GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

A PHASE 1A/1B TRIAL OF TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMORS

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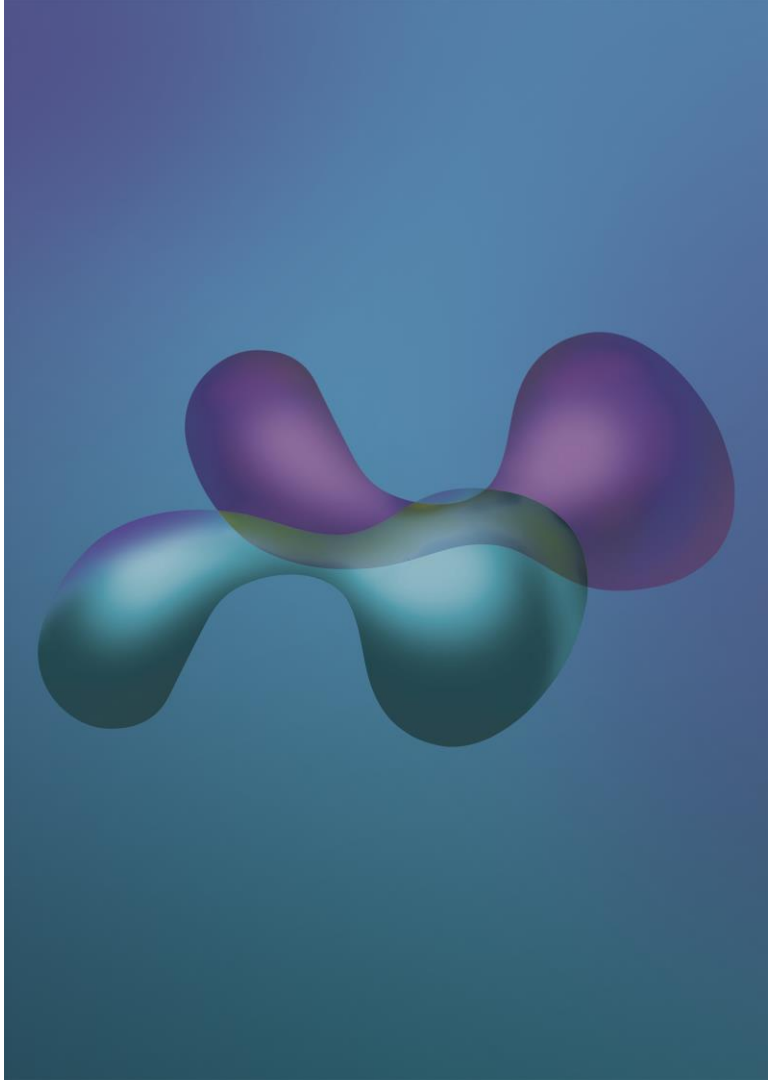


DISCLOSURE SLIDE

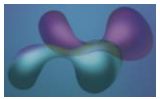
Chia-Chi Lin

Consultant or Advisory Role:

AbbVie, Boehringer-Ingelheim, Merck, Novartis

Honoraria:

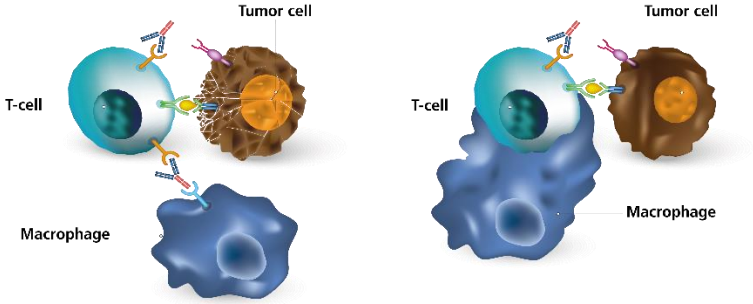
Novartis, Roche



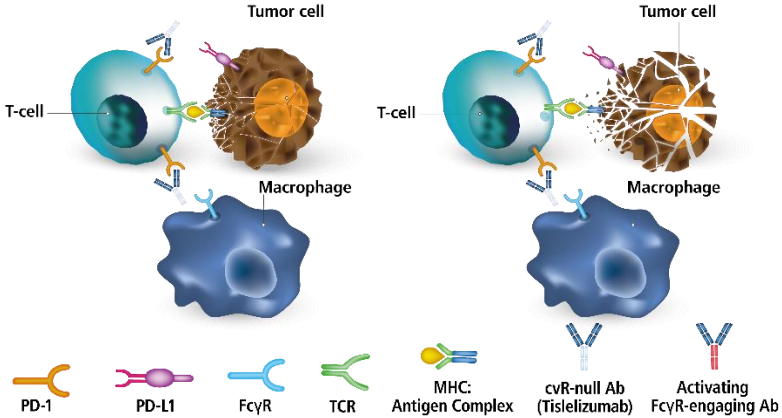
TISLELIZUMAB

AN INVESTIGATIONAL ANTI-PD-1 ANTIBODY

PD-1 monoclonal antibody ***with*** FCγR binding

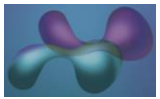


PD-1 monoclonal antibody ***without*** FCγR binding



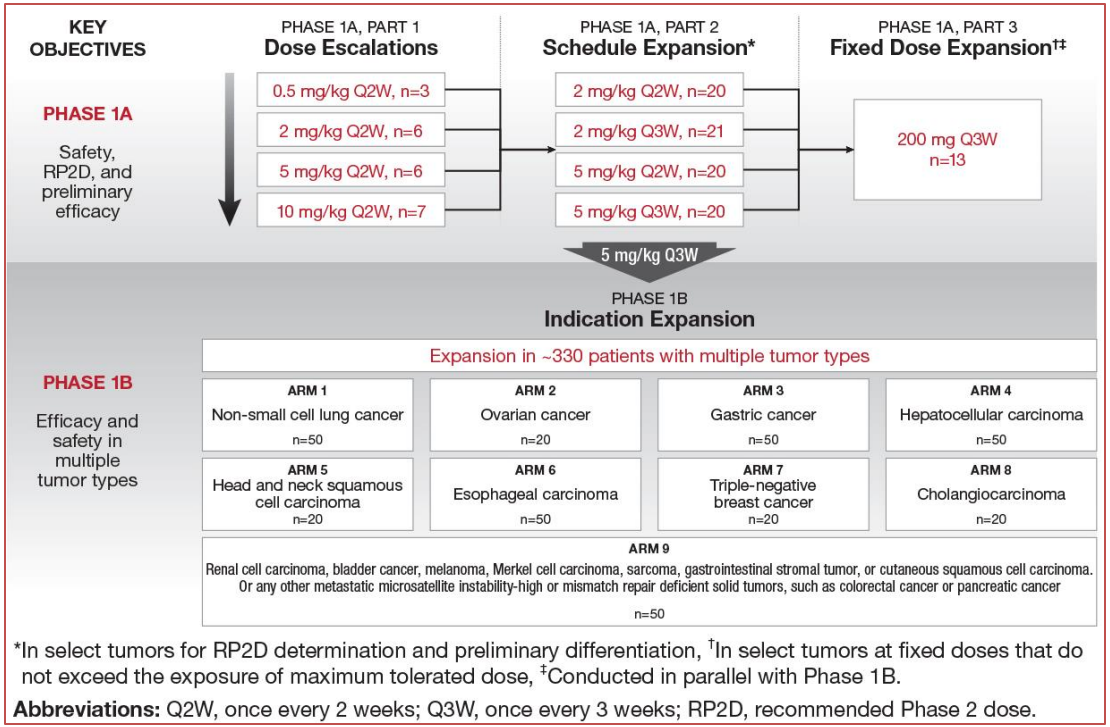
- Tislelizumab (BGB-A317) is an investigational, humanized IgG4 monoclonal antibody that has been shown to have high affinity and binding specificity for PD-1[1]
- Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis,[1] a potential mechanism of resistance to anti-PD-1 therapy

[1]Zhang et al. *Cancer Immunol Immunother.* 2018. 67:1079–1090.



TISLELIZUMAB PHASE 1A/1B STUDY

(NCT02407990)

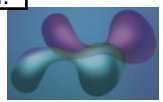


- In phase 1A, 10 mg/kg Q2W was the maximum administered dose; the maximum tolerated dose (MTD) was not reached
- All patients in phase 1B received tislelizumab 5 mg/kg IV infusion Q3W
- Radiographic assessment was performed every 8 to 9 weeks per RECIST v1.1
- Tumor cell (TC) and immune cell (IC) PD-L1 expression were retrospectively assessed with the VENTANA PD-L1 (SP263) assay
- Here we report the effects of tislelizumab in patients with esophageal (EC), gastric (GC), hepatocellular (HCC), and non-small cell lung (NSCLC) cancers

DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

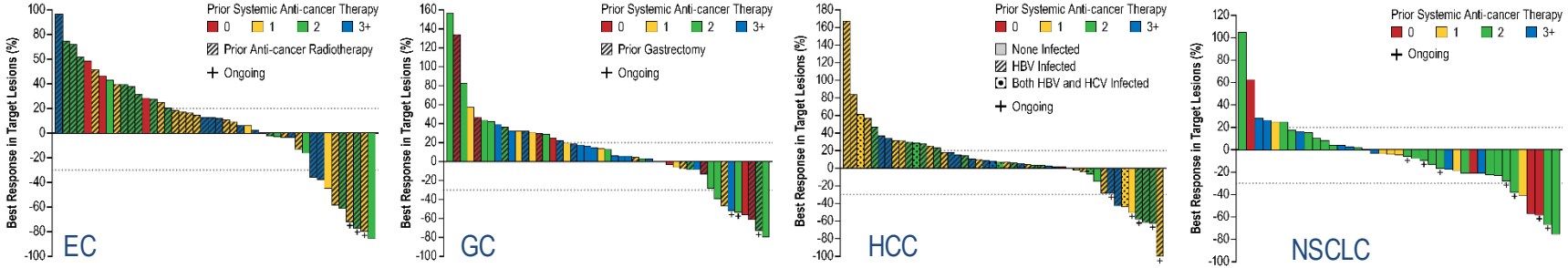
	EC (N=54)	GC (N=54)*	HCC (N=50)†	NSCLC (N=49)‡
Median age, years (range)	62.0 (30, 80)	61.5 (22, 81)	55.5 (28, 76)	62.0 (39, 78)
Sex, n (%)				
Male	41 (75.9)	31 (57.4)	41 (82.0)	27 (55.1)
Female	13 (24.1)	23 (42.6)	9 (18.0)	22 (44.9)
Race, n (%)				
White	28 (51.9)	23 (42.6)	4 (8.0)	23 (46.9)
Asian	21 (38.9)	25 (46.3)	44 (88.0)	21 (42.9)
Other	5 (9.3)	6 (11.1)	2 (4.0)	5 (10.2)
Median prior systemic treatments, (range)	2.0 (0, 7)	1.0 (0, 9)	2.0 (0, 6)	1.0 (0, 7)
Histology, n (%)				
Adenocarcinoma	26 (48.1)	50 (92.6)	NA	29 (59.2)
Squamous	26 (48.1)	0		14 (28.6)
Mixed	1 (1.9)	0		0
Mucinous	0	0		1 (2.0)
Other/Missing	1 (1.9)	4 (7.4)		5 (10.2)
Nicotine use status, n (%)				
Never	16 (29.6)	27 (50.0)	26 (52.0)	15 (30.6)
Former	33 (61.1)	24 (44.4)	16 (32.0)	27 (55.1)
Current	4 (7.4)	1 (1.9)	8 (16.0)	7 (14.3)
Missing	1 (1.9)	2 (3.7)	0	0
Still on treatment, n (%)	3 (5.6)	3 (5.6)	5 (10)	7 (14.3)
Median study follow-up, months (range)	5.2 (0.2, 22.7)	4.9 (0.9, 25.4)	10.8 (0.7, 31.6)	11.2 (0.5, 25.9)

*One patient was HER2 positive; †92% of patients were positive for HBV; ‡two patients were EGFR ex19del mutation positive.
Abbreviations: EC, esophageal cancer; GC, gastric cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer.



ANTITUMOR ACTIVITY OF TISLELIZUMAB

Maximum Tumor Reduction in Evaluable Patients



Best Overall Response, Confirmed	EC (N=54)	GC (N=54)	HCC (N=49)	NSCLC (N=46)
CR, n (%)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
PR, n (%)	5 (9.3)	7 (13.0)	6 (12.2)	6 (13.0)
SD, n (%)	14 (25.9)	9 (16.7)	19 (38.8)	23 (50.0)
PD, n (%)	25 (46.3)	31 (57.4)	23 (46.9)	12 (26.1)
Not evaluable/missing, n (%)	9 (16.7)	7 (13.0)	1 (2.0)	5 (10.9)
ORR, % (95% CI)	**11.1 (4.2, 22.6)**	**13.0 (5.4, 24.9)**	**12.2 (4.6, 24.8)**	**13.0 (4.9, 26.3)**
DCR, % (95% CI)	**37.0 (24.3, 51.3)**	**29.6 (18.0, 43.6)**	**51.0 (36.3, 65.6)**	**63.0 (47.6, 76.8)**

ORR=CR+PR; DCR= CR+PR+SD.

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD stable disease.

ANTITUMOR ACTIVITY OF TISLELIZUMAB

Confirmed Best Overall Response by PD-L1 Status

Best Overall Response by PD-L1 Status, Confirmed	EC (N=54)			GC (N=54)			HCC (N=50)			NSCLC (N=49)		
	PD-L1+ (n=33)	PD-L1– (n=17)	Missing (n=4)	PD-L1+ (n=22)	PD-L1– (n=23)	Missing (n=9)	PD-L1+ (n=26)	PD-L1– (n=19)	Missing (n=5)	PD-L1+ (n=16)	PD-L1– (n=21)	Missing (n=12)
CR, n (%)	1 (3.0)	0	0	0	0	0	0	0	0	0	0	0
PR, n (%)	3 (9.1)	1 (5.9)	1 (25.0)	5 (22.7)	1 (4.3)	1 (11.1)	6 (23.1)	0	0	3 (18.8)	2 (9.5)	1 (8.3)
SD, n (%)	6 (18.2)	6 (35.3)	2 (50.0)	3 (13.6)	4 (17.4)	2 (22.2)	9 (34.6)	8 (42.1)	2 (40.0)	11 (68.8)	8 (38.1)	4 (33.3)
PD, n (%)	16 (48.5)	9 (52.9)	0	12 (54.5)	13 (56.5)	6 (66.7)	10 (38.5)	11 (57.9)	2 (40.0)	1 (6.3)*	7 (33.3)	4 (33.3)
NE/ missing, n (%)	7 (21.2)	1 (5.9)	1 (25.0)	2 (9.1)	5 (21.7)	0	1 (3.8)	0	1 (20.0)	1 (6.3)	4 (19.0)†	3 (25.0)
ORR, %	**12.1**	**5.9**	**25.0**	**22.7**	**4.3**	**11.1**	**23.1**	**0**	**0**	**18.8**	**9.5**	**8.3**
DCR, %	**30.3**	**41.2**	**75.0**	**36.4**	**21.7**	**33.3%**	**57.7**	**42.1**	**40.0**	**87.5**	**47.6**	**41.7**

*Subject carries *EGFR* mutation; †One subject carries *EGFR* mutation.
ORR=CR+PR; DCR=CR+PR+SD.
EC/GC tumors were considered PD-L1+ if: ≥25% TC exhibited PD-L1 membrane staining or IC >1% in tumor area and ≥25% IC exhibit PD-L1 staining, or IC ≤1% in tumor area and 100% IC exhibit PD-L1 staining.
HCC tumors were considered PD-L1+ if ≥1% IC in tumor area exhibited PD-L1 membrane staining.
NSCLC tumors were considered PD-L1+ if ≥25% TCs exhibited PD-L1 membrane staining.
Abbreviations: DCR, disease control rate; IC, immune cells; NE, not evaluable; ORR, objective response rate; TC, tumor cell.

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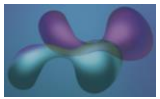
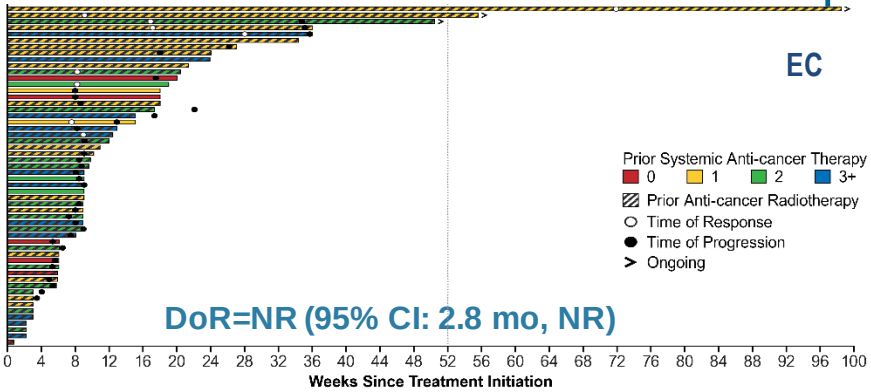
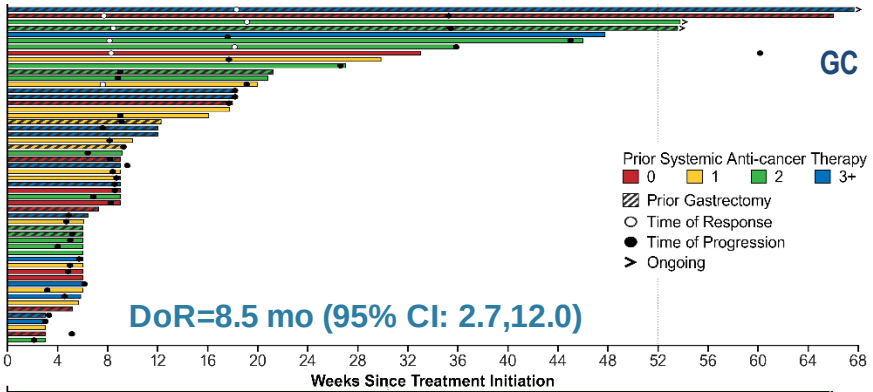
Data cut-off 31 Aug 2018

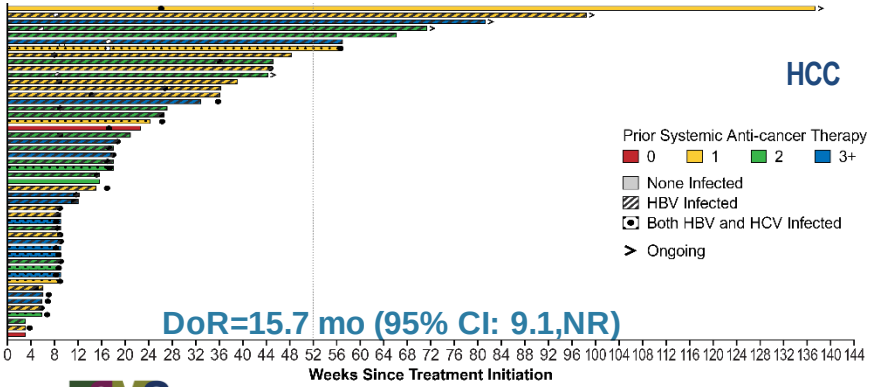


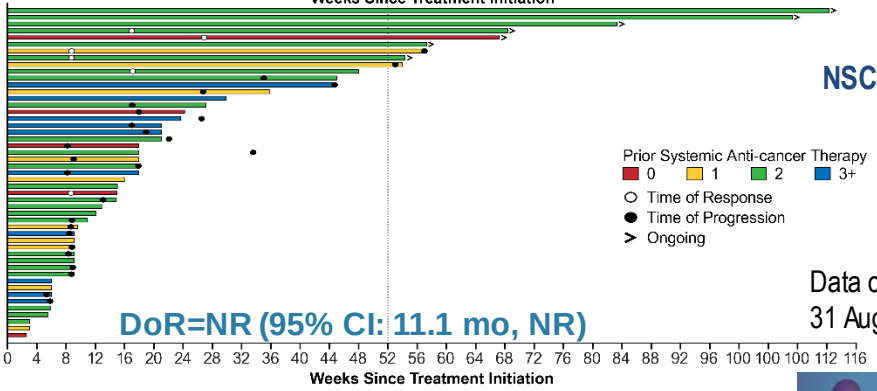
ANTITUMOR ACTIVITY

Duration of Treatment and Response









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31 Aug 2018

Dotted line indicates 1 year. DoR was estimated from Kaplan-Meier analyses. **Abbreviations:** CI, confidence interval; EC, esophageal cancer; DoR, duration of response; GC, gastric cancer; HCC, hepatocellular carcinoma; mo, months; NR, not reached; NSCLC, non-small cell lung cancer.

SAFETY AND TOLERABILITY OF TISLELIZUMAB

Treatment-related AEs Occurring in ≥2% of Patients Across Cohorts, n (%)	All Grades (N=207)
Fatigue	18 (8.7)
Pruritus/generalized pruritus	16 (7.7)
Hypothyroidism	15 (7.2)
Decreased appetite	14 (6.8)
Rash	14 (6.8)
Nausea	13 (6.3)
Hyperthyroidism	9 (4.3)
Infusion-related reaction	9 (4.3)
Proteinuria	8 (3.9)
Diarrhea	7 (3.4)
Increased AST	6 (2.9)
Arthralgia	5 (2.4)
Increased ALT	5 (2.4)
Pneumonitis	5 (2.4)
Vomiting	5 (2.4)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Commonly reported treatment-related AEs were mild to moderate in severity

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Data cut-off 31 Aug 2018

SAFETY AND TOLERABILITY OF TISLELIZUMAB

Treatment-related AEs Occurring in ≥2 Patients Across Cohorts, n (%)	TRAE Grade ≥3 (N=207)
Increased AST	4 (1.9)
Increased ALT	3 (1.4)
Pneumonitis	2 (1.0)
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.	

Serious Adverse Events and Deaths Related to Tislelizumab

- Ten patients experienced ≥1 serious adverse event considered related to tislelizumab (pneumonitis [n=3]; acute hepatitis; dermatitis; diarrhea; increased ALT; increased AST; infusion-related reaction; pyrexia; vomiting [all n=1])
- Two fatal treatment-related adverse events were reported
    - Acute hepatitis in a patient with HCC confounded by rapidly progressive disease
    - Pneumonitis in a NSCLC patient with compromised pulmonary capacity at baseline

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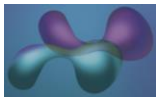

SUMMARY

- As of 31 Aug 2018, 18 patients (8.7%) remained on treatment and median study follow-up was 8.0 months (range: 0.2, 31.6)
- Single-agent tislelizumab antitumor activity was observed in EC, GC, HCC, and NSCLC
- Tislelizumab was generally well tolerated
  - Adverse events reported in patients across these cohorts were generally of mild or moderate severity and were consistent with prior reports for tislelizumab monotherapy
- The safety profile and antitumor activity observed in this study support the further development of tislelizumab
- Tislelizumab, as monotherapy and in combination, is further being evaluated in these indications in the following eight clinical studies:
  - Phase 2 (GC, NCT03469557; HCC, NCT03419897; NSCLC/SCLC, NCT03432598)
  - Phase 3 (ESCC, NCT03430843; HCC, NCT03412773; NSCLC, NCT03358875, NCT03594747, NCT03663205)

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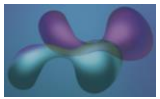

The authors would like to acknowledge and thank our patients and their families for their participation in the study, and also thank all the research personnel for their support of this trial

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