK2/STAT3轴扩大PD-L1表达，抑制T细胞的活性；
- IL-6招募并激活髓源性抑制细胞， 形成非PD-1/PD-L1 依赖的多重免疫抑制网络。抑制IL-6同时可能减轻PD-1/PD-L1可能带来的免疫毒性





1. Wischhusen J, et al. Front Immunol. 2020;11:951. 2. Journal for immunotherapy of cancer vol. 13,3 e010612. 6 Mar. 2025

GFS202A的未来临床开发方向：I/O增效



接受Visugromab联合nivolumab治疗的非小细胞肺癌患者肿瘤应答情况

Melero I, et al. Nature. 2025;637(8048):1218-1227.

研究主要结果：

既往接受抗PD-(L)1治疗出现耐药的晚期NSCLC患者，接受Visugromab联合Nivolumab治疗后：

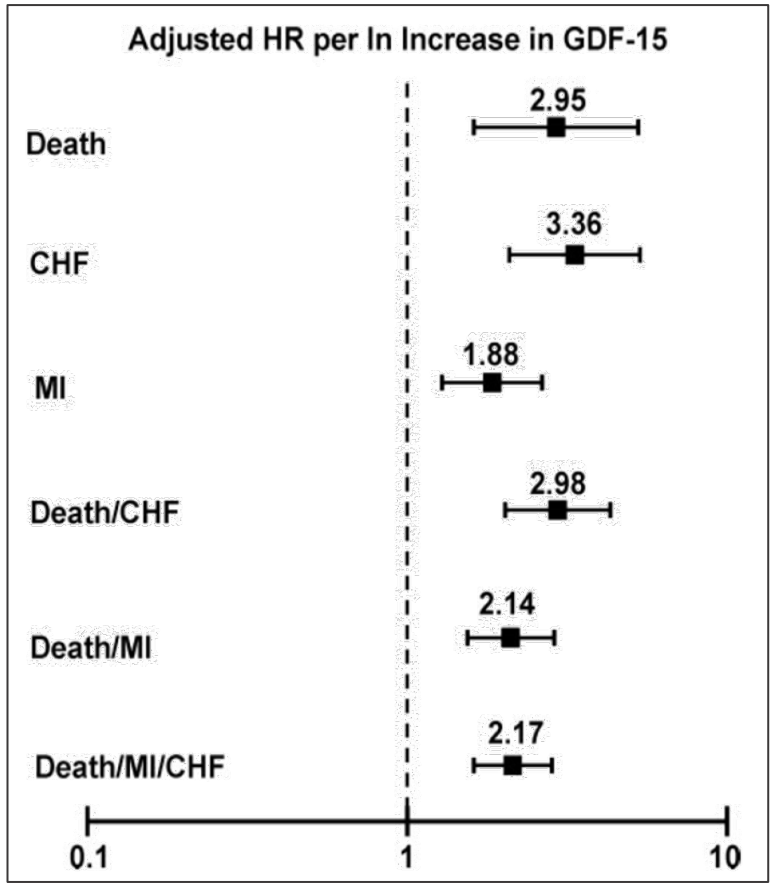
- ORR为14.8%，mDOR达15.3个月；
- 超过一半获得应答的患者在研究治疗中达到的肿瘤缩小程度超过了此前在一线抗PD-(L)1治疗中的最佳效果。
- 在治疗过程中，观察到免疫抑制性肿瘤微环境被逆转

启示：

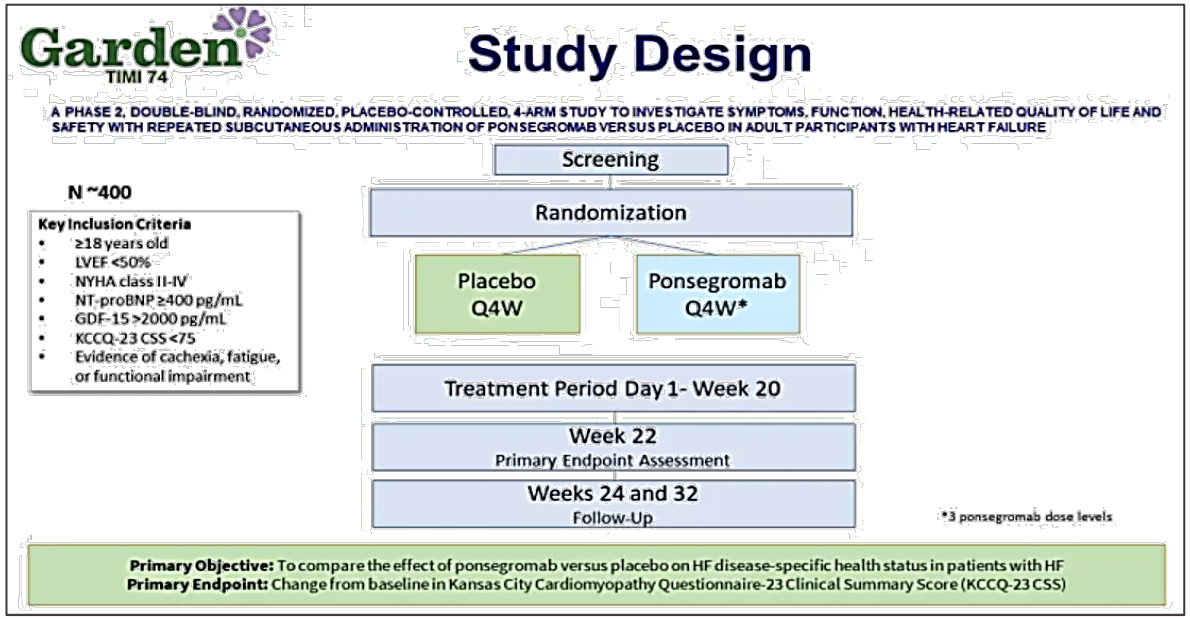
研究证明GDF15/IL-6共同参与PD-(L)1耐药机制，GSF202A联合抗PD-(L)1方案，可能通过阻断GDF15及IL-6双靶点，逆转PD-(L)1耐药，为对抗PD(L)-1耐药的肿瘤患者带来潜在获益。

GFS202A的未来临床开发方向：心力衰竭

GDF15升高会增加心力衰竭的发病风险及对应的死亡风险



1. Bonaca MP, et al. Arterioscler Thromb Vasc Biol. 2011;31(1):203-210 2. Burger PM, et al. J Am Coll Cardiol. 2023;82(5):414-426.



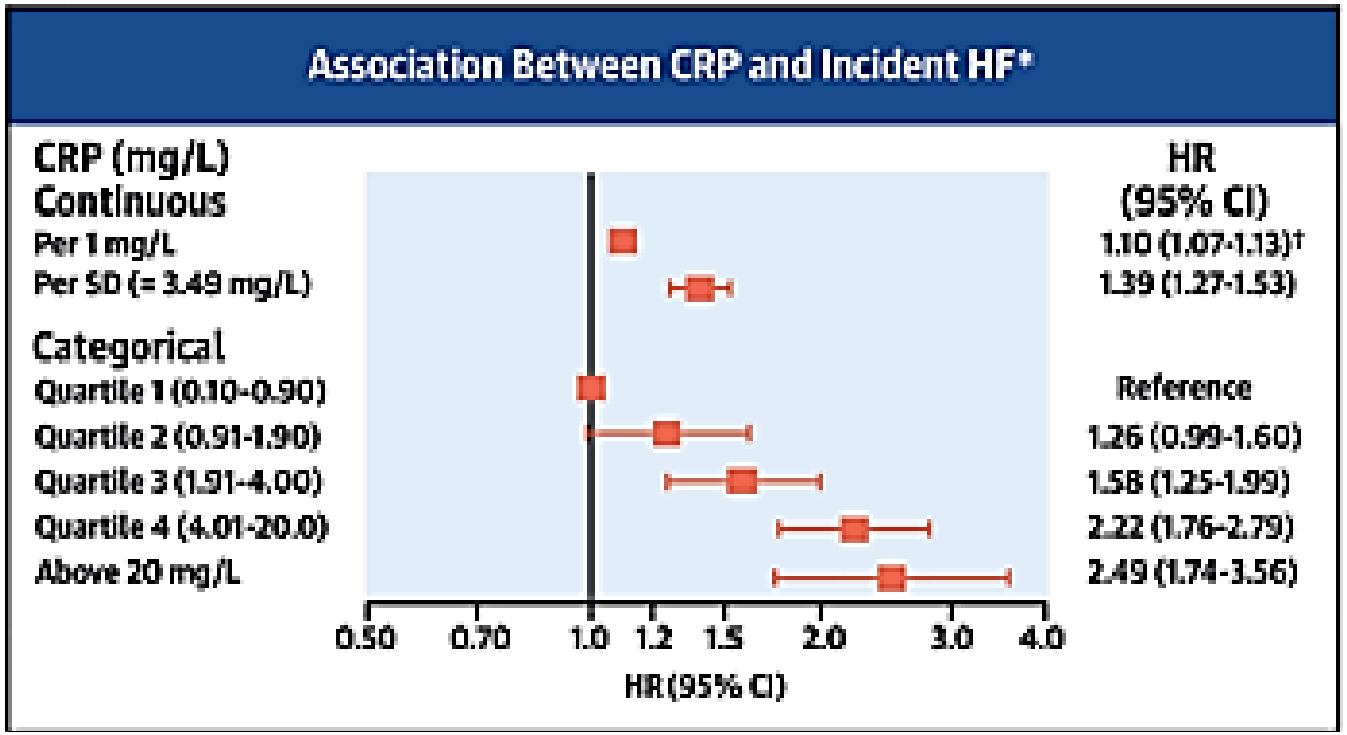
研究主要结果：

- 22周随访中，ponsegromab组心血管死亡或心力衰竭恶化事件发生率达19.8%（安慰剂组11.6%）。
- 尽管所有ponsegromab剂量组均实现了超过96%的GDF-15抑制，并且体重增加均值1.4kg（第4周-第22周），但**CRP较基线增加约1.3倍**。

GFS202A的未来临床开发方向：心力衰竭

CRP升高与心力衰竭风险增加显著相关

CRP每升高1mg/L，心衰风险增加10%



启示：

- GSF202A可能通过阻断GDF-15及IL-6双靶点，同时抑制慢性心衰伴随的恶病质及炎性状态，带来潜在获益。

1. Bonaca MP, et al. Arterioscler Thromb Vasc Biol. 2011;31(1):203-210 2. Burger PM, et al. J Am Coll Cardiol. 2023;82(5):414-426.

总结

恶病质存在巨大未满足医学需求，市场巨大

GFS202A是全球首个进入临床的恶病质双抗产品，
初步临床数据令人鼓舞

辉瑞在晚期胰腺癌的临床II/III期设计和终点使得
GDF15相关靶向药的临床注册途径清晰

GFS202A具有巨大的治疗扩展空间

后续研发将逐步推进

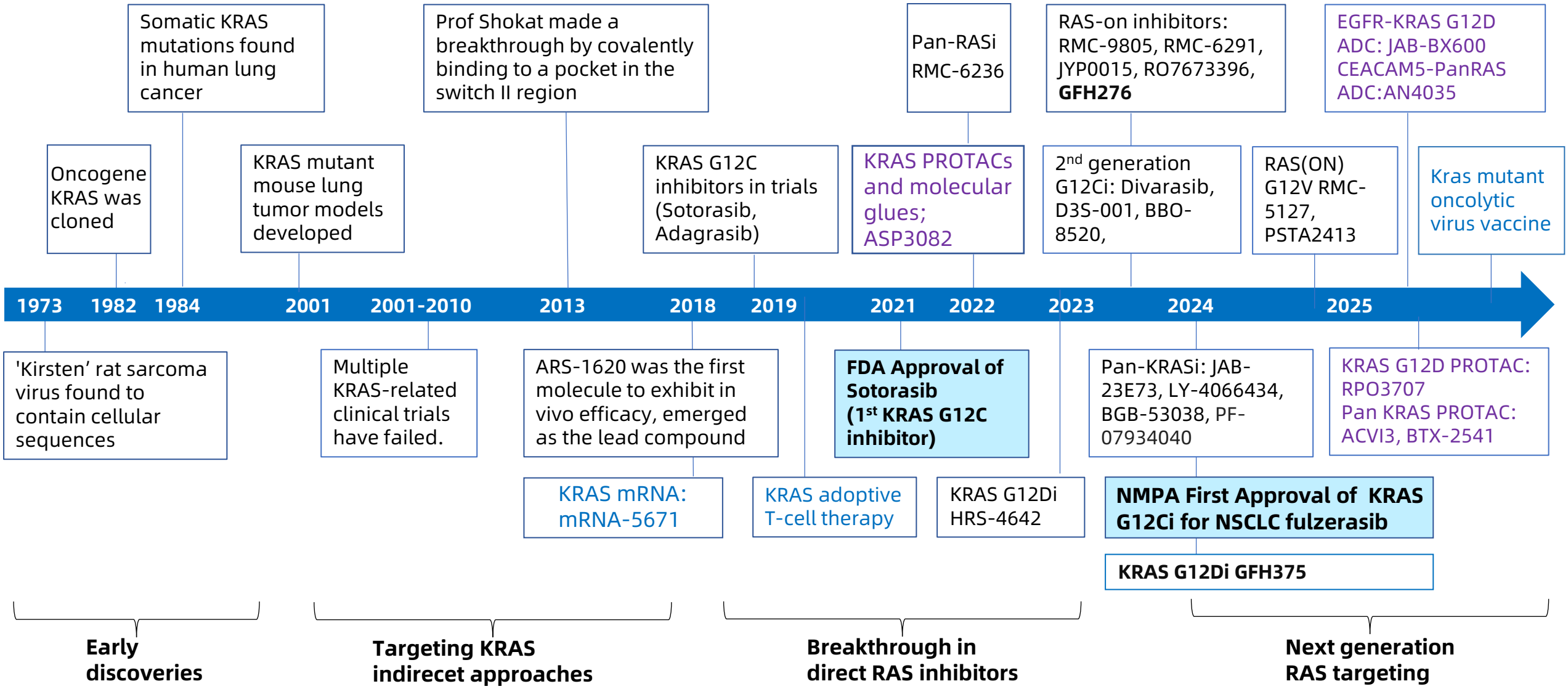

風飛浪勁·据義履方

GFH375治疗非小细胞肺癌临床开发进展

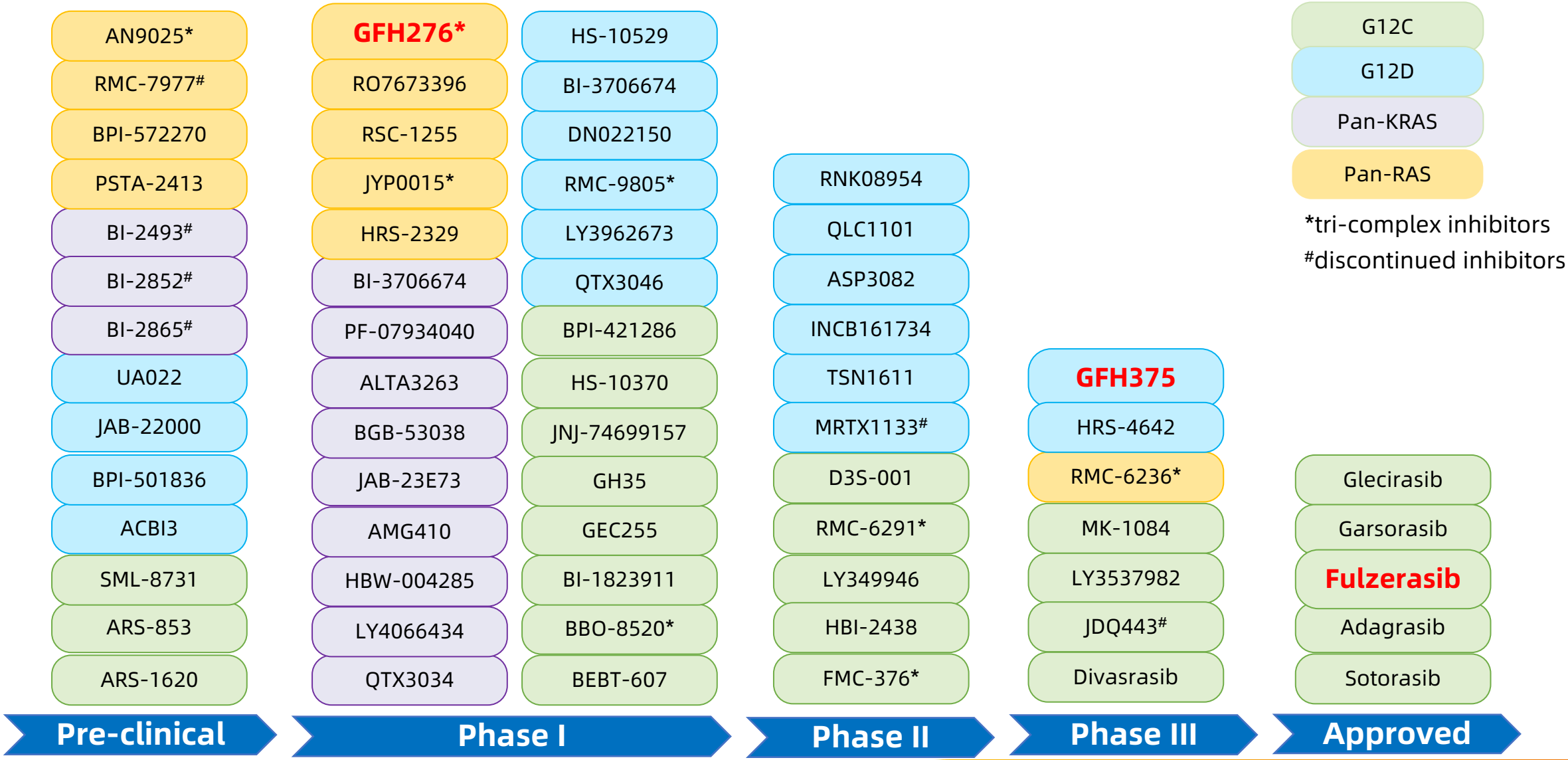
陆舜教授
上海胸科医院

目录 Contents

Historical Timeline of Major Milestones in RAS Discovery and Therapeutic Development



Clinical Stages of RAS Inhibitors



Phase I/II Study of GFH375 in Advanced Solid Tumors (NCT06500676)

Key eligibility criteria

- Advanced solid tumors with KRAS G12D mutation
- Previously treated with standard therapies

  NSCLC previously treated with ICI and/or platinum-based chemo therapies
- ECOG PS 0 - 1

Phase I: Dose escalation and expansion

900mg QD
750mg QD
600mg QD
300mg BID
400mg QD
200mg QD
100mg QD

Escalate with accelerated titration and BOIN design + backfilling

RP2D

Phase II: Indication expansion

- Cohort 1: NSCLC
- Cohort 2: PDAC
- Cohort 3: CRC
- Cohort 4: Other solid tumors

Treatment until disease progression, intolerable toxicity or other reasons

Phase I endpoints:

- Safety/tolerability and MTD/RP2D: AEs, etc.
- Anti-tumor activity: ORR, DOR, DCR, PFS (per RECIST 1.1) and OS
- Pharmacokinetics
- Biomarkers

Phase II endpoints:

- Efficacy: ORR, DOR, DCR, PFS (per RECIST 1.1) and OS
- Safety: AEs, etc.
- Biomarkers

Abbreviations: AE, adverse event; BID, twice daily; BOIN, Bayesian optimal interval; CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; ECOG PS, eastern cooperative oncology group performance status; ICI, immune checkpoint inhibitor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression of survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.

NSCLC Baseline Characteristics & Patient Disposition

- 28 NSCLC patients with local tumor testing KRAS G12D+ were treated with GFH375 single agent, including 16 at 600 mg QD.
- Majority (60.7%) were never smokers.
- Among the 22 patients with baseline PD-L1 TPS data available, **none had high expression (TPS ≥ 50%).**
- 17.9% had baseline brain metastases.
- Majority (64.3%) had received at least 2 prior lines of therapies; all received prior platinum-based chemo therapies; **96.4% received prior ICIs.**
- Most patients were ongoing; the longest follow-up was 55.6 weeks.

	All NSCLC (n=28)	NSCLC at 600 mg QD (n=16)
Discontinued n(%)	12 (42.9)	4 (25.0)
Adverse event	1 (3.6)	1 (6.3)
Progress disease	8 (28.6)	2 (12.5)
Patient's decision	2 (7.1)	1 (6.3)
Physician's decision	1 (3.6)	0

Source: 2025 WCLC

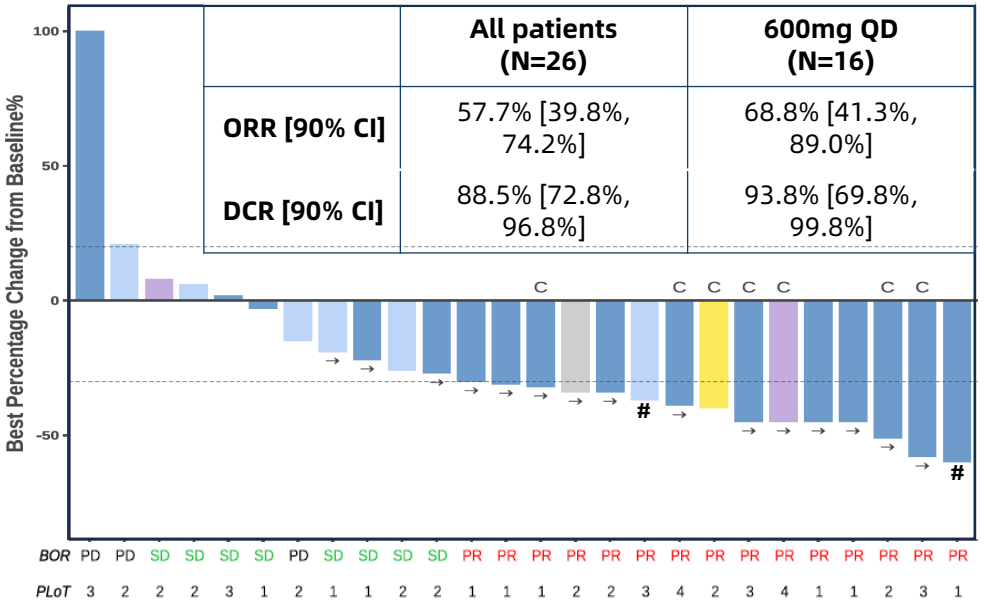
	All NSCLC (n=28)	NSCLC at 600 mg (n=16)
Age, median (range), years	61 (36-74)	60.5 (36-74)
Female, n(%)	13 (46.4)	8 (50)
Smoking status, n(%)		
Current or former	11 (39.3)	8 (50)
Never	17 (60.7)	8 (50)
ECOG PS, n(%)		
1	26 (92.9)	14 (87.5)
Pathology adenocarcinoma, n(%)	28 (100)	16 (100)
Baseline metastasis, n(%)	28 (100)	16 (100)
Bone	12 (42.9)	4 (25.0)
Brain	5 (17.9)	1 (6.3)
Liver	3 (10.7)	2 (12.5)
PD-L1 TPS, n(%)		
Known	22 (78.6)	11 (68.8)
< 1%	*13 (59.1)* [1]	*6 (54.5)* [2]
1-49%	*9 (40.9)* [1]	*5 (45.5)* [2]
≥ 50%	**0**	**0**
Prior lines of therapies, median (range)*	2 (1-4)	1.5 (1-4)
Prior ICI, n(%)	**27 (96.4)**	**16 (100)**
Prior platinum, n(%)	28 (100)	16 (100)
Prior ICI +platinum concurrent, n(%)	25 (89.3)	16 (100)

[1] Percentage denominator is 22. [2] Percentage denominator is 11.
* A neoadjuvant and adjuvant therapy would be counted as a line of system therapy if patient relapsed or progressed during treatment or within 6 months of last dose.

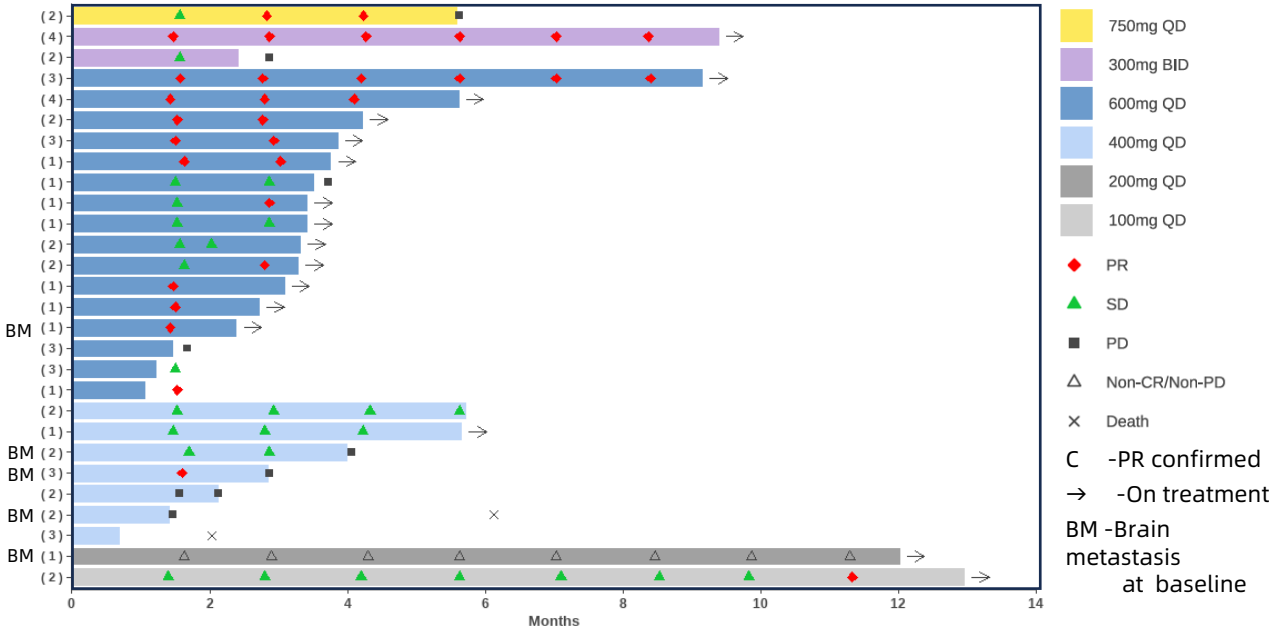
Efficacy in NSCLC

- ORR is 57.7% in 26 evaluable patients, and 68.8% in 16 patients at 600 mg QD *.

	All patients (N=26)	600mg QD (N=16)
ORR [90% CI]	57.7% [39.8%, 74.2%]	68.8% [41.3%, 89.0%]
DCR [90% CI]	88.5% [72.8%, 96.8%]	93.8% [69.8%, 99.8%]



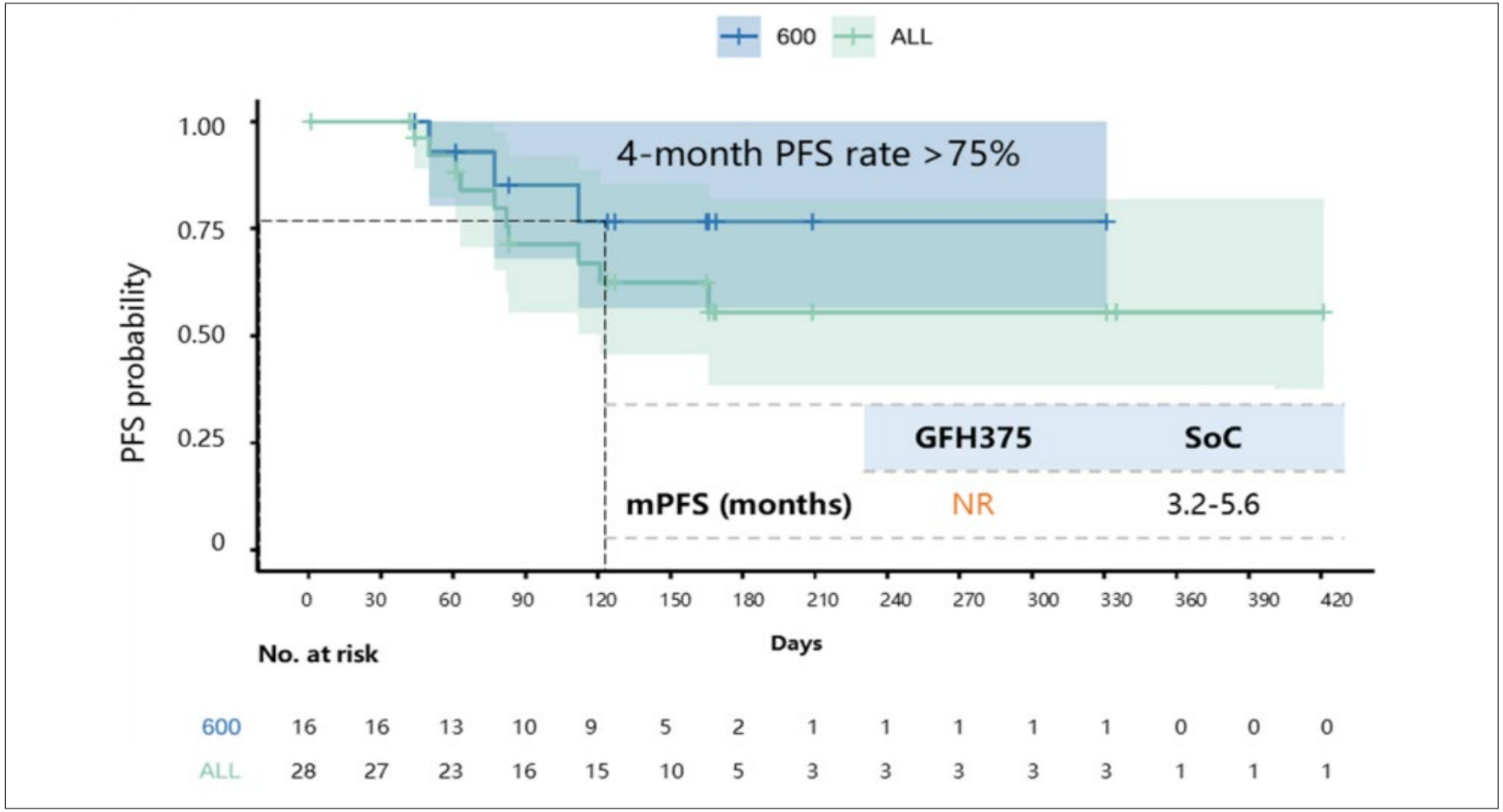
- Median (range) time on treatment: 15.1 weeks (range: 4.6 - 55.6)
- Median (range) time to response: 6.3 weeks (range: 6.0 - 48.1)



Source: 2025 WCLC
All patients received first dose of GFH375 at least 10 weeks prior to data cut-off date. Median follow-up 21.8 weeks (range: 8.3 - 55.6).
* One patient (200 mg QD) had no target lesion at baseline but remains stable; one patient (400 mg QD) dropped out early without post-baseline tumor assessment due to patient's decision and died 41 days after last dose due to disease progression.
# Two patients achieved PR but discontinued before response confirmation. One (400 mg QD) had PD at the 2nd assessment. The other dropped out due to G4 hepatic function abnormal (recovered after discontinuation).
Abbreviation: BOR, best overall response; CI, confidence interval; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; PLoT: number of prior lines of therapies.

Progression Free Survival

- mPFS was not reached with Median follow up time of all dose levels 5.5 months and 600 mg QD 4.2 months.
- 4-month PFS rate was >75%.

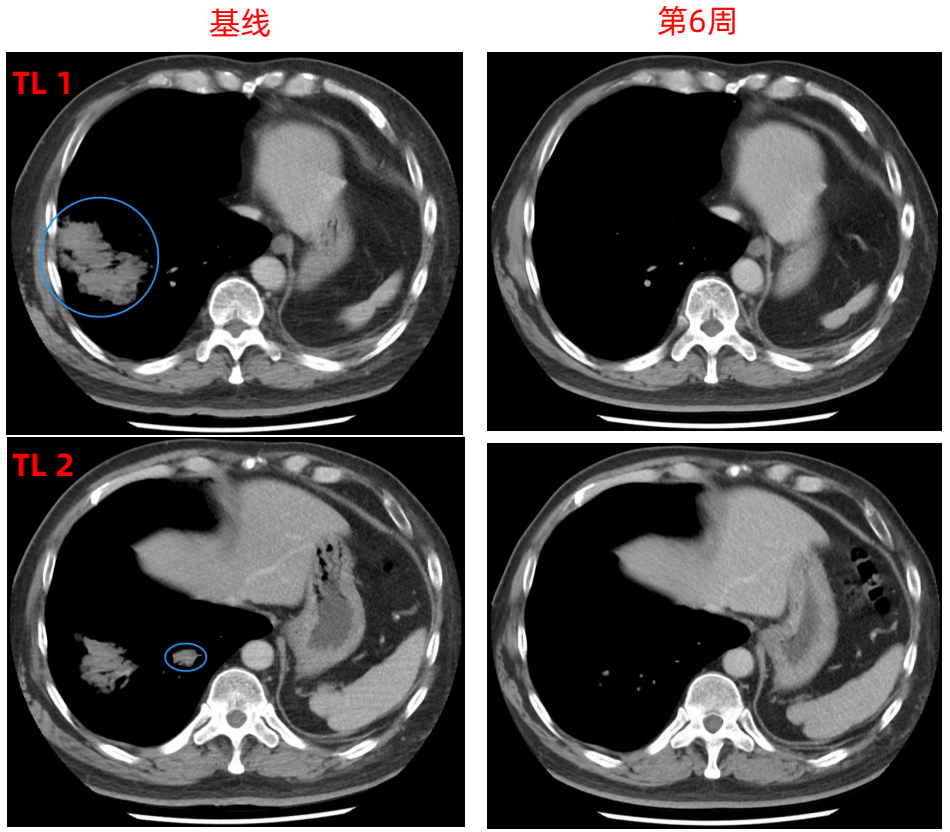


Source: 2025 WCLC

成功案例

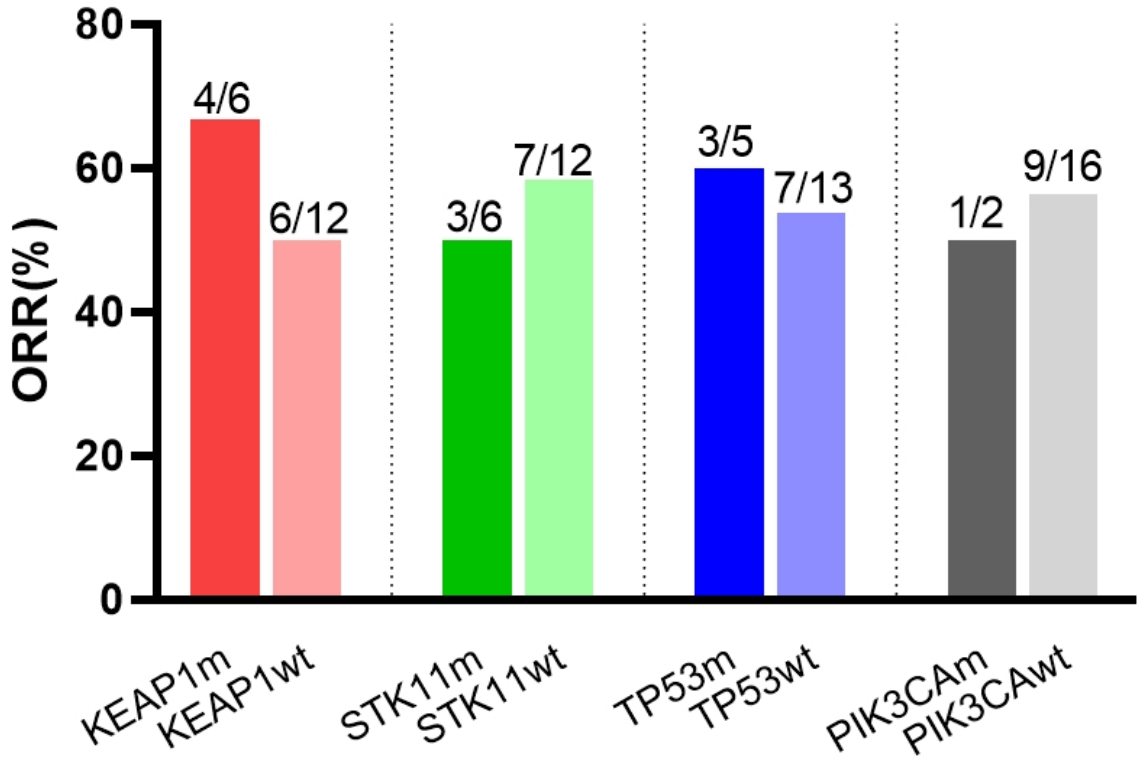
- 受试者31002，52岁，男性，从未吸烟。2024年4月22日确诊NSCLC（腺癌），PD-L1中表达。
- 基线IVA期(T4N0M1a)，双肺、胸膜转移伴胸水。基线KRAS G12D突变频率为26.74% (组织检测，2025年7月4日检测)。
- 既往治疗：
  - 手术：2024年4月22日行肺叶切除术；2024年6月复发
  - 既往治疗：培美曲塞+卡铂+替雷利珠单抗一次，换培美曲塞+卡铂+信迪利单抗4个周期，最佳疗效为SD，2025年9月19日疾病进展。
- 2025年9月30日首次给药，至今未发生TEAE。

	基线 (2025年9月19日)	第6周 (2025年11月12日)
右肺下叶靶病灶1	79.3 mm	5 mm
右肺下叶靶病灶2	17.1 mm	5 mm
SoD	96.4 mm	10 mm
非靶病灶	肺、胸膜、胸水	non-CR, non- PD
新病灶	NA	无
疗效	NA	PR (-89.6%)



Baseline Co-Mutated Genes and Response

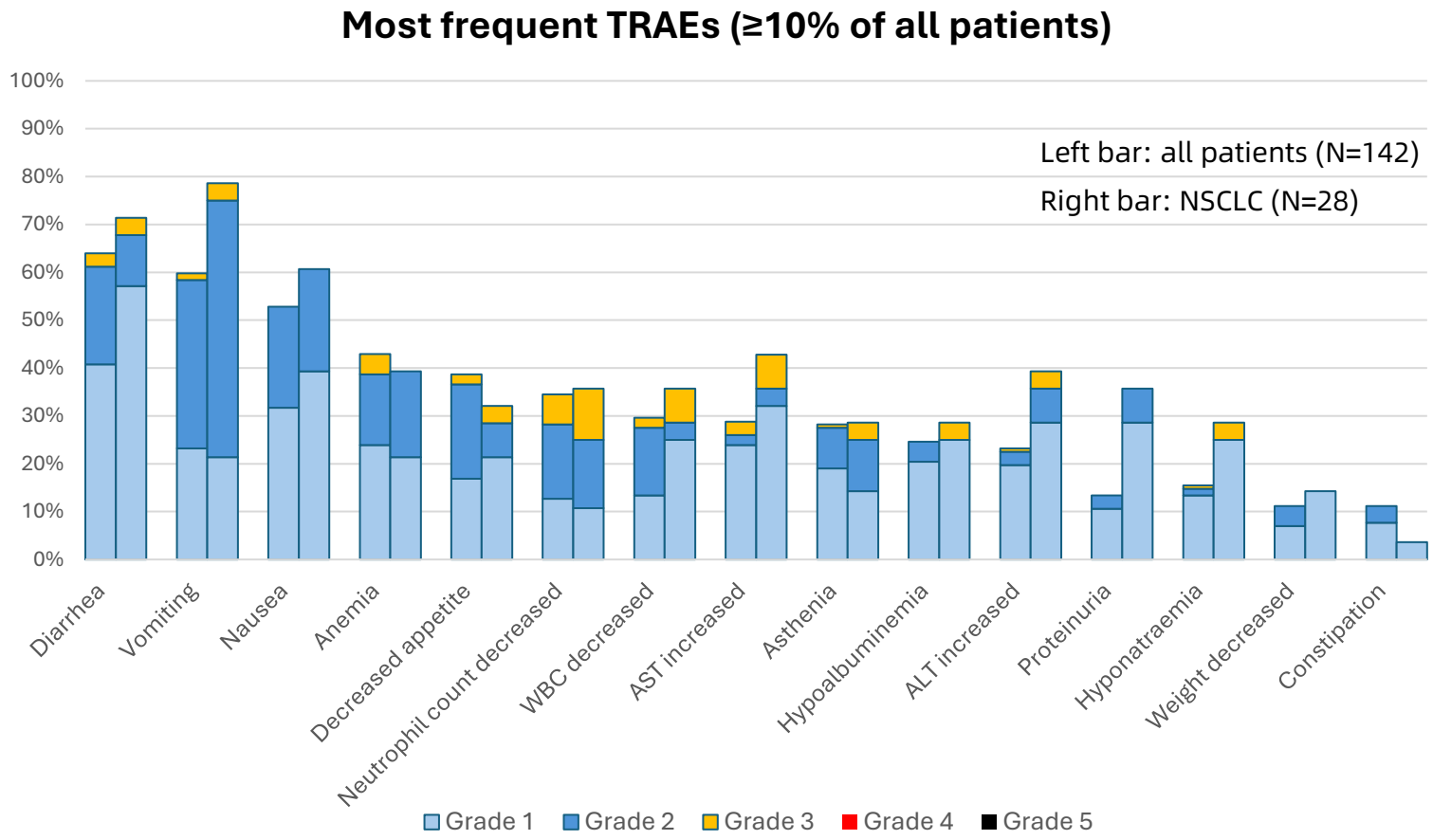
- 18 of the 28 patients had baseline ctDNA central testing results:
  - 9 had a detectable KRAS G12D mutation and 6 (66.7%) achieved PR.
  - The potential pathogenic co-mutations included KEAP1 (33.3%, 6/18), STK11 (33.3%, 6/18), TP53 (27.8%,5/18) and PIK3CA (11.1%, 2/18).
  - No significant difference in tumor response was observed between patients with and without the co-mutations.



Source: 2025 WCLC

Safety in All Patients and NSCLC

- No new safety signals were observed.
- The most frequent TRAEs were gastrointestinal AEs (diarrhea, vomiting, and nausea) and hematological AEs (anemia and neutropenia), mainly grade 1/2 and manageable with supportive medications.
- Most frequent G3/4 TRAEs were neutropenia (6.3%) and anemia (4.2%).
- Multiple AEs had higher rates in NSCLC patients, potentially due to prior use of ICIs.
  - 96.4% pts with NSCLC had received ICIs before GFH375 treatment.
  - The median time of last dose of ICIs to first administration of GFH375 was 2.8 months (range: 1.0 - 40.0); the median time of ICI treatment was 4.3 months (range: 0.7 – 26.5).

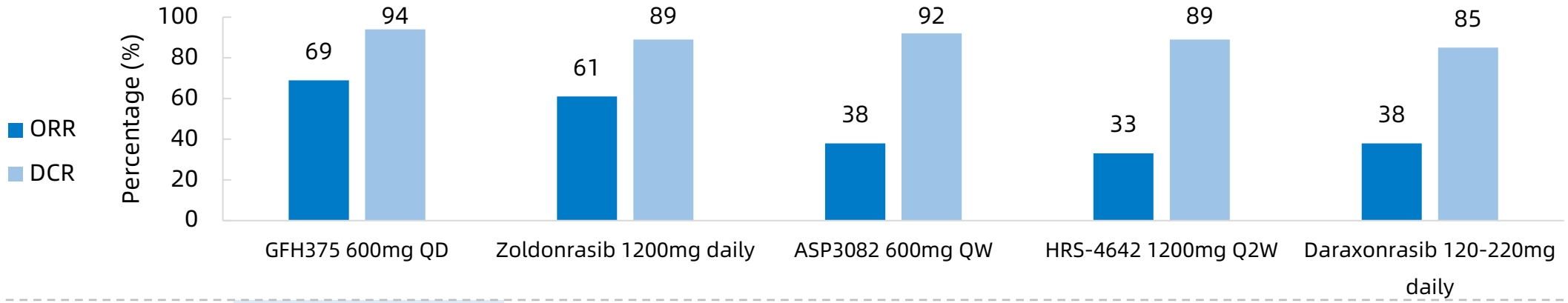


Source: 2025 WCLC

Abbreviations: ALT, alanine transaminase; AST, aspartate transferase; TRAE, treatment related adverse event; WBC, white blood cell.

GHF375 Improved Efficacy Compared to Competitors (Cross-trial comparison)

- **Potential best-in-class as G12D monotherapy for NSCLC**
- **Supporting single-arm accelerated approval for 2L+ NSCLC**



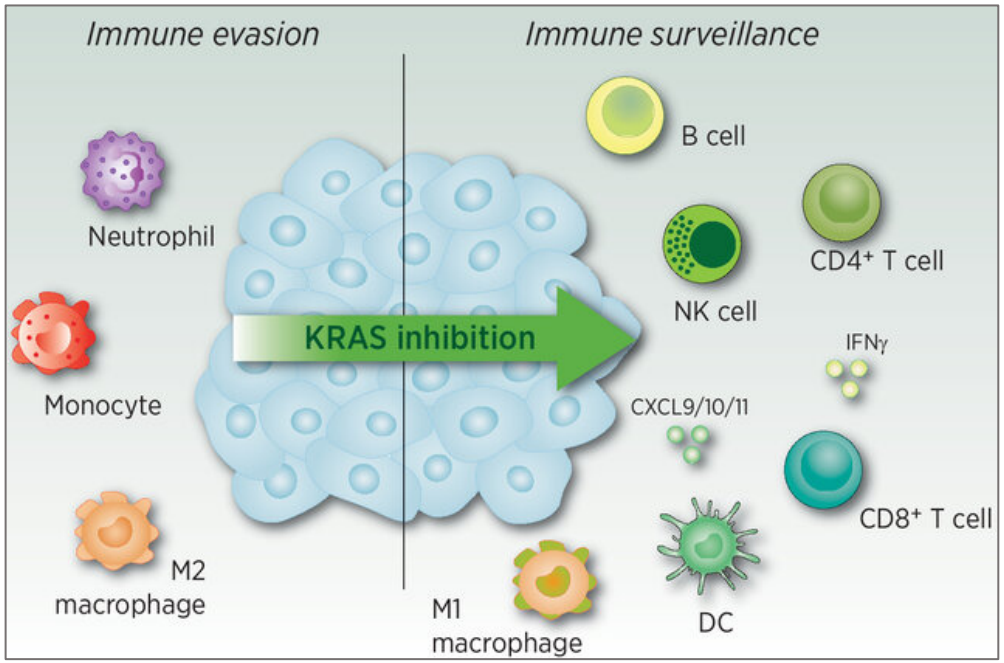
Population	2L+ NSCLC with KRAS G12D[1]	2L+ NSCLC with KRAS G12D[2]	2L+ NSCLC with KRAS G12D[3]	2L+ NSCLC with KRAS G12D[4]	2/3L NSCLC with KRAS G12X[5]
Sample size	16	18	25	9	40
ORR	69%	61%	38%	33%*	38%*
DCR	94%	89%	92%	89%*	85%*
PFS, months	NR	NA	8.3(2/3L)/3.3(4L+)	8.4	9.8
OS, months	NR	NA	NA	NR	17.7
Median follow-up time, months	4.2	NA	NA	NA	10.8

Cross-trial comparison. Source: [1]WCLC 2025. [2]AACR 2025. [3]AACR-NCI-EORTC 2025. [4]ESMO 2025. [5]ELCC 2025 (participants were required not have received docetaxel previously). *confirmed.
Abbreviations: 2L+, second line and beyond. DCR, disease control rate. DoR, duration of response. NA, not available. NR, not reached. ORR, objective response rate. OS, overall survival. PFS, progression-free survival.

G12D Inhibitors in Combination with ICIs

PROS

- Treatment with KRAS inhibitors leads to remodeling of the immune TME composition
- Clinical synergy of G12Ci + ICIs combination



CONS

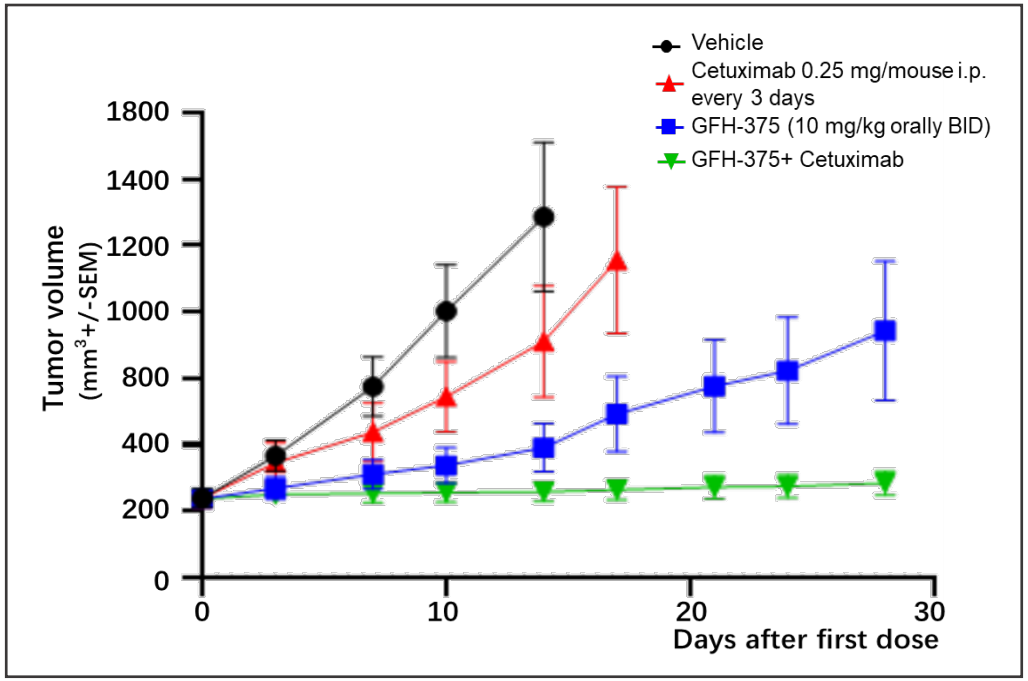
- KRAS G12D mutation creates an immunosuppressive microenvironment by downregulating PD-L1/CXCL10/CXCL11 and reducing $CD8^+$ TILs.
- GFH375 study found significantly higher PD-L1 negative/low expression than in KRAS G12C-mutated NSCLC.
- Common co-mutations in KEAP1 and/or STK11 may promote immunologically “cold” TME
- Toxicity of combination (e.g. hepatoxicity)

Boumelha J, et al, Clin Cancer Res 2023;29:5012-20

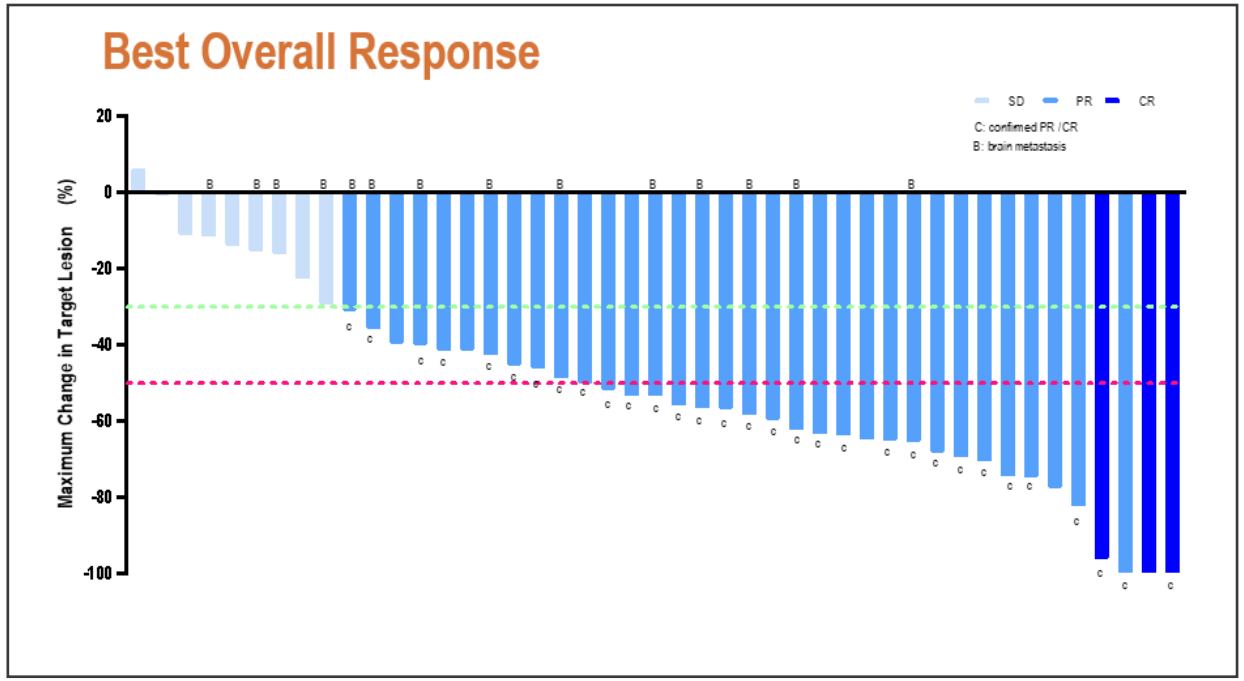
Combination with EGFR Inhibitors

- RTK signaling promotes cycling of RAS from inactive →active conformation
- KRAS inhibition suppresses negative feedback to rebound in EGFR signaling
- EGFR antibodies (cetuximab and panitumumab) interfere with ligand binding and disrupt signaling.
- GFH375 in combination with Cetuximab showed a synergetic activity in KRAS G12D mutant NSCLC models in vivo. [1]
- The combination has been confirmed by the KROCUS study (Fulzerasib + cetuximab).[2]

Tumor growth curve of GFH375 combined with cetuximab in lung cancer PDX models[1]



KROCUS study (Fulzerasib + cetuximab) ORR[2]



1. *Cancer Res (2025) 85 (8_Supplement_1): 4394.* ; *2. JTO 2025 20 (3 _Supplement_1): S1-S97*

Other Combinations

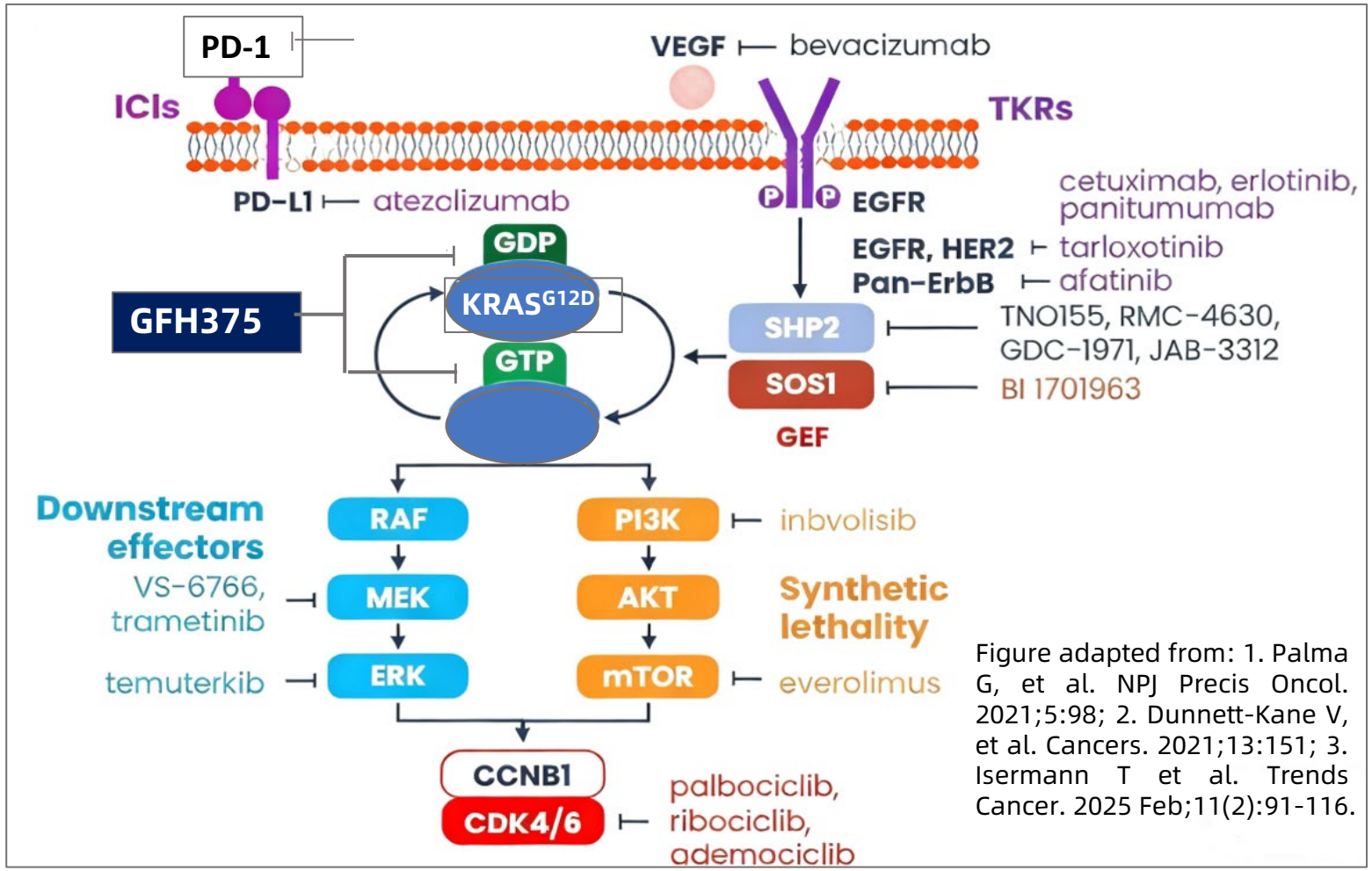
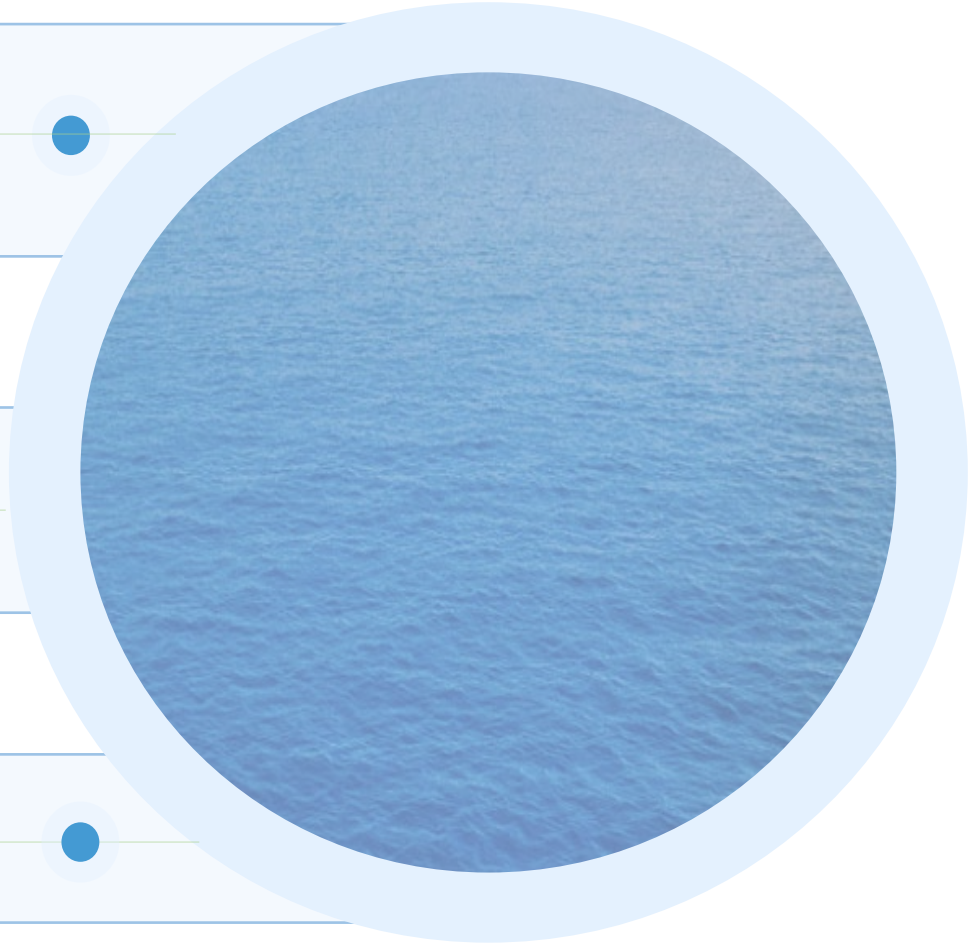


Figure adapted from: 1. Palma G, et al. NPJ Precis Oncol. 2021;5:98; 2. Dunnett-Kane V, et al. Cancers. 2021;13:151; 3. Isermann T et al. Trends Cancer. 2025 Feb;11(2):91-116.

- Chemotherapy
  - Combine with chemo to advance to 1st-line setting.
- Upstream effectors:
  - EGFR antibody
  - RTKs inhibitors
  - SHP2 inhibitors
  - SOS inhibitors
  - Others
- Downstream effectors
  - PI3K-AKT-mTOR pathway inhibitors
  - BRAF/MEK/ERK inhibitors
  - Others
- Cyclin-Dependent Kinase inhibitors
- RAS inhibitor doublets

Summary

- The RAS inhibitor therapy landscape is evolving rapidly, featuring numerous mutant-selective, pan-KRAS, and pan-RAS inhibitors in clinical development.
- GFH375 exhibits promising anti-tumor activity in previously treated KRAS G12D-mutated NSCLC, with good tolerability, manageable safety profile.
- GFH375 monotherapy and combination regimens will advance to frontline setting.




風飛浪勁·据義履方

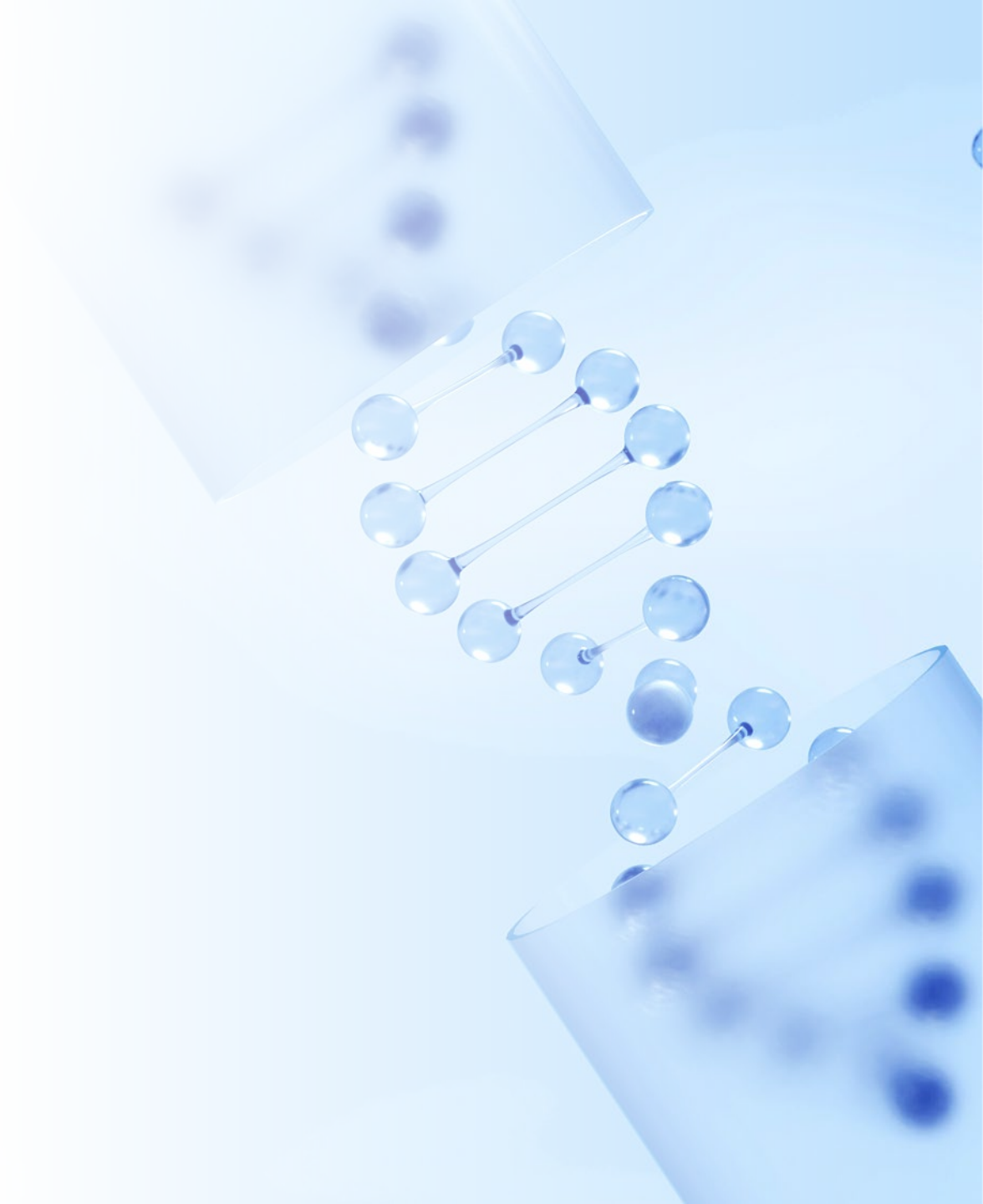
劲方医药临床开发规划及展望

汪裕博士
劲方医药首席医学官

CONTENTS

PART 01

Refreshing ESMO Data of GFH375 for PDAC



PDAC: ESMO Reported Baseline Characteristics

10:15 - 11:45 Proffered paper session 2: GI tumours, upper digestive

CHAIRS: MAEVE LOWERY, CHRISTOPH BENEDIKT WESTPHALEN

LBA84 : GFH375 Monotherapy

Advanced, KRAS G12D mutated, previously treated PDAC, n=66 patients

	GFH375 600mg QD (N=66)
Age, median (range), years	60 (35, 74)
≥60, n (%)	35 (53.0%)
Male, n (%)	35 (53.0%)
ECOG PS 1, n (%)	66 (100%)
Histological type, n (%)	
Adenocarcinoma	64 (97.0%)
Adenosquamous carcinoma	2 (3.0%)
Stage IV at study entry, n (%)[c]	63 (95.5%)
Baseline metastasis, n (%)	
Liver	52 (78.8%)
Lung	19 (28.8%)
Peritoneum	19 (28.8%)
Bone	12 (18.2%)

	GFH375 600mg QD (N=66)
Number of prior lines of anticancer therapy, (range)	(1, 5)
1, n (%)	21 (31.8%)
≥2, n (%)	45 (68.2%)
Prior anticancer therapy, n (%)	
Gemcitabine-containing	61 (92.4%)
Fluorouracil-containing	50 (75.8%)
Irinotecan-containing	35 (53.0%)
Immune checkpoint inhibitors	22 (33.3%)

Real world data : < 10% of PDAC patients receive 3rd line chemotherapy*

Maeve A Lowery

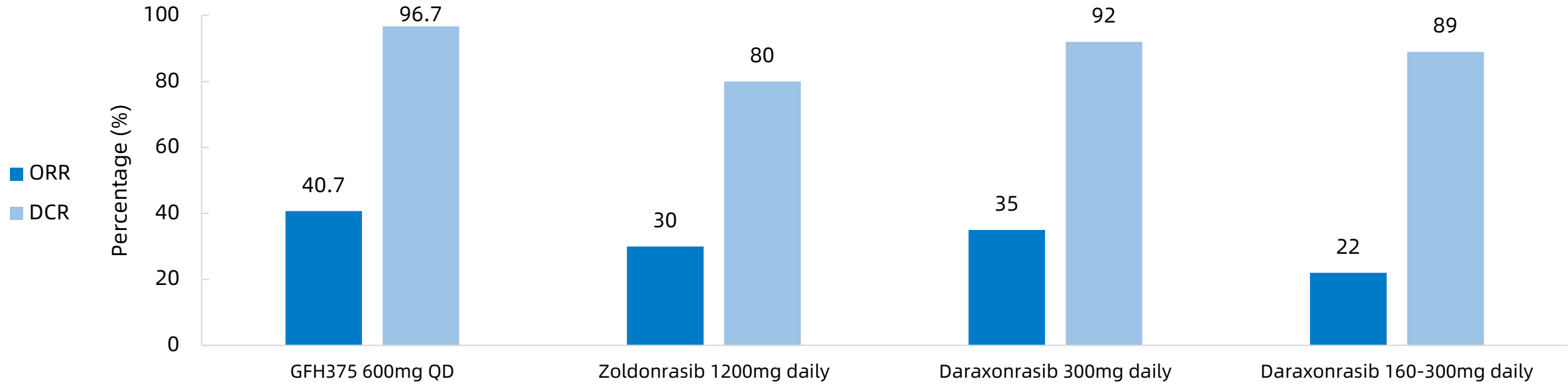
*Macarulla et al, ESMO Real World Data & Digital Oncology 2025

Maeve Lowery

Invited Discussant LBA84 and 22150

BERLIN AUDITORIUM - HUB 27

PDAC: Improved Efficacy Compared to Competitors



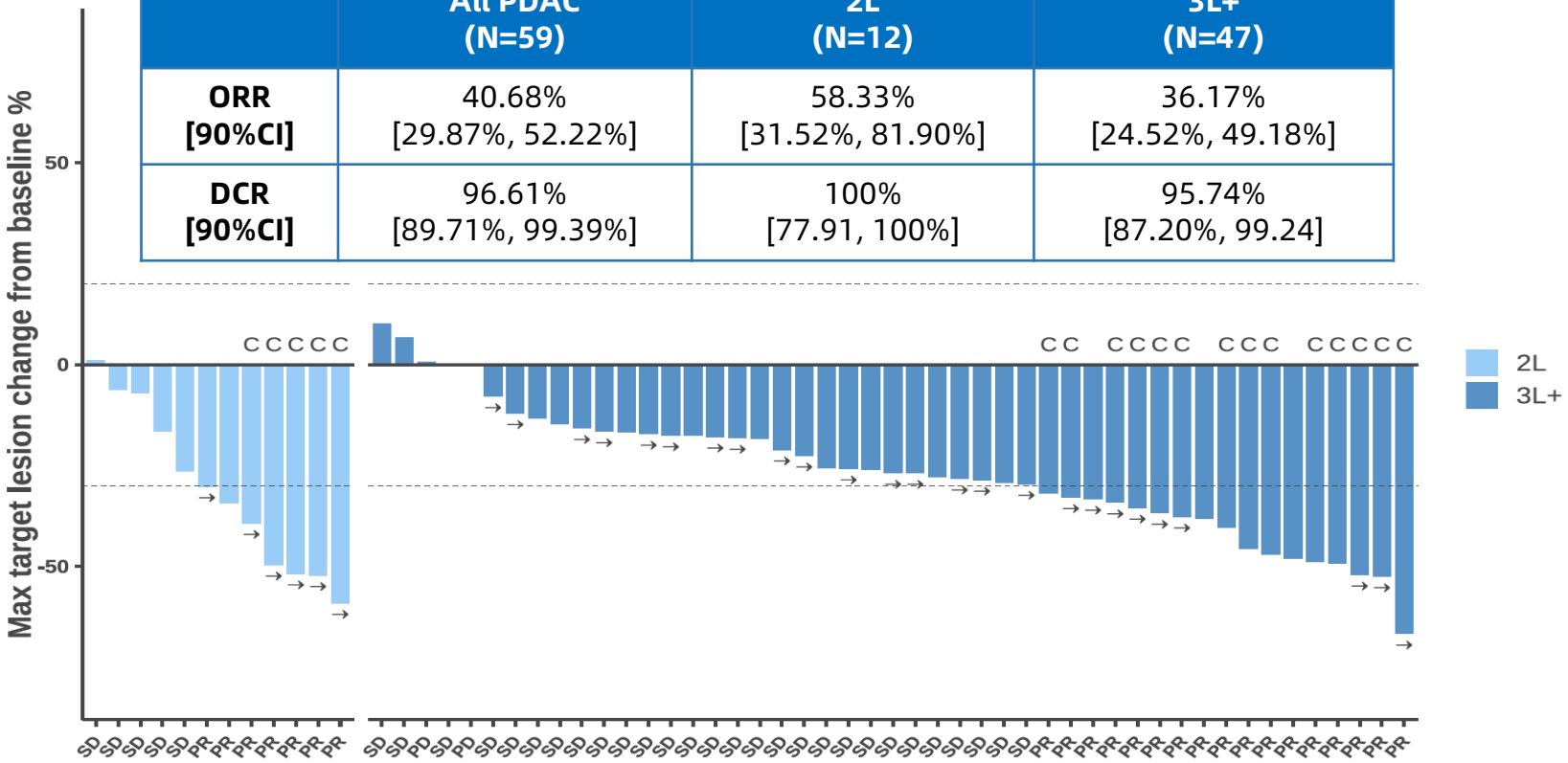
Population	2L+ PDAC with KRAS G12D$_m$[1]	2L+ PDAC with KRAS G12D$_m$[2]	2L PDAC with KRAS G12X$_m$[3]	3L+ PDAC with KRAS G12X$_m$[4]
Sample size	**66**	40	26	63
ORR	**40.7%**	30%	35%	22%
DCR	**96.7%**	80%	92%	89%
PFS	**5.52 months**	NA	8.5 months	4.4 months
OS	**NR; 4-months rate 92.2%**	NA	13.1 months	NA
Median follow-up time	**5.65 months**	NA	16.7 months	5.7 months*

Cross-trial comparison. Source: [1]ESMO 2025. [2]ASCO GI 2025. [3]Events & Presentations | Revolution Medicines. [4]ENA 2024. *For both KRAS G12 and RAS mutant.
Abbreviations: 2L+, second line and beyond. ORR, objective response rate. DCR, disease control rate. PFS, progression-free survival. OS, overall survival. NR, not reached. NA, not available.

GFH375 for PDAC: Subgroup Analysis - ORR

- 59 participants had measurable disease at baseline and at least one post-baseline tumor assessment.

	All PDAC (N=59)	2L (N=12)	3L+ (N=47)
ORR [90%CI]	40.68% [29.87%, 52.22%]	58.33% [31.52%, 81.90%]	36.17% [24.52%, 49.18%]
DCR [90%CI]	96.61% [89.71%, 99.39%]	100% [77.91, 100%]	95.74% [87.20%, 99.24]



Data cut-off date: September 27, 2025. All participants received first dose of GFH375 for at least 4 months prior to the cut-off date. Seven participants had no post-treatment tumor assessments due to early dropout: 2 due to AEs not related to GFH375 (1 upper gastrointestinal hemorrhage and 1 respiratory failure); 1 started new anticancer therapy; 4 early discontinued due to participant decision. Figure: "C " represents confirmed responders. Arrows indicate treatment ongoing. The bars for 3 participants are not shown in the waterfall plot: [a]1 had best overall response (BOR) as SD, and the best percentage change from baseline in was 0%. [b]2 had progressive disease as their BOR: one had a target lesion decrease by 0.4% from baseline with non-target lesion progression; the other had target lesions increase by 0.7% from baseline with non-target lesion progression. Abbreviations: CI, confidence interval. DCR, disease control rate. ORR, objective response rate.

Cross-Trial Comparisons of Safety in PDAC

- **The overall safety/tolerability of GFH375 is better than that of daraxonrasib.**

	GFH375 600mg QD[1]	Daraxonrasib 300mg daily[2]	
	2L+ PDAC, N=66	2L+ PDAC, N=83	1L PDAC, N=40
TRAE	100%	96%	95%
G3 or above	**31.8%**	34%	35%
Leading to discontinuation	**3.0%**	0	10%
Leading to reduction	**6.1%**	30%	33%
Leading to interruption	**27.3%**	43%	53%
Mean dose intensity*	**93%**	86%	85%

Source: [1]ESMO 2025. [2]Events & Presentations | Revolution Medicines. *Refers to the average amount of a drug administered per unit of time. It is used to assess treatment adherence and drug exposure and directly influences therapeutic efficacy and the risk of adverse events.
Abbreviations: 1L, first line. 2L+, second line and beyond. TRAE, treatment-related adverse event.

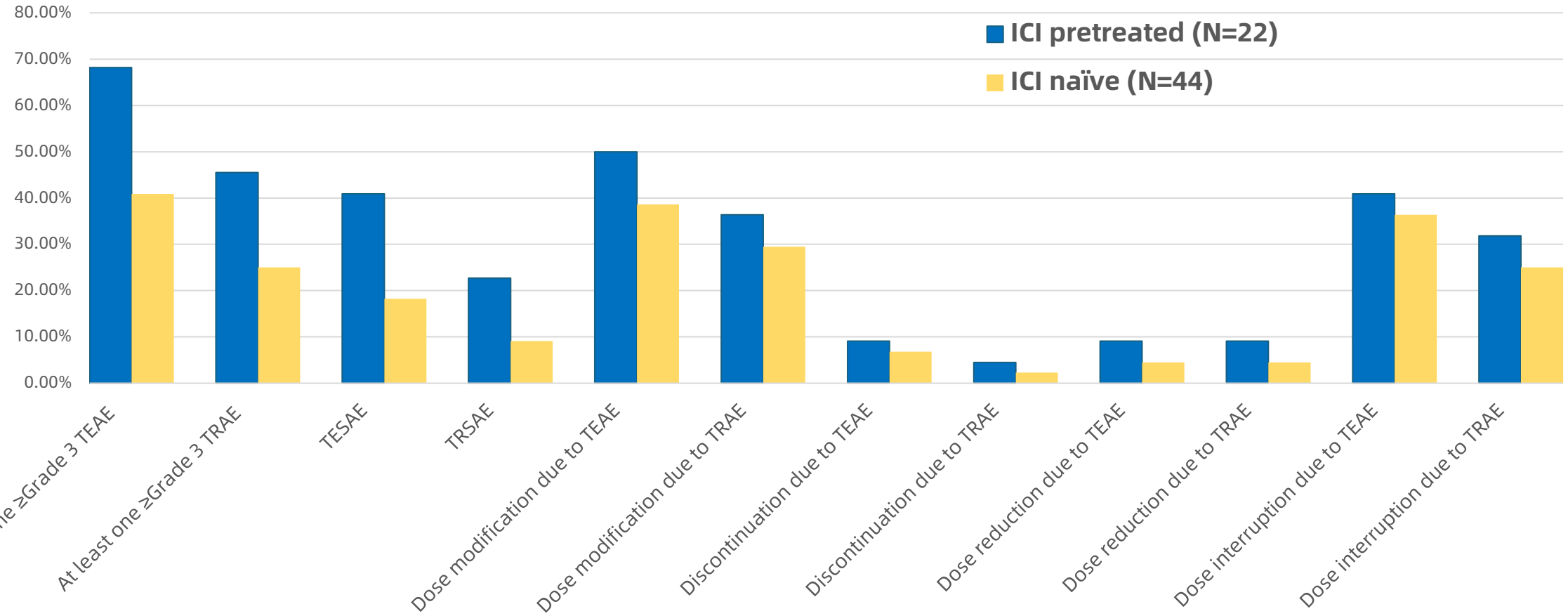
Common TRAEs in PDAC

	GFH375 600mg QD[1] 2L+ PDAC, N=66		Daraxonrasib 300mg daily[2] 2L+ PDAC, N=83		1L PDAC, N=40	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Gastrointestinal disorders						
Diarrhea	56.1%	3.0%	52%	4%	58%	10%
Vomiting	47.0%	1.5%	36%	0	50%	5%
Nausea	47.0%	0	39%	0	50%	3%
Decreased appetite	33.3%	3.0%	NA	NA	15%	0
Hematological toxicities						
Neutrophil count decreased	48.5%	**7.6%**	6%	**4%**	0	**0**
Anemia	42.4%	**7.6%**	8%	**7%**	5%	**3%**
WBC count decreased	36.4%	**1.5%**	NA	**NA**	NA	**NA**
PLT decreased	28.8%	**1.5%**	10%	**4%**	8%	**0**
Liver enzyme abnormalities						
AST increased	24.2%	**1.5%**	10%	**4%**	8%	**0**
ALT increased	22.7%	**0**	7%	**2%**	8%	**0**
Skin toxicities						
Rash	3.0%	0	90%	7%	88%	8%

Source: [1]ESMO 2025. [2]Events & Presentations | Revolution Medicines.
Abbreviations: 1L, first line. 2L+, second line and beyond. WBC, white blood cell. PLT, platelet. AST, aspartate transaminase. ALT, alanine transaminase. NA, not available.

Prior ICI Treatment May Worsen Later-line Safety

- The incidence of grade ≥3 TEAEs/TRAEs, TEAEs/TRAEs leading to treatment interruption, and SAEs/TRSAEs were higher in participants with prior ICI than in the ICI naïve participants (ESMO 2025 data)



Combination Strategies of GFH375

In combination with cetuximab

Regimen A: Solid tumors with KRAS G12D mutation

Phase Ib – Dose escalation

Dose Level Escalation
GFH375 600 mg QD

BOIN design, 3-6 pts per dose level

GFH375 400 mg QD+ Cetuximab, every 2 wks

RP2D

Phase II – Expansion

From late- line to 1st line PDAC and CRC

Regimen A:
Progressed after standard of care or not suitable for SOC
Cohort 1: PDAC 20-30 pts
Cohort 2: mCRC 20-30 pts

In combination with chemo

Regimen B: KRAS G12D-mutated PDAC pts eligible for AG

Phase Ib – Dose escalation

Dose Level Escalation
GFH375 600 mg QD

BOIN design, 3-6 pts per dose level

GFH375 400 mg QD + gemcitabine, d1, 8, 15; nab-paclitaxel, d1, d8, d15, every 4 wks

RP2D

Phase II – Expansion

1st line PDAC

Regimen A:
Progressed after standard of care or not suitable for SOC
Cohort 1: PDAC 20-30 pts
Cohort 2: mCRC 20-30 pts

PART 02

Clinical Development Plan for GFH375, GFS202A and GFH276

Clinical Development Plan for GFH375 (KRAS G12D Inhibitor)

	2nd line and above	1st line	Perioperative
PDAC	Phase I/II mono FIH ⇩ Phase III **Monotherapy** vs chemotherapy	Phase II combo study + cetuximab or + AG ⇩ Phase III study vs 1st line chemotherapy	• Neo/adjuvant Local advanced • Adjuvant for resectable
NSCLC	Phase I/II FIH ⇩ Single-arm study for conditional approval ⇩ Confirmatory study Phase III: **monotherapy** vs docetaxel	⇨ Phase III: **Combination** vs Chemo+/-PD-1 or **Mono** vs Chem+/-PD-1 • Cetuximab • Chemotherapy • PD-1/PD-L1?	**PD-L1 expression** • TPS 1-49% • TPS>=50%?
CRC	Phase II (single-arm) in 3rd line: • Cetuximab+GFH375 or chemo+GFH375 Phase III in 2nd line: • Cetuximab+GFH375 vs chemo		
BTC	Phase II single arm for conditional approval	⇨ Phase III: SOC+GFH375 vs SOC	

Other types of tumors

Clinical Development Plan for GFS202A (GDF15/IL-6 Bispecific Antibody)

Phase II ⇨ **Phase III**

Oncology

- Cancer associated cachexia ⇨ Phase IIb/III combined with chemo in mPDAC; Phase IIb/III combined SOC in other tumor types ⇨ Primary Endpoints: Weight gain; Anorexia 5-items score
- Immunomodulatory for PD-1 resistance ⇨ Combing withPD-1/PD-L1: Primary resistance; Acquired resistance ⇨ Endpoints: Anti-cancer Efficacy
- Reducing immune-related toxicities

Non-oncology

- Heart failure
- COPD associated cachexia
- Autoimmune disease
- Anorexia nervosa

Cachexia in PC is likely multifactorial. GDF15 produces nausea, vomiting, anorexia, and cachexia.[44] Ponsegromab, a monoclonal antibody that targets circulating GDF15, promoted dose-dependent weight gain in a recent Phase II trial of advanced cancer patients with cachexia, including patients with PC.[7] Nearly all patients in our study had sufficient GDF15 (>1,500 pg/mL) to qualify for the ponsegromab trial. Unlike cisplatin-based chemotherapy regimens, Gem/Nab and Gem/Nab/Toc did not change GDF15 levels, consistent with preclinical data showing low/no cachexia-inducing effects of Gem/Nab.[45] Furthermore, these results indicate that GDF15 is either upstream or independent of IL-6. Thus, combination therapy against both targets might be more effective than inhibition of one or the other. Further studies

J Clin Oncol . 2025 Jun 20;43(18):2107-2118

Clinical Development Plan with Timeline for GFH375 and GFS202A

劲方医药 GENFLEET

● Proof of concept ★ NDA submission

Clinical Development Plan of GFH276 (Pan RAS Inhibitor)

	2nd line and above	1st line	Perioperative
PDAC	Phase I/II mono FIH ⇩ Phase III Monotherapy vs chemotherapy • KRAS mutation • KRAS mutation after G12D resistance	Phase II combo study • Cetuximab • AG regimen ⇩ Phase III study vs 1st line chemotherapy • Cetuximab preferred	• Neo/adjuvant Local advanced • Adjuvant for resectable
CRC	Phase II (single-arm) in 3rd line: • **Cetuximab**+GFH276 Phase III in 2nd line: • **Cetuximab**+/-chemo+GFH276 vs chemo		Adjuvant for resectable • S1+GFH276
NSCLC	Phase I/II FIH ⇩ Single-arm study for conditional approval in **G12C or G12D** resistance ⇩ Confirmatory study Phase III: **monotherapy** vs docetaxel	⇨ Phase III: **Combination** vs Chemo+/-PD-1 or **Mono** vs Chem+/-PD-1 • **Cetuximab** • Chemotherapy • PD-1/PD-L1? **PD-L1 expression** • TPS 1-49% • TPS>=50%?	
BTC	Phase II single arm for conditional approval	⇨ Phase III: SOC+GFH276 vs SOC	

Other types of tumors

- HRAS,NRAS mutant cancers: Bladder cancer, thyroid cancer, melanoma
- TKI resistant cancers
- Non-oncology

规划总结及展望

1. GFH375成药性明确
   预计未来3年内提交2个NDA（ PDAC、NSCLC）， 后续适应症继续开展

2. GFS202A初步数据令人鼓舞
   适应症广泛、市场前景巨大

3. GFH276早期数据有待后续临床进展及观察
   临床药代初步数据接近临床前研究；临床思路与6236有差异化

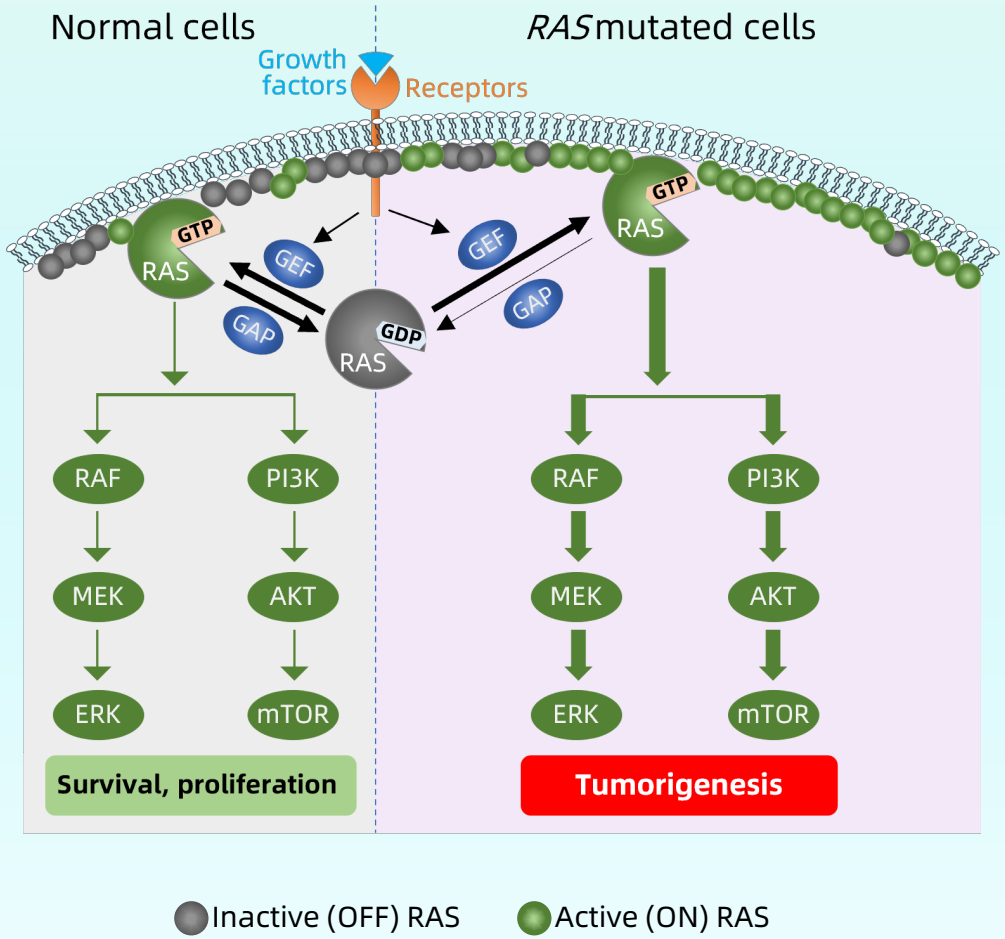

風飛浪勁·据義履方

劲方医药临床前开发规划及展望

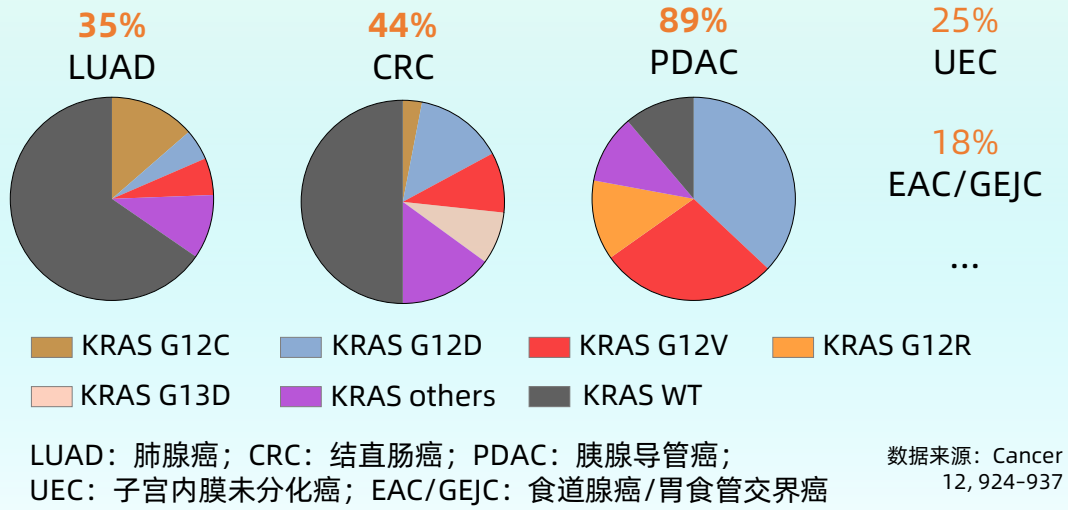
周福生博士
劲方医药药物研发部副总裁

狙击“不可成药靶点”：全球癌症患者约30%出现RAS突变

RAS突变促进肿瘤发生的机制



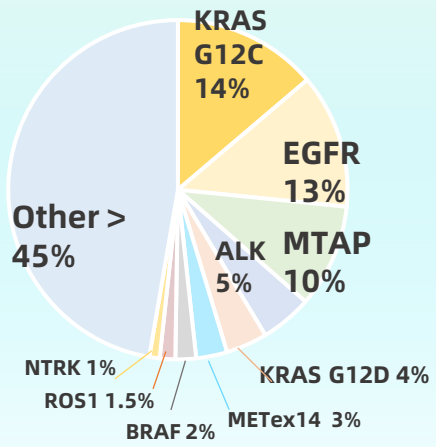
RAS突变在胰腺癌、肺癌、结直肠癌等瘤种高发

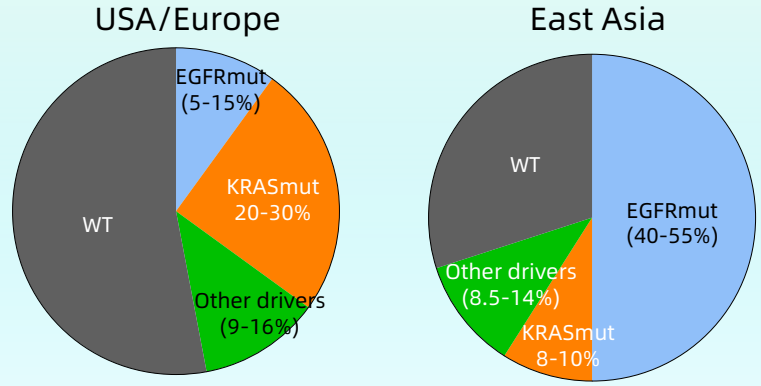


LUAD：肺腺癌；CRC：结直肠癌；PDAC：胰腺导管癌；
UEC：子宫内膜未分化癌；EAC/GEJC：食道腺癌/胃食管交界癌

数据来源：Cancer Discov 12, 924-937 (2022)

全球转移性NSCLC患者基因突变统计





数据来源：BMS, Transl Lung Cancer Res 4 156-164 (2015)

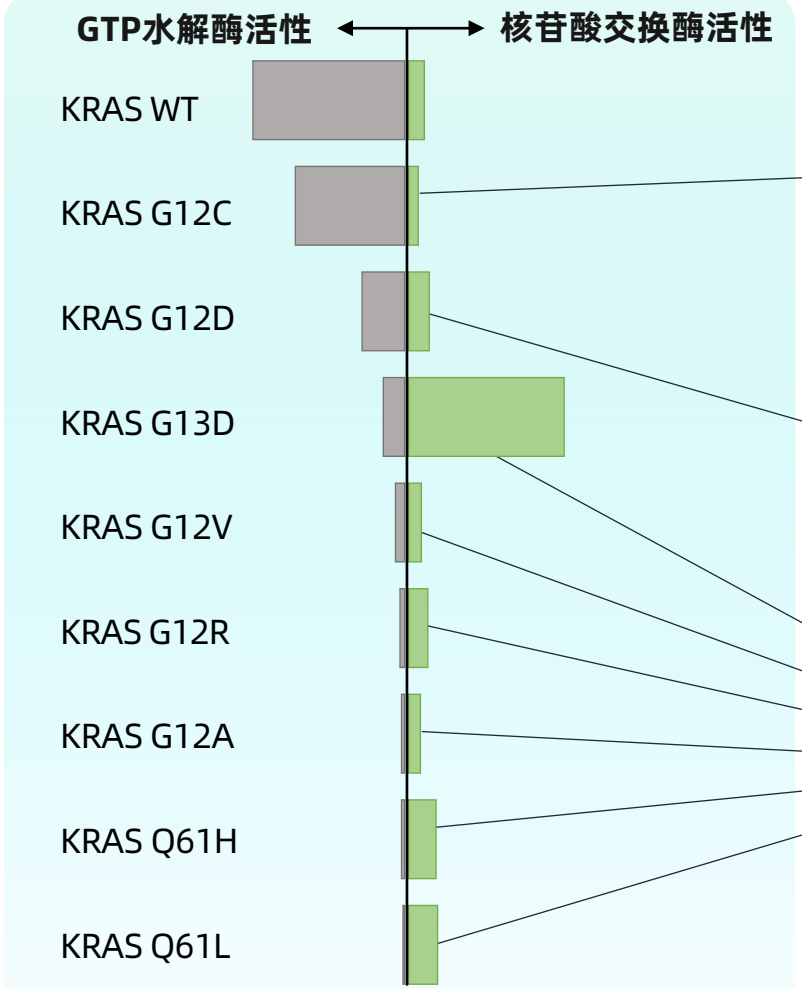
直击多层次未满足临床需求，塑造全球最全面RAS疗法矩阵企业之一

现状	全球5款**KRAS G12C**抑制剂获批	**特定共突变人群**对现有产品**反应率较低**	现有产品**单药**均治疗**后线非小**	多数药物针对**RAS突变**患者开发
劲方策略	**更多突变型**	**更多共突变人群**	**各线、多种RAS突变癌症**	**RAS依赖（如EGFR突变）**
	多种选择性、泛RAS抑制剂覆盖几乎所有突变型	开发新分子类型或新靶点靶向药	新型单药和联用疗法治疗后线及一线患者	开发功能型抗体+协同性靶向药载荷的新型偶联药物

产品	开发阶段					RASmut NSCLC, CRC, PDAC				EGFRmut NSCLC	
（代码及靶点）	临床前	I期	II期	III期	上市	$KRAS^{G12C}$	$KRAS^{G12D}$	$KRAS^{G12V}$	RAS^{other}	TKI naive	TKI resist
GFH925（KRAS G12Ci） 单药、联合疗法	单药2L+ 非小					✓					
	+cetux 1L 非小					✓					
GFH375（KRAS G12Di） 单药、联合疗法	单药2L+ 胰腺癌						✓				
	+化疗 1L PDAC						✓				
	+cetux 2L+ PDAC、CRC						✓				
GFH276 (泛RAS抑制剂)	实体瘤					✓	✓	✓	✓		
GFS784 (EGFR-Pan RAS)						✓	✓	✓	✓	✓	✓
GFH603（小分子激活剂）						✓	✓	✓	✓	✓	✓

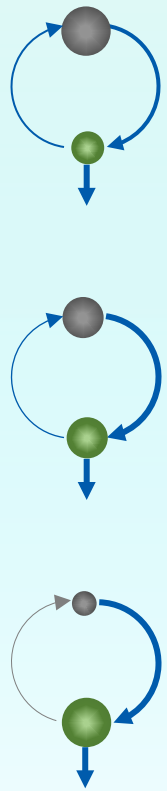
基于KRAS生物学机理的差异化药物设计与开发

KRAS突变体活性差异



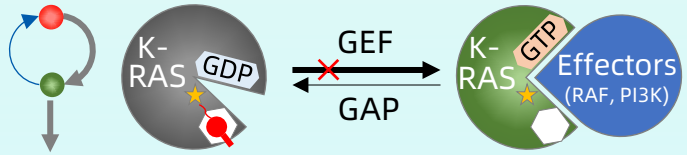
数据来源：Mol Cancer Res 13, 1325-35 (2015)

KRAS ON/OFF比例

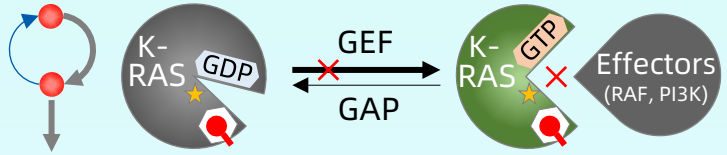


靶向抑制策略

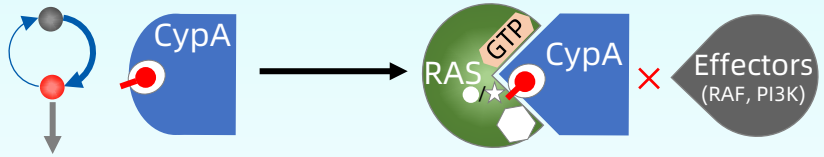
GFH925: SIIP类KRAS G12C (OFF)共价抑制剂



GFH375: SIIP类KRAS G12D (ON&OFF)双机制抑制剂



GFH276: 分子胶类泛RAS (ON)抑制剂

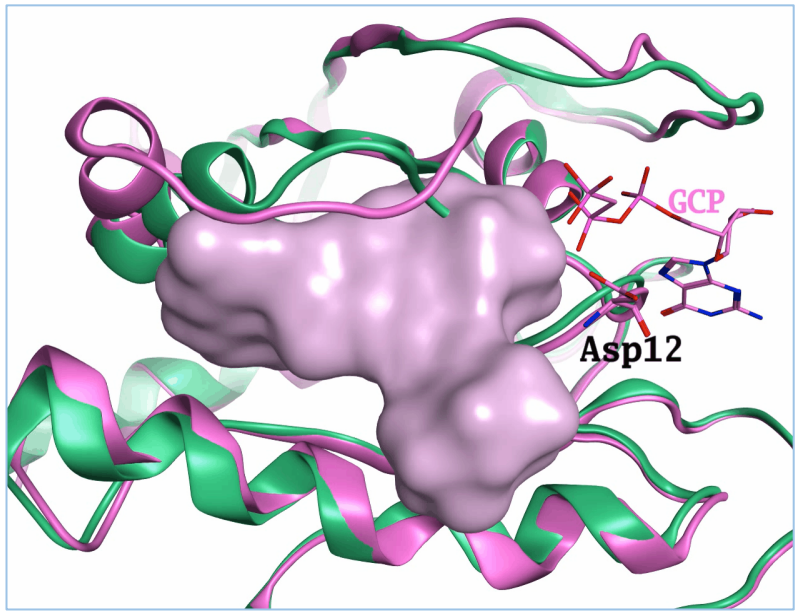


Inactive (OFF) RAS　Active (ON) RAS　Occupied RAS　Inhibitor

GFH375：全球领先的Switch II Pocket KRAS G12D抑制剂
开发进度位于口服KRAS G12D抑制剂第一梯队

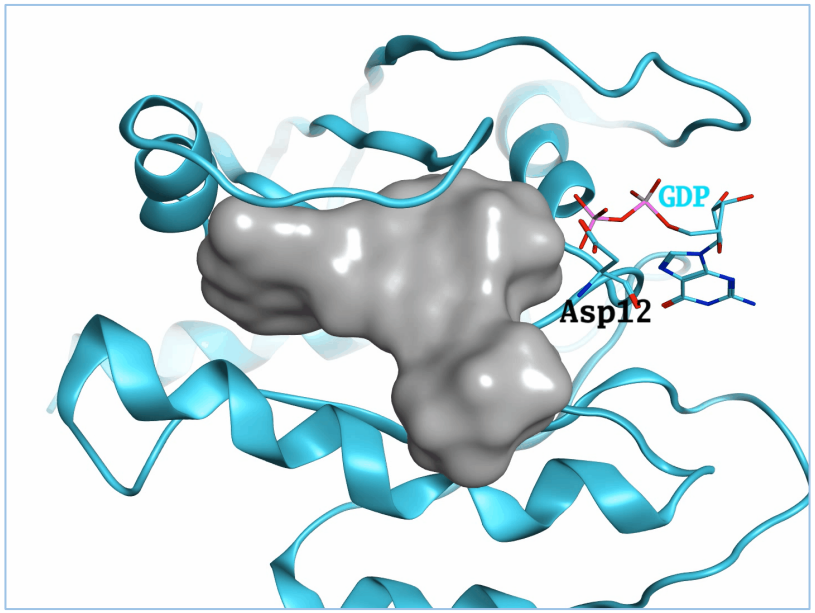
劲方医药 GENFLEET

解析共晶结构，指导分子设计



Active KRAS^{G12D}, 劲方化合物1, GCP (分辨率1.15Å)

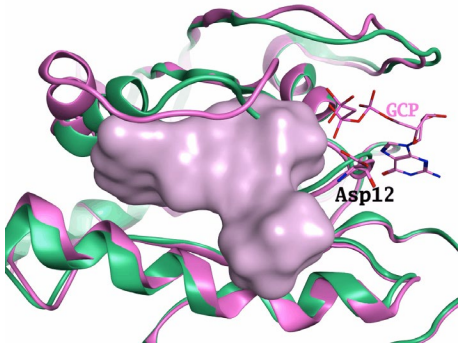
Active KRAS^{G12D}, APO , GCP (4DSN)



Inactive KRAS^{G12D}, 劲方化合物2, GDP (分辨率1.78Å)

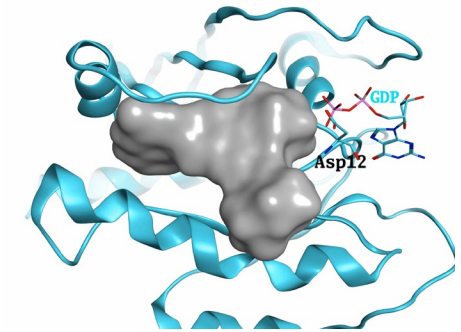
GFH375：ON/OFF双重抑制及优效抑瘤活性显示BIC潜力+广阔联用前景

解析共晶结构，指导分子设计



Active KRAS^{G12D}, 劲方化合物1, GCP (分辨率1.15Å)

Active KRAS^{G12D}, APO , GCP (4DSN)



Inactive KRAS^{G12D}, 劲方化合物2, GDP
(分辨率1.78Å)

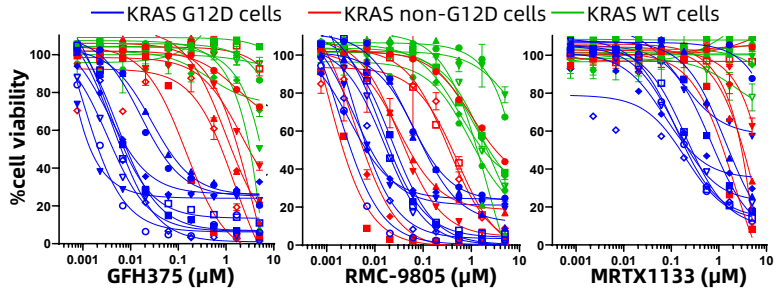
➢ ON/OFF双重抑制

GFH375对靶蛋白亲和力			
KRAS^{G12D} state	SPR K_D	KRAS^{G12D}/RAF1 binding	KRAS^{G12D} nucleotide exchange
'ON' targeting	18 pM	2 nM	/
'OFF' targeting	12 pM	/	6 nM

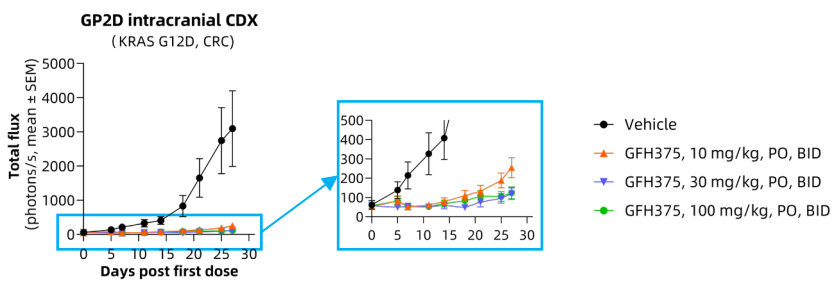
➢ 高稳定性及生物利用度

Category	GFH375	MRTX1133
Stability (pH=1.2)	Stable	Unstable
Bioavailability (%F) (Ms/R/D)	41/19/23	1.0/NA/NA

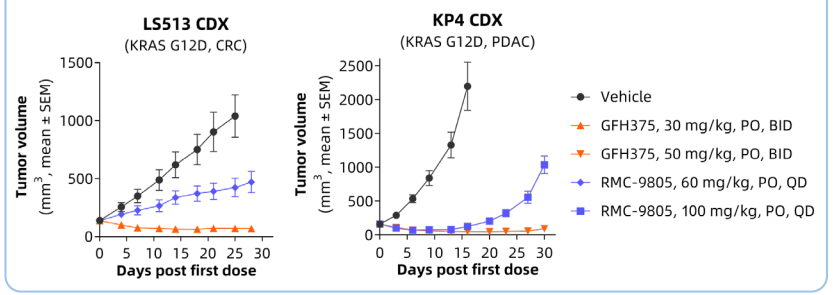
➢ 高选择性及抑瘤活性



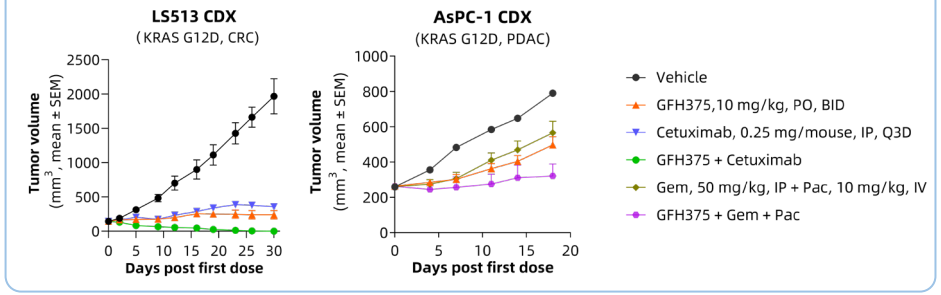
➢ 脑通透性



单药药效同类最佳

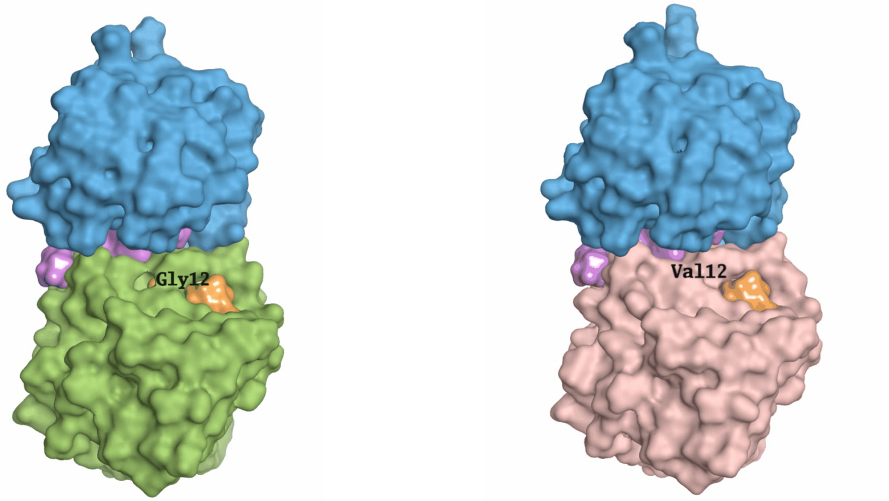


联用前景广阔



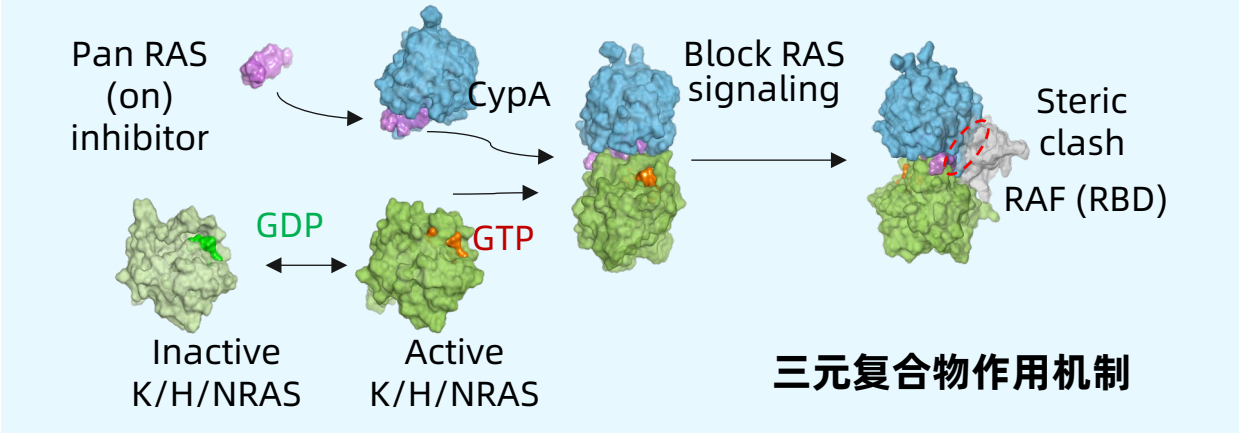
数据来源：AACR2024, EORTC-NCI-AACR2025

分子胶泛RAS（ON）抑制剂——GFH276的独特结构及作用机制



$KRAS^{G12V}$-CYPA · GF4962 · GCP (分辨率1.85 Å)

$KRAS^{WT}$-CYPA · GF4962 · GCP (分辨率1.95 Å)



三元复合物作用机制

独有大环结构及“变色龙”效应

- 基于三元复合物共晶结构，获得独特大环母核
- 强化大环“变色龙”效应，展现卓越PK性质
- 新颖母核结构，专利期可到2044年

CypA依赖的泛RAS(ON)抑制剂

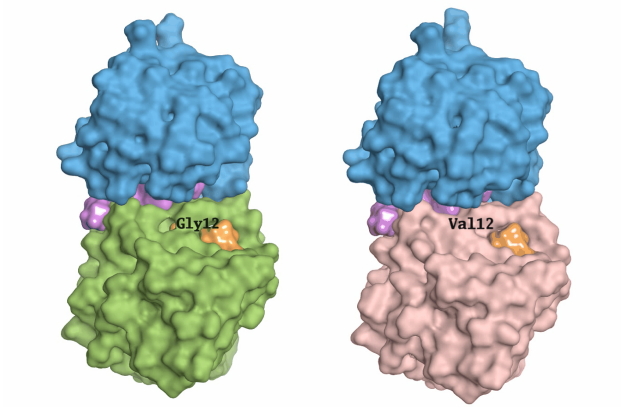
GFH276对RAS/RAF1结合抑制IC_{50} (nM)						
Assay	$KRAS^{G12C}$	$KRAS^{G12D}$	$KRAS^{G12V}$	$KRAS^{WT}$	$HRAS^{WT}$	$NRAS^{WT}$
CypA+	71	304	38	210	144	82
CypA-	>10000	>10000	>10000	>10000	>10000	>10000

低清除率、高生物利用度

PK in Ms/R/D		
PK parameter	GFH276	RMC-6236
CL (mL/min/kg)	5.60/0.70/2.95	54/19/16
Bioavailability (%)	53/113/20	22/7.8/9.8

数据来源：AACR2025

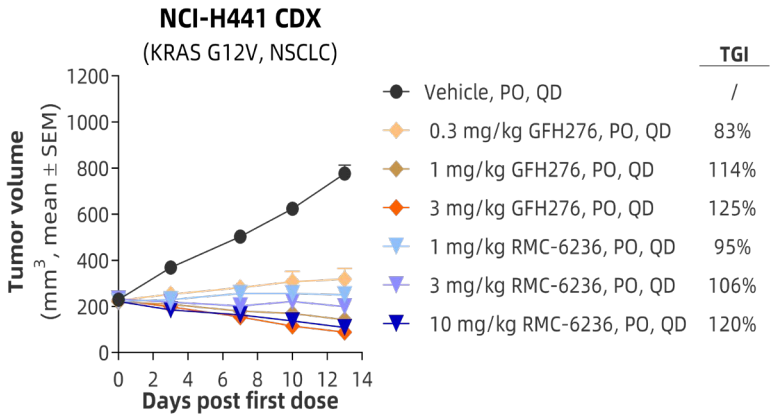
GFH276：靶向不同亚型活化RAS蛋白，分子性能优越并抵抗多重耐药

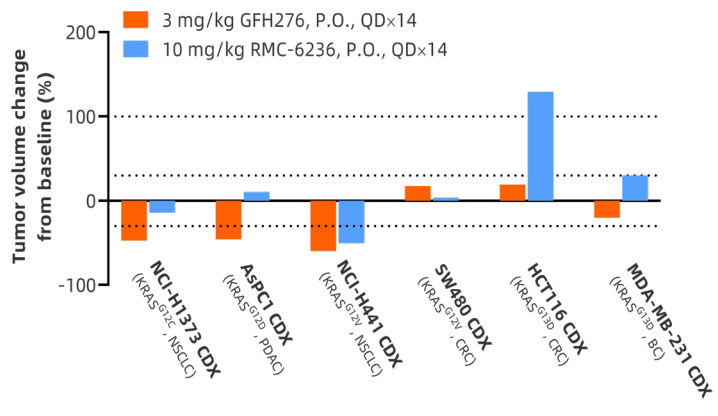


$KRAS^{G12V}$-CYPA · GF4962 · GCP (分辨率1.85 Å)

$KRAS^{WT}$-CYPA · GF4962 · GCP (分辨率1.95 Å)

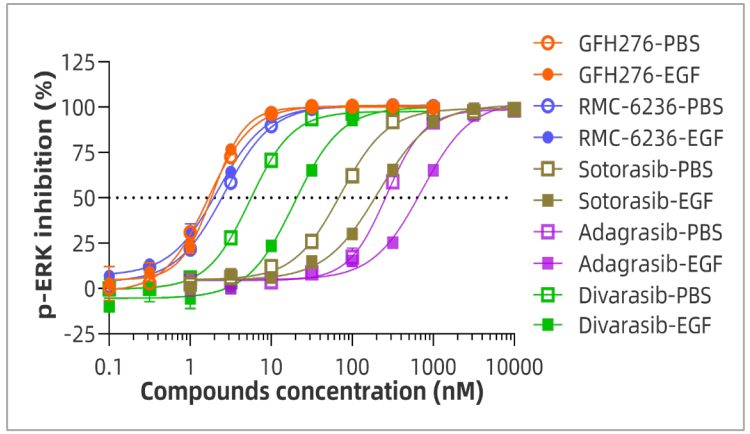
低起效剂量，深度抑制肿瘤生长





多种机理诱导的KRAS抑制剂耐药细胞系中：均保持强效活性、显示多重抗耐药潜力

不易受适应性耐药影响



克服KRAS G12C抑制剂获得性耐药

GFH276对Ba/F3细胞抑制IC_{50} (nM)

Ba/F3 cell line	GFH276	RMC-6236	Adagrasib
KRAS G12C	0.38	0.25	7.0
KRAS G12C&R68S	4.06	1.67	306
KRAS G12C&H95Q	0.27	0.21	549
KRAS G12C&Y96C	0.33	0.24	757

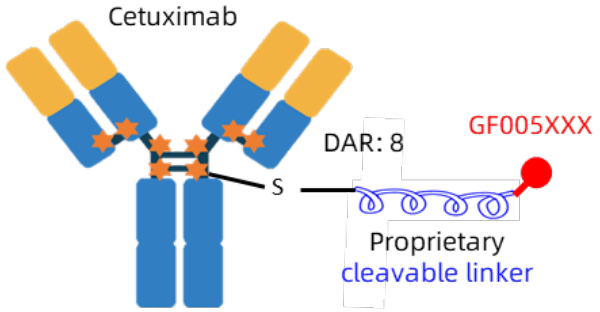
GFH276对H358细胞抑制IC_{50} (nM)

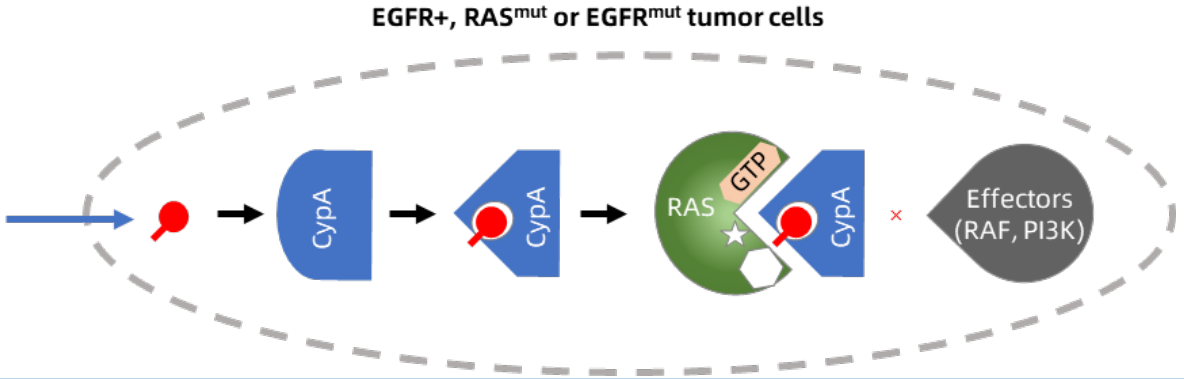
Compound	GFP	$EGFR^{A289V}$		FGFR2-TACC2		FGFR3-TACC3	
GFH276	0.14	0.81	*5.9x*	0.82	*6.0x*	2.8	*20x*
RMC-6236	0.20	0.74	*3.7x*	0.74	*3.7x*	3.7	*18x*
Sotorasib	1.1	26	*24x*	95	*86x*	4310	*3918x*
Adagrasib	1.8	21	*12x*	52	*29x*	679	*378x*
Divarasib	0.071	1.3	*18x*	2.7	*38x*	226	*3160x*

数据来源：AACR2025

GFS784：全球首个泛RAS抑制剂载荷ADC，结合功能性EGFR抗体同时靶向RAS突变及EGFR突变、耐药肿瘤

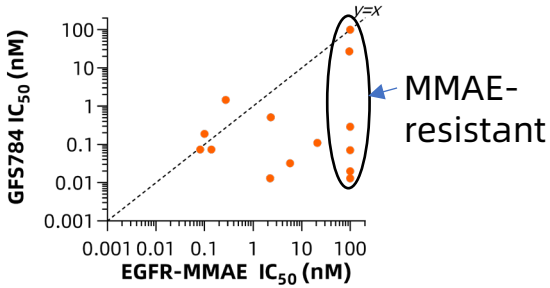
基于FAScon平台：
全球首创功能性抗体
+协同性靶向药载荷的
偶联药物平台
FUNCTIONAL Antibody &
SYNERGISTIC conjugate

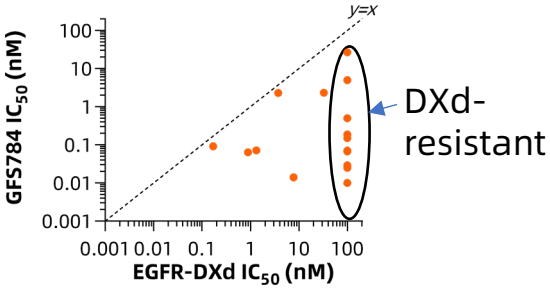




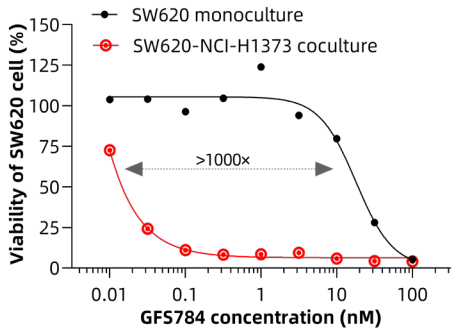
体外活性

皮摩尔级活性，对细胞毒载荷耐药细胞系仍可保持高效抑制





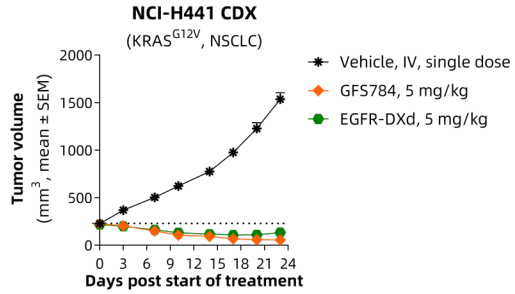
强效旁观者杀伤效应

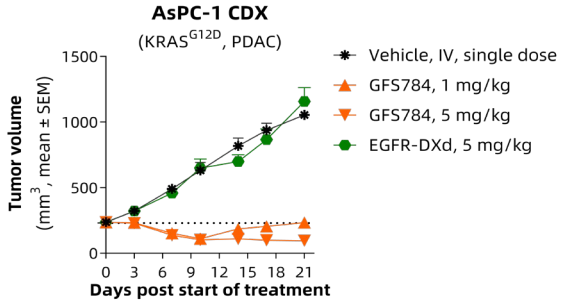


Cell line	EGFR copy/cell
SW620	17
NCI-H1373	116846

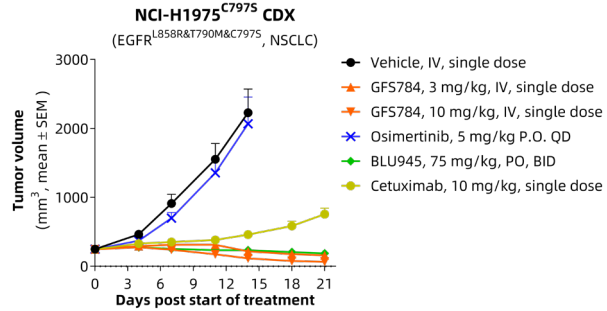
体内药效

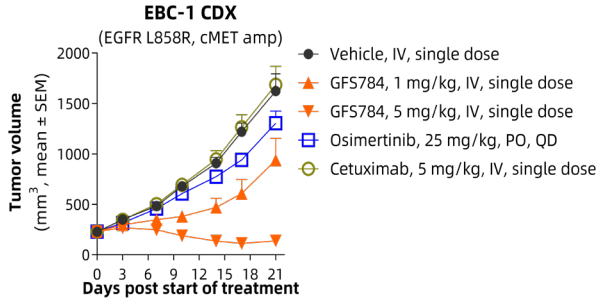
抑制多种KRAS突变亚型





高效抑制 TKI 耐药肿瘤生长





立足成药性验证的新药开发闭环，构建下一代大、小分子开发平台

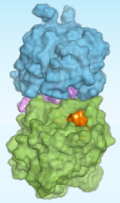
劲方医药 GENFLEET

新型口服小分子
如环肽、双功能小分子

传统小分子

口服TPD

大环分子胶

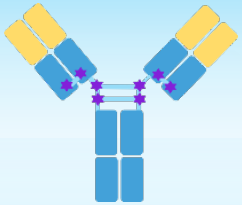


多抗

双抗

多元载荷ADC

RAS-ADC



依托多分子类型的先进平台，以协同性靶向疗法矩阵瞄准大适应症市场

瞄准非肿瘤领域的炎症性疾病——
GFH946：口服STAT6降解剂，解决二型炎症临床巨大的未满足需求

Kymera本周股价因KT-621的Ib期数据披露上涨超30%

传统固醇类药物、JAK抑制剂安全风险及副反应较大

乌帕替尼 JAK1抑制剂：FDA 2021黑框警告
风险、包括静脉血栓、恶性肿瘤、心梗等

口服糖皮质激素类药物可导致代谢紊乱、骨质疏松、低血钾等

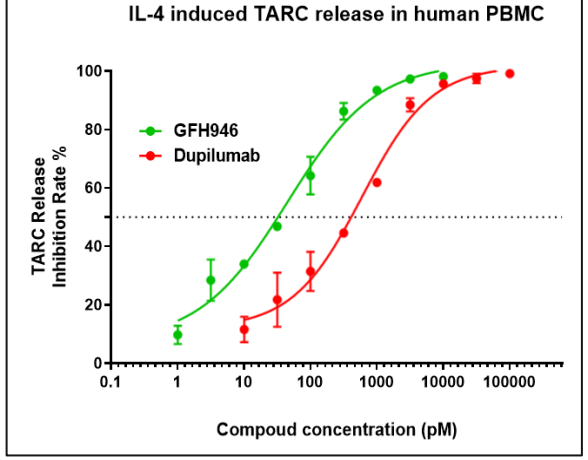
临床阶段STAT6降解剂KT-621在AD病人展现卓越疗效

Metric	KT-621 Overall Day 29 (4 weeks, n=22)	Dupilumab 300 mg Q2W D28 Ph3 (n=457)
EASI-50	76%	57%
EASI-75	29%	28%
vIGA-AD 0 and 1	19%	12%
Mean % Change in SCORAD - Itch	-44%	NR
POEM Responders	73% at Week 4	69% at Week 16
DLQI Responders	61% at Week 4	69% at Week 16

GFH946：更优的体外活性
DDI和心脏毒性风险低，可口服给药

	KT-621*	GFH946
STAT6 degradation (PBMC) DC_{50} (pM)	13	6
IL-4 induced TARC (PBMC) IC_{50} (pM)	62	21-32
CYP IC_{50} (μM)	NA	>10 (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4)
hERG inhibition	NA	Negative
Oral Bioavailability (%F) (Ms/R)	NA	14/43

GFH946在PBMC中呈现pmol级TARC诱导抑制



*参考Kymera公司报道及数据


風飛浪勁·据義履方

劲方医药董事长吕强博士致辞

今天观众最关心的话题——

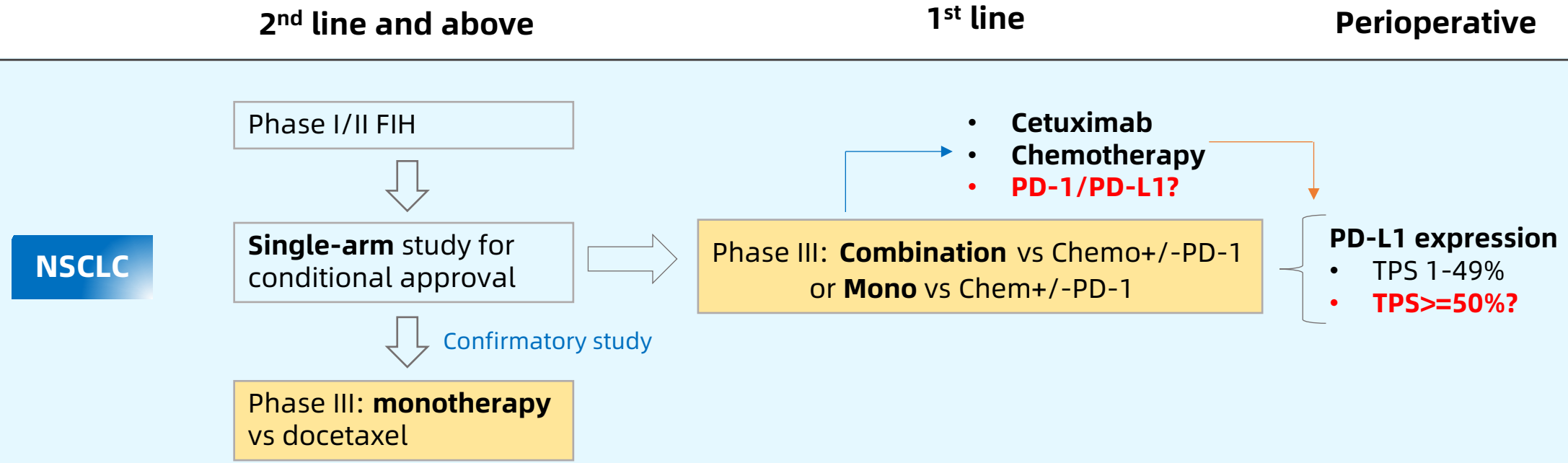
选项	小计	比例
GFH375 胰腺癌临床开发	188	83.19%
2026年临床开发计划	169	74.78%
GFH375/VS-7375 海外临床进展分享	156	69.03%
GFH375 非小细胞肺癌临床开发	154	68.14%
2026年临床前项目开发策略	132	58.41%
GFS202A 临床开发进展	122	53.98%
本题有效填写人次	226	(截至12月9日18：00)

GFH375: PDAC Trials are More Straightforward

	2nd line and above	1st line	Perioperative
PDAC	Phase I/II mono FIH ↓ Phase III **Monotherapy** vs chemotherapy	Phase II combo study + **cetuximab** or + **AG** ↓ Phase III study vs 1st line chemotherapy	• Neo/adjuvant Local advanced • Adjuvant for resectable

- for 2L+, “train has left the station”
- for 1L combo, Cetuximab synergy being proven clinically, while Chemo being an approved therapy - as a safe bet

GFH375: NSCLC Trials are Trickier



- for 2L+, monotherapy/single-arm pivotal is on track
- for 1L, good news: monotherapy has a chance, at least for low/mid-TPS patients

  bad news: I/O be a friend... or foe?

Leading to the First Two Pivotal Trials for GFH375: Well Choreographed Timeline with Powerful Execution

Start Point of Clinical Dev't

单药IND获批
2024.6.19

(D+7.5 Months)

单药II期FPI
2025.2.26

2024 | 2025-2026 | 2027 | 2028 | 2029

FDA FTD获批
2025.7

联合疗法启动（两项方案，包括一项1L PDAC方案）
2025.10

单药 2L及以上

PDAC

(D+16.5M)
单药关键性研究启动（随机对照）
主要终点：PFS/OS dual
2025.11

(D+36M)
优先审评 + NDA提交
2027.6（E）

(D+45M)
完全获批上市
2028.3（E）

进入医保
2029

NSCLC

关键性研究启动（单臂试验）
主要终点：ORR
2026 Q1

NDA提交
2027.9（E）

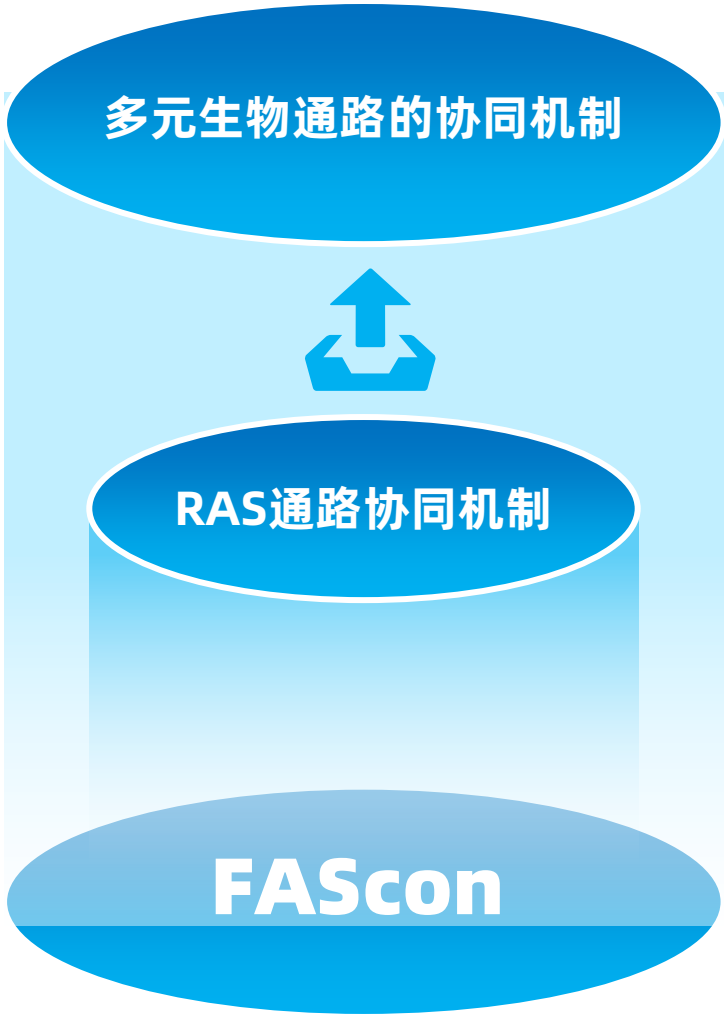
有条件获批上市
2028.3（E）

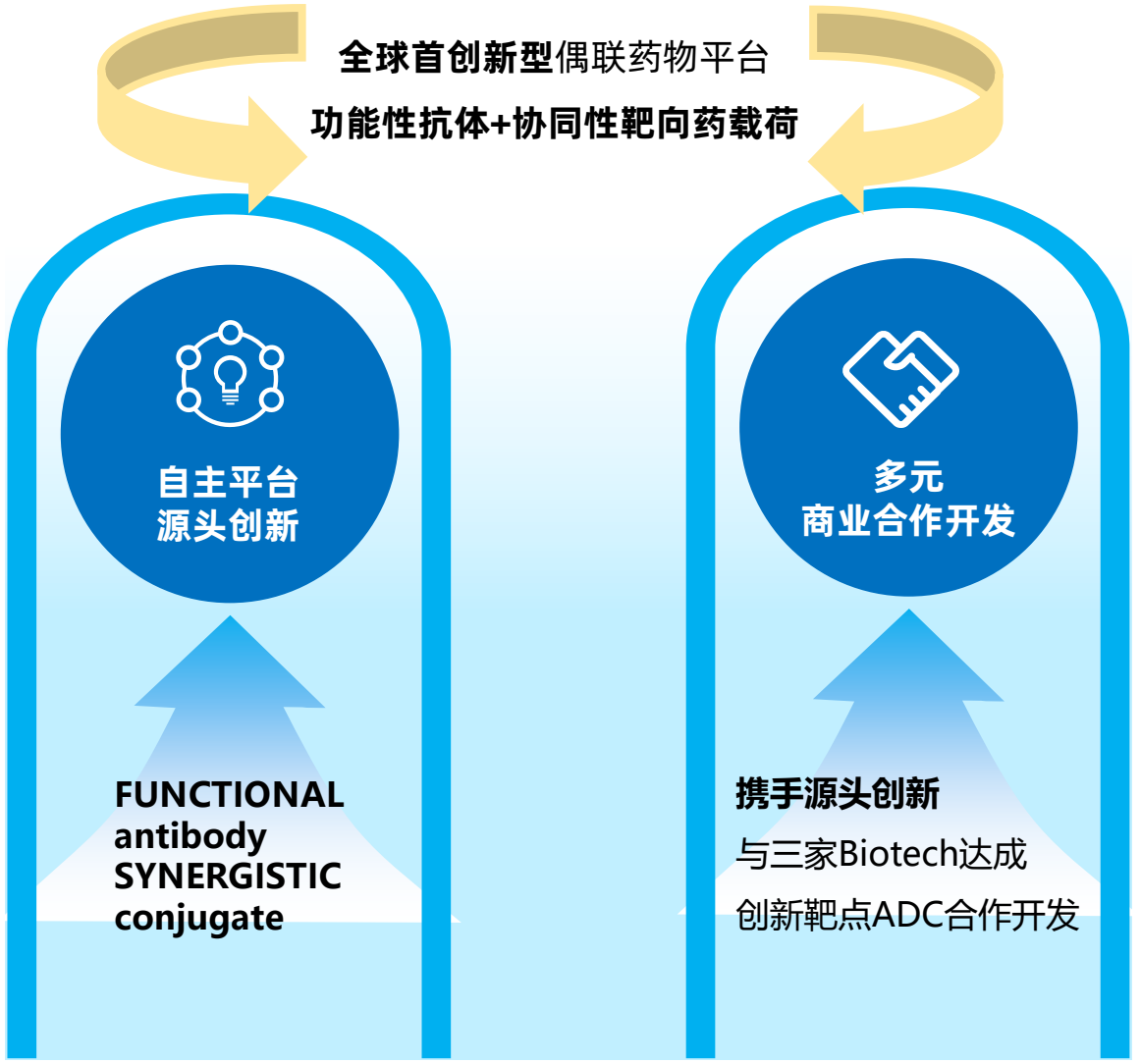
随机对照确证性研究

劲方管线一年内预期开发进展及数据披露

		2025 Q3-Q4	2026 Q1	2026 Q2	2026 Q3
GFH375	2L+ PDAC	ESMO报告（PFS）✓ 关键性研究启动✓			
	2L+ NSCLC	WCLC报告（最新ORR）✓	关键性研究启动		WCLC报告（详细数据）
	2L+ 其他适应症			ASCO摘要/壁报（胆管癌及其他适应症）	
	1L PDAC（combo）	Ib/II期首例入组✓			ESMO报告（疗效数据）
GFS202A	肿瘤恶病质	剂量爬坡结束		ASCO报告（安全性数据）	中报（初步有效性）
GFH276	实体瘤	I期首例入组✓		I期研究结束	ESMO报告（I期研究数据）
GFS784	实体瘤		完成I期首例入组		
GFH312	PBC		完成II期首例入组		
临床前进展		3款临床前候选化合物✓		2款临床前候选化合物	2款临床前候选化合物 中报（1项IND）

劲方技术平台开发策略：技术方面迅速拓展，推进方面双轮驱动





劲方管线布局策略：
平台已经临床POC验证、开发进度有把握领先、同时考虑商业化协同性

劲方医药 GENFLEET

全球最全面RAS疗法矩阵企业之一

- KRAS G12C
- KRAS G12D
- Pan RAS
- FAScon (RAS-ADC)

全球最首款恶病质双抗疗法

- GDF15/IL-6

协同性多元靶向疗法，面向大适应症的广阔市场

大瘤种	胰腺癌	非小细胞肺癌	结直肠癌
恶病质	肿瘤	心衰	慢阻肺

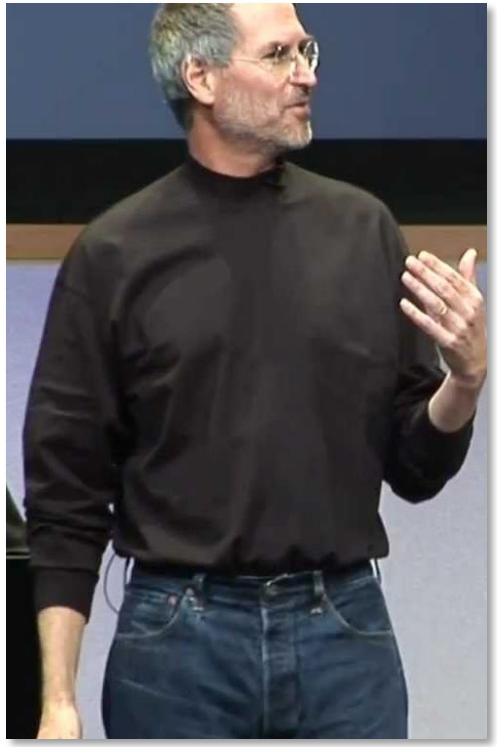
CMC：完整生产质控 跑通IND-NDA

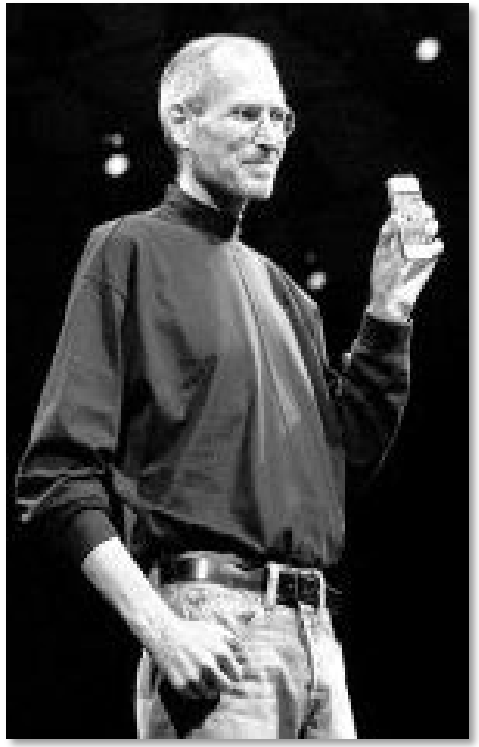
劲方一体化新药开发体系

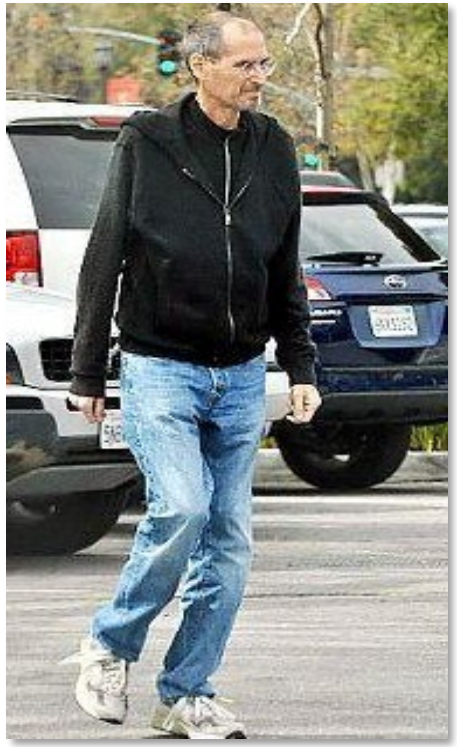
立项 → 临床前候选化合物（PCC） → 临床试验获批（IND） → 早期临床开发 → 注册性临床研究 → NDA与获批上市 → 商业化

瞄准非肿瘤领域的炎症性疾病——恶病质在胰腺癌等瘤种患者中高发

恶病质前期 | 恶病质期 | 难治期/顽固性恶病质期







1. 中国临床肿瘤学会 肿瘤厌食-恶病质综合征诊疗指南 2025 2.肿瘤恶液质临床诊断与治疗指南（2020版）

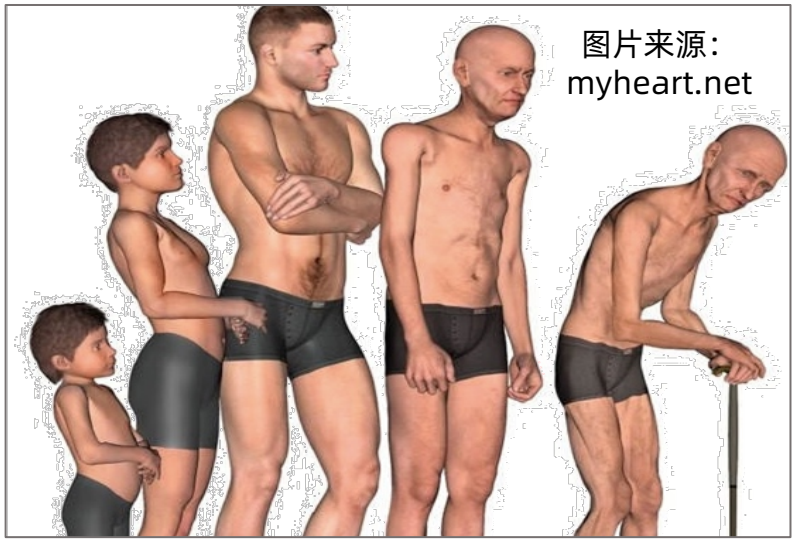
劲方在GDF15治疗肿瘤恶病质赛道的差异化布局

- 目前临床阶段在研治疗肿瘤恶病质的药物均为单靶向GDF15或GFRAL。
- **GFS202A是全球首个GDF15/IL-6双抗产品及恶病质双靶向疗法（First-in-class）。**

研发公司	化合物	靶点	开发阶段
Pfizer	Ponsegromab	GDF15mAb	IIb/III期
CATALYM	Visugromab	GDF15mAb	II/III期
AVEO ONCOLOGY	AV-380	GDF15mAb	Ib期
Kexing Biopharm 科兴制药	GB18	GDF15纳米抗体	I期
NGMBio	NGM120	GFRAL	II期
JMT-BIO	JMT-203	GFRAL	I/II期
劲方医药 GENFLEET	GFS202A	GDF15mAb+IL-6mAb	I期

1. https://www.clinicaltrials.gov/ 2.药物临床试验登记与信息公示平台

瞄准恶病质之外的大适应症领域——e.g. 老年性肌少症（sarcopenia）



全球高发病率	
60岁以上老年人	10-16%
不可切除食管癌患者	66%
糖尿病患者	18%
主要症状：肌肉组织减少、功能衰退； 与多种老年综合征并发症关联	

相关病因

- 生理退行性改变
- 生活习惯及作息不规律等
- **肿瘤、慢性肾病、慢阻肺、糖尿病等慢性病相关的炎症因子影响**

治疗手段缺乏

- 机制研究及临床试验挑战显著
- 营养补充效果有限
- 专业康复治疗可及性低

1. Epidemiology of sarcopenia: Prevalence, risk factors, and consequences, https://pubmed.ncbi.nlm.nih.gov/36907247/
2. Emerging Therapeutic Strategies in Sarcopenia: An Updated Review on Pathogenesis and Treatment Advances, Int J Mol Sci. 2024 Apr 12;25(8):4300. doi: 10.3390/ijms25084300.

劲方医药：上升期biotech，充满期待的后续发展，强劲的国外对标

2017

公司成立

劲方医药 GENFLEET

2024

首个新药上市

中国**第一**、全球**第三**个

KRAS G12C抑制剂获批

2028（E）

第二个新药上市

GFH375
KRAS G12D抑制剂

位于口服G12Di**第一**梯队

2030（E）

EBITA转正

氟泽雷塞联合疗法
国际**一线**疗法获批

GFH375
国内**数个**适应症获批

REVOLUTION MEDICINES **>$150亿 市值**
（2025/11/28数据）

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