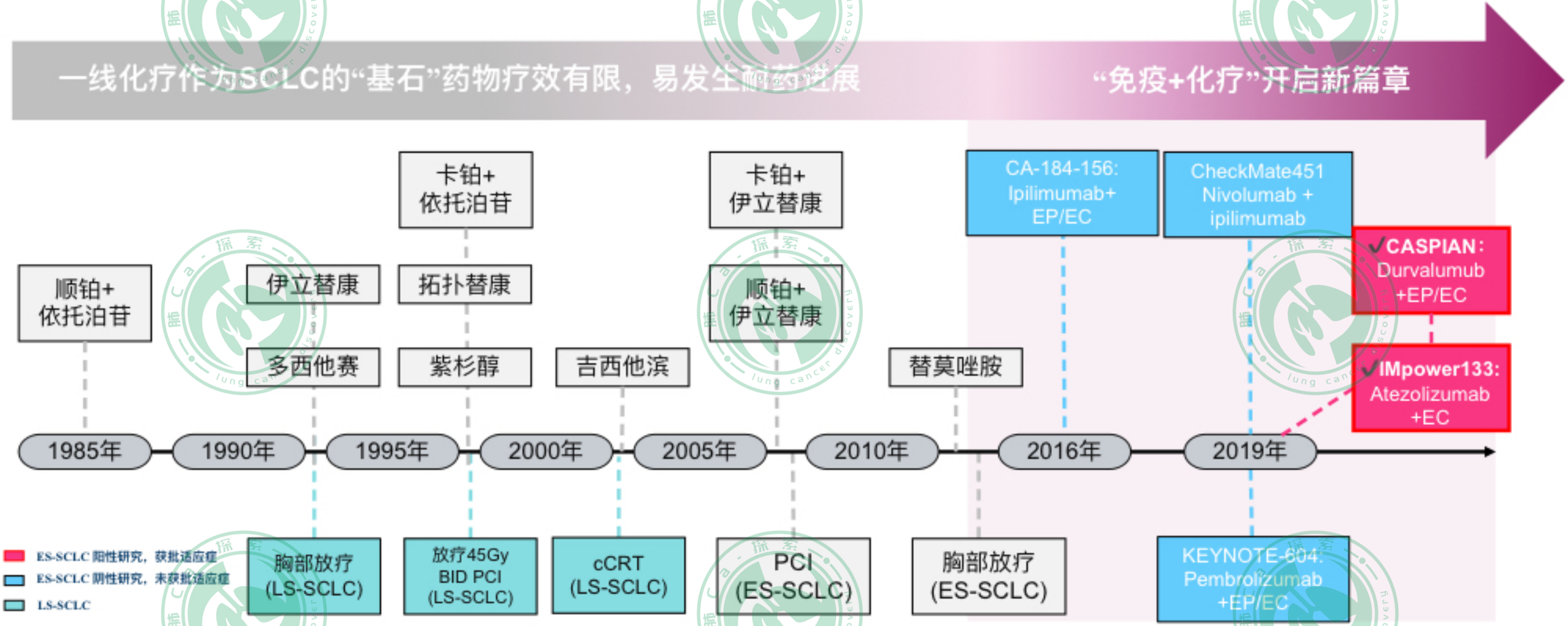
广泛期小细胞肺癌后线选择

高雯

2023-3-30

SCLC治疗策略演变

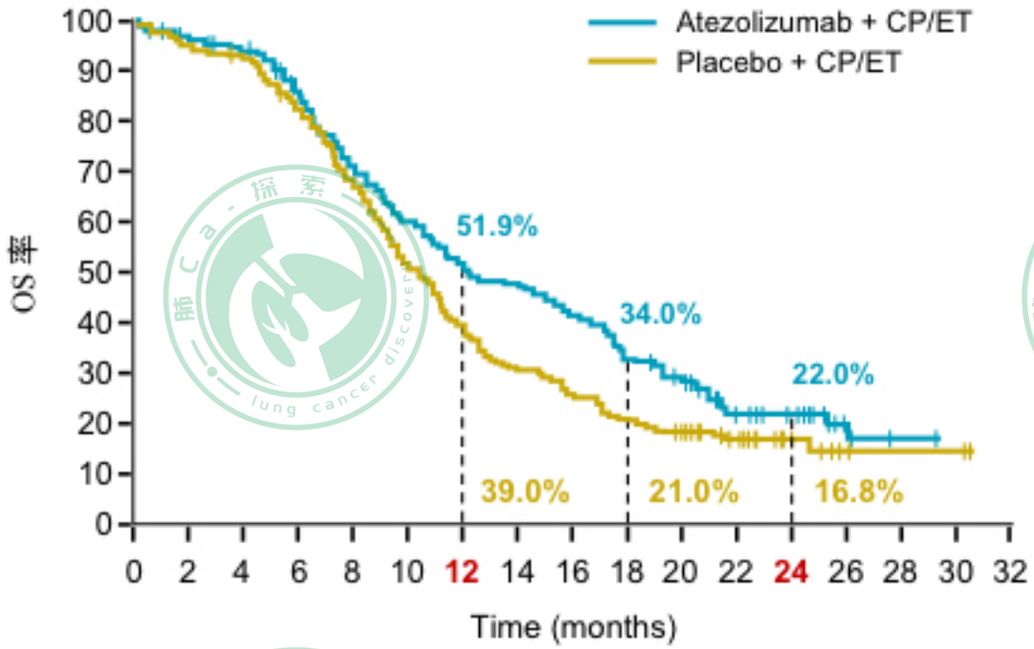


1. Sabari, et al. Nat Rev Clin Oncol. 2017 September ; 14(9): 549–561.
2. Reck M, et al. J Clin Oncol. 2016 Nov 1;34(31):3740-3748.
3. Owonikoko. ELCC 2019. Abstr LBA1_PR.
4. N Engl J Med
5. .1992 Dec 3;327(23):1618-24.
6. Rudin CM, et al. J Clin Oncol. 2020 Jul 20;38(21):2369-2379.
7. Paz-Ares L, et al. Lancet. 2019;394(10212):1929-1939.
8. Martin Reck presented at ESMO 2019:IMpower133 Updated OS Analysis
9. Takada. JCO. 2002;15:3054
10. ANDREW T.The New England Journal of Medicine 1999

ES-SCLC 1L :PD-L1+化疗建立治疗新标准,提高长期生存获益

IMpower133

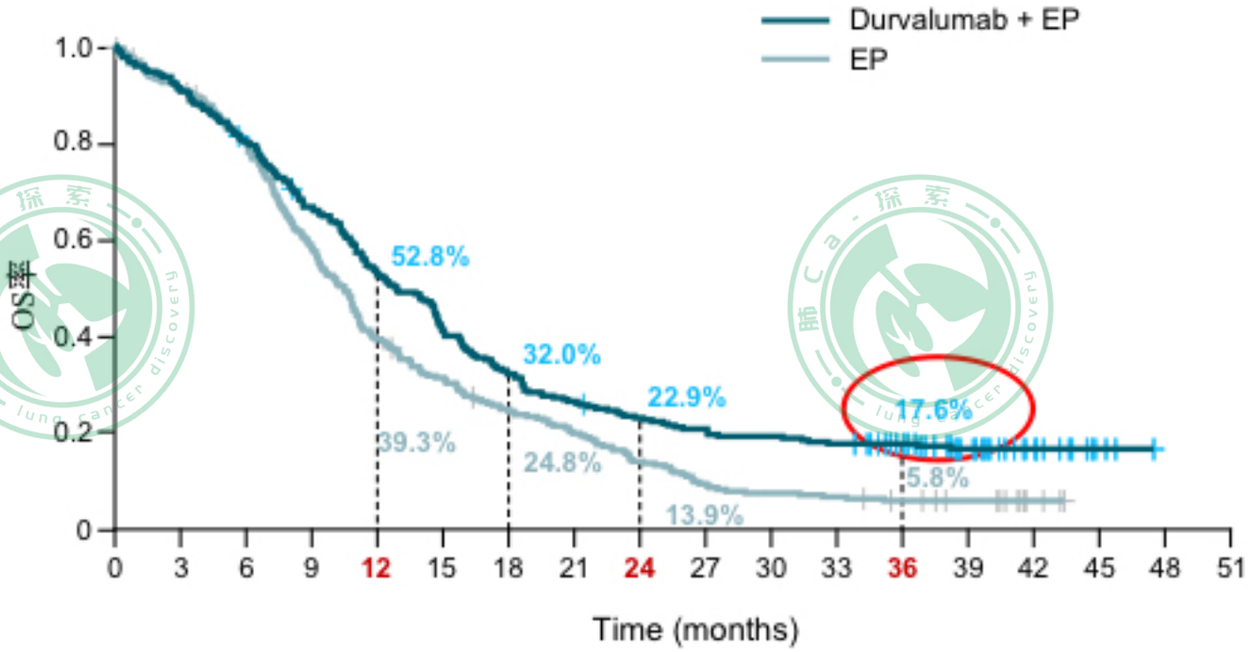
mF/U：**22.9 months**



mOS **12.3** vs **10.3** mo
HR 0.76 (0.60, 0.95) P=0.0154

CASPIAN

mF/U：**39.4 months**

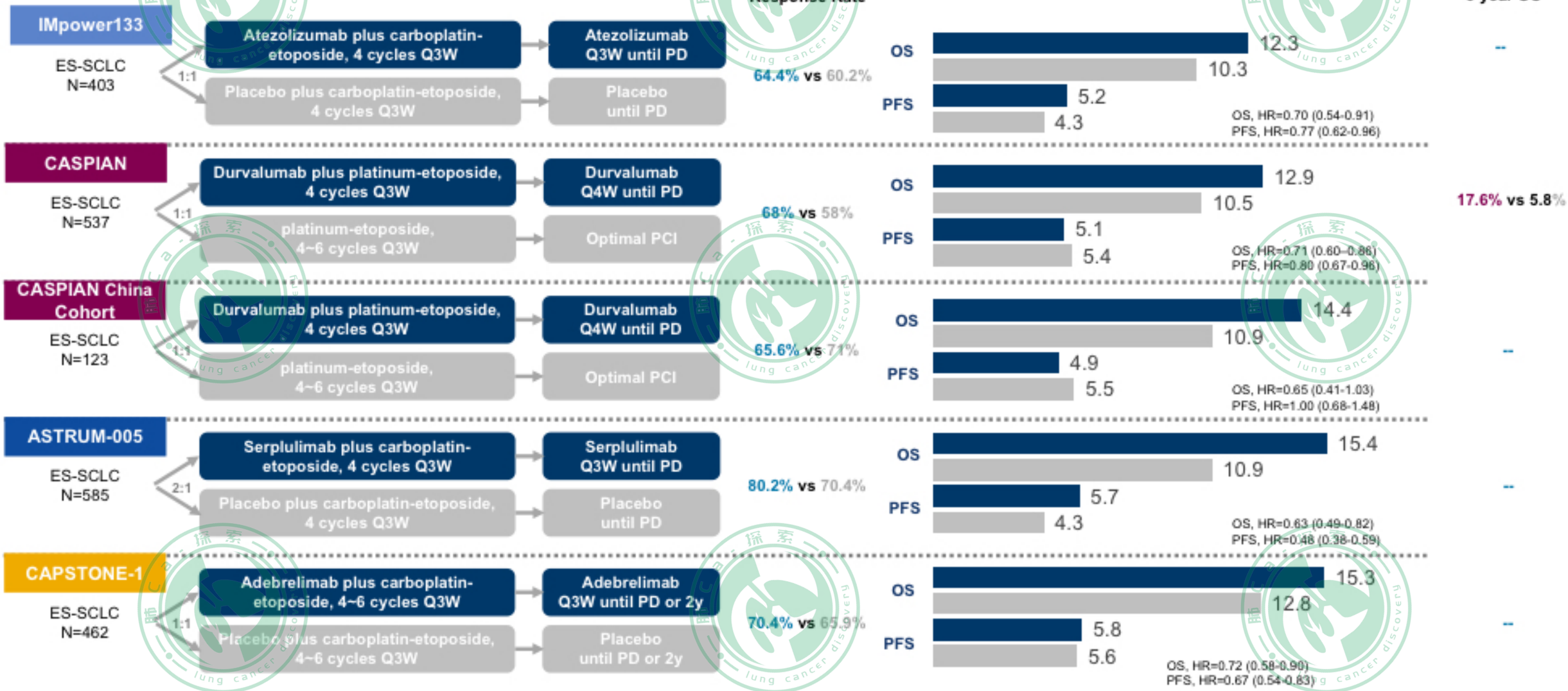


mOS **12.9** vs **10.5** mo
0.71 (0.60–0.86) P=0.0003
3年OS率 17.6% vs 5.8%

Data listed are from different clinical trials; not for cross-trial comparison
CP, carboplatin; EP, platinum-etoposide; ES-SCLC, extensive-stage small cell lung cancer; ET, etoposide; HR, hazard ratio; IO, immuno-oncology; mOS, median overall survival; ns, not significant; OS, overall survival

1.Martin Reck presented at ESMO 2019:IMpower133 Updated OS Analysis
2. Lancet Oncol. 2021 Jan;22(1):51-65. ESMO Open. 2022 Mar 10;7(2):100408.

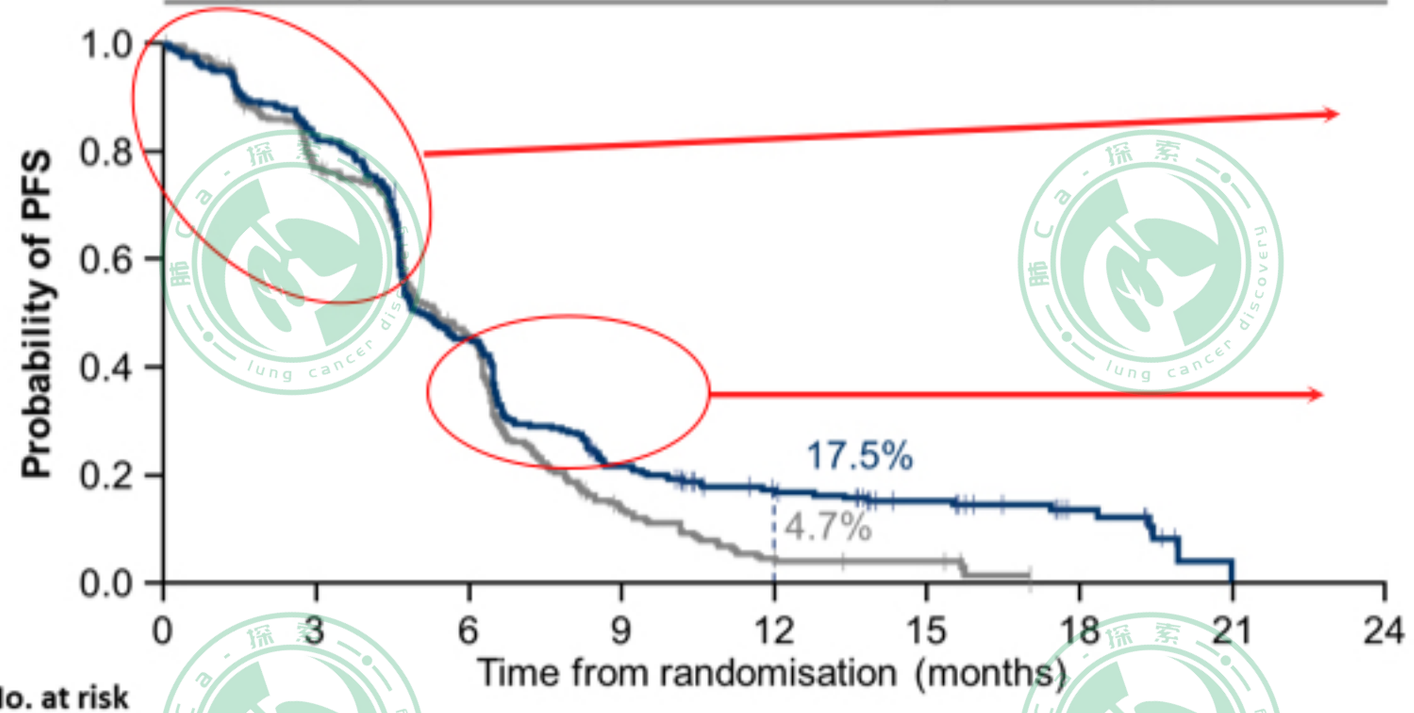
ES-SCLC一线关键临床研究



1.阿替利珠单抗注射液说明书, 2021年10月13日版. 2.度伐利尤单抗注射液说明书, 2021年7月12日版. 3.Ying Cheng. 2022 ASCO. Abstr 8505. 4. Wang J, et al. Lancet Oncol. 2022;23(6):739-747.

如何应对耐药?

	Durvalumab + EP	EP
事件, n/N (%)	226/268 (84.3)	233/269 (86.6)
mPFS*, 月 (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	



No. at risk

D + EP	268	220	119	54	34	22	10	0	0
EP	269	194	109	30	9	7	0	0	0

原发性耐药 (primary resistance)：也称固有耐药，指肿瘤对于免疫治疗自始至终均无反应

获得性耐药 (acquired resistance)：患者存在抗肿瘤免疫反应，起始对免疫治疗有反应或者在治疗的过程中，肿瘤进展，抵抗性瘤细胞亚群可能是治疗起始阶段就存在，也可能是治疗过程中被编辑出来

1. Paz-Ares L, et al. Lancet. 2019 Nov 23;394(10212):1929-1939.
2. Sharma P et al, Cell. 2017;168(4):707-723

复发性SCLC-指南提示

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Small Cell Lung Cancer

NCCN Guidelines Index
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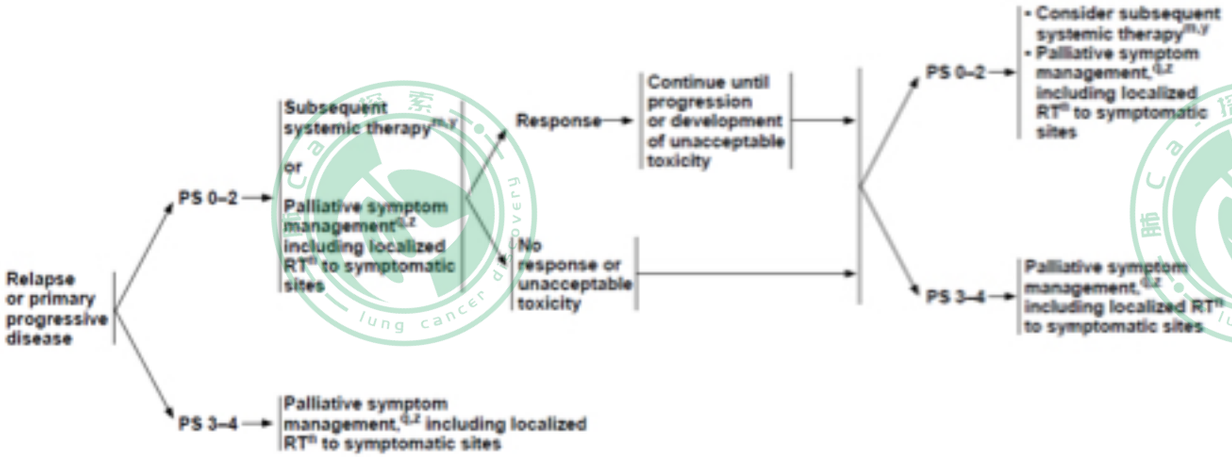
PROGRESSIVE DISEASE　　SUBSEQUENT THERAPY/PALLIATIVE THERAPY



（一）小细胞肺癌的二线治疗

分层	Ⅰ级推荐	Ⅱ级推荐	Ⅲ级推荐
≤ 6 个月复发	拓扑替康（1 类）[1-3] 参加临床试验	伊立替康（2A 类）[4] 紫杉醇（2A 类）[5, 6] 多西他赛（2A 类）[7] 吉西他滨（2A 类）[8, 9] 口服依托泊苷（2A 类）[10, 11] 长春瑞滨（2A 类）[12, 13] 替莫唑胺（2A 类）[14, 15]	苯达莫司汀（2B 类）[16]
>6 个月复发	选用原方案*		

*. 不适用于一线应用免疫靶向药物治疗的患者，对于使用 atezolizumab 或 durvalumab 维持治疗 >6 个月后复发的患者，建议再次使用卡铂 + 依托泊苷或顺铂 + 依托泊苷。

拓扑替康及其新型制剂

VOLUME 24 · NUMBER 34 · DECEMBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY

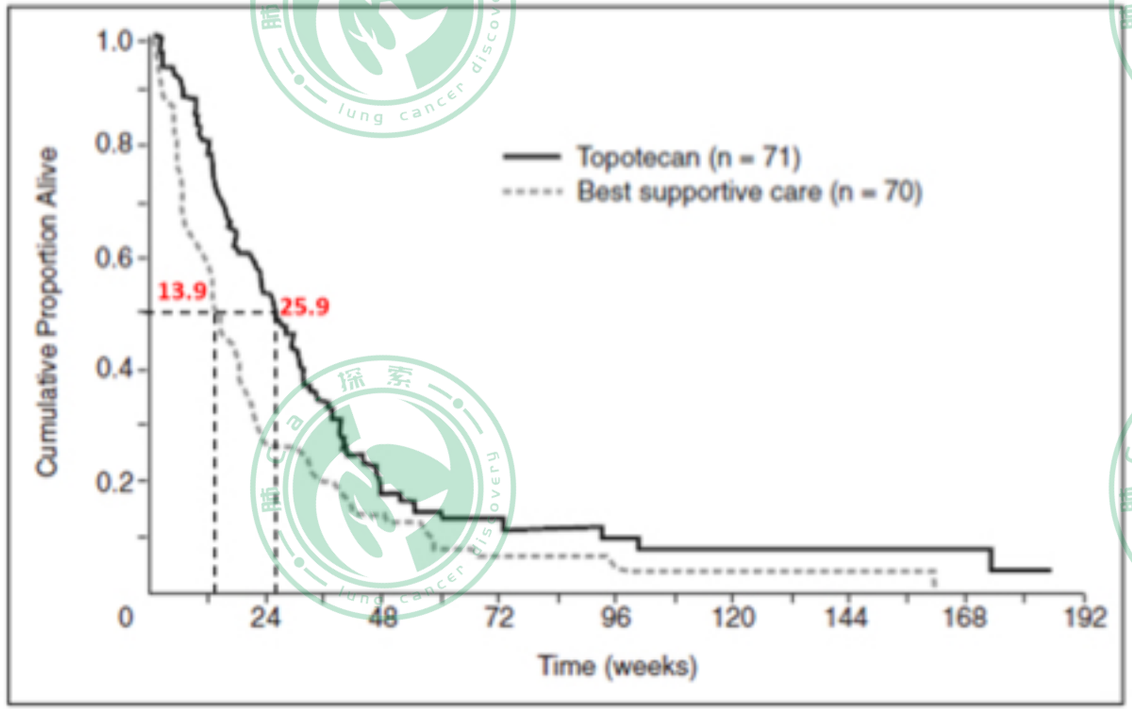
ORIGINAL REPORT

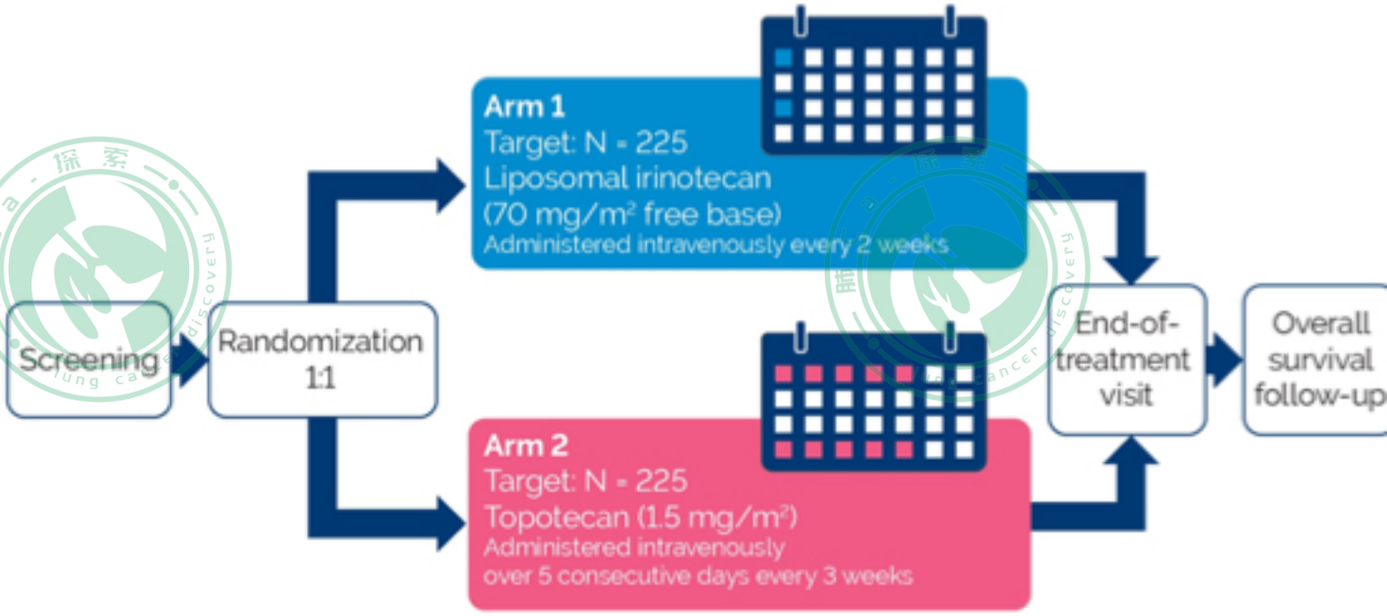
Phase III Trial Comparing Supportive Care Alone With Supportive Care With Oral Topotecan in Patients With Relapsed Small-Cell Lung Cancer

Mary E.R. O'Brien, Tudor-Eliade Ciuleanu, Hristo Tsekov, Yaroslav Shparyk, Branka Čučević, Gabor Juhasz, Nicholas Thatcher, Graham A. Ross, Graham C. Dane, and Theresa Crofts

From the Royal Marsden Hospital, Sutton; Christie Hospital, Manchester; GlaxoSmithKline, Harlow, United King

A B S T R A C T





其他化疗方案

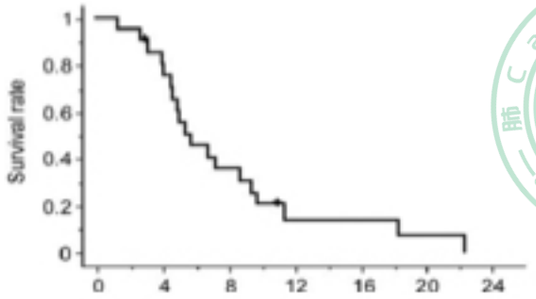
Phase II Study of Weekly Paclitaxel for Relapsed and Refractory Small Cell Lung Cancer

NOBUYUKI YAMAMOTO[1,2], JUNJI TSURUTANI[1], NARUO YOSHIMURA[3], GYO ASAI[1,2], AZUSA MORIYAMA[1], KAZUHIKO NAKAGAWA[1], SHINZO KUDOH[3], MINORU TAKADA[4], YOSHIAKI MINATO[5] and MASAHIRO FUKUOKA[1]

Table III. *Response data.*

		No. of patients					Response rate (%)
		CR	PR	NC	PD	NE	
Total	21	0	5	4	11	1	23.8
Sensitive	11	0	3	3	5	0	27.3
Refractory	10	0	2	1	6	1	20.0

CI = confidence interval; CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; NC = no change.



Phase II Trial of Gemcitabine/Irinotecan in Refractory or Relapsed Small-Cell Lung Cancer

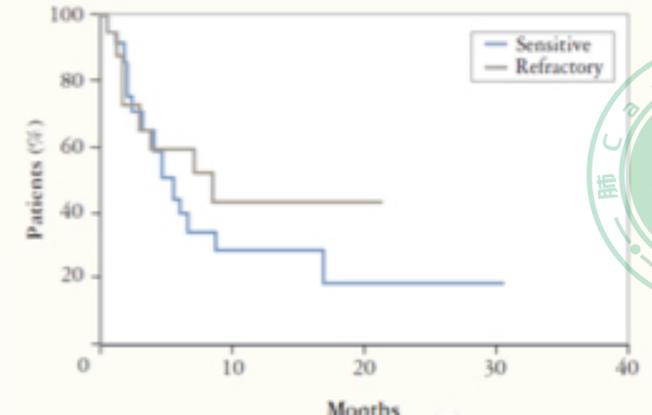
Wolfgang Schuette,[1] Sylke Nagel,[1] Stefan Juergens,[1] Ines Bork,[2] Bettina Wollschlaeger,[2] Steffen Schaedlich,[1] Thomas Blankenburg[1]

Table 2 Response to Treatment for All Patients and for Patients with Sensitive and Refractory Disease

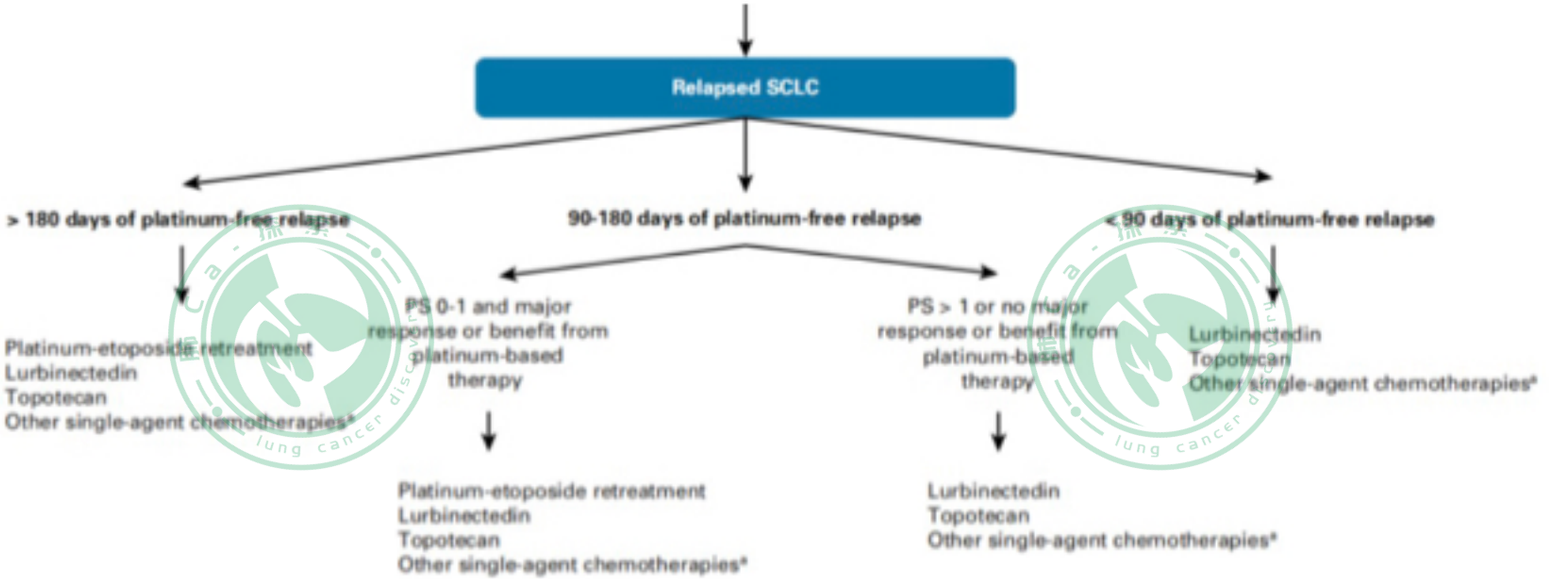
Response	All Patients (N = 35)	Sensitive (n = 20)	Refractory (n = 15)
Complete Response	2 (6)	1 (5)	1 (7)
Partial Response	4 (11)	1 (5)	3 (20)
Stable Disease	7 (20)	4 (20)	3 (20)
Progressive Disease	22 (63)	14 (70)	8 (53)

Values in parentheses are percentages

Figure 3 Overall Survival for Patients with Refractory Disease Versus Patients with Sensitive Disease



其他化疗方案

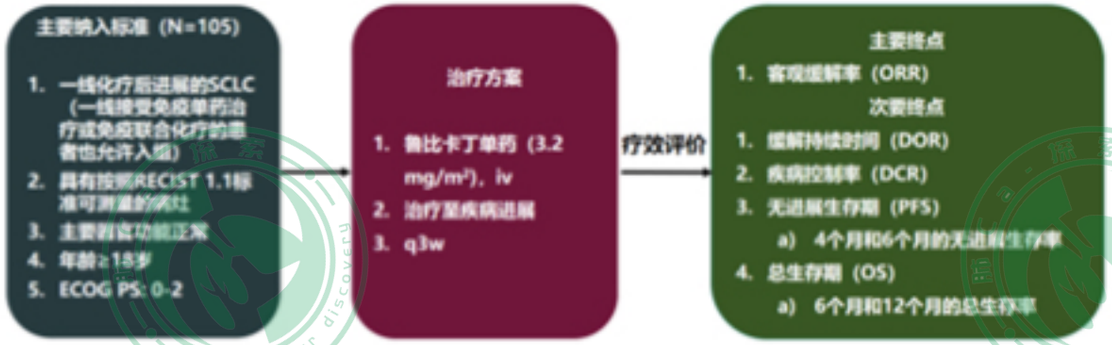


- 对于敏感性复发患者，含铂化疗再挑战已被广泛用于临床实践；
- 法国研究：敏感性复发后，卡铂联合依托泊苷化疗患者的中位PFS优于单药，晚期复发大于180天患者获益最岷县，OS无差异；
- 日本研究：含铂三药OS显著延长，18.2个月 vs 12.5个月；，PFS OS均有意义，AE多，不是经典推荐

Lubrinectedin及其联合探究

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo, Vivek Subbiah*, Benjamin Besse, Victor Moreno, Rafael López, María Ángeles Galo, Solange Peters, Santiago Ponce, Cristian Fernández, Vicente Alfaro, Javier Gómez, Carmen Kahatt, Ali Zeaiter, Khalil Zaman, Valentina Boni, Jennifer Arrondeau, Maite Martínez, Jean-Pierre Delord, Ahmad Awada, Rebecca Kristeleit, María Eugenia Olmedo, Luciano Wannesson, Javier Valdivia, María Jesús Rubio, Antonio Anton, John Sarantopoulos, Sant P Chawla, Joaquín Mosquera-Martínez, Manolo D'Arcangelo, Armando Santoro, Víctor M Villalobos, Jacob Sands, Luis Paz-Ares*



疗效	患者（n=105）	CTFI≥90天（n=60）	CTFI＜90天（n=45）
CR	0	0	0
PR	37 (35%)	27 (45%)	10 (22%)
SD	35 (33%)	22 (37%)	13 (29%)
PD	28 (27%)	10 (17%)	18 (40%)
无法评价	5 (5%)	1 (2%)	4 (9%)
ORR，% (95% CI)	**35.2% (26.2–45.2)**	**45.0% (32.1–58.4)**	**22.2% (11.2–37.1)**
DCR，% (95% CI)	**68.6% (58.8–77.3)**	**81.7% (69.6–90.5)**	**51.1% (35.8–66.3)**
DOR，月 (95% CI)	**5.3 (4.1–6.4)**	**6.2 (3.5–7.3)**	**4.7 (2.6–5.6)**
PFS，月 (95% CI)	**3.5 (2.6–4.3)**	**4.6 (2.8–6.5)**	**2.6 (1.3–3.9)**
4个月PFS率 (95% CI)	46.6% (36.7–56.5)	59.9% (47.1–72.7)	29.1% (15.3–42.8)
6个月PFS率 (95% CI)	32.9% (23.3–42.5)	43.5% (30.1–56.9)	18.8% (6.8–30.9)
OS，月 (95% CI)	**9.3 (6.3–11.8)**	**11.9 (9.7–16.2)**	**5.0 (4.1–6.3)**
4个月OS率 (95% CI)	67.1% (57.6–76.7)	83.6% (73.7–93.5)	45.8% (30.4–61.3)
6个月OS率 (95% CI)	34.2% (23.2–45.1)	48.3% (32.5–64.1)	15.9% (3.6–28.2)

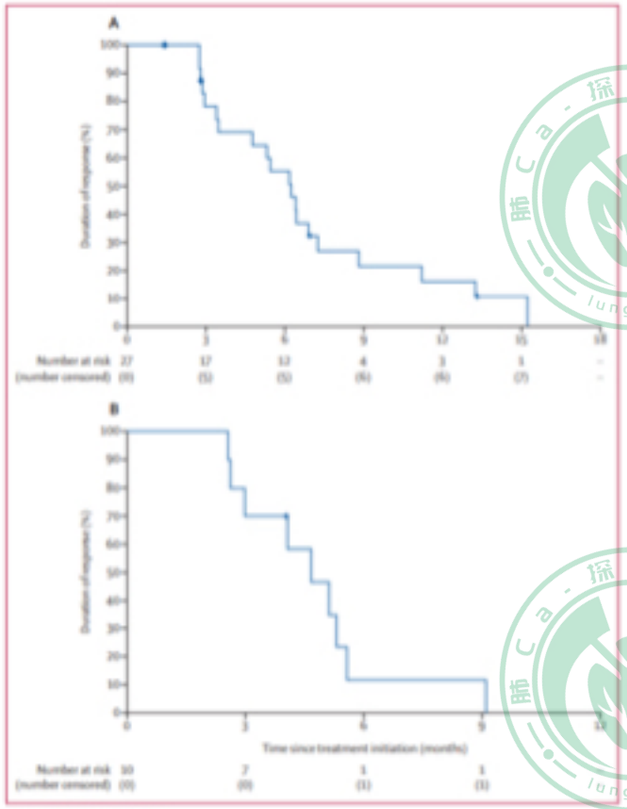
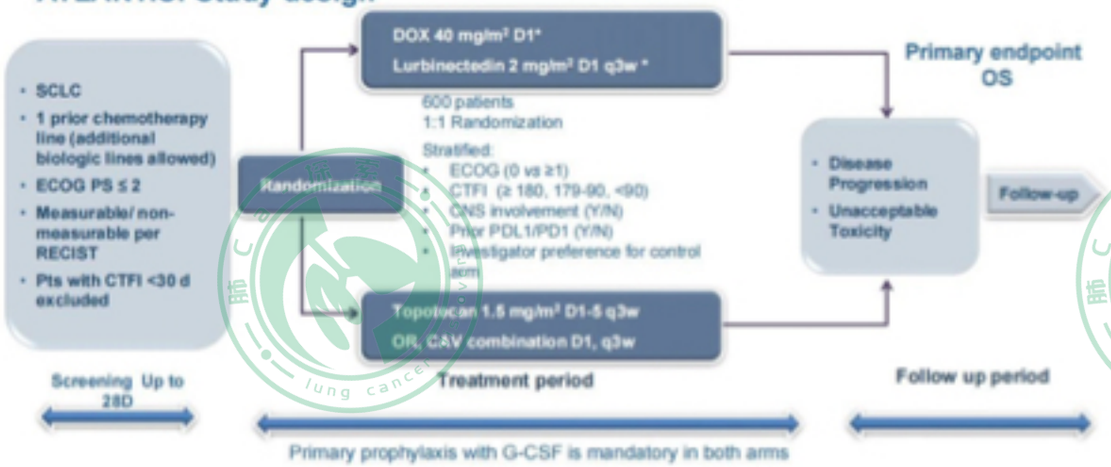


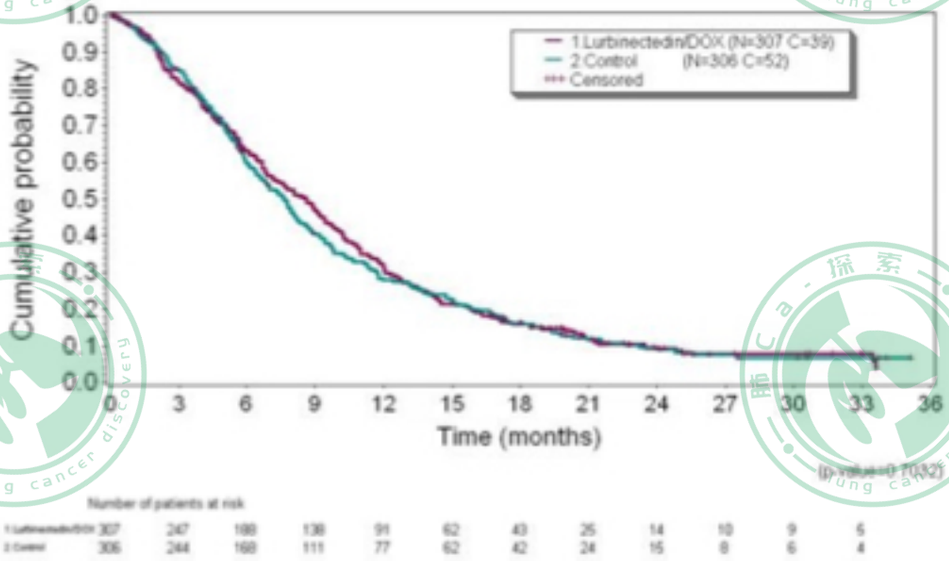
Figure 2: Duration of response
(A) Patients with sensitive disease (chemotherapy-free interval ≥90 days). (B) Patients with resistant disease (chemotherapy-free interval <90 days).

Lubrinectedin及其联合探究

ATLANTIS: Study design



Overall Survival (ITT population)



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	8.6 (7.1, 9.4)	7.6 (6.6, 8.2)	HR : 0.967 (0.815, 1.148)	0.7032
Mean OS, months	10.6	9.9		

免疫联合鲁比卡丁带来新的探索方向

鲁比卡丁联合帕博利珠单抗治疗复发SCLC(LUPER)：一项前瞻性、多中心I/II期临床研究

研究设计：

I期：剂量递增，采用3+3剂量爬坡，主要探索DLT和RP2D

II期：剂量扩展，探索鲁比卡丁联合帕博利珠单抗的有效性

主要入组人群：

- 既往接受化疗后疾病进展（研究开始前≥4周）
- 既往**未接受过免疫治疗**
- ECOG PS 为0-1
- 允许经治疗稳定和无症状脑转移患者入组

Phase 1:
Pembrolizumab 200 mg Q3w + lurbinectedin 起始剂量 2.4 mg /m² Q3w

→

Phase 2:
Pembrolizumab 200 mg Q3w + lurbinectedin RD Q3w

主要研究终点：

- I期：鲁比卡丁MDT和RD
- II期：鲁比卡丁联合帕博利珠单抗的有效性

研究结果：

Figure 1. Best Overall Response according to RECIST v.1.1 N=13

Related TEAE

Overall (N=13)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
TEAEs*	11 (84.6)	7 (53.9)	2 (15.4)
Haematologic	8 (61.5)	3 (23.1)	2 (15.4)
Neutropenia	7 (53.9)	3 (23.1)	2 (15.4)
Thrombocytopenia	3 (23.1)	1 (7.7)	0 (0.0)
Anaemia	2 (15.4)	0 (0.0)	0 (0.0)

- 中位DoT 3.1m(0-14.6)；ORR 30.8%；中位DoR未达到
- 在DL1(2.4 mg/m²)队列中发生1例剂量限制毒性（3级乏力）和1例4级中性粒细胞减少症，持续＞3天
- 在DL2(3.2 mg/m²)队列中未报告剂量限制毒性。RP2D确定为鲁比卡丁3.2 mg/m2和帕博利珠单抗200 mg IV Q3W。

鲁比卡丁联合帕博利珠单抗二线治疗复发SCLC安全性可耐受，有效性有待进一步验证

鲁比卡丁联合度伐利尤单抗治疗复发SCLC：一项前瞻性II期临床研究

研究设计：

入组人群：含铂的化学治疗联合免疫治疗后进展的ES-SCLC患者

治疗方案：

- **第1组**(铂类药物敏感患者)：度伐利优单抗（1500 mg，IV，Q3W）+托泊替康（1.25 mg/m²/天IV，连续5天，Q3W）
- **第2A组**(铂类药物敏感患者)：度伐利尤单抗+鲁比卡丁（3.2 mg/m² IV，每个21天周期的第1天）
- **第2B组**（铂类药物耐药患者）：度伐利尤单+鲁比卡丁（3.2 mg/m² IV，每个21天周期的第1天）

Group 1* (platinum-sensitive†)	Group 2A* (platinum - sensitive†)	Group 2B* (platinum - resistant†)
Treatment with durvalumab (1500 mg given as an intravenous [IV] infusion once every 3 weeks) and topotecan (1.25 mg/m2/day IV for 5 consecutive days every 3 weeks)	Treatment with durvalumab (1500 mg given as an intravenous [IV] infusion once every 3 weeks) and lurbinectedin (3.2 mg/m2 IV on Day 1 of every 21-day cycle).	Treatment with durvalumab (1500 mg given as an intravenous [IV] infusion once every 3 weeks) and lurbinectedin (3.2 mg/m2 IV on Day 1 of every 21-day cycle).

*治疗组的选择基于患者既往含铂治疗疗效：

†含铂治疗疗效：

主要终点：

- **6个月OS率 (组 1)**
- **6个月PFS率 (组 2A&2B)**

- 铂敏感：完成治疗后＞90天 (3个月) 复发
- 铂耐药：完成治疗后≤ 90天 (3个月) 复发

研究从设计更符合临床实际，探索PD-L1抑制剂治疗在SCLC二线的作用

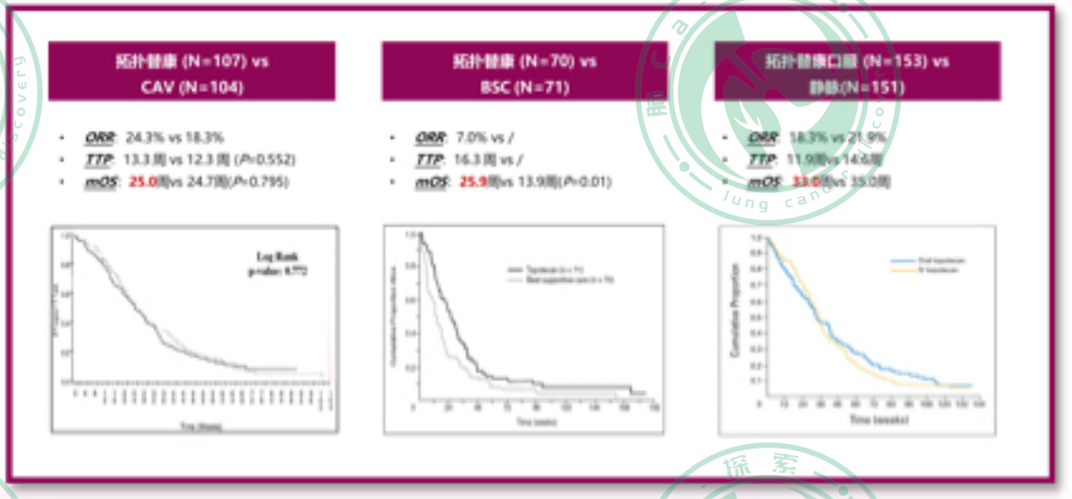
1.Antonio Calles. 2022 ASCO. Abstr 8581. 2.Konstantinos Leventakos. 2022 ASCO. Abstr TPS8604

复发SCLC：拓扑替康疗效有限，VEGFR-TKI后线治疗获益明确

尽管SCLC对于初始治疗敏感，但多数患者在短期内复发及耐药

对于复发后SCLC患者，**目前药物治疗进展缓慢且选择有限**

- ✔ 二线：拓扑替康或原方案（除一线应用免疫）
- ✔ ≥三线：安罗替尼



ALTER 1202：安罗替尼三线治疗复发SCLC

多中心、随机、双盲II期研究

- 18~75岁
- 组织学确诊的SCLC
- 既往至少接受过2次化疗
- ECOG PS 0~2

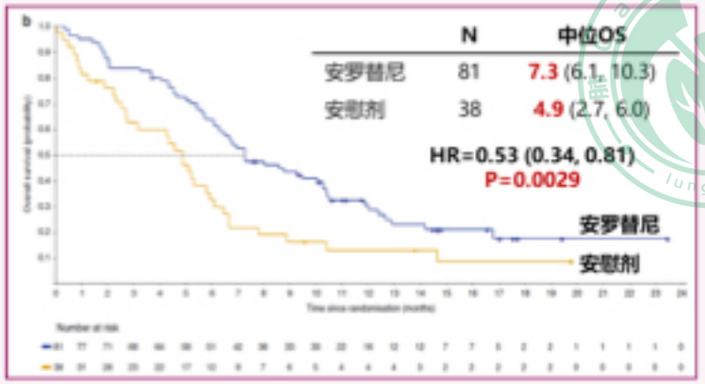
R 2:1

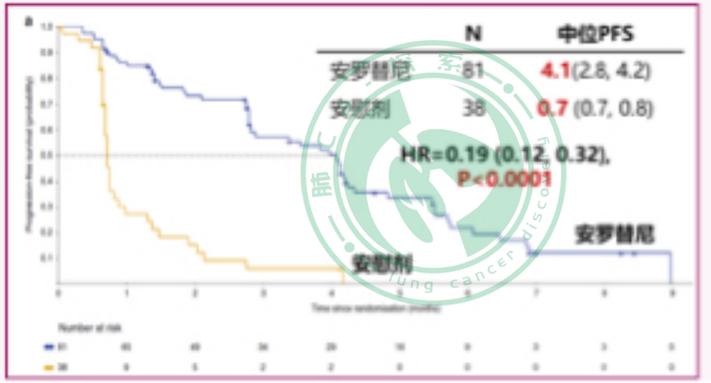
安罗替尼 12mg qd 第1-14天 Q3W N=81

安慰剂 12mg qd 第1-14天 Q3W N=38

分层因素：疾病分期（局限期/广泛期），复发（敏感/耐药）

主要研究终点：PFS；次要研究终点：OS、ORR、DCR、QOL、安全性





1.J Clin Oncol. 1999 Feb;17(2):658-67. 2.J Clin Oncol. 2006 Dec 1;24(34):5441-7. 3.J Clin Oncol. 2007 May 20;25(15):2086-92.

指南优先级推荐及现有临床研究提示

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Small Cell Lung Cancer

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PRINCIPLES OF SYSTEMIC THERAPY

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[c]
Consider dose reduction or growth factor support for patients with PS 2.

Relapse ≤6 months	Relapse >6 months
Preferred Regimens • Topotecan PO or IV[14-16] • Lurbinectedin[17] • Clinical trial **Other Recommended Regimens** • Paclitaxel[18,19] • Docetaxel[20] • Irinotecan[21] • Temozolomide[22,23] • Cyclophosphamide/doxorubicin/vincristine (CAV)[14] • Oral etoposide[24,25] • Vinorelbine[26,27] • Gemcitabine[28,29] • Nivolumab[b,d,30,31] • Pembrolizumab[b,d,32-34] • Bendamustine (category 2B)[35]	**Preferred Regimens** • Original regimen[d,36,37] **Other Recommended Regimens** • Topotecan PO or IV[14-16] • Paclitaxel[18,19] • Docetaxel[20] • Irinotecan[21] • Temozolomide[22,23] • CAV[14] • Oral etoposide[24,25] • Vinorelbine[26,27] • Gemcitabine[28,29] • Nivolumab[b,d,30,31] • Pembrolizumab[b,d,32-34] • Lurbinectedin[38] • Bendamustine (category 2B)

TABLE 2. Efficacy of Selected Non–Immune-Based Treatment Strategies for Relapsed SCLC

Agent	Study (ref)	Design	No.	Response Rates (%)		Median PFS (months)		Median OS (months)	
				Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant
Carboplatin plus etoposide	Baize et al[27]	Phase III	82	49	NA	4.7	NA	7.5	NA
Lurbinectedin	Trigo et al[38]	Single-arm phase II	105	45	22.2	4.6	2.6	11.9	5
Topotecan*	Von Pawel et al[29]	Phase III	213	23.1	9.4	4.3	2.6	9.9	5.7
Amrubicin	Von Pawel et al[29]	Phase III	424	40.9	20.1	5.5	2.8	9.2	6.2
Irinotecan	Masuda et al[30]	Single-arm phase II	15	47		NR		6.2	
Paclitaxel	Smit et al[31]	Single-arm phase II	24	NA	29	NA	2.1	NA	3.3
	Yamamoto et al[32]	Single-arm phase II	22	27.3	20	NR		5.8	
Temozolomide	Pietanza et al[33]	Single-arm phase II	64	23	13	1.6	1	6	5.6
Liposomal irinotecan (nal-IRI)	Paz-Ares et al[34]	Single-arm phase II	25	44		NR		NR	
Lurbinectedin plus doxorubicin	Calvo et al[35]	Phase I	28	91.7	28.5	5.8	NR	NR	NR
	Olmedo et al[36]	Phase I	28	50	10	5.7	1.3	11.5	4.6
Lurbinectedin plus irinotecan	Ponce-Aix et al[37]	Phase Ib-II	21	69	50	8.1	4.8	NR	NR
Temozolomide plus veliparib	Pietanza et al[38]	Randomized phase II	55	41	37	3.8		8.2	
Temozolomide plus olaparib	Farago et al[39]	Phase I-II	50	47.1	28.6	4.5	2.9	9.4	7.4
M6620 plus topotecan	Thomas et al[40]	Single-arm phase II	25	60	30.5	NR		NR	

Abbreviations: NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.
*The efficacy of topotecan has been evaluated in multiple studies. The study by Von Pawel et al is selected in this table as a reference, as this is one of the largest trials conducted in patients with relapsed SCLC.

免疫治疗在复发性SCLC中的尝试

TABLE 3. Efficacy of PD-1 Axis Blockade and Other Immune-Based Treatment Strategies in Relapsed SCLC

				Response Rates (%)		Median PFS (months)		Median OS (months)	
Study (ref)	**Design**	**Treatment**	**No.**	**Sensitive**	**Resistant**	**Sensitive**	**Resistant**	**Sensitive**	**Resistant**
CheckMate 032[41]	Randomized phase I-II	Nivolumab	147	11.6		1.4		7.6	3.1
		Nivolumab plus ipilimumab	96	21.9		1.5		8.5	3.1
CheckMate 331[42]	Phase III	Nivolumab	284	13.7		1.4		7.5	
		Chemotherapy (topotecan-amrubicin)	285	16.5		3.8		8.4	
KEYNOTE-028/158[43]	Single-arm phase Ib-II	Pembrolizumab	83	19.3		2		7.7	
IFCT-1603[44]	Randomized phase II	Atezolizumab	49	2.3		1.4		9.5	
		Chemotherapy (topotecan-platinum retreatment)	24	10		4.3		8.7	
NCT03319940[45]	Phase I	AMG757	64	20		NR		NR	

Abbreviations: NR, not reported; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; SCLC, small-cell lung cancer.

SCLC耐药机制

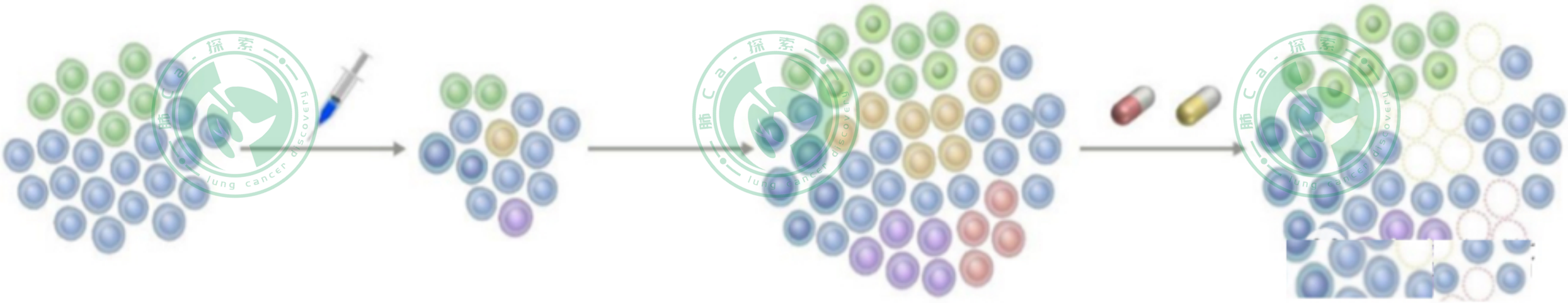
Second Line

Treatment naïve

Responding

Relapsed

Limited Response



免疫联合抗血管疗效初显

信迪利单抗联合安罗替尼二线或后线治疗ES-SCLC，一项前瞻性、单臂II期临床研究

主要入选标准：（N=42）

- 经组织学或细胞学证实的广泛期SCLC
- 经过≥1线含铂化疗
- 年龄≥18
- ECOG PS 0-2

治疗：

安罗替尼（12mg po d1-14）

+

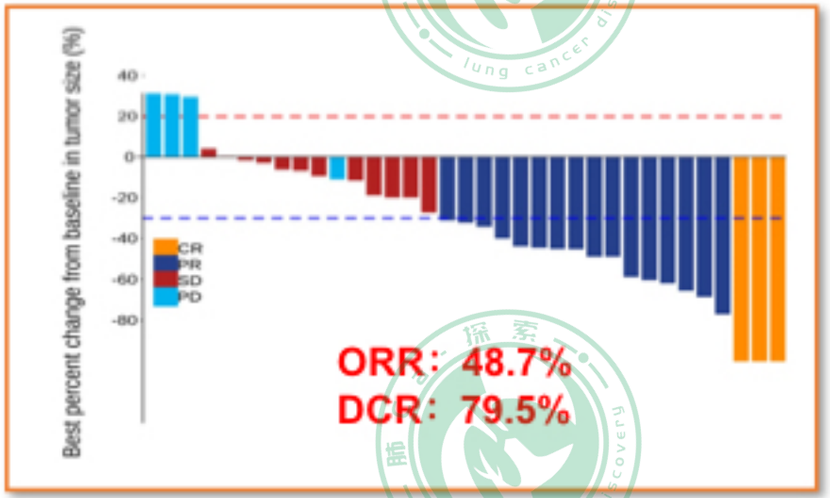
信迪利单抗（200 mg iv d1）

Q3W

- 至疾病进展
- 或不可耐受的毒性
- 最多2年

主要研究终点：PFS

次要研究终点：OS, ORR, DCR, 安全性



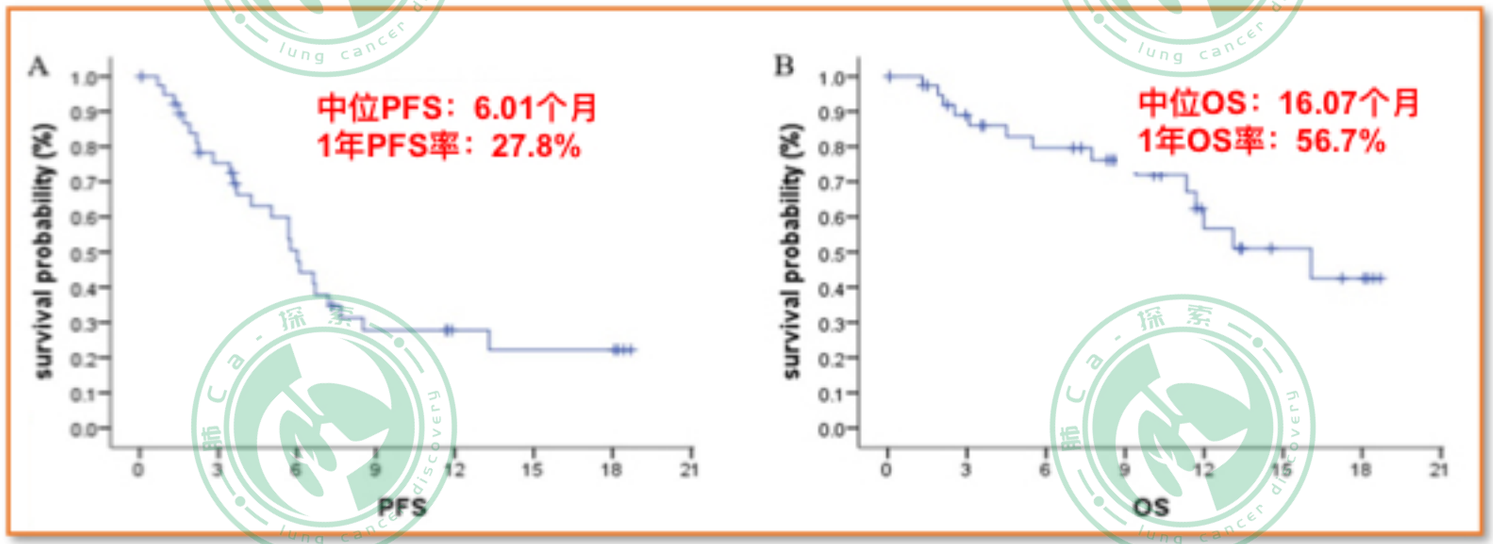


Table 3. Overview of Treatment Related Adverse Events (TRAEs) (n=42)

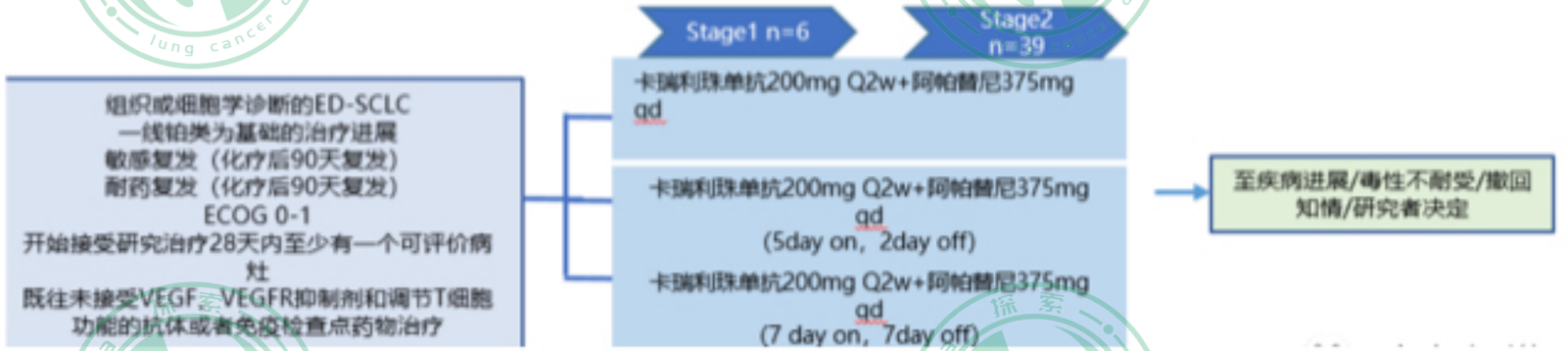
Any TRAE	40(95.2)
Most common TRAEs(≥10% of patients)	
hypothyroidism	19(45.2)
hypoproteinemia	17(40.5)
GGT increased	16(38.1)
Grade 3-4 TRAEs	22(52.4)
elevated GGT	5(11.9)
elevated bilirubin	3(7.1)
elevated ALT	2(4.8)
TRAE leading to drug discontinuation	3(11.5)

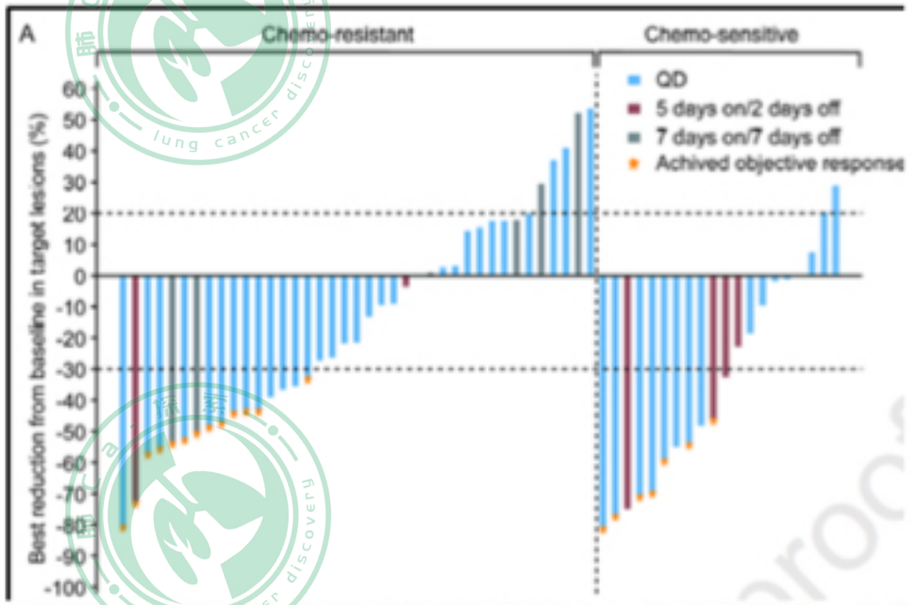
信迪利单抗联合安罗替尼治疗复发SCLC显示出可观的疗效，未来需随机对照研究验证

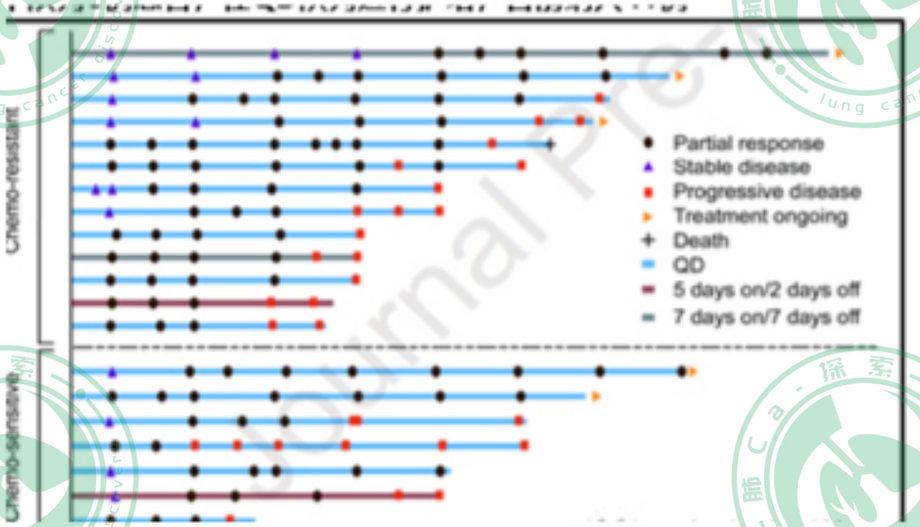
1.Shuxiang Ma. 2022 ASCO. Abstr 8516.

免疫联合抗血管疗效初显

卡瑞利珠单抗联合阿帕替尼二线ES-SCLC, 多中心 两临床研究阶段II期（PASSION）





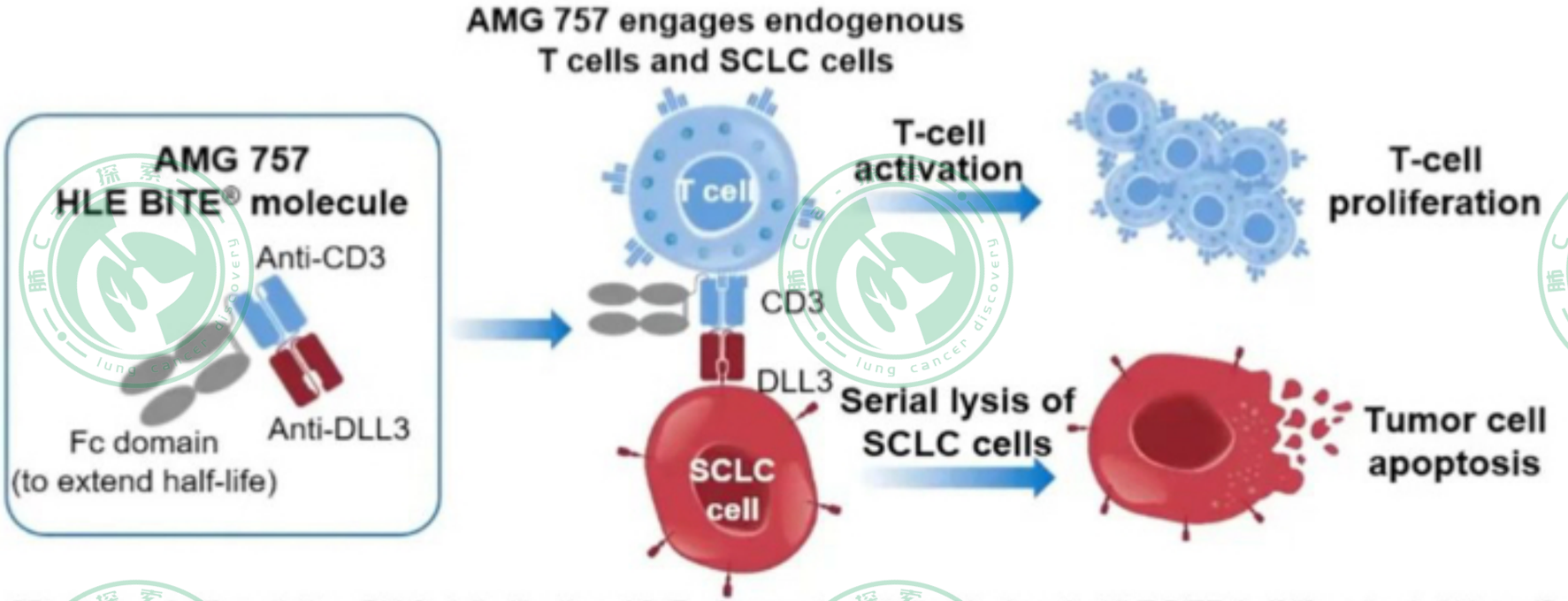


主要终点：ORR，基于第一阶段耐受性和疗效一哥队列选为扩展队列，进行45例扩增

2018年4月20日-2019年3月12日：共纳入59例，第一阶段每个队列6例患者，在QD队列进行扩增，目前纳入41例

双抗在复发性SCLC中的探索

AMG 757: A Half-life Extended BiTE® (bispecific T-cell engager) Immuno-oncology Therapy Targeting DLL3 for SCLC



CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

- BiTE molecules engage a patient's own T cells to attack and eradicate cancer cells[1–3]

1.Stieglmaier J, et al. *Expert Opin Biol Ther*. 2015;15:1093-1099. 2. Einsele H, et al. *Cancer*. 2020;126:3192-3201. 3. Bargou R, et al. *Science*. 2008;321:974-977.

First-in-human Study of AMG 757 in SCLC

Primary Objectives
- Evaluate safety and tolerability in SCLC
- Determine MTD or RP2D

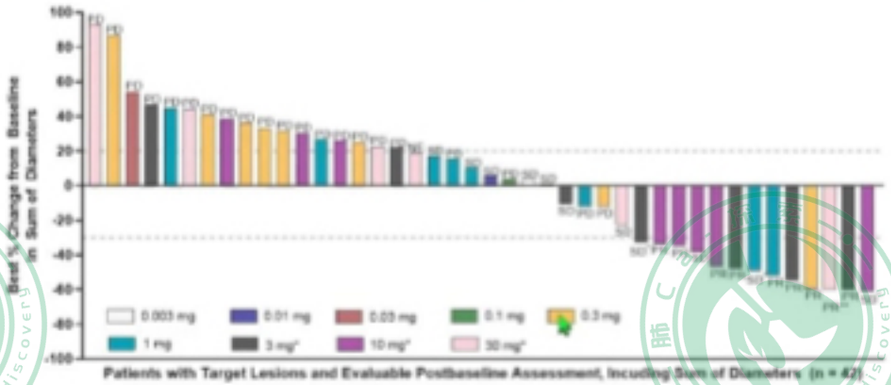
Secondary Objectives
- Characterize PK
- Evaluate preliminary antitumor activity

Exploratory Objectives
- Evaluate immunogenicity, biomarkers, target protein & outcomes

- **Study design** – NCT03319940: open-label, multi-center study of AMG 757 (dose escalation ranging from **0.003 mg to 30 mg** as of data cutoff [*3 November 2020*]), administered by IV infusion every 2 weeks, with/without step dosing
- **Disease assessment** – Antitumor activity assessed using modified RECIST 1.1 every 8 ± 1 weeks

Baseline Characteristic	All Patients (N = 52)
Median age, years (range)	64 (32–80)
Current/former smoker, n (%)	8 (15) / 36 (69)
ECOG performance status: 0–1, n (%)	51 (98)
Prior lines of therapy	
1–2, n (%)	39 (75)
≥ 3, n (%)	13 (25)
Median (range)	2 (1–6)
Prior PD-1 or PD-L1 treatment, n (%)	23 (44)
Extensive-stage disease at initial diagnosis, n (%)	50 (96)
Brain / liver metastases, n (%)	13 (25) / 25 (48)

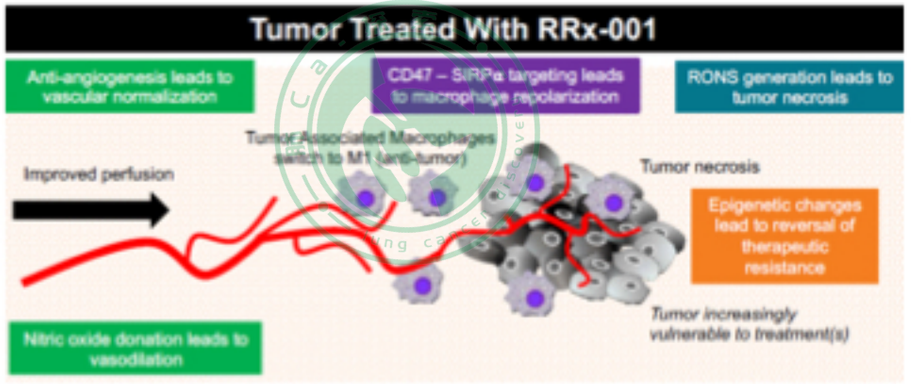
AMG 757 Demonstrates Antitumor Activity in Patients with SCLC



PR** indicates the PR is unconfirmed. SD* indicates patients who had an initial PR but did not have confirmation of PR on the subsequent scan. PD indicates PD in the post-baseline scan and came off study without further confirmation scan. *Step dosing. †Includes patients who received ≥ 1 dose of AMG 757 and had at least 8 weeks follow-up. NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

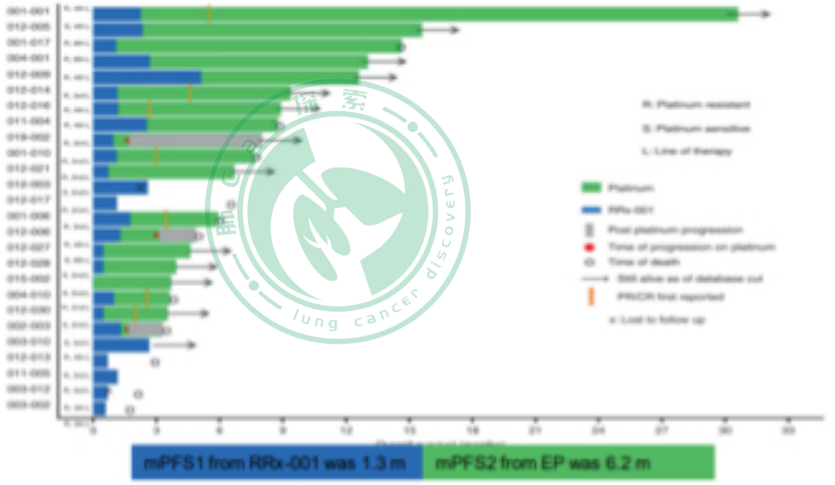
- Confirmed PR in 7 (14%) patients
- Unconfirmed PR in 1 patient
- Stable disease in 11 (22%) patients
- Disease control rate was 37%
- Tumor (any) shrinkage was seen in 17/42 (40%) patients
- 10/52 (20%) patients have completed 24 weeks of treatment
  - 4/7 patients with confirmed PR are still receiving therapy and have on-going response
- For patients with confirmed PR
  - Median time to response was 1.8 months
  - Estimated duration of response was > 6 months in 83% of patients with confirmed PR
  - Median follow-up was 11.5 months

前身是炸药和火箭燃料的“合成中间体”靶向TAM



Quadruple THREAT (Phase II) （n=26, published on BJC 2019）

疗效 (OS 8.6m, PFS 6.2m, ORR 26.9%, DCR 61.5%)



ITT分析	N=19	ORR
CR	1	
PR	6	
SD	9	
PD	3	
ORR	7	26.9%
DCR	16	61.5%

*British Journal of Cancer volume 121, pages211–217(2019)

其中，铂类耐药人群数据*积极：

14例铂类耐药的三线及后续治疗的SCLC患者，在9例（64.2%）接受了后续EP方案的患者中，3例（21.4%）达到了PR，4例（28.5%）达到了SD。

- mOS为8.6m，mPFS为5.8m

*探索性数据

普那布林(BPI-2358)+纳武利尤单抗和伊匹木单抗治疗复发性SCLC的I期临床试验

- 普那布林（BPI-2358）是首个通过诱导刺激树突状细胞成熟、激活T细胞发挥免疫抗肿瘤作用的选择性免疫调节微管结合剂（SIMBA），能够增强纳武利尤单抗和伊匹木单抗的细胞毒性。
- 普那布林可以抑制磷酸二酯酶-4（PDE4），减少CPI引起的免疫相关AEs。

研究设计

N=16
Day 1,第1-4周期
（1个周期=21天）
纳武利尤单抗：1mg/kg
伊匹木单抗：3mg/kg
普那布林:
- (-1)13.5mg/m²
- (start)20mg/m²
- (+1)30mg/m²

63%患者既往曾接受过检查点抑制剂治疗

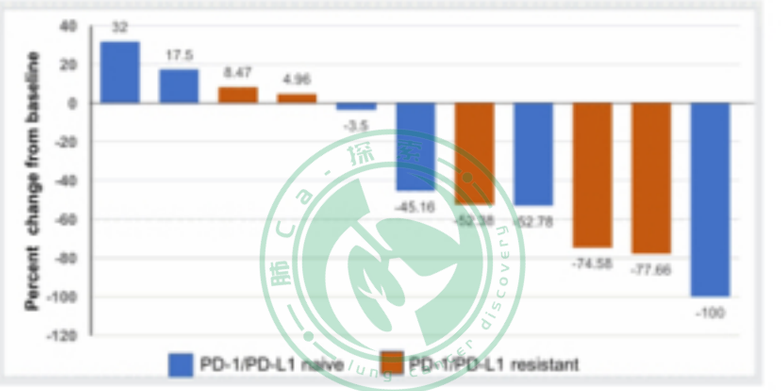
Day 1,第5+周期
（1个周期=14天）
纳武利尤单抗：240mg
普那布林：如上所述

直到疾病进展或无法耐受的毒性
主要终点：DLT、 RP2D
次要终点：ORR、PFS 和 irAEs

研究结果

治疗相关不良反应

	任意级别	≥3级
恶心	10（63%）	0
输液反应	8（50%）	1（6%）
呕吐	7（44%）	0
腹泻	7（44%）	1（6%）
疲劳	6（32%）	1（6%）
发热	4（25%）	0
皮疹	3（19%）	0
高血压	3（19%）	1（6%）



- 普那布林+纳武利尤单抗+伊匹木单抗的**安全性和耐受性良好**，ORR为46%
- 在既往接受免疫治疗失败的患者中，联合治疗能使患者对检查点抑制剂治疗重新和持续应答，ORR达43%。

BMS-986012+纳武利尤单抗治疗复发/难治性SCLC的I/II期研究

BMS-986012+nivo治疗SCLC的1/2期研究

Key eligibility criteria[a]

- Patients ≥ 18 years old with histologically or cytologically confirmed pulmonary SCLC
- No prior treatment with anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, anti–CTLA-4 or any other antibody targeting T-cell costimulation or checkpoint pathways
- ECOG PS 0-1
- Part 1: ≥ 1 prior line of therapy (dose escalation); Part 2: relapsed or refractory[b] to only 1 prior line of therapy (dose expansion)

Part 1: dose escalation IV Q3W	Part 2: dose expansion IV Q3W
BMS-986012 400 mg + nivolumab 360 mg n = 8	BMS-986012 400 mg + nivolumab 360 mg n = 13
BMS-986012 1000 mg + nivolumab 360 mg n = 8	

Primary endpoint: Safety

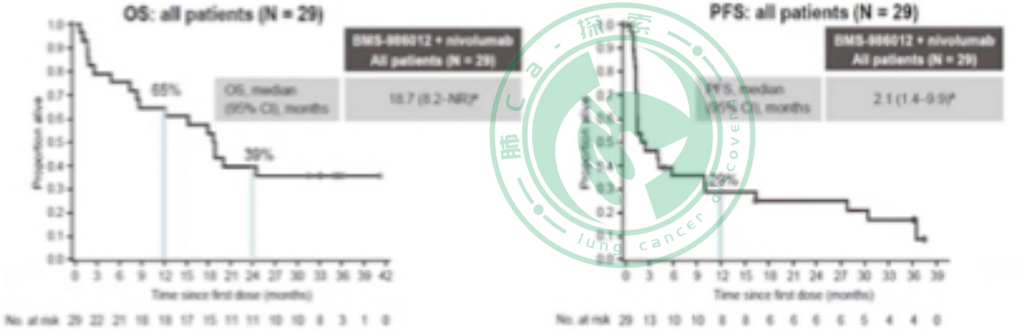
Secondary endpoints: investigator-assessed ORR, median DOR, median PFS[a]

Exploratory endpoint: median OS

	BMS-986012 400 mg + nivolumab 360 mg n = 21	BMS-986012 1000 mg + nivolumab 360 mg n = 8	BMS-986012 + nivolumab All patients N = 29	Nivolumab monotherapy (Ready et al.[3,4]) N = 147
ORR, n (%)	9 (43)	2 (25)	11 (38)	17 (12)
CR	1 (5)	0	1 (3)	2 (1)
PR	8 (38)	2 (25)	10 (34)	15 (10)
SD	2 (10)	1 (13)	3 (10)	25 (17)
DCR (CR + PR + SD), n (%)	11 (52)	3 (38)	14 (48)	42 (29)

7例患者治疗超过12个月，DOR：26.4个月

- SCLC中高表达单唾液酸神经节苷Fucosyl-GM1
- BMS-986012是一种与Fucosyl-GM1有高特异性亲和力的单克隆抗体，通过巨噬细胞的吞噬作用、NK介导的ADCC作用等发挥抗肿瘤作用

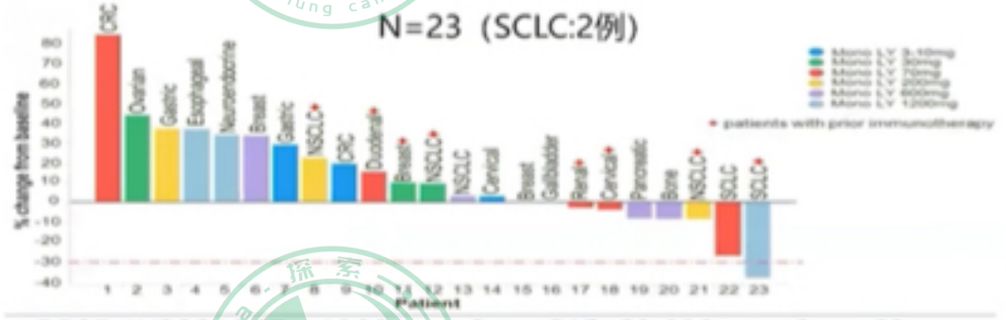


- ➤ BMS-986012联合纳武利尤单抗，**mOS为18.7个月**，mPFS为2.1个月；24-weeks PFS为39.3% ;是一种耐受性良好、潜在的治疗复发或难治性SCLC的新方法。
- ➤ BMS-986012与卡铂、依托泊苷和Nivolumab联合用于广泛期SCLC的一线治疗的研究正在进行中（NCT04702880）

TIM3抑制剂在SCLC中的研究

LY3321367单药或联合PD-L1抑制剂治疗实体瘤的I期研究

研究设计



RP2D:LY3321367：1200mg q2w，C1和C2,600mg q2w，C3

Sabatolimab(MBG453) 单独/联合Spartalizumab（PDR001）在晚期实体瘤的 I/Ib 期研究

- Sabatolimab (MBG453) 和 Spartalizumab（PDR001）分别是与TIM3和PD-1结合的单克隆抗体

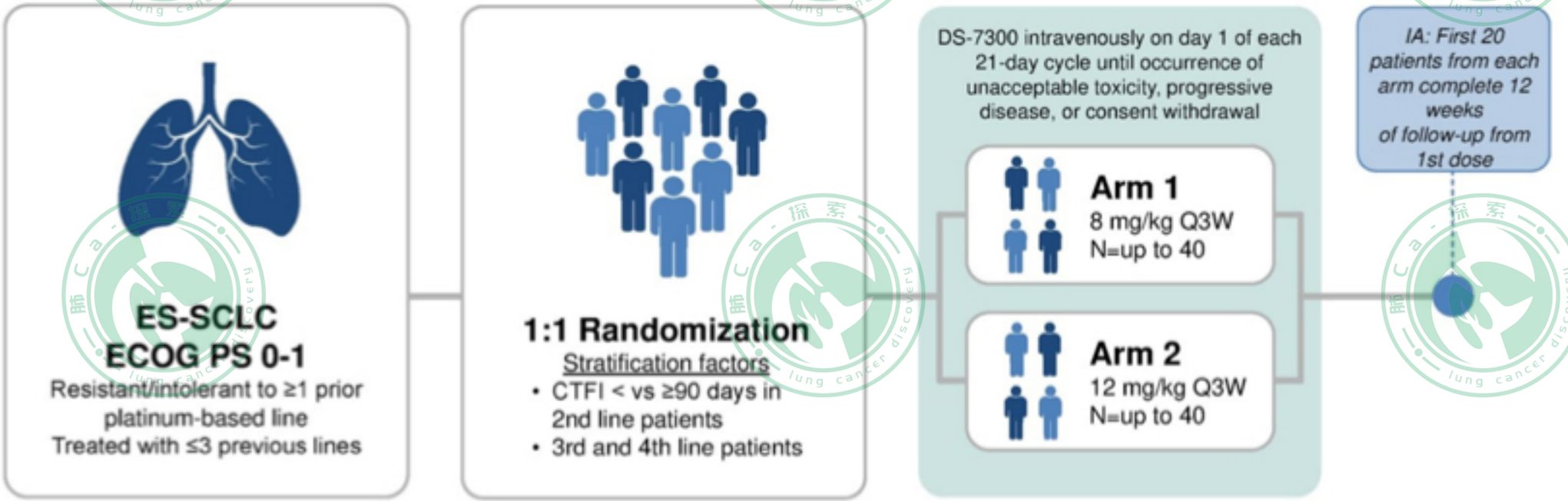
Table 1. Baseline patient demographics and characteristics, by treatment group.

	Dose-escalation part		DRP	
	Sabatolimab single agent (*n* = 87)	Sabatolimab + spartalizumab (*n* = 86)	Sabatolimab single agent (*n* = 46)	All patients (*N* = 219)
Median age, years (range)	60.0 (23-84)	58.5 (25-86)	55.5 (32-85)	59.0 (23-86)
Sex, *n* (%)				
Female	45 (51.7)	39 (45.3)	37 (80.4)	121 (55.3)
Male	42 (48.3)	47 (54.7)	9 (19.6)	98 (44.7)
Race, *n* (%)				
Caucasian	58 (66.7)	59 (68.6)	41 (89.1)	158 (72.1)
Asian	27 (31.0)	24 (27.9)	2 (4.3)	53 (24.2)
Black	0	2 (2.3)	2 (4.3)	4 (1.8)
Other/unknown	2 (2.3)	1 (1.2)	1 (2.2)	4 (1.8)
ECOG performance status, *n* (%)				
0	35 (40.2)	28 (32.6)	18 (39.1)	81 (37.0)
1	47 (54.0)	53 (61.6)	26 (56.5)	126 (57.5)
2	5 (5.7)	5 (5.8)	2 (4.3)	12 (5.5)
Number of prior therapies, median (range)	3 (1-12)	3 (1-12)	3 (1-18)	3 (1-18)
Prior PD-1/PD-L1 therapy, *n* (%)				
Prior PD-1	11 (12.6)	21 (24.4)	0	32 (14.6)
Prior PD-L1	1 (1.1)	2 (2.3)	2 (4.3)	5 (2.3)
No prior PD-1/PD-L1	75 (86.2)	63 (73.3)	44 (95.7)	182 (83.1)
Disease diagnosis, *n* (%)				
Ovarian cancer	2 (2.3)	5 (5.8)	30 (65.2)	37 (16.9)
Colorectal cancer	9 (10.3)	6 (7.0)	0	15 (6.8)
Mesothelioma	2 (2.3)	3 (3.5)	7 (15.2)	12 (5.5)
Pancreatic cancer	10 (11.5)	2 (2.3)	0	12 (5.5)
NSCLC	4 (4.6)	6 (7.0)	0	10 (4.6)
SCLC	0	3 (3.5)	6 (13.0)	9 (4.1)
Cholangiocarcinoma	3 (3.7)	2 (2.3)	0	7 (3.2)

- TIM3抑制剂联合PD-1/PD-L1对SCLC表现出初步的抗肿瘤活性，且耐受性良好
- TIM-3和PD-1的双重阻断比单独靶向更为有效

ADC领域：DS-7300(B7-H3ADC)治疗经治的广泛期小细胞肺癌多中心、随机、开放标签的II期临床研究

组织或细胞学确诊的、经治的ES-SCLC的国际、多中心、开放标签、II期临床研究



- 本研究的目的是在疗效和安全性的基础上优化DS-7300（B7-H3 ADC，通过可切割的四肽连接子，将拓扑异构酶I抑制剂（DXd）连接到人源化抗B7-H3单克隆抗体上。）在ES-SCLC预处理患者中的剂量
- 每剂量水平40例患者的样本量将为客观缓解率(ORR)的推断提供足够的统计精度
- 主要终点：ORR
- 次要终点：OS, PFS, DoR, TTP et al.

*BICR，盲态独立中心评估；CTFI，无化疗间隔期；ES-SCLC，广泛期小细胞肺癌；ECOG PS，美国东部肿瘤协作组体力状态评分；IA，中期分析；Q3W，每3周1次。

免疫联合化疗：纳武利尤单抗+替莫唑胺治疗免疫联合化疗进展的ES-SCLC的多队列、开放标签、单臂、单中心II期研究

Sample size: 15 patients for efficacy analysis
- Cohort 1: If 2 or more responses seen, enroll total of 25 patients
- Cohort 2: If 3 or more responses seen, enroll total of 28 patients

Cohort 1: Extensive Stage Small Cell Lung Cancer (n=25)
- Refractory/recurrent to platinum chemo-immunotherapy
- Any PD-L1
- Treated CNS disease allowed

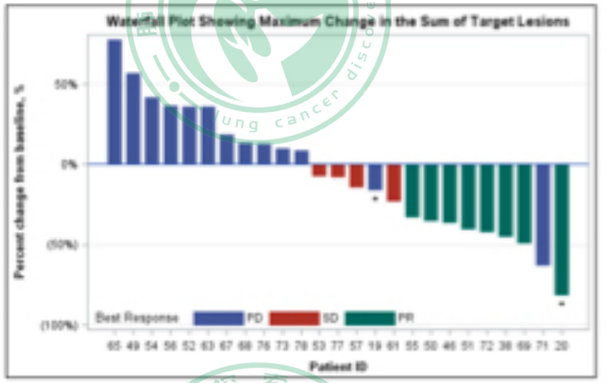
Cohort 2: Metastatic neuroendocrine carcinoma (n=28)
- WHO Grade 1-3
- Any PD-L1
- Any line of therapy

Eligibility and consent → Cycle #1 (28 days): Nivolumab 480 mg IV q4 weeks; Temozolomide 150 mg/m2 PO daily (D1-5) → Cycle #2 Onward: Tumor imaging (and q8 weeks); Tumor markers (and q4 weeks) (Cohort 2)

25例化免经治患者 ORR率28%

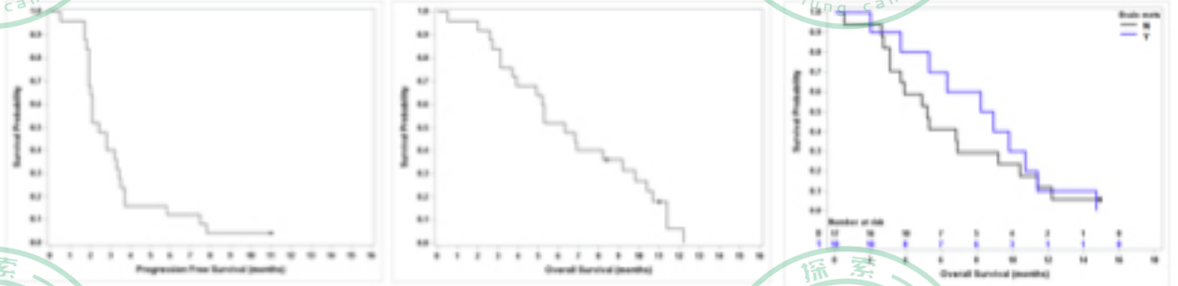
- Among 25 patients previously treated with first

		ORR	95% CI	p-value
All patients		7/25 (28%)	12% - 49%	
Platinum resistant	Y	0/10 (0 %)	0 – 31%	0.057
	N	7/15 (47%)	21 – 73%	
Brain metastases	Y	2/10 (20%)	3% - 56%	0.659
	N	5/15 (33%)	12% - 62%	



* Patients not evaluable for primary endpoint due not receiving prior chemo-immunotherapy

- With a median follow up of 6.3 months, the median PFS of all 27 patients was 2.4 months (95% CI: 1.9, 3.4)
- The median OS for all patients was 6.3 months (95% CI 3.7, 9.2).



Patient Characteristics for ES-SCLC Cohort (N=27)[1]

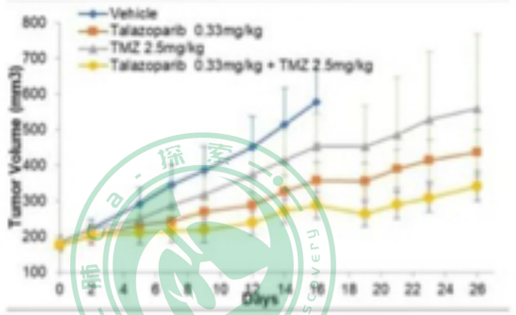
Age	Median (range)	65 (56-78)
Sex	Male	17 (63%)
	Female	10 (37%)
ECOG	0	3 (11%)
	1	23 (85%)
	2	1 (4%)
Platinum resistant[2]	Yes	11 (41%)
	No	16 (59%)
Smoking	Yes	27 (100%)
Brain Metastasis	Yes	10 (37%)
	No	17 (63%)
Line of therapy	2	21 (75%)

[1]Two patients were included under prior amendment and had not received first line chemo-immunotherapy and not eligible for primary objective
[2]Platinum resistance was defined as progression within 90 days of completion of platinum chemotherapy

➤ 纳武利尤单抗联合替莫唑胺在既往一线接受过免疫联合化疗治疗进展的ES-SCLC患者中：ORR为28%（仅见于对铂敏感患者，铂耐药患者客观缓解率低），mPFS 2.4m，mOS 6.3m

靶向联合化疗：拉唑帕尼(talazoparib)联合低剂量替莫唑胺治疗复发或难治性ES-SCLC1期临床研究

背景



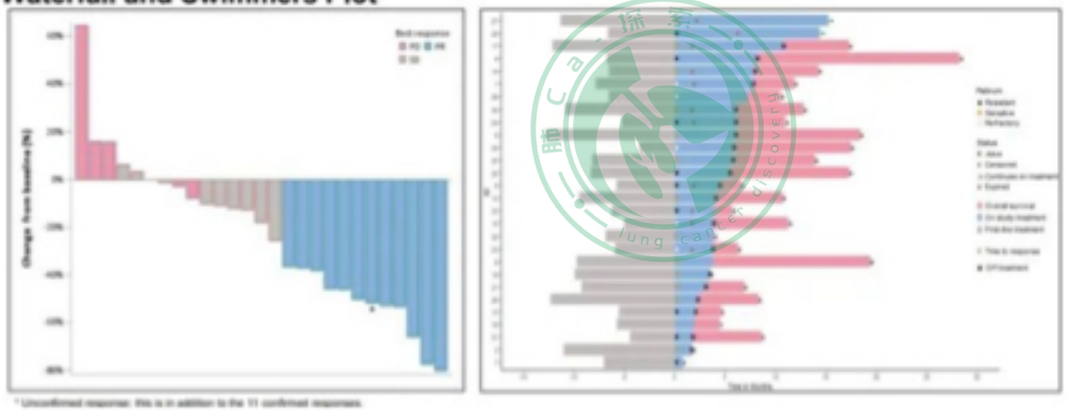
卵巢癌细胞系RMG1小鼠异种移植使用他拉唑帕尼，替莫唑胺，或联合疗法治疗。联合组在抑制肿瘤增殖方面更有效

试验设计

主要终点：ORR对比历史对照（拓扑替康二线ORR15%）
28例入组中如果≥8例患者缓解零假设被拒绝
次要终点：PFS，OS，DoR和TTR
探索性终点包括标志物分析与患者报告
缓解率基于RECIST1.1标准评价，需要≥4week确认扫描

- 28例可评估患者确认的PR 39.3%
- mTTR 1.8m，mDoR 4.3m，mPFS 4.3m，mOS 11.9m
- 各亚组ORR率相似，铂难治50% (3/6)，铂耐受44%(4/9)，铂敏感31%(4/13)

Waterfall and Swimmers Plot

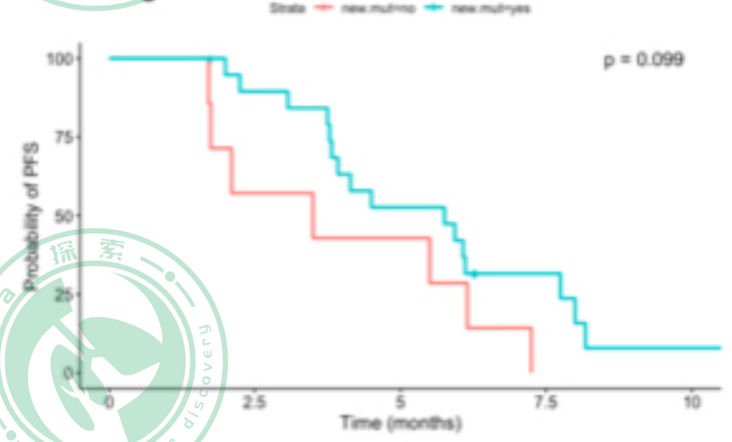


靶向联合化疗：拉唑帕尼(talazoparib)联合低剂量替莫唑胺治疗复发或难治性ES-SCLC1期临床研究

探索分析：治疗引发突变患者有更长PFS

Figure 1. DDR mutation characterization, grouped by best response

Figure 2. Kaplan-Meier Curve for Progression-Free Survival by presence of treatment emergent mutations



- 对于 27 名反应可评估患者 (pts)，收集了 78 个 ctDNA 样本。
- 没有DDR 胚系突变的患者
- 最常见的基线体细胞突变是TP53 (23 pts, 85.2%)、RB1 (8 pts, 29.6%)、ATM (5 pts, 18.5%) 和 BRCA2 (5 pts, 18.5%) 突变。
- **在 18/27 (66.7%) 的患者中发现了 DDR体细胞突变**（图 1）
- 在≥2 个时间点收集的患者中，**13/17 (76.4%) 的患者有≥ 1 个治疗引发突变**，最常见的是 ATM (7 pts)
- **治疗引发突变与疾病控制呈现一定相关性(P = 0.042) 并具有改善 PFS 的趋势**，5.8 个月 (95% CI 3.9-8.2) vs 3.5 个月 (95% CI 1.8-NE), P = 0.099) (图 2)

DDR：DNA damage repair

免疫联合靶向：氟唑帕利+阿得贝利单抗治疗复发性SCLC的耐受性、安全性和初步抗肿瘤活性
一项多中心、开放标签、两阶段、Ib期试验

- 在SCLC 中PARP高表达和细胞周期控制缺陷与 RB 损失，使 SCLC 对 PARP 抑制剂敏感 1,2
- 临床前研究表明，**PARP抑制剂可能增强免疫检查点抑制剂的抗肿瘤活性**，并导致协同临床活性。3，4

主要入组标准
- 组织学/细胞学诊断SCLC
- 既往一线铂类治疗进展
- ECOG PS 0-1

N=23

数据截止2021年4月23日

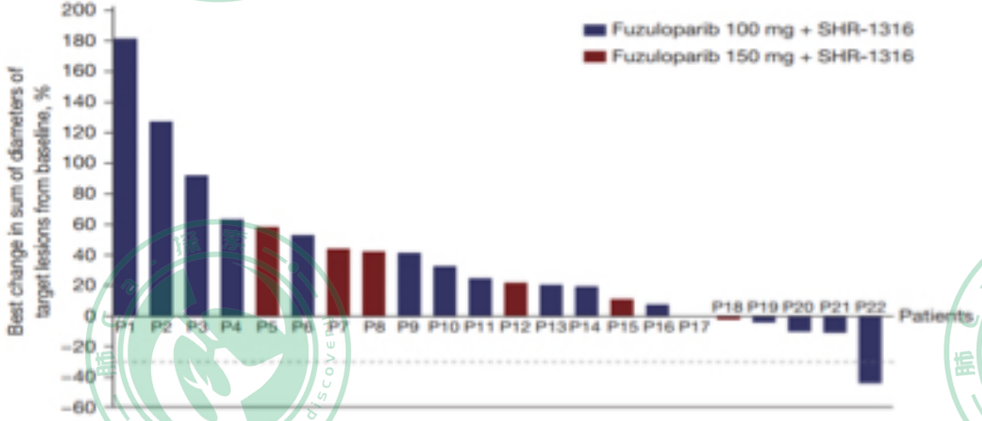
氟唑帕利100 mg bid，
阿得贝利单抗600 mg q2w
N=16

氟唑帕利150 mg bid，
阿得贝利单抗600 mg q2w
N=7

第一阶段
主要终点：
安全性、RP2D

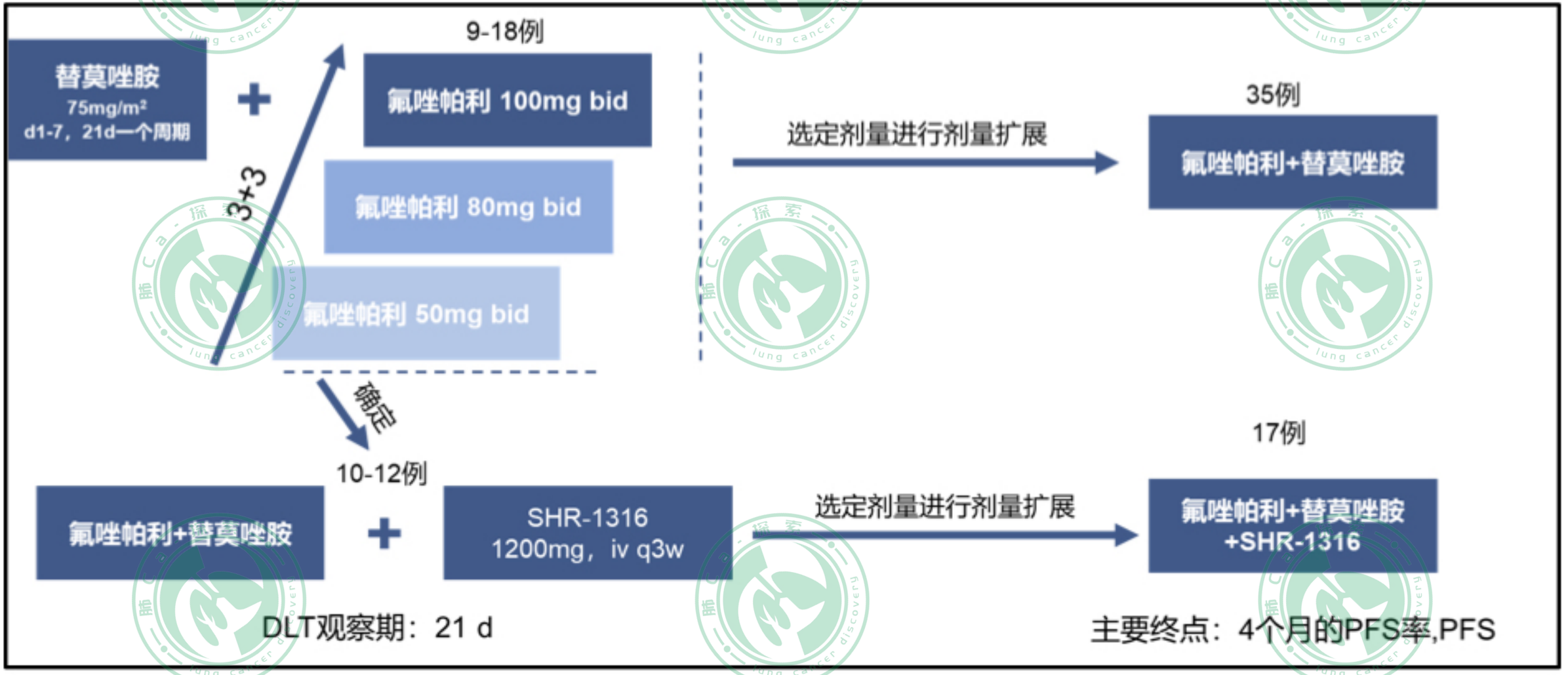
RP2D:
氟唑帕利100 mg +
阿得贝利单抗

第二阶段
主要终点：ORR
次要终点：安全性、DOR、DCR、PFS、OS



- 与标准化疗或单独免疫治疗相比，**氟唑帕利联合阿得贝利单抗治疗复发小细胞肺癌安全性可耐受，但未能改善未选择的复发SCLC患者的预后**（ORR为6.3%，mPFS为1.4个月，mOS为5.6个月），。
- 探索PARP抑制剂联合免疫抑制剂的获益人群，需进行生物标志物分析或PD-L1的表达。
- 研究结果与度伐利尤单抗联合奥拉帕利治疗复发SCLC的II期临床试验一致

免靶化：氟唑帕利+TMZ＋阿得贝利单抗治疗复发性SCLC的Ib/II期研究



复发SCLC :关键临床研究，新的联合方案或可改变治疗格局

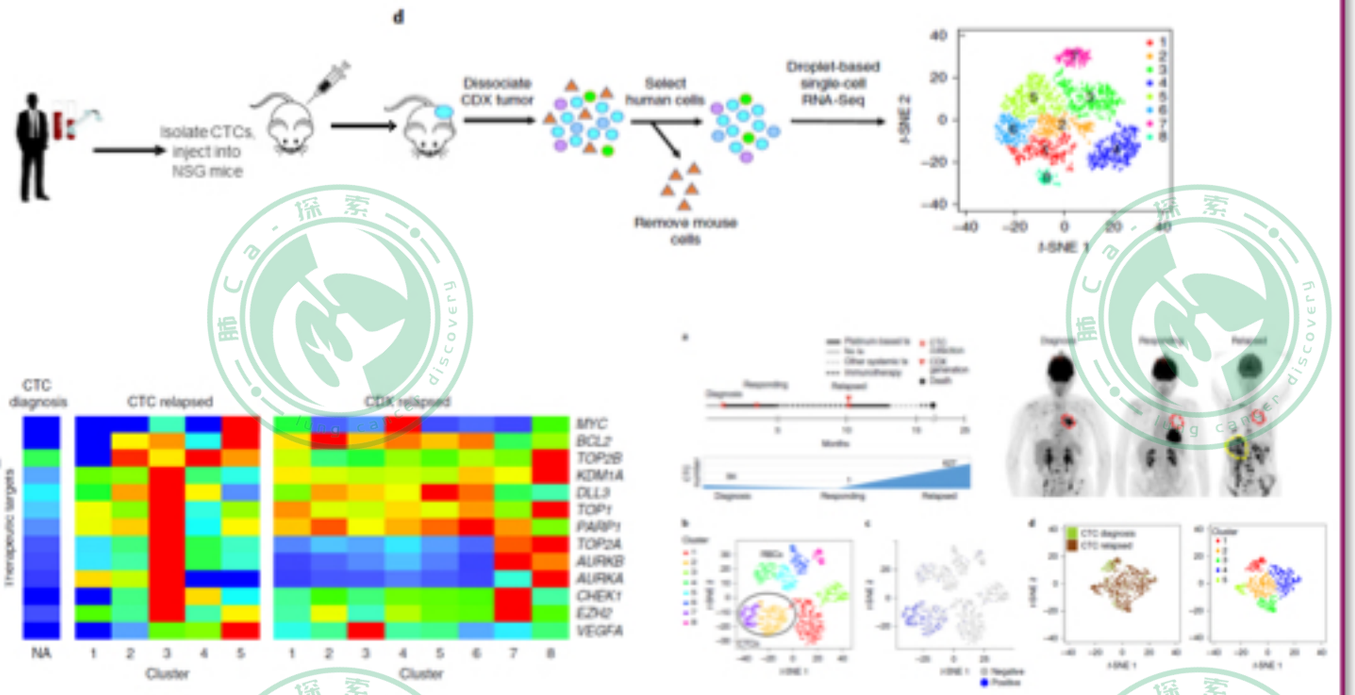
Trial	Phase	MoA	Drug	ORR	PFS	OS
von Pawel 1999	2	化疗	Topotecan IV	24%	~3.1 mo	-
von Pawel 1999	2	化疗	CAV	18%	~2.9 mo	-
Eckardt 2007	3	化疗	Topotecan PO	18%	~2.8 mo	~7.7 mo
Pietanza 2012	2	化疗	Temozolomide	20%	1.6 mo	5.8 mo
Pietanza 2018	2	化疗+PARP 抑制剂	**Temozolomide+Veliparib**	**39%**	3.8 mo	**8.2 mo**
Farago 2019	2	化疗+PARP 抑制剂	**Temozolomide+ Olaparib**	**41.7%**	4.2 mo	**8.5 mo**
Checkmate 032, 2020	2	免疫	Nivolumab	11.6%	1.4 mo	5.7 mo
Checkmate 032,2020	2	双免疫联合	Nivolumab + Ipilimumab	21.9%	1.5 mo	4.7 mo
Trigo 2020	2	新型化疗 (RNA-polymerase-II)	**Lurbinectedin**	**34.7%**	3.9 mo	**9.3 mo**
ATLANTIS.2021	3	新型化疗联合	**Dox+lurbi 2mg/m²**	**31.6%**	4.0 mo	**8.6 mo**
			Topotecan or CAV	29.7%	4.0 mo	7.6 mo
ASCO 2022						
#8516: ma,et al.	2	免疫+VEGFR-TKI	**Sintilimab + Anlotinib**	**48.7%**	6 mo	**16 mo**
#8517:goldman,et al.	2	化疗+PARP 抑制剂	**Talazoparib+ Temozolomide**	**39.3%**	4.5 mo	**11.9 mo**
#8581:Antonio ,et al.	2	免疫+新型化疗	**Pembrolizumab+ Lurbinectedin**	**30.8%**	-	-
#TPS8604:Konstantinos,et al.	2	免疫+化疗/新型化疗	**Durvalumab+Topotecan** **Durvalumab+Lurbinectedin**	-	-	-

1. Ryan D, 2022 ASCO A4315

瘤内异质性研究引发联合治疗的理论基础

nature cancer ARTICLES

Single-cell analyses reveal increased intratumoral heterogeneity after the onset of therapy resistance in small-cell lung cancer



尽早应用联合方案（最大程度地靶向尚未接受治疗、异质性相对弱的SCLC肿瘤细胞），或可最大程度克服耐药，提高疗效

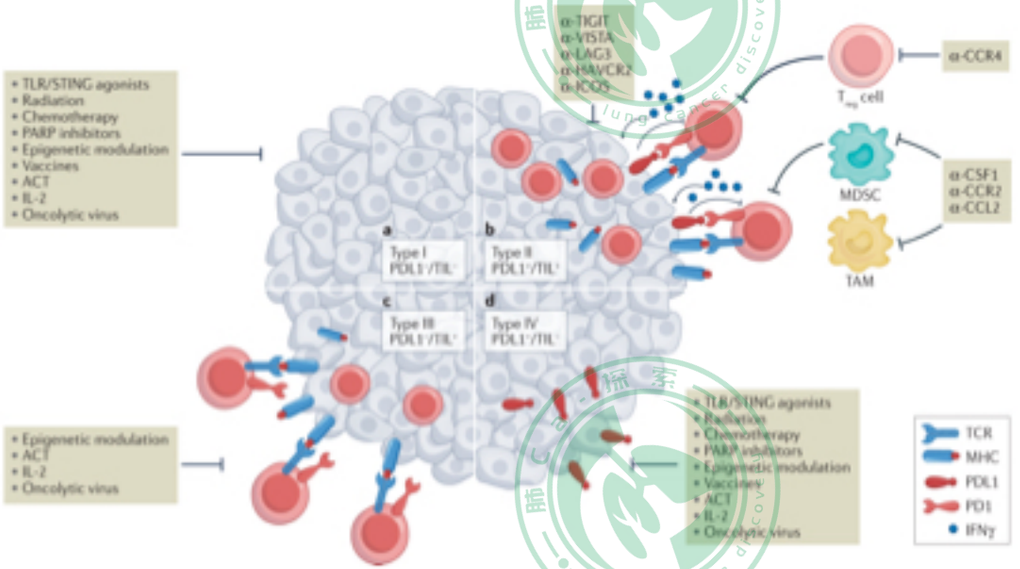
Adaptive immune resistance at the tumour site: mechanisms and therapeutic opportunities

Tae Kon Kim, Esten N. Vandsemb, Roy S. Herbst and Lieping Chen

nature reviews drug discovery

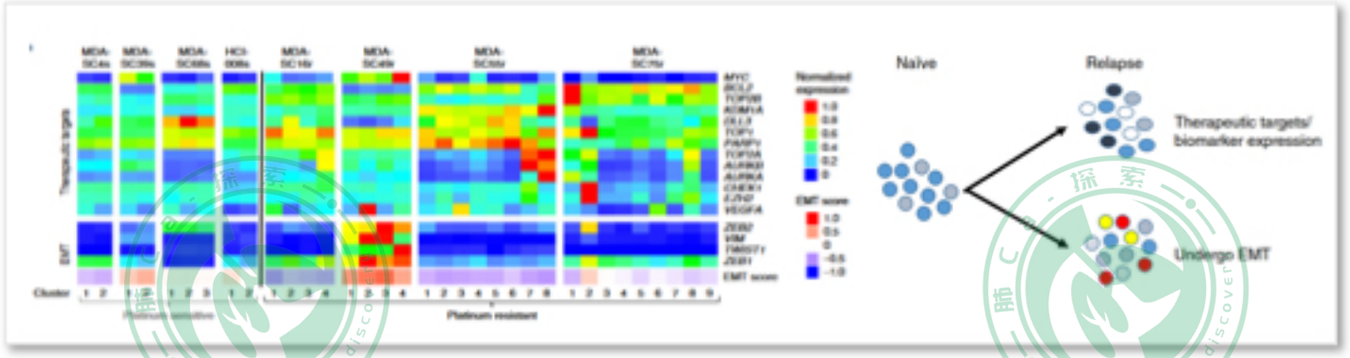
肿瘤微环境免疫状态（TIME）分型法：

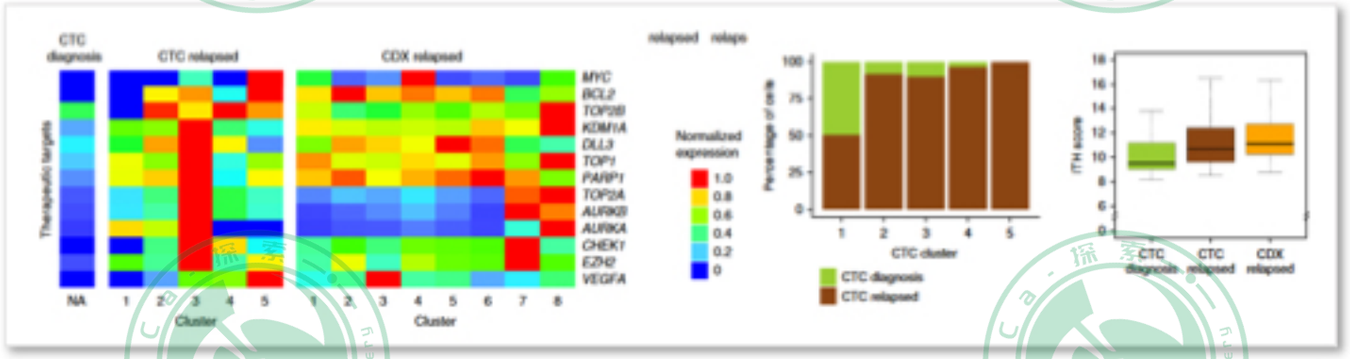
I型：PDL1−/TIL−,PD-1/PD-L1疗效差，靶点缺失耐药,冷肿瘤
II型：PDL1+/TIL+,PD-1/PD-L1理应有效，原发性耐药
III型：PDL1−/TIL+,PD-1/PD-L1疗效差，靶点缺失耐药,T细胞功能异常
IV型：PDL1+/TIL−,PD-1/PD-L1疗效差，靶点缺失耐药,冷肿瘤



1. Sharma P et al, Cell. 2017;168(4):707-723
2. Nature Cancer | VOL 1 | April 2020 | 423–436
3. Chen LP et al. Nature Reviews,2022 July

SCLC化疗进展后肿瘤异质性增加，提示针对多种耐药机制的一线联合疗法或可最大程度改善SCLC患者生存





肿瘤组织

- 铂耐药 vs 铂敏感：潜在治疗靶点基因和耐药途径相关基因表达增多，提示铂耐药后的SCLC肿瘤内异质性增加

循环肿瘤细胞

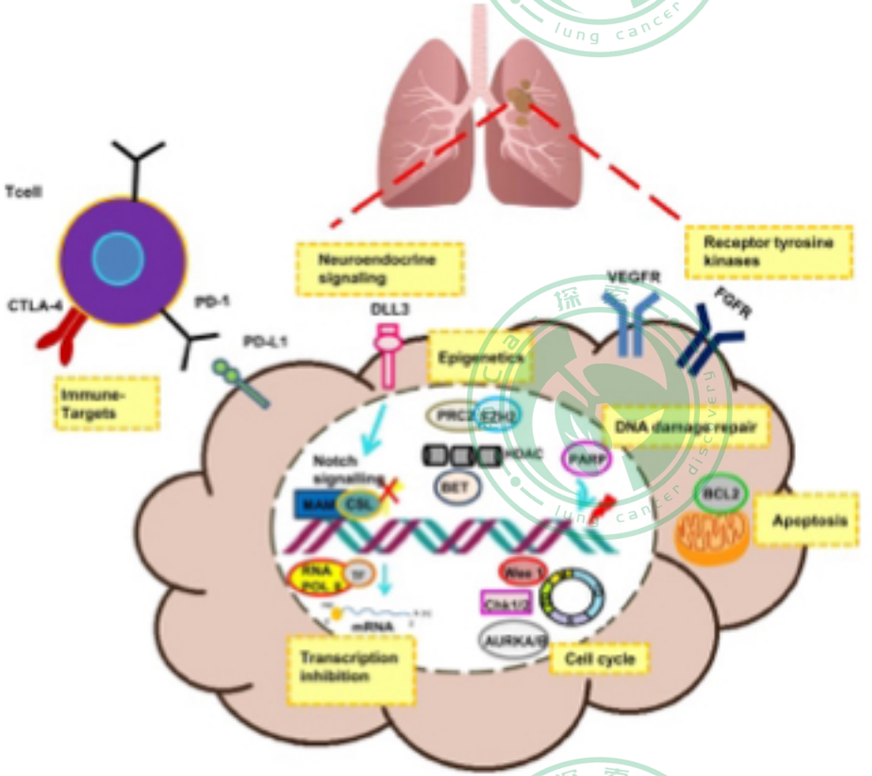
- 基因表达特征与肿瘤组织相似，进一步证实复发后肿瘤内异质性增加

Stewart CA, et al. Nat Cancer. 2020 Apr;1:423–436

联合治疗方案正在探索中

SCLC进入免疫治疗时代，为协同强化免疫治疗疗效，一系列联合治疗方案正处于临床探索阶段

靶点	药物
DNA damaging agent	Lurbinectedin
VEGFR inhibitors	Apatinib, anlotinib, bevacizumab
AURKB inhibitor	AZD2811
WEE1 inhibitor	Adavosertib
DNA Repair (PARP inhibitor)	Olaparib, Veliparib
Delta-like protein-3	Rovalpituzumab teserine (ADC)
BiTE (Bispecific T-cell engager)	AMG 757 (anti-DLL3 x anti-CD3)
Immune checkpoint inhibitor (TIGIT CD39)	Tiragolumab IPH5201



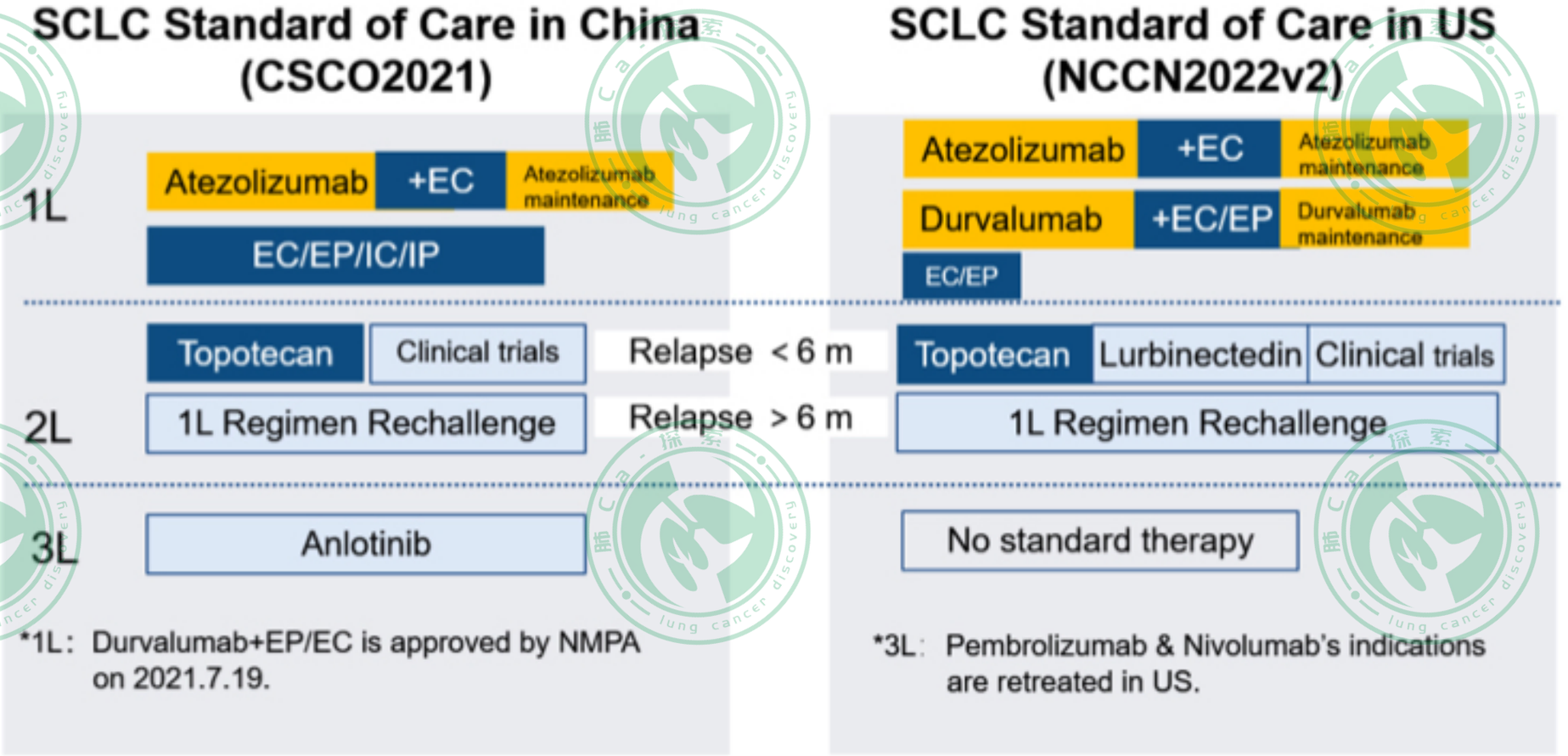
ICIs 与不同MoA药物联合治疗或可增益疗效

以PD-L1+化疗为基础，一些新兴的药物，如奥拉帕利、Rova-T、双抗、ADC等，可能是未来免疫联合治疗SCLC的联合优选

ADC, antibody-drug conjugate; PARP, poly-ADP ribose polymerase; SCLC, small-cell lung cancer; TIGIT, T cell immunoreceptor with Ig and ITIM domains; VEGFR, vascular endothelial growth factor receptor

1. Wei Huang, et al. Transl Oncol. 2021 Jan;14(1):100889.
2. J. Meijer et al. Seminars in Cancer Biology 2022.5

谢谢



更多挑战：复合型，特殊类型。。。。