BeiGene

POST-ESMO —晚期胃癌治究进展与思考

概览（这一页在最终幻灯中不会呈现）

HER-2 + GC： An Endless Story

引子：DESTINY-Breast03

ADC：DESTINY-Gastric01 & RC-48 ADC

BsAB：ZWI-ZW25-201

IO+Anti-HER-2：INTEGA & KEYNOTE – 811

新的方向：1线ADC，IO + BsAB/ADC

HER-2 – GC: End of The Beginning

IO + Chemo：

- ORIENT-16数据解读
- 一线研究结果思辨（KN-062, CM-649，RN-205)
- 有所期待: RATIONALE-305, KEYNOTE-859

IO mono/IO + IO

- KN-062, CheckMate – 649

新的探索： DisTinGuish, +TKI, CRT……

DESTINY-Breast03——ESMO头号LBA，引爆抗HER-2未来

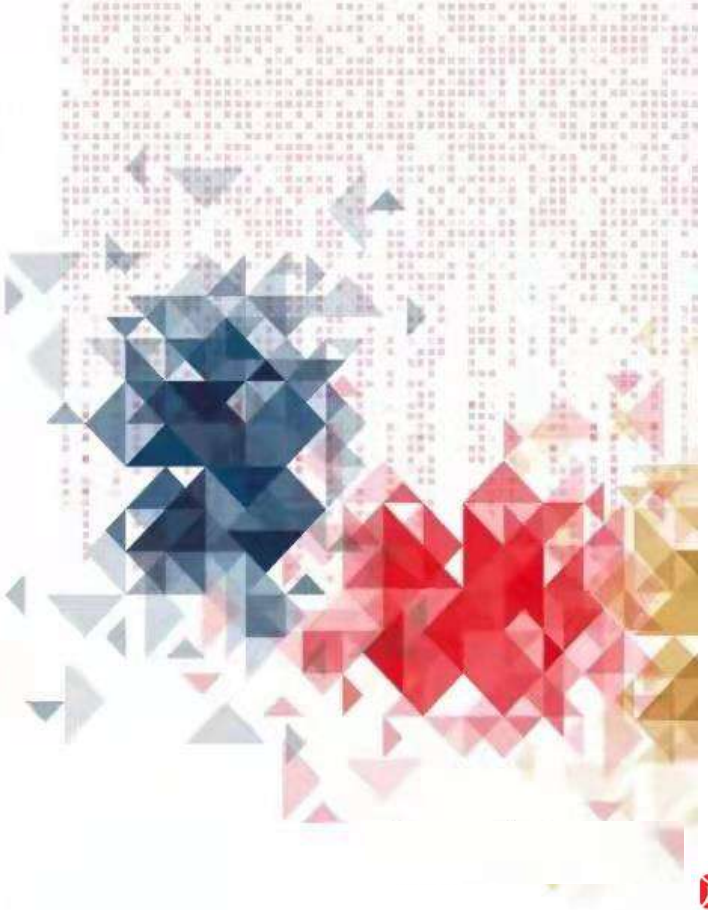
2021 ESMO congress

Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Results of the Randomized, Phase 3 Study DESTINY-Breast03

Javier Cortés, MD[a], Sung-Bae Kim, Wei-Pang Chung, Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung, Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee, Yali Liu, Jillian Cathcart, Emarjola Bako, Sunil Verma, Sara Hurvitz

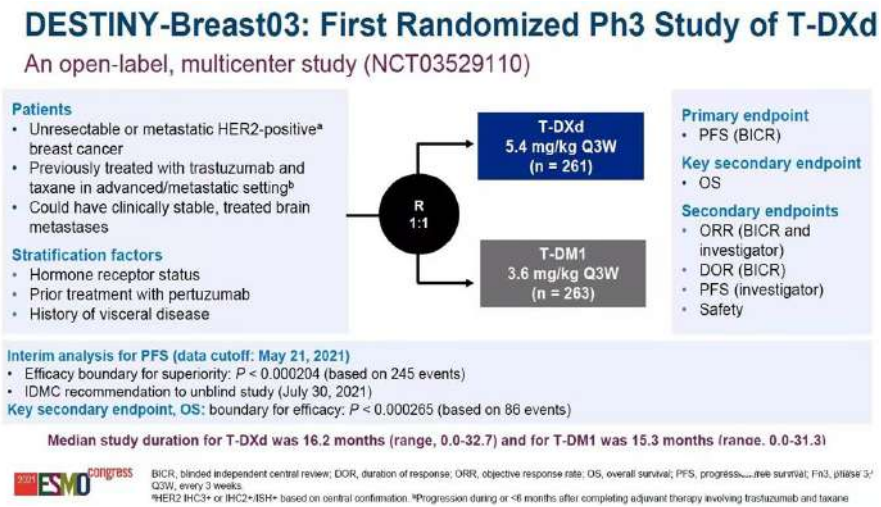
On behalf of the DESTINY-Breast03 investigators

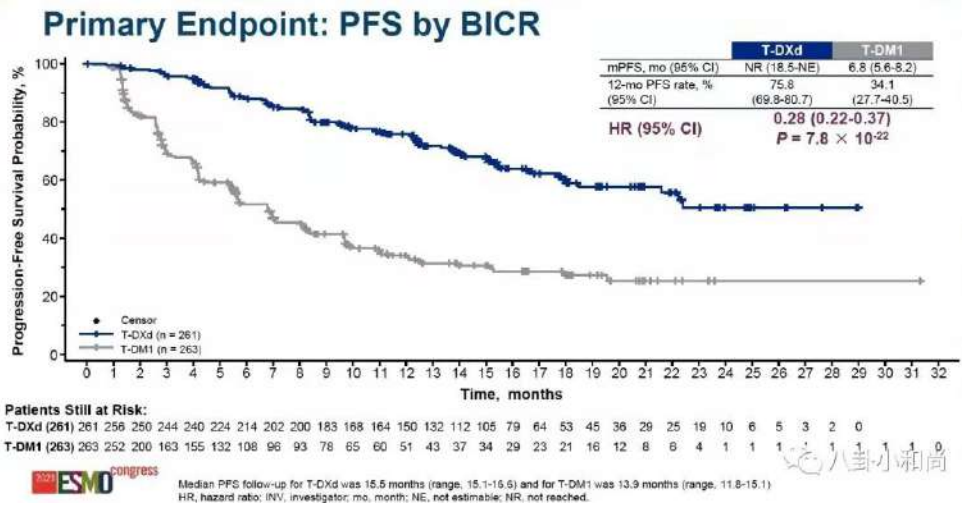
[a]Medical Oncology, International Breast Cancer Center (IBCC), Quironsalud Group, and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain.



BeiGene

DESTINY-Breast03：T-DXd相比T-DM1显著降低疾病复发或死亡风险72%

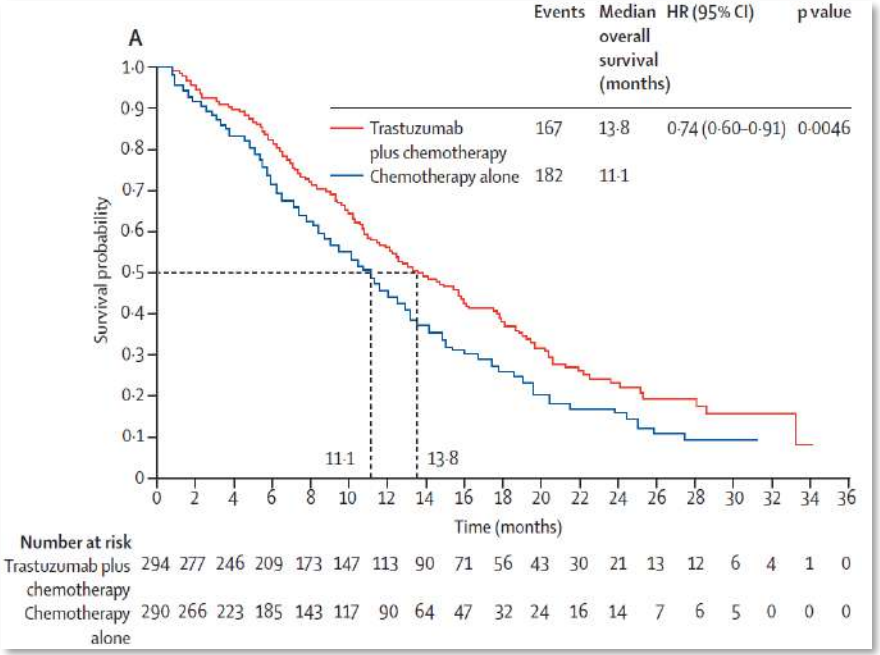




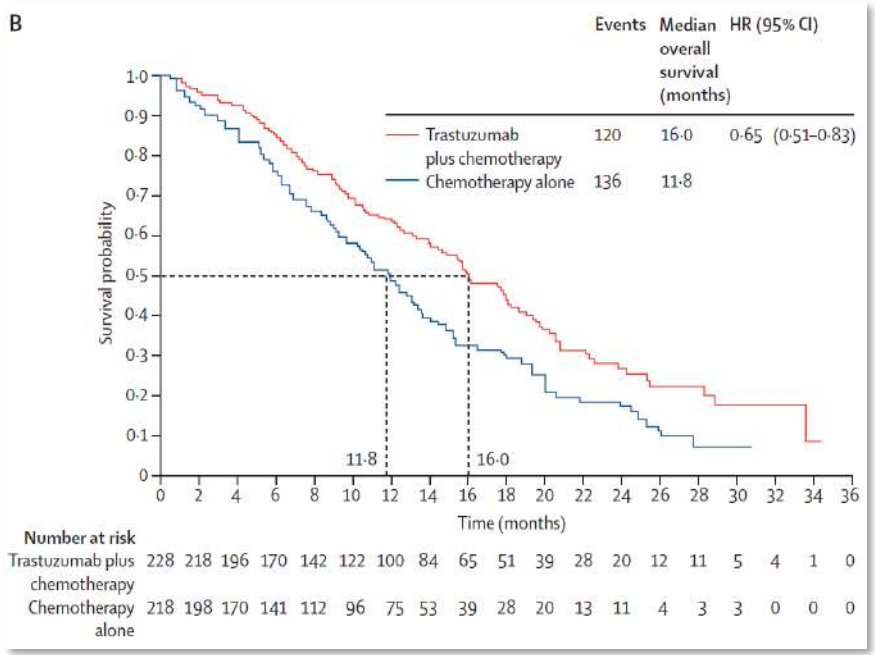
- T-DXd组的中位PFS仍为未达到（95% CI 18.5-NE）,T-DM1组的中位PFS为6.8个月（95% CI 5.6-8.2）；
- 两组间PFS具有高度显著的统计学差异（P=7.8*10-22）且具有显著临床意义的改善;
- T-DXd相比T-DM1，降低疾病复发或死亡风险达72%（HR 0.2840, 95% CI 0.2165-0.3727

胃癌抗HER-2治疗的基石：ToGA研究 OS结果 晚期胃癌一线

OS: primary analysis population

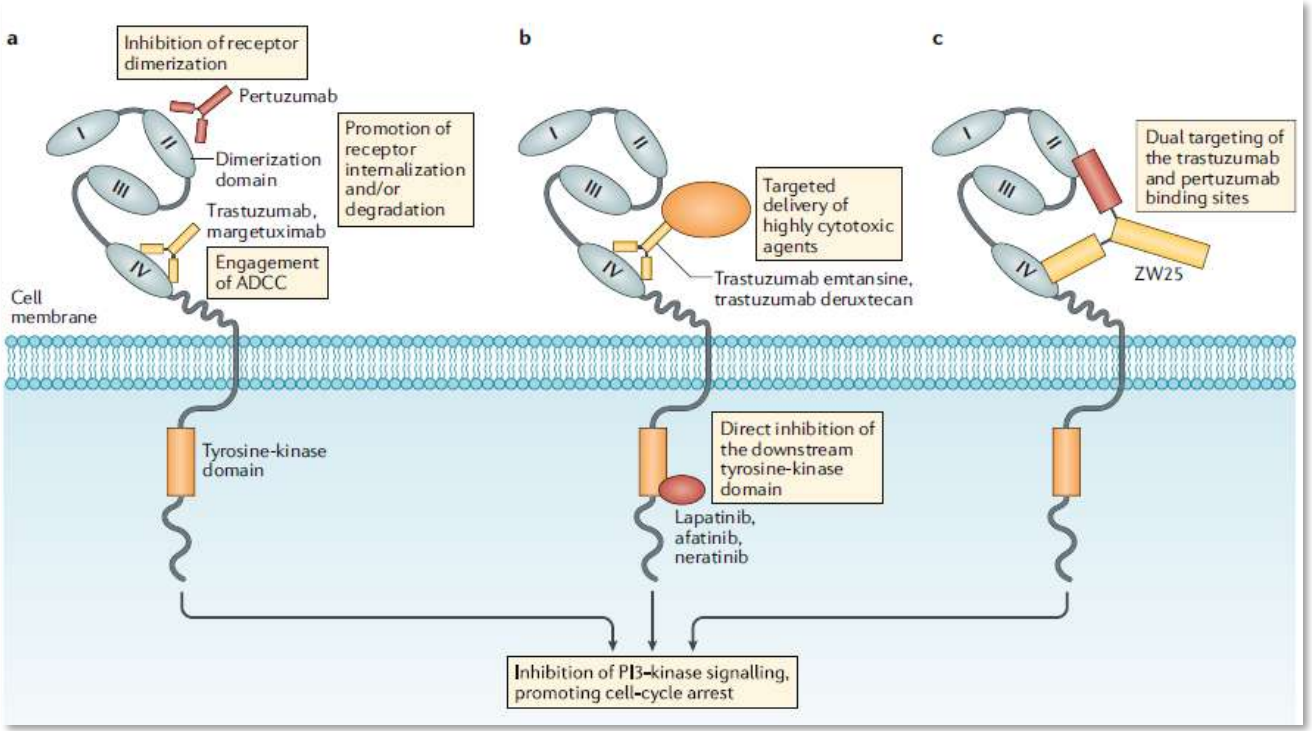


OS: HER2 IHC2 +/FISH+ or IHC 3+ population



BeiGene

常见的抗HER2药物类型及的作用机制

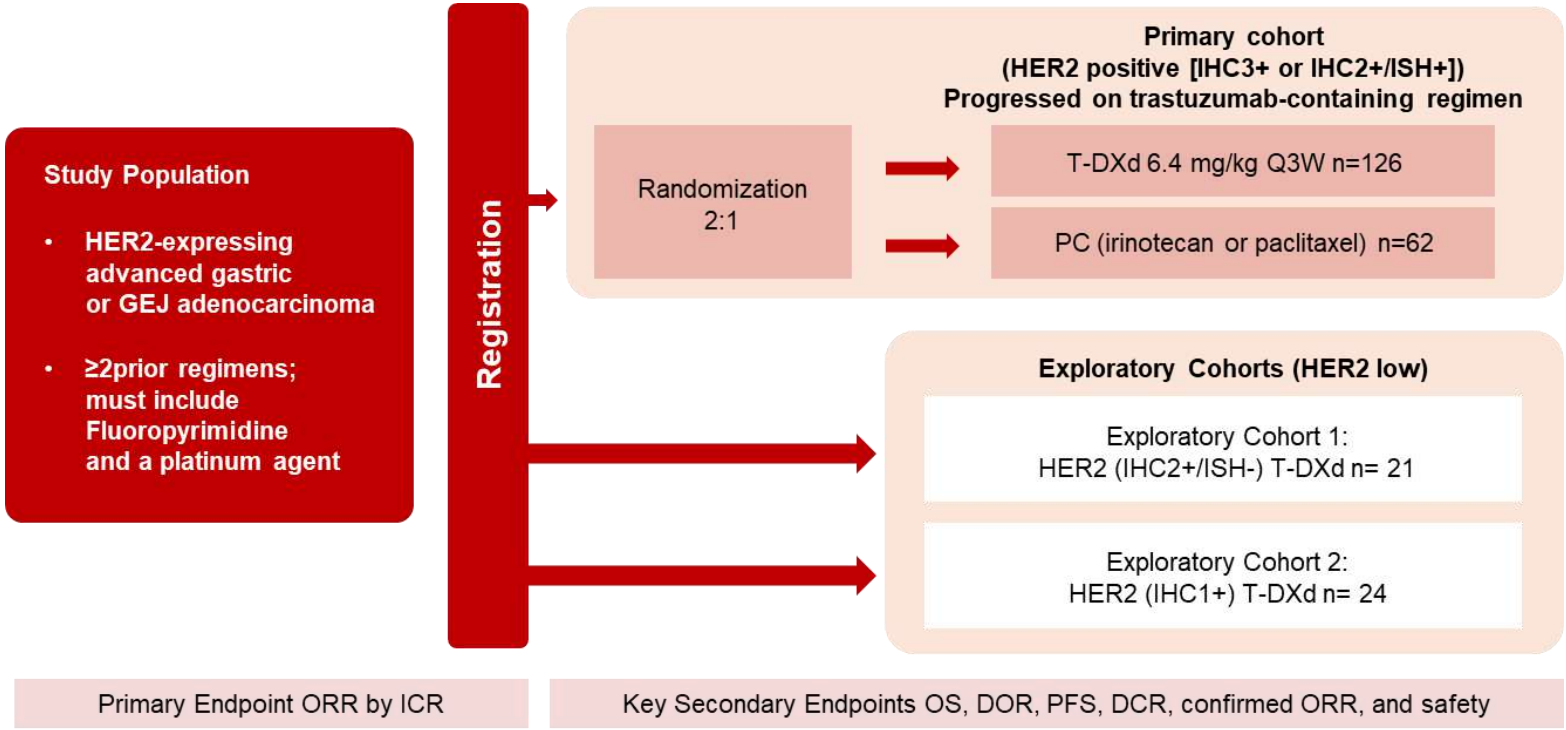


- 单克隆抗体
  - **曲妥珠单抗**
  - 帕妥珠单抗
- 抗体偶联药物
  - T-DM1
  - **T-DXd**
  - **RC-48**
- 小分子TIK
  - 拉帕替尼
  - 吡咯替尼
- 双特异性抗体
  - **ZW25**

BeiGene

ADC: DESTINY-Gastric01研究（2020ASCO/2021ASCO）

一项随机、多中心、开放、II期研究，评估Trastuzumab deruxtecan(T-DXd;DS-8201)治疗HER2+晚期胃或胃食管交界处(GEJ)腺癌的有效性和安全性。



187例治疗患者中，按2:1的比例随机分配，125例接受trastuzumab deruxtecan，62例接受化疗（55例接受伊立替康，7例接受紫杉醇）

BeiGene

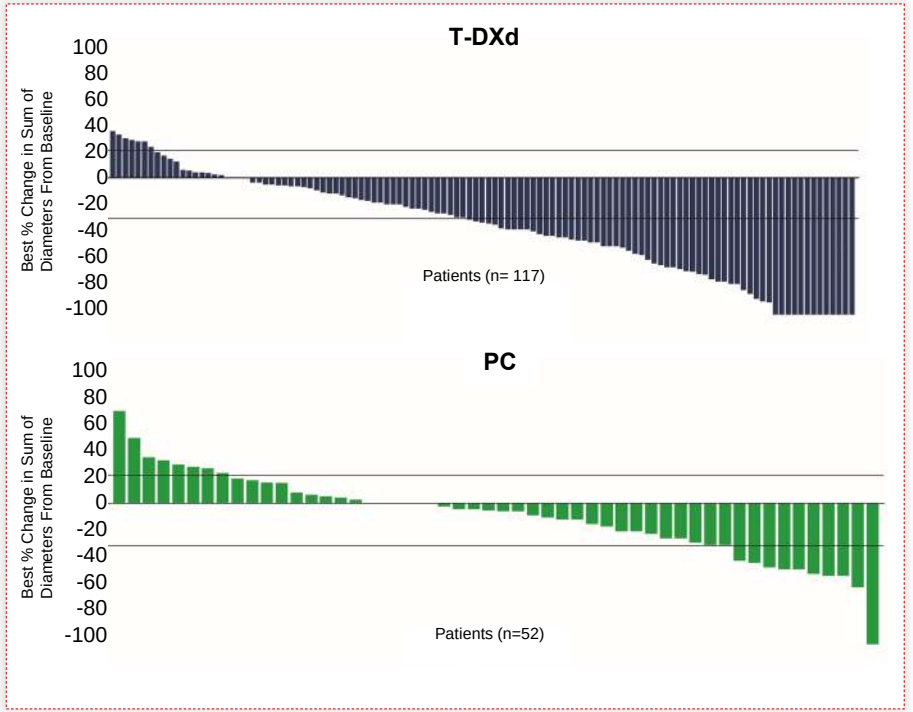
研究结果- ORR, DCR, PFS…

T-DXd 显示出更高的抗肿瘤反应（ORR：T-DXd vs 化疗， 51% vs. 14%, P<0.001）

Results: ORR and Other Efficacy Endpoints

	T-DXd n=119	PC Overall n=56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3)** 95% CI, 41.9-60.5	8 (14.3) 95% CI, 6.4-26.2
	P< 0.0001[b]	
CR	11(9.2)	0
PR	50(42.0)	8(14.3)
SD	42(35.3)	27(48.2)
PD	14(11.8)	17(30.4)
Not evaluable	2(1.7)	4(7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	**50 (42.0)** 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10(8.4)	0
PR	40(33.6)	7(12.5)
SD	52(43.7)	28(50.0)
PD	14(11.8)	17(30.4)
Not evaluable	3(2.5)	4(7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	**102 (85.7)** 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	**12.5** 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
PFS, median, months	**5.6** 95% CI, 4.3-6.9	3.5 95% CI, 2.0-4.3
	P= 0.0003[c]	
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI,1.3-1.7

Best Percentage Change from Baseline in Tumor Size

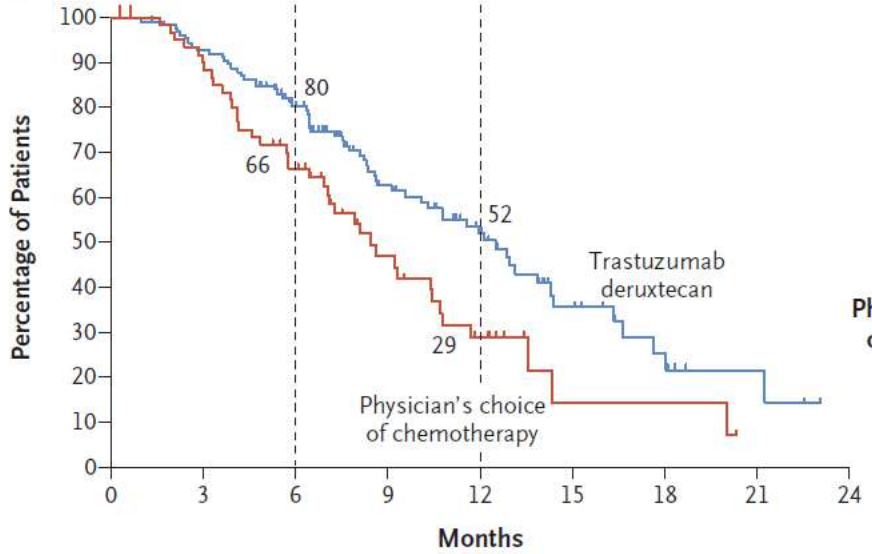


CR, complete response; DCR, disease control rate; DOR, durationof response; ICR, independent central review, NE, not estimable; ORR, objective response rate; PC, physician's choice; PD, progressive disease; PFS, progression-free response; PR, partial Response SD,stable disease;T-DXd,trastuzumab deruxtecan;TTR,time to response.[a]Includes data for the response-evaluable set:all randomized patients who received ≥1 dose of study drug and had measurable tumorsbased on ICR at baseline. [b]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratifed by region.[c]Comparison between T-DXd and PC overall using stratifed Log-rank test stratifed by region.

研究结果-OS

T-DXd的总生存期长于化疗组（中位OS： 12.5个月vs.8.4个月；死亡风险下降41%）

A Overall Survival



No. at Risk									
Trastuzumab deruxtecan	125	115	88	54	33	14	7	3	0
Physician's choice of chemotherapy	62	54	37	19	10	2	2	0	0

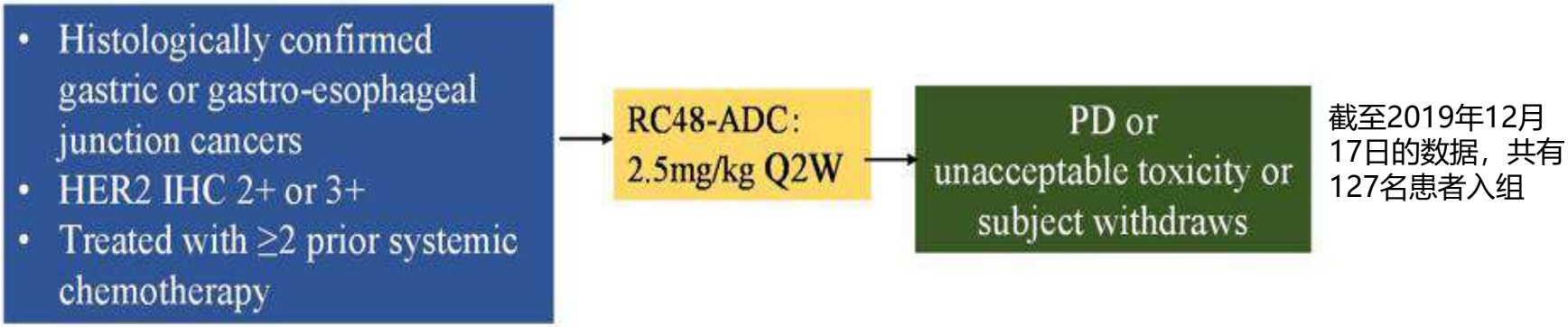
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Trastuzumab Deruxtecan	62/125	12.5 (9.6–14.3)
Physician's Choice of Chemotherapy	39/62	8.4 (6.9–10.7)

Hazard ratio for death, 0.59
(95% CI, 0.39–0.88)
P=0.01

BeiGene

ADC: RC48-ADC胃癌研究（2020ASCO）

一项评价RC48-ADC在HER2过度表达（IHC2 + 或3 +）胃癌或胃食管交界处癌强化治疗患者中的疗效和安全性的开放标签、多中心、单臂、II期研究



主要终点： 客观缓解率 (ORR)

次要终点： 无进展生存期 (PFS)、总生存期(OS)和安全性

RC48-ADC是一种抗体-药物偶联物(ADC)药物，由新型人源化抗HER2 IgG1、连接子和微管抑制剂MMAE组成。MoA包括抑制HER2信号通路和MMAE RC48-ADC的细胞毒性，已在临床前和早期临床研究中证明其具有良好的抗肿瘤活性。

研究结果—主要终点 ORR

独立疗效评价委员会（IRC）评效的主要疗效指标客观缓解率（ORR）为23.6%，（95% CI：16.5%、32.0%）；研究者评估的2线和 3 线以上患者的亚组 ORR 分别为 19.4% 和 16.9%。

对于 111 名接受 ≥ 2 个疗效评估周期（即 12 周）监测的患者，ORR 为 20.7%（95% CI：13.6%、29.5%）

Figure 2. Best Overall Response

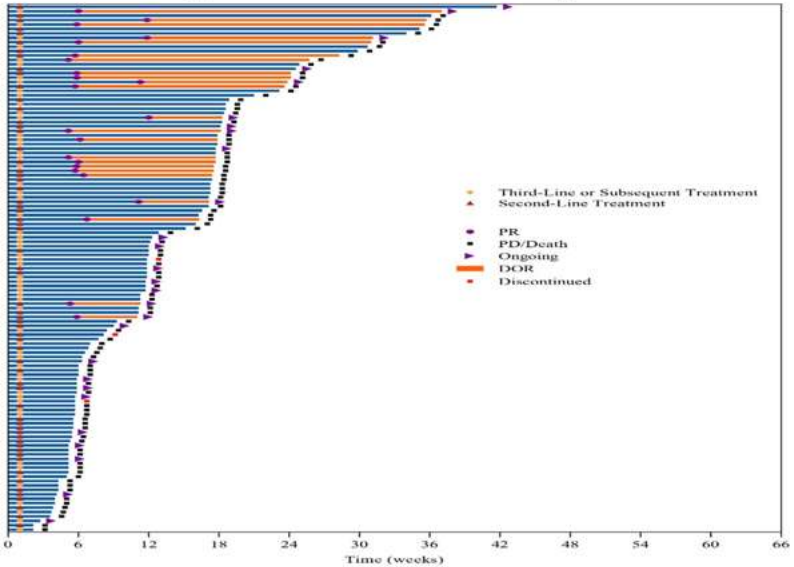
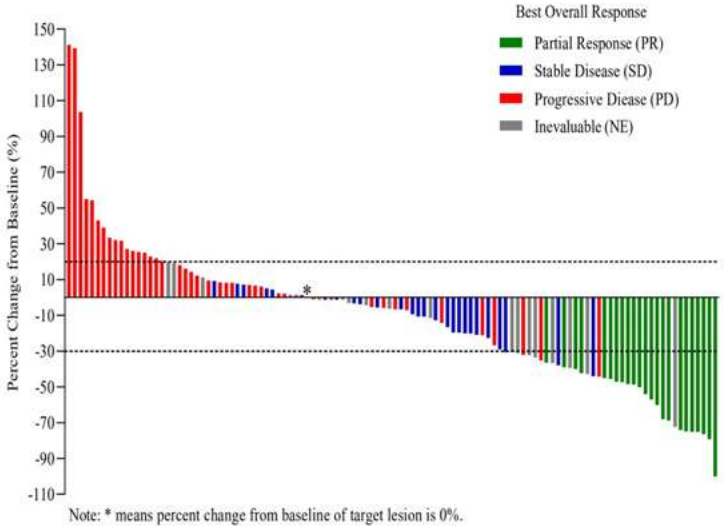


Figure 3. Best Change of Target lesion from Baseline



研究结果—次要研究终点：PFS、OS及安全性

对于 127 名患者，mPFS 为 3.8 个月（95% CI：2.7、4.0、89 个事件 [70.1%]），mOS 为 7.6 个月（95% CI：6.6、9.2）

Figure 4 .Kaplan-Meier estimates of progression-free survival

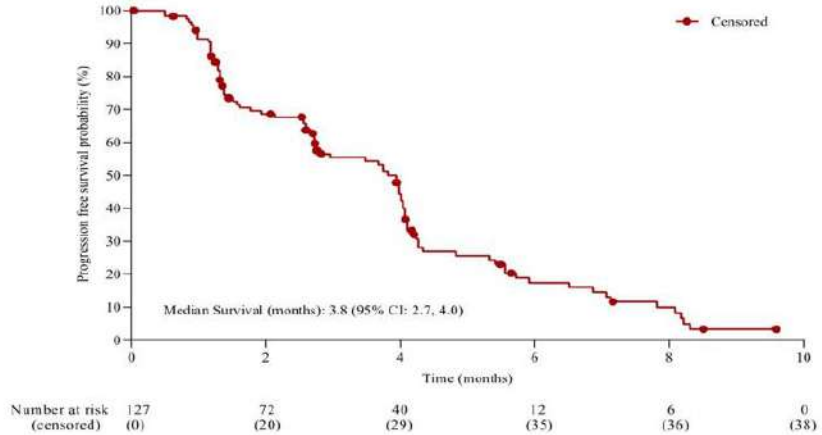
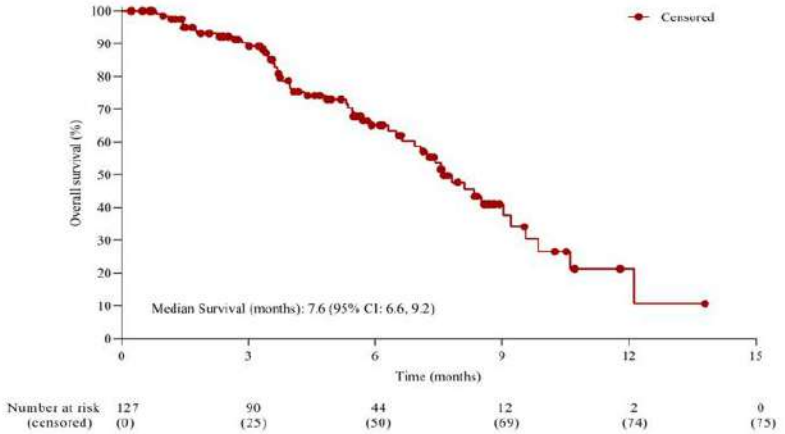


Figure 5 .Kaplan-Meier estimates of overall survival

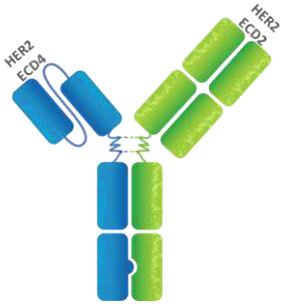


安全性最常报告的治疗相关AE为白细胞减少(52.0%)、脱发(51.2%)、中性粒细胞减少(48.0‰)、疲乏(42.5%)、感觉减退(55.8‰)和恶心(34.6%)。

最常报告的3/4级TRAE为中性粒细胞计数降低(14.2‰)、白细胞减少(11.8%)和贫血(6.3%)。

BsAB: ZWI-ZW25-201研究

全球多中心、II 期、开放标签、一线研究（NCT03929666），评估 Zanidatamab +化疗治疗一线 HER2+胃食管腺癌(GEA) 的疗效及安全性研究

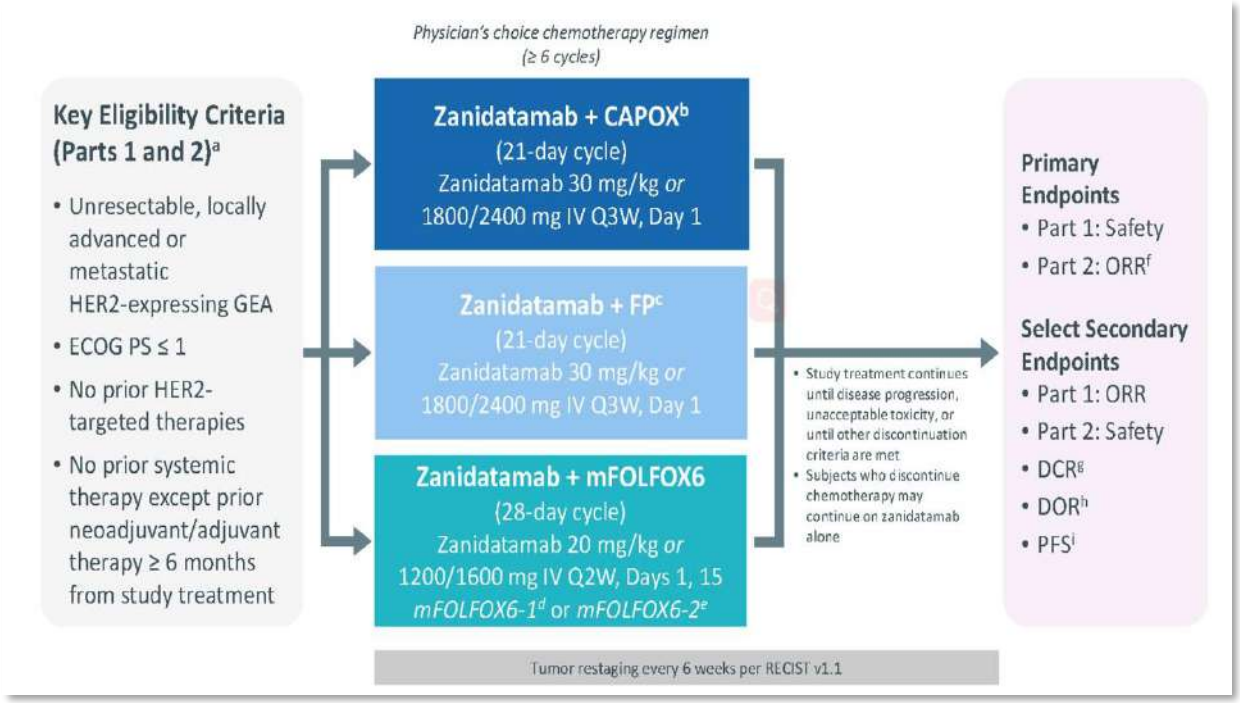


ZW25

ZW25, 全称Zanidatamab，

- 是一种 HER2 靶向双特异性抗体，
- 增强Her2结合和内吞
- 耐受性良好，具有持久反应

（I 期研究显示：单药治疗的确认客观缓解率[cORR]为33%；联合化疗的cORR为54%）



在Her2+GEA患者中，ZW25联合一线化疗观察到初步的疗效和安全性数据

截止2021年7月28日，36例GEA患者中，19例(53%)继续接受研究治疗;12例(33%)因疾病进展而停止治疗，4名(11%)因临床进展而停止治疗，1例(3%)由医生决定停止治疗；

Table 2: Zanidatamab and/or Chemotherapy TRAEs

	Zanidatamab + CAPOX (n = 14)		Zanidatamab + FP (n = 2)		Zanidatamab + mFOLFOX6 (n = 20)		Total (N = 36)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
TRAE,[a] n (%)	14 (100)	8 (57)	2 (100)	1 (50)	20 (100)	16 (80)	36 (100)	25 (69)
Treatment-related SAE[b]	2 (14)	2 (14)	1 (50)	1 (50)	4 (20)	4 (20)	7 (19)	7 (19)
TRAEs leading to treatment discontinuation	0	0	0	0	4 (20)	1 (6)	4 (11)	1 (3)

TRAEs：腹泻是观察到的最常见的TRAE，门诊可控制，并可通过预防减轻，未观察到严重(3级以上)输液相关反应或心脏事件；
5例患者因TRAE而停止治疗(**均为ZW25+ mFOLFOX6**)，没有治疗相的死亡病例。

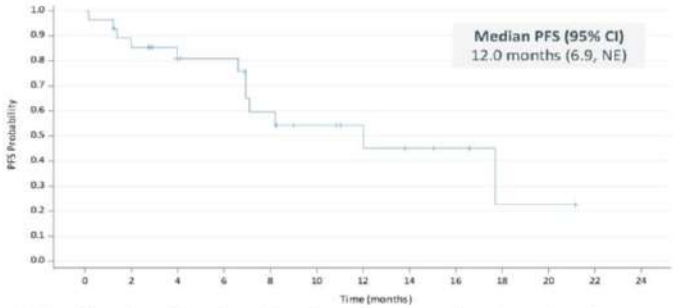
所有治疗方案的cORR为75%，中位DOR为16.4个月

Table 3: Response Rates and DOR

HER2-positive subjects[a]	Zanidatamab + CAPOX (n = 12)	Zanidatamab + FP (n = 2)	Zanidatamab + mFOLFOX6 (n = 14)	Total (N = 28)
cORR,[b] % (95% CI)	92 (61.5, 99.8)	100 (15.8, 100)	57 (28.9, 82.3)	75 (55.1, 89.3)
CR, n (%)	0	0	1 (7)	1 (4)
PR, n (%)	11 (92)	2 (100)	7 (50)	20 (71)
SD, n (%)	1 (8)	0	3 (21)	4 (14)
PD, n (%)	0	0	3 (21)	3 (11)
DCR, % (95% CI)	100 (73.5, 100)	100 (15.8, 100)	79 (49.2, 95.3)	89 (71.8, 97.7)
Median DOR (range), months	NR (2.7, 15.2+)	NR (6.8, 12.5+)	16.4 (1.4, 19.8+)	16.4 (1.4, 19.8+)

中位无进展生存时间为**12.0个月。**

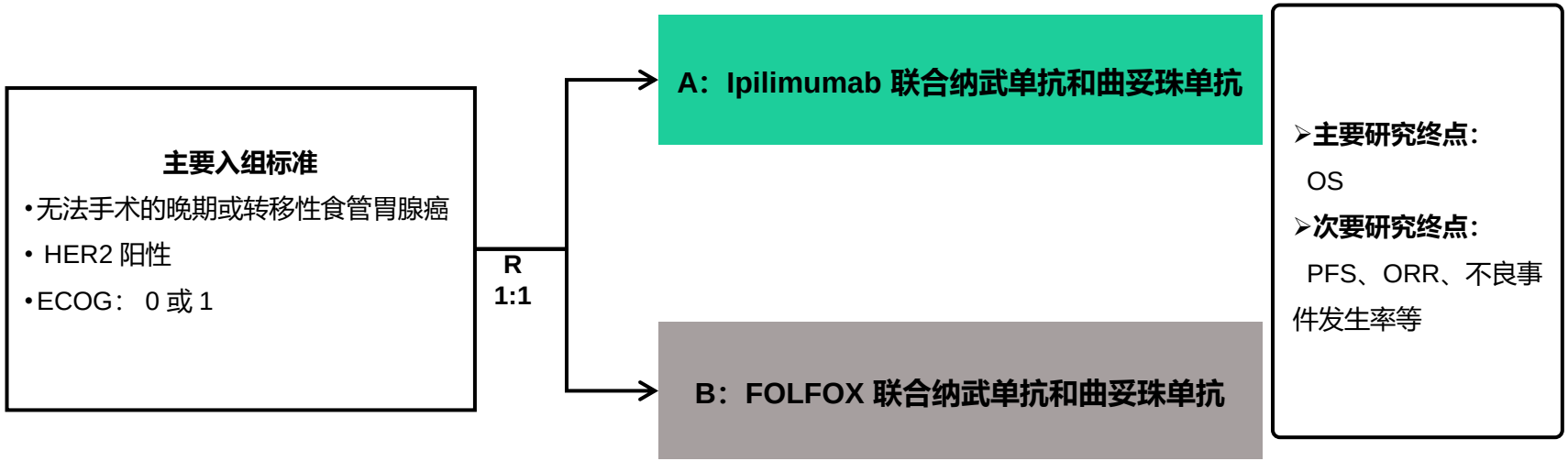
Figure 5: Progression-free Survival



基于该结果，一项**评估ZW25+化疗±替雷丽珠单抗**一线治疗晚期Her2阳性GEA的全球3期研究计划开展中

IO+Anti-HER-2: INTEGA 研究

IPI 或 FOLFOX 联合纳武单抗和曲妥珠单抗治疗先前未经治疗的 HER2 阳性局部晚期或转移性食管胃腺癌(EGA)——随机 II 期临床研究（NCT03409848.）



A：第 1-12 周 曲妥珠单抗 6mg/kg d1 每 3 周（负荷剂量 8mg/kg）；Nivolumab 1mg/kg iv d1 每 3 周 Ipilimumab 3mg/kg iv d1 每 3 周 第 13 周至 EOT（最长治疗期 12 个月） 曲妥珠单抗 4mg /kg d1 每 2 周一次 Nivolumab 240mg iv d1 每 2 周一次

B：曲妥珠单抗 4mg/kg d1 每 2 周一次（负荷剂量 6mg/kg） Nivolumab 240mg iv d1 每 2 周 mFOLFOX6 每两周一次 奥沙利铂 85 mg/m2 静脉注射 2 小时（第 1 天） 5-FU 400 mg/m2静脉推注（第 1 天） LV 剂量为 400 mg/m2 静脉注射超过 2 小时（第 1 天） 5-FU 剂量为 2400 mg/m2 静脉注射超过 46 小时（第 1-3 天）

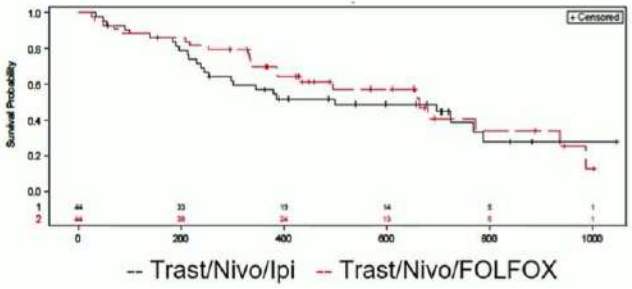
研究结果

Trast+nivo+FOLFOX组显示了更高的疗效，而Trast+nivo+ ipi组疗效不明显。

	All (n=88) ITT		CPS>=1 (n=59)		CPS>=5 (n=46)		HER2+ central (n=76)	
	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX
	N=44	N=44	N=31	N=28	N=24	N=22	N=40	N=36
ORR	32%	**56%**	36%	**63%**	33%	**67%**	35%	**63%**
mPFS	3.2 mo	**10.7 mo**	2.2 mo	**10.7 mo**	2.2 mo	**11 mo**	3.4 mo	**10.7 mo**
PFSR@12	15%	**37%**	14%	**33%**	7%	**38%**	17%	36%
mDOR	5.8 mo	9.2 mo	na	na	na	na	na	na
mOS	16.4 mo	21.8 mo	16.4 mo	**21.6 mo**	12.5 mo	**21.6 mo**	16.4 mo	**22.4 mo**
OSR@12	57%	70%	54%	71%	53%	72%	58%	74%

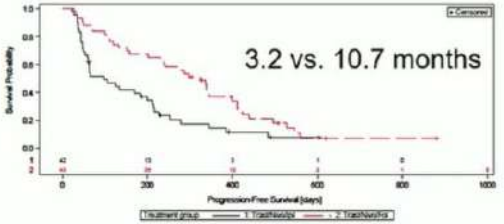
Efficacy – overall and progression free survival

Overall survival



Overall Survival	Rate after 12 months (%)	Median (months)
Trast/Nivo/Ipi	57%	16.4
Trast/Nivo/FOLFOX	70%	21.8

Progression free survival



2021 ESMO Abstract LBA54

IO+Anti-HER-2: KEYNOTE-811

KEYNOTE-811是一项随机、安慰剂对照、双盲、3期研究，目的是评估帕博利珠单抗 +曲妥珠单抗联合SOC化疗 vs. 曲妥珠单抗联合SOC化疗对先前未经治疗、局部晚期不可切除或转移性HER2+ G/GEJ腺癌患者的疗效和安全性

全球队列

患者
- 晚期G/GEJ腺癌
- 晚期疾病先前未接受治疗
- HER2+

分层
- 地理区域
- PD-L1状态
- 化疗方案(FP或CAPOX)

1:1 随机化 N=692

帕博利珠单抗 200mg IVQ3W +曲妥珠单抗+FP或CAPOX

安慰剂+曲妥珠单抗+FP或CAPOX

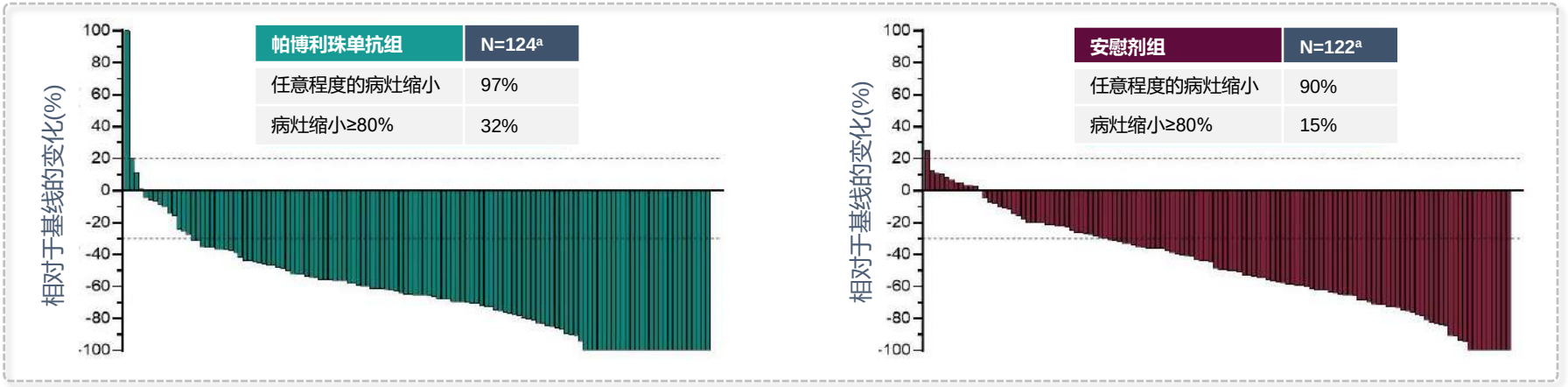
治疗直至35个周期(~2年)或疾病进展或不耐受毒性

电话随访生存状态直至死亡或撤回同意或研究结束

- 主要终点：无进展生存期(RECIST v1.1)和总生存期。
- 次要终点：客观缓解率(ORR)、缓解持续时间(DOR)、安全性和耐受性
- 探索性终点：PFS和ORR(mRECIST v1.1)、生活质量(EORTC QLQ-C30和QLQ-STO22)、EQ-5D、PD-1/PD-L1/PD-L2表达、分子生物标志物
- 计划招募约692例患者

CAPOX：卡培他滨+奥沙利铂；FP：5-氟尿嘧啶+顺铂；G/GEJ：胃/胃食管结合部；HER2：人表皮生长因子受体2；IV：静脉注射；PD-L1：程序性死亡配体1;Q3W，每3周一次

KEYNOTE-811：确认的缓解(IA1)



ORR和DCR，%(95%CI)	帕博利珠单抗组 (N=133)	安慰剂组 (N=131)
ORR	**74.4%** (66.2-81.6)	51.9% (43.0-60.7)
ORR差异[b]	22.7%(11.2-33.7)	P=0.00006
DCR	**96.2%** (91.4-98.8)	89.3% (82.8-94.0)

最佳缓解，n(%)	帕博利珠单抗组 (N=133)	安慰剂组 (N=131)
CR	15(11%)	4(3%)
PR	84(63%)	64(49%)
SD	29(22%)	49(37%)
PD	5(4%)	7(5%)
不可评估	0	2(2%)
未评估	0	5(4%)

缓解持续时间[c]	帕博利珠单抗组 (N=99)	安慰剂组 (N=68)
中位值[d]	**10.6个月**	9.5个月
范围	1.1+-16.5+	1.4+-15.4+
持续≥6月[d]	70.3%	61.4%
持续≥9月[d]	58.4%	51.1%

帕博利珠单抗+曲妥珠单抗+化疗的应答更深、持久

[a]在基线时有RECIST可测量病灶，在基线后有21个可测量靶病灶。[b]用Miettinen和Nurminen法进行随机分层因素计算。[c]计算最佳应答患者CR或PR. [d]Kaplan-Meier etimation。两组治疗方案均包括曲妥珠单抗和化疗。数据截止时间: 2020年6月17日

晚期HER-2阳性胃癌疗效汇总

一线	ORR（%）	DOR（m）	PFS（m）	OS（m）
ToGA	T+C：47.3 C：34.5	-	-	T+C：13.5 C：11.1
ZWI-ZW25-201	75	16.4	12.0	-
INTEGA	T+V+I：32% T+V+C：56%	T+V+I：5.8 T+V+C：9.2	T+V+I：3.2 T+V+C：10.7	T+V+I：16.4 T+V+C：21.8
KEYNOTE-811	P+T+C：74.4 T+C：51.9	-	-	-

三线＋ ADC	ORR（%）	DOR	PFS（m）	OS（m）
RC48-ADC	23.6	-	3.8	7.6
DESTINY-Gastric01	T-DXd ： 51 化疗：14	T-DXd ： 12.5 化疗：3.9	T-DXd ： 5.6 化疗：3.5	T-DXd ： 12.5 化疗：8.4

BeiGene

小结

HER2+晚期胃癌研究全面突破

- **ADC方案：** DESTINY-Gastric01研究：与化疗相比，T-DXd 显示出更高的抗肿瘤反应（**ORR**：T-DXd vs 化疗， **51%** vs. 14%, P<0.001）；更长的生存周期，**死亡风险下降41%；** RC48-ADC研究进一步验证ADC 可使HER2 过表达胃癌或胃食管交界处癌患者表现出抗肿瘤反应和生存获益
- **双抗治疗：** ZWI-ZW25-201研究：在her2+GEA的患者中，ZW25联合标准一线化疗显示了令人鼓舞的抗肿瘤活性（**cORR为75%**，**中位DOR为16.4**个月）
- **PD-1+：** KEYNOTE 811研究等为免疫联合其它靶向药物在胃癌一线治疗进行了成功的探索
- 抗HER-2治疗的多方向突破为该类型患者的临床治疗和新的研究探索带来更多的选择。

IO+Chemo vs Chemo：ORIENT-16研究

信迪利单抗联合化疗与化疗作为晚期胃或胃食管交界处 (G/GEJ) 的一线治疗：一项随机、双盲、3 期研究

Statistical considerations

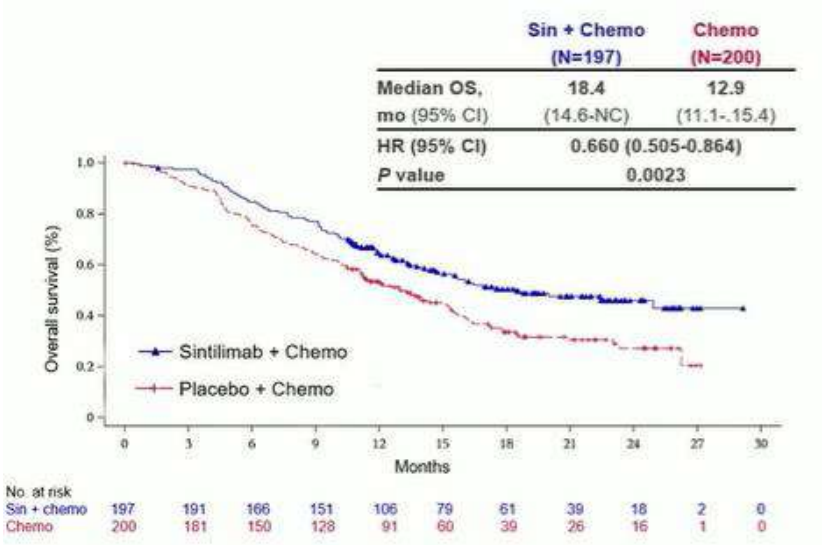
- Type I error is strictly controlled using fixed sequence test. OS in CPS≥5 and all randomized are tested hierarchically
- One interim analysis is planned, and O'Brien-Fleming is used for the alpha boundary (alpha=0.0148).

BeiGene

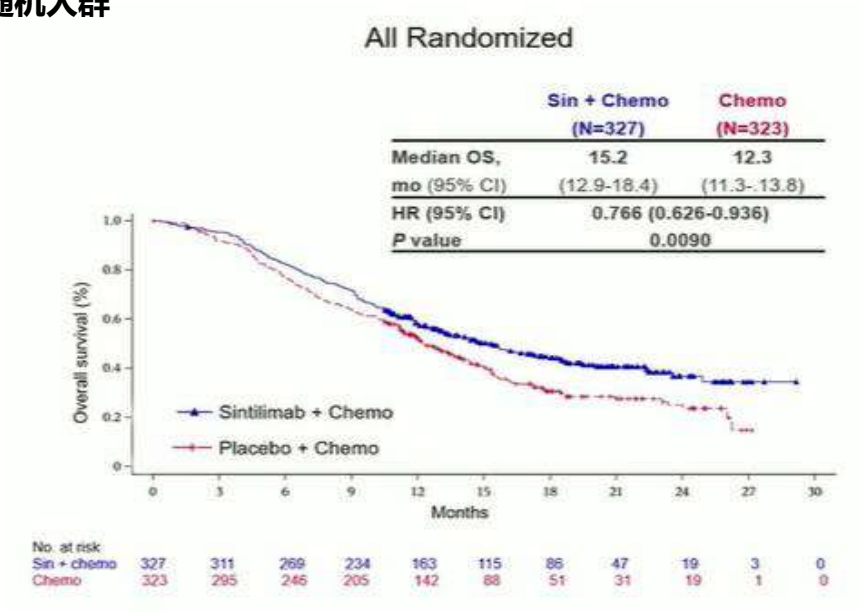
期中结果分析--主要研究终点OS

信迪利单抗联合化疗组和对照组的中位OS分别为：（PD-L1 CPS≥5）：18.4个月 vs. 12.9个月，HR 0.660 (0.505-0.864), P=0.0023；全随机人群：15.2个月 vs. 12.3个月，HR 0.766 (0.626-0.936), P=0.0090。

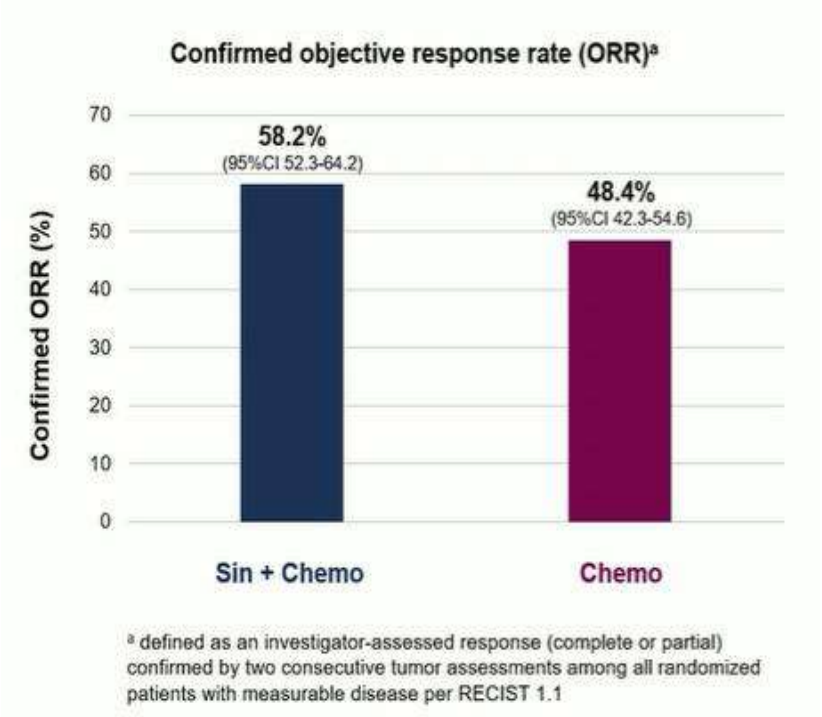
PD-L1 CPS≥5

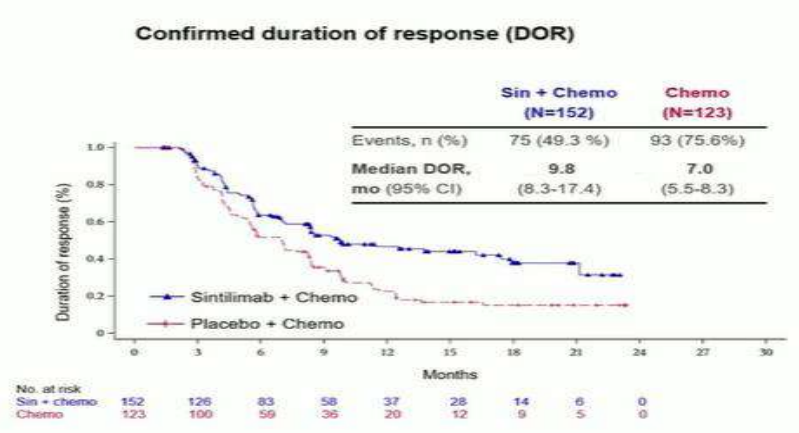


全随机人群



期中结果分析—ORR和DOR免疫联合组均优于单纯化疗组，且安全性可控





Adverse events in safety population

	Sin + Chemo (N=328)	Chemo (N=320)
Any TRAEs	319 (97.3)	308 (96.3)
Grade ≥3 TRAEs	196 (59.8)	168 (52.5)
Serious TRAEs	86 (26.2)	70 (21.9)
AEs leading to discontinuation of any study treatment, n (%)	38 (11.6)	25 (7.8)
AEs leading to interruption of any study treatment, n (%)	245 (74.7)	223 (69.7)
TRAEs leading to death	6 (1.8)	2 (0.6)

- The most common any-grade TRAEs (≥ 20%) across both groups include Platelet count decreased, Neutrophil count decreased, White blood cell count decreased, Anaemia, Nausea, Vomiting, AST or ALT increased, and Decreased appetite.

BeiGene

2021: HER-2-晚期胃癌临床研究数据汇总(ESMO会议前)

	CheckMate 649 Global		KEYNOTE-062 Global		ATTRACTION-4 Asia
化疗方案	FOLFOX/CapeOX		PEMBRO + 5-FU/Cape+cis		SOXb /CapeOXc
	所有随机人群	CPS ≥5	All (CPS≥1)	All (CPS≥10)	所有随机人群
N	1581	955 (Asia: 24%)	507	189	724
mOS (月)	13.8 vs 11.6	14.4 vs 11.1 Asia: 15.6 vs 11.8	12.5 vs 11.1	12.3 vs 10.8	17.5 VS. 17.2
HR	0.80 (0.68-0.94)	0.71 (0.59-0.86) Asia: 0.64 (0.47-0.87)	0.85 (0.70–1.03)	0.85 (0.62-1.17)	0.90 (0.75-1.08)
mPFS (月)	7.7 vs 6.9	7.7 vs 6.0	6.9 vs 6.4	5.7 vs 6.1	10.45 vs. 8.34
HR	0.77 (0.68-0.87)	0.68 (0.56-0.81)	0.84	0.73	0.68 (0.51-0.90)
ORR (%)	-	60 vs 45	49 vs 37	53 vs 38	57.5 vs 47.8
DOR (月)	-	9.5 vs 7.0	6.8 vs 6.8	8.3 vs 6.8	12.91 vs 8.67

1.Moehler M, et al. LBA .ESMO2020；2.KEYNOTE-062 study. Oral presentation at ASCO 2019. Abstract LBA4007.；3. Boku N. et al. ESMO 2020; LBA 7；4. 2021 ESMO Abstract LBA53

BeiGene

2021: HER-2-晚期胃癌临床研究数据汇总(基于ESMO会议更新)

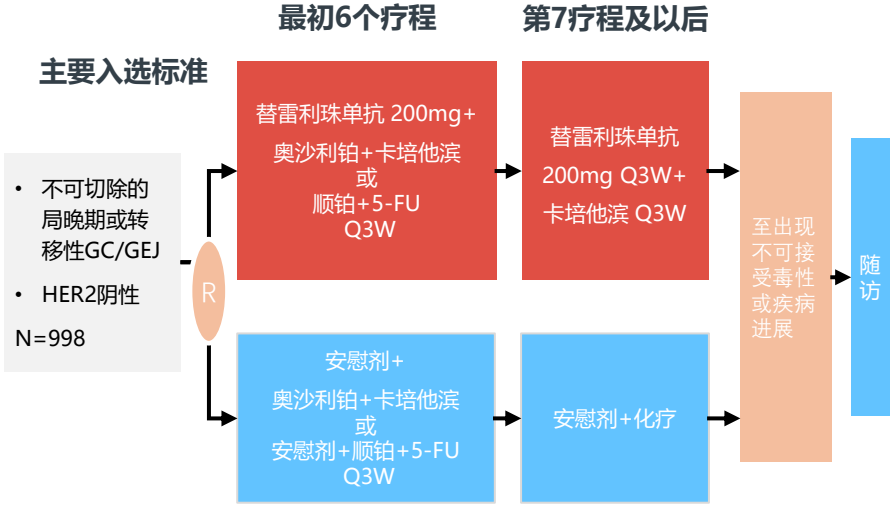
	CheckMate 649 Global		KEYNOTE-062 Global		ATTRACTION-4 Asia	ORIENT-16 China	
化疗方案	FOLFOX/CapeOX		PEMBRO + 5-FU/Cape+cis		SOXb /CapeOXc	XELOX+Cape	
	所有随机人群	CPS ≥5	All (CPS≥1)	All (CPS≥10)	所有随机人群	所有随机人群	CPS ≥5
N	1581	955 (Asia: 24%)	507	189	724	650	
mOS (月)	13.8 vs 11.6	14.4 vs 11.1 Asia: 15.6 vs 11.8	12.5 vs 11.1	12.3 vs 10.8	17.5 VS. 17.2	15.2 vs. 12.3	18.4 vs. 12.9
HR	0.80 (0.68-0.94)	0.71 (0.59-0.86) Asia: 0.64 (0.47-0.87)	0.85 (0.70–1.03)	0.85 (0.62-1.17)	0.90 (0.75-1.08)	0.77 (0.63-0.94)	0.66 (0.51-0.86)
mPFS (月)	7.7 vs 6.9	7.7 vs 6.0	6.9 vs 6.4	5.7 vs 6.1	10.45 vs. 8.34	7.1 vs 5.7	7.7 vs 5.8
HR	0.77 (0.68-0.87)	0.68 (0.56-0.81)	0.84	0.73	0.68 (0.51-0.90)	0.64 (0.53-0.77)	0.63 (0.50-0.81)
ORR (%)	-	60 vs 45	49 vs 37	53 vs 38	57.5 vs 47.8	58.2 vs 48.4	72.8 vs 59.6
DOR (月)	-	9.5 vs 7.0	6.8 vs 6.8	8.3 vs 6.8	12.91 vs 8.67	8.4 vs 5.5	8.6 vs 5.5

影响因素：地域差异/化疗方案/统计假设/样本量/免疫药物？

1.Moehler M, et al. LBA .ESMO2020；2.KEYNOTE-062 study. Oral presentation at ASCO 2019. Abstract LBA4007.；3. Boku N. et al. ESMO 2020; LBA 7；4. 2021 ESMO Abstract LBA53

更多的一线IO + Chemo 研究仍在探索中

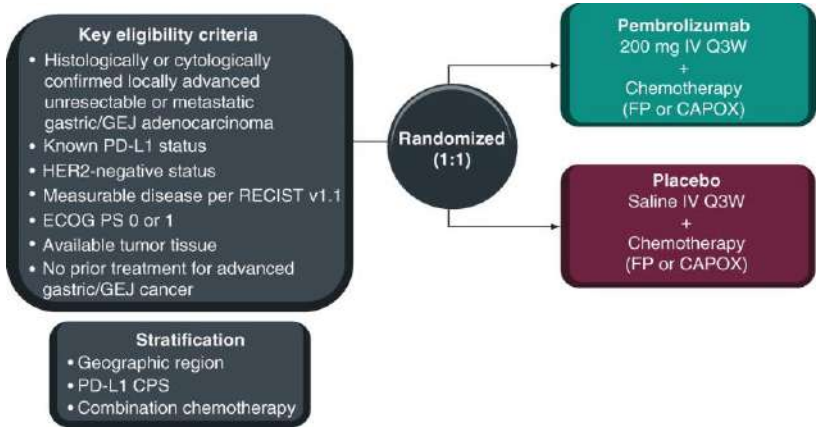
RATIONALE-305研究：替雷利珠联合化疗或单独化疗用于晚期胃癌/胃腺癌Ⅲ期研究，**兼顾各地区人群；兼顾不同化疗方案**



分层因素：
- ✓ PD-L1表达
- ✓ 腹膜转移
- ✓ 研究者选择的化疗

- **主要终点：**OS
- **次要终点：**PFS，ORR、DoR（研究者评估）、生活质量、安全性

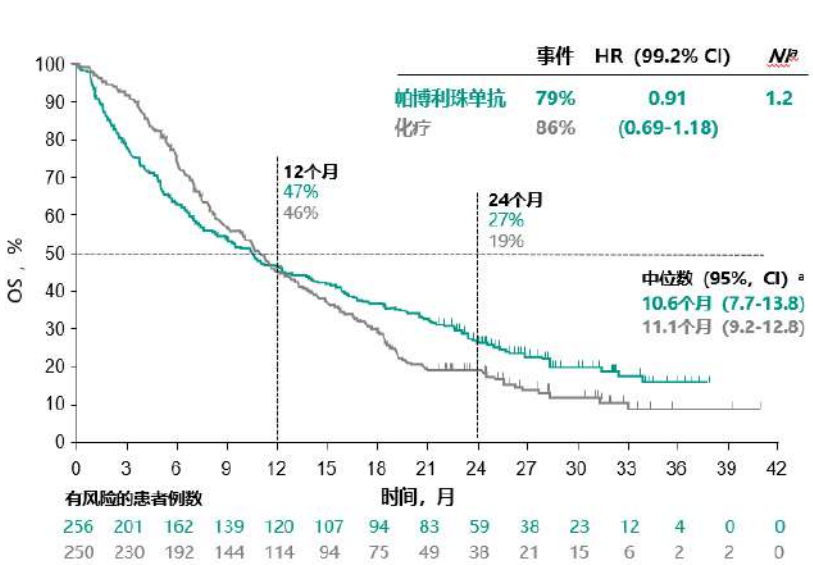
KEYNOTE-859: Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma



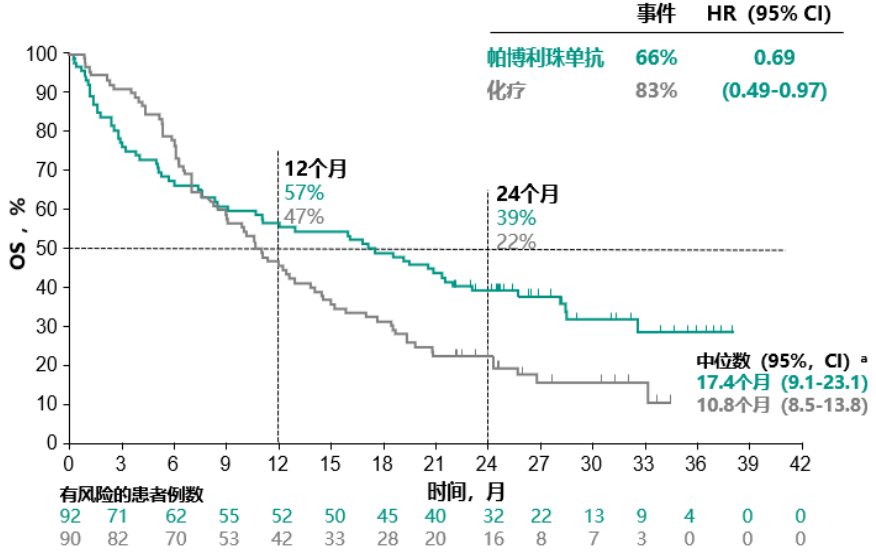
- **Build on the knowledge learned from KEYNOTE-062**
- **Use a different standard-of-care chemotherapy backbone**
- **Use a modified statistical design**
- **N = 1542**

IO mono： KEYNOTE-062

OS：帕博利珠单抗 vs. 化疗 (CPS≥1)



OS：帕博利珠单抗 vs. 化疗 (CPS≥10)



对于CPS≥ 1的晚期胃癌，帕博利珠单药对比化疗达到非劣效终点

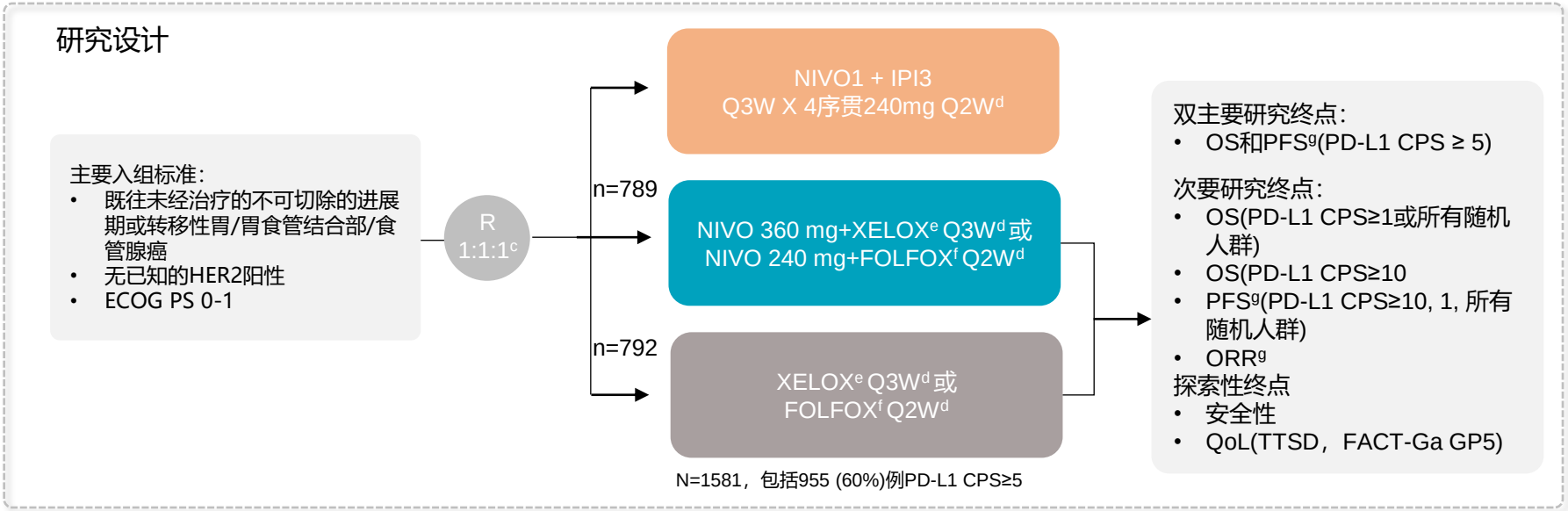
- 非劣效边界设置1.2，统计学的成功≠临床价值
- KM曲线交叉时间出现晚

数据截止日期：2019年3月26号

BeiGene

IO + IO vs Chemo: CheckMate 649

CheckMate 649研究是一项全球多中心，开放标签，Ⅲ期临床研究



- 数据截止日期2020年5月27日，最短随访时间为12.1个月[h]

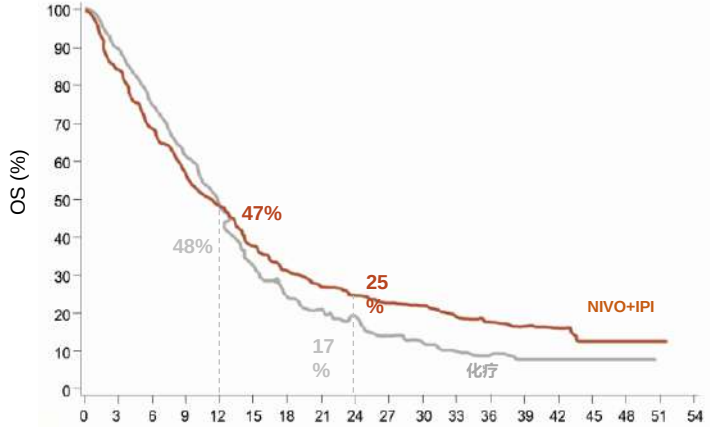
[a]ClinicalTrials.gov：NCT02872116；[b]<1% 包含不确定的肿瘤细胞PD-L1表达；采用PD-L1 IHC 28-8(Dako)检测；[c]在增加NIVO联合化疗组之前，且在NIVO联合IPI3组新患者入组之前关闭；[d]直到疾病进展(同意NIVO联合化疗治疗进展后继续治疗除外)，不可耐受的毒性，撤回知情同意，或研究结束。NIVO最多治疗至满2年；[e]奥沙利铂130mg/m^2 IV(D1)，卡培他滨100mg/m^2，口服，每天2次(D1-14)；[f]奥沙利铂 85mg/m^2，四氢叶酸 400mg/m^2，FU 400 mg/m^2 IV(D1)，FU 1200mg/m^2 IV 每天1次(D1-2)；[g]BIRC 评估；[h]最后1例患者随机到数据截止日期。

主要终点OS：CPS≥5和所有随机人群中，NIVO+IPI对比化疗未显示出优势

OS曲线

PD-L1 CPS≥5患者

	NIVO+IPI(n=234)	化疗(n=239)
mOS，月	11.2(9.2-13.4)	11.6(10.1-12.7)
HR (96.5%CI)	0.89(0.71-1.10)	
P值	0.2302	

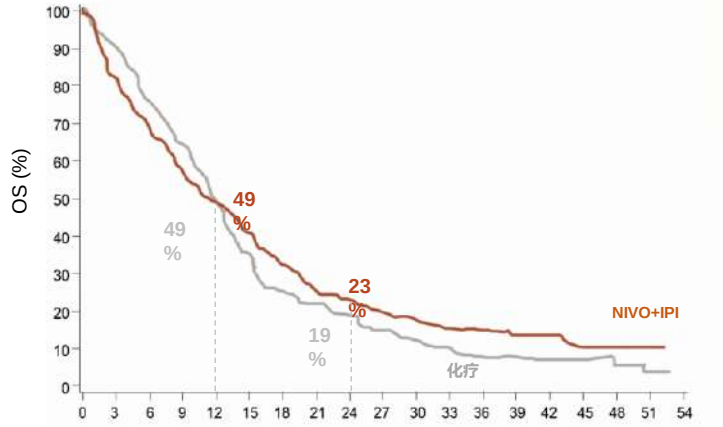


处于风险的患者数

NIVO+化疗	234	193	156	131	106	85	70	60	56	51	48	42	39	25	18	6	3	2	0
化疗	239	211	176	143	110	74	56	45	39	31	27	22	19	12	7	2	1	1	0

所有随机分组患者

	NIVO+IPI(n=409)	化疗(n=404)
mOS，月	11.7(9.6-13.5)	11.8(11.0-12.7)
HR (96.5%CI)	0.91(0.77-1.07)	
P值	暂无结果	



处于风险的患者数

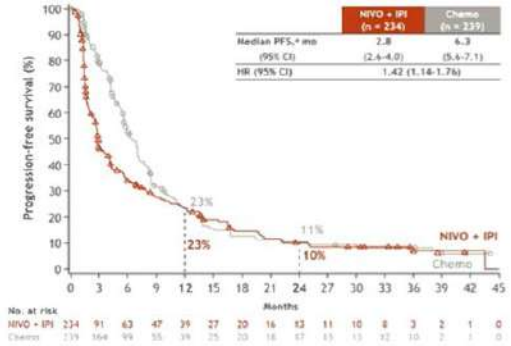
NIVO+化疗	409	332	279	235	197	162	132	102	90	79	68	62	59	39	25	10	5	3	0
化疗	404	359	305	255	189	134	98	84	71	56	43	36	31	23	15	9	3	2	0

OS：总生存；PFS：无进展生存；HR：风险比

次要终点PFS：CPS≥5和所有随机人群中，NIVO+IPI对比化疗未显示出优势

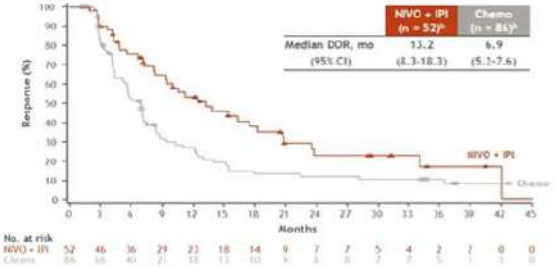
ORR、DOR：NIVO+IPI的ORR低于化疗，但 CPS≥5和所有随机人群的DOR更长

PD-L1 CPS ≥ 5



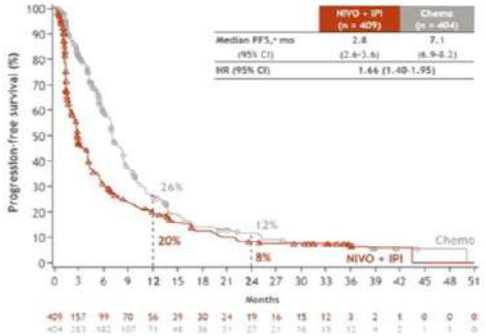
	NIVO + IPI (n = 234)	Chemo (n = 239)
Median PFS,[a] mo	2.8	6.3
(95% CI)	(2.6-4.0)	(5.6-7.1)
HR (95% CI)	1.42 (1.14-1.76)	

Response per BICR	NIVO + IPI (n = 196)[a]	Chemo (n = 183)[a]
ORR, % (95% CI)	27 (20-33)	47 (40-54)
CR	5	8
PR	21	39
SD	27	35
PD	32	10



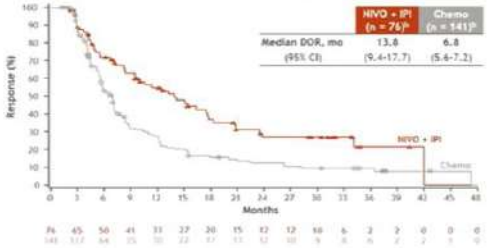
	NIVO + IPI (n = 52)[b]	Chemo (n = 86)[b]
Median DOR, mo	13.2	6.9
(95% CI)	(8.3-18.3)	(5.2-7.6)

所有随机的人群



	NIVO + IPI (n = 409)	Chemo (n = 404)
Median PFS,[a] mo	2.8	7.1
(95% CI)	(2.6-3.6)	(6.9-8.2)
HR (95% CI)	1.66 (1.40-1.95)	

Response per BICR	NIVO + IPI (n = 333)[a]	Chemo (n = 299)[a]
ORR, % (95% CI)	23 (18-28)	47 (41-53)
CR	6	8
PR	17	39
SD	27	34
PD	34	9



	NIVO + IPI (n = 76)[b]	Chemo (n = 141)[b]
Median DOR, mo	13.8	6.8
(95% CI)	(9.4-17.7)	(5.6-7.2)

思考：双免方案是否可行？

INTEGA 研究

	All (n=83) ITT		CPS>=1 (n=59)		CPS>=5 (n=46)		HER2+ central (n=76)	
	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX	Trast/Nivo/ Ipi	Trast/Nivo/ FOLFOX
	N=44	N=44	N=31	N=28	N=24	N=22	N=40	N=36
ORR	32%	56%	36%	63%	33%	67%	35%	63%
mPFS	3.2 mo	10.7 mo	2.2 mo	10.7 mo	2.2 mo	11 mo	3.4 mo	10.7 mo
PFSR@12	15%	37%	14%	33%	7%	38%	17%	36%
mDOR	5.8 mo	9.2 mo	na	na	na	na	na	na
mOS	16.4 mo	21.8 mo	16.4 mo	21.6 mo	12.5 mo	21.6 mo	16.4 mo	22.4 mo
OSR@12	57%	70%	54%	71%	53%	72%	58%	74%

INTEGA 研究：IPI 或 FOLFOX 联合纳武单抗和曲妥珠单抗治疗先前未经治疗的 HER2 阳性局部晚期或转移性食管胃腺癌 (EGA)——随机 II 期临床研究

CheckMate 649研究

	NIVO + chemo	Chemo	NIVO + IPI	Chemo
PD-L1 CPS ≥ 5	N = 473	N = 482	N = 234	N = 239
mOS, mo (95% CI)	14.4 (13.1–16.2)	11.1 (10.0–12.1)	11.2 (9.2–13.4)	11.6 (10.1–12.7)
HR	0.70 (95% CI 0.61–0.81)	0.89 (96.5% CI 0.71–1.10; P = 0.2302)		
ORR [a]	N = 378	N = 390	N = 196	N = 183
% (95% CI)	60 (55-65)	45 (40-50)	27 (20-33)	47 (40-54)
All randomized	N = 789	N = 792	N = 409	N = 404
mOS, mo (95% CI)	13.8 (12.4–14.5)	11.6 (10.9–12.5)	11.7 (9.6–13.5)	11.8 (11.0–12.7)
HR	0.79 (95% CI 0.71–0.88)	0.91 (96.5% CI 0.77–1.07; P not tested)		
TRAEs, %	N = 782	N = 767	N = 403	N = 389
Any	95	89	80	92
Grade 3–4	60	45	38	46
Led to discontinuation	38	25	22	26

[a]Per BICR m, median; ORR, objective response rate; TRAE, treatment-related adverse event

CheckMate 649研究：一项全球多中心，开放标签，III期临床研究，评估Nivolumab (NIVO) +化疗(Chemo)或Ipilimumab (IPI) vs化疗作为一线(1L)治疗进展期胃癌/胃食管交界处癌/食管腺癌疗效

GASTROINTESTINAL CANCERS

Upper GI tumours: survival benefits with PD-1 inhibitors plus chemotherapy, but not nivolumab plus ipilimumab

19 Sep 2021 **ESMO Congress 2021**

BeiGene

新的探索1：DisTinGuish研究— PD-1 + Chemo + anti-DKK1

一项 IIa 期非随机、开放标签、多中心干预性研究，评估DKN-01联合替雷丽珠单抗和化疗作为一线治疗未经治疗的晚期胃食管腺癌的有效性和安全性。

主要纳入标准

- 不能手术、局部晚期或转移性 G/GEJ 腺癌患者
- 患者可能已经接受过先前的新辅助或辅助治疗，只要完成后至少 6 个月没有疾病复发

治疗方案

1、DKN-01：300 毫克，D1、D15 静脉注射）
2、替雷利珠单抗：200 毫克，D1静脉注射
3、奥沙利铂：130 毫克/平方米，D1静脉注射
4、卡培他滨：1000 毫克/平方米，D 1-15 天，口服，2次/天。

每 21 天为1个周期

主要终点： 6个月客观缓解率 (ORR)

次要终点： 缓解持续时间 (DoR)、疾病控制率 (DCR) 和无进展生存期 (PFS) 在改良意向治疗 (mITT) 人群 (完成 ≥ 1 个周期) 以及 DKK1 高 (H-score ≥35) 和低组之间的比较。

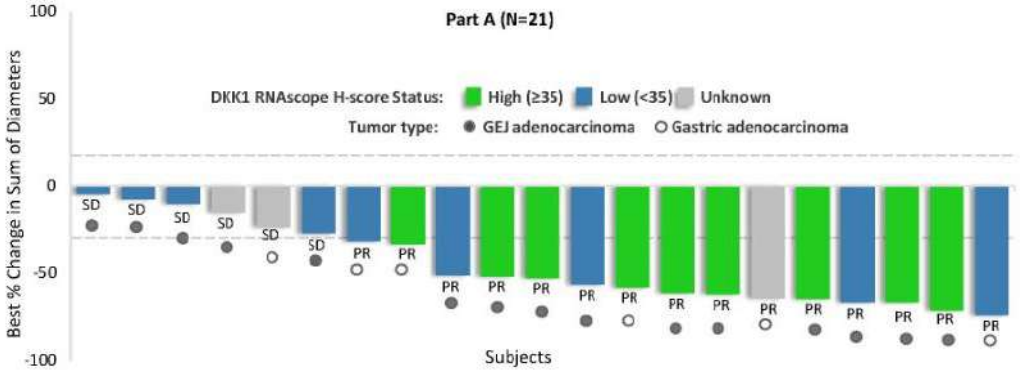
DKK1在多种肿瘤中高度表达，它通过激活Akt信号通路，可以上调VEGFR2的表达，从而促进血管增生，为肿瘤的生存和增殖提供养分。另一方面，它通过调节Wnt信号通路，增强髓源性抑制细胞（MDSC）的免疫抑制能力。DKN-01是一款靶向DKK1的潜在“first-in-class”抗体，通过与DKK1相结合，可以降低血管增生，并且上调IFNγ，IL-15 and IL-33等关键细胞因子的水平，促进肿瘤细胞的死亡。它同时可以通过激活Wnt信号通路，对MDSC细胞进行重编程，降低它们的免疫抑制活性。

研究结果：D + T + CAPOX 方案主要研究终点 ORR:68.2%，DKK1-high组ORR：90%

- 25例GEA患者入选，胃食管交界区(GEJ)腺癌17例(68%)，8例胃癌患者(32%)；21例患者可获得RNAscope DKK1表达
- 平均治疗持续时间为 3 个月，迄今为止最长的研究持续时间为 7 个月，19 名患者仍在接受治疗。

	D + T + CAPOX 方案 (mITT人群，N=22)
客观缓解(ORR)	68.2% (15 PR, 6 SD, 1 NE)
DKK1-high	90%
DKK1-low	55.6%
疾病控制(DCR)	95.5%
PFS（95% CI: ）	未达到
缓解持续时间 (DOR)	未达到

Best Overall Response, n (%)				
	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
mITT population (N=22)	15 (68.2%)	6 (27.3%)	0	1 (4.5%)
DKK1-high (N=10)	9 (90.0%)	0	0	1 (10.0%)
DKK1-low (N=9)	5 (55.6%)	4 (44.4%)	0	0
DKK1 unknown (N=3)	1 (33.3%)	2 (66.7%)	0	0



D + T + CAPOX 方案不良反应：TEAE 为 G1/2：主要为贫血、血小板减少、疲劳、腹泻、恶心。没有相关的 G3/4 毒性；总共4例G5； 1 相关事件肺栓塞。

mITT人群包括22例患者;可评价应答(RE)的mITT人群为21例

新的探索2： PD-1 + Chemo + anti-VEGF TKI

一项多中心、开放标签、II期临床研究，评估卡瑞利珠单抗+化疗序贯卡瑞利珠单抗+阿帕替尼一线治疗晚期G/GEJ腺癌的抗肿瘤活性和安全性。

主要终点： 6个月客观缓解率 (ORR)

次要终点： 缓解持续时间 (DoR)、总生存期(OS) 、无进展生存期 (PFS) 及安全性。

BeiGene

研究结果

卡瑞利珠单抗+化疗序贯卡瑞利珠单抗+阿帕替尼一线治疗晚期G/GEJ腺癌，具有良好的抗肿瘤活性和生存期，安全性可控。

	卡瑞利珠单抗+化疗序贯卡瑞利珠单抗+阿帕替尼方案 (mITT人群，N=48)
客观缓解率(ORR)	**58.3%** (95% CI, 43.2-72.4)
中位总生存期（mOS）	14.9个月 (95% CI, 13.0-18.6)
中位无进展生存期 (mPFS)	6.8个月 (95% CI, 5.6-9.5)
中位缓解持续时间(mDOR)	5.7个月 (95% CI, 4.4-8.3)


CLINICAL CANCER RESEARCH

Home About Articles For Authors Alerts News COVID-19 Webinars Search

Clinical Trials: Immunotherapy

Camrelizumab Combined with Chemotherapy Followed by Camrelizumab plus Apatinib as First-line Therapy for Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

Zhi Peng, Jia Wei, Feng Wang, Jiaer Ying, Yanhong Deng, Kangsheng Gu, Ying Cheng, Xianglin Yuan, Juxiang Xiao, Yanfei Tai, Linna Wang, Jianjun Zou, Yanqiao Zhang, and Lin Shen

Add to Cart ($50)

DOI: 10.1158/1078-0432.CCR-20-4691 Published June 2021 Check for updates

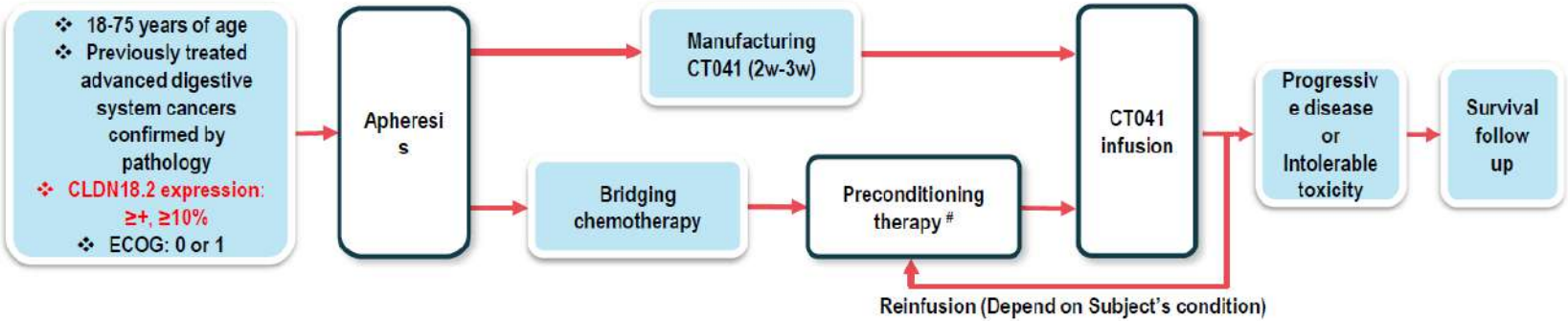
最常见的≥3级治疗相关不良事件(>10%)是血小板计数下降(20.8%)、中性粒细胞计数下降(18.8%)和高血压(14.6%)。

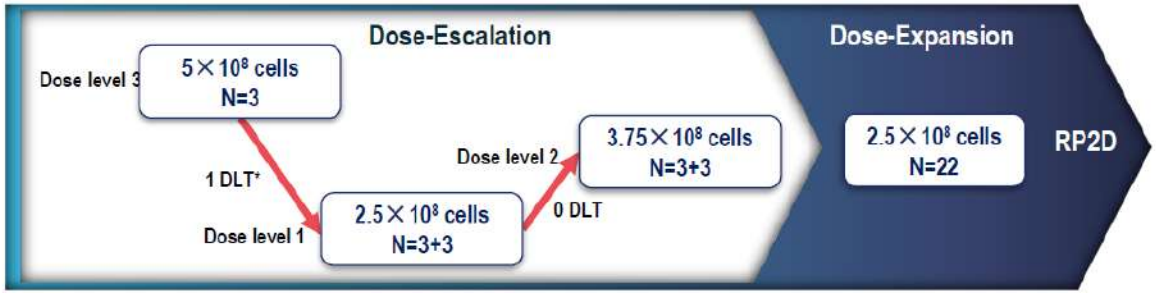
1例患者(2.1%)因肝功能异常和肺间质疾病发生治疗相关死亡。

BeiGene

新的探索3：CLDN 18.2-targeted CAR-T

研究设计





Primary Objectives: Safety and tolerability

Secondary Objectives : Efficacy, Pharmacokinetics

Explorative Objectives : Covariate analysis for efficacy, biodistribution of CT041

#Fludarabine 25 mg/m²/day(D–4~D–3)+Cyclophosphamide 250 mg/m²/day (D–4~D–2)+Nab-paclitaxel 100mg or gemcitabine 1000mg (D–3)

*One patient suffered gastrointestinal hemorrhage in D51 after reinfusion, which was considered to be caused by obvious tumor regression. After discussion among the investigators, DMC and partners, it was decided to lower the dose to 2.5×10⁸ cells.

BeiGene

研究结果--安全性：耐受性良好

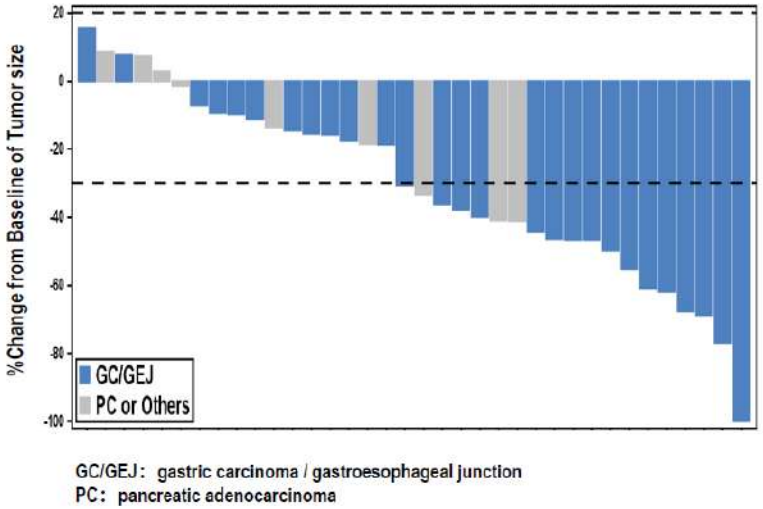
总体耐受性良好

- 最常见的3级AEs是血液学毒性，并在2周内恢复。
- 1/2级CRS 35例(94.5%)，3级CRS无1例
- 没有CRES /ICANS
- 第2次输注后第51天DLT胃肠道出血导致进一步纳入的剂量减少。
- 6例报告粘膜损伤，1例为3级。
- 3种剂量水平的安全性无明显差异。
- 无治疗相关死亡

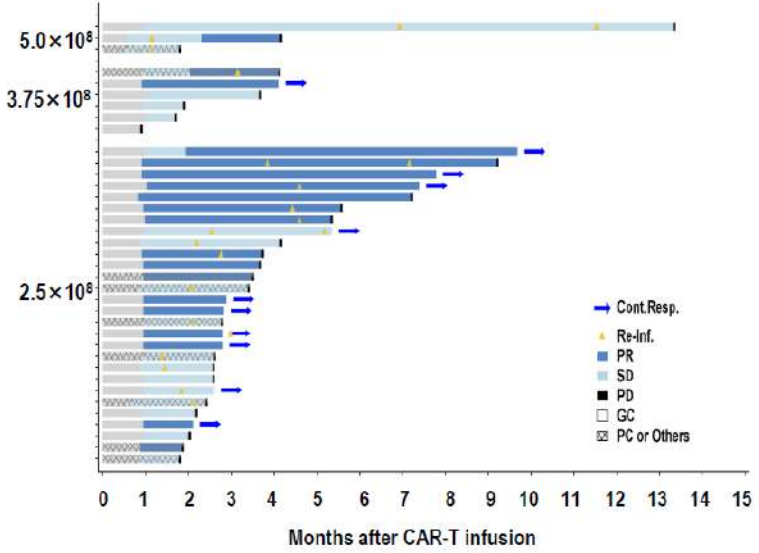
	Dose Escalation			Dose Expansion	Total
	$2.5x10^8$ (N=6)	$3.75x10^8$ (N=6)	$5x10^8$ (N=3)	$2.5x10^8$ (N=22)	(N=37)
ALL AEs	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
DLT	0	0	1 (33.3)	0	1 (2.7)
AE leading to study withdrawal	0	0	0	0	0
AE leading to drug withdrawal	0	0	1 (33.3)	0	1 (2.7)
AE leading to death	0	0	0	0	0
Treatment related SAE	0	0	1 (33.3)	2 (9.1)	3 (8.1)
Treatment related AEs	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
≥Grade 3 fever	1 (16.7)	0	1 (33.3)	1 (4.5)	3 (8.1)
Grade 3	1 (16.7)	0	1 (33.3)	1 (4.5)	3 (8.1)
Grade 4	0	0	0	0	0
≥Grade 3 hematological toxicity	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
Grade 3	6 (100)	6 (100)	3 (100)	22 (100)	37 (100)
Grade 4	5 (83.3)	6 (100)	3 (100)	21 (95.5)	35 (94.6)
CRS	5 (83.3)	6 (100)	3 (100)	21 (95.5)	35 (94.6)
Grade 1	2 (33.3)	4 (66.7)	0	11 (50.0)	17 (45.9)
Grade 2	3 (50.0)	2 (33.3)	3 (100)	10 (45.5)	18 (48.6)
≥Grade 3 neurotoxicity	0	0	0	0	0
≥Grade 3 infections	0	0	0	0	0
Gastric mucosal injury	0	0	0	6 (27.3)	6 (16.2)
≥Grade 3	0	0	0	1 (4.5)	1 (2.7)

研究结果--ORR和DCR

37名受试者中有36人有靶病灶。31例患者靶病灶有不同程度的收缩。
根据RECIST 1.1, ORR和DCR分别达到48.6%(18/37)和73.0%(27/37)。



GC/GEJ：gastric carcinoma / gastroesophageal junction
PC：pancreatic adenocarcinoma



小结

HER2-晚期胃癌研究步步为营

- CheckMate 649、ATTRACTION-4为晚期胃癌一线治疗带来了革命性的突破；
- ORIENT-16 进一步验证了免疫联合化疗在中国人群中的获益；
- PD-1联合化疗的疗效影响因素仍需进一步研究；
- Pembro单药、Nivo 联合 IPI 未能为晚期胃癌患者带来优于化疗的生存获益；
- PD-1+化疗联合其它免疫/靶向药物及CAR-T治疗等晚期胃癌领域丰富的探索及研究布局可能为胃癌治疗提供新的前进方向。

谢谢聆听!