SINGLE-AGENT TISLELIZUMAB, AN ANTI-PD-1 ANTIBODY: RESULTS FROM A PHASE 1 EXPANSION COHORT IN NON-SMALL CELL LUNG CANCER PATIENTS

Paula Barlow[1], Michael Jameson[2], Chia-Chi Lin[3], Jiang Li[4], Andrea Pirkzall[4], Liang Liang[5], Jong-Seok Lee[6]

[1]Auckland City Hospital, Auckland, New Zealand; [2]Regional Cancer Centre, Waikato Hospital, and the University of Auckland Waikato Clinical Campus, Hamilton, New Zealand; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]BeiGene USA, Inc., San Mateo, California, USA; [5]BeiGene (Beijing) Co., Ltd., Beijing, China; [6]Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea

367
World Congress on Lung Cancer
7-10 September 2019 | Gran Via, Fira de Barcelona, Spain

BACKGROUND

- Lung cancer remains a major worldwide health problem, with an estimated 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing nearly one in five cancer deaths[1]
- Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancers and has a poor prognosis at later stages[2]
- While chemotherapy is the backbone of treatment for patients with advanced NSCLC, newer therapeutics include those that target the immune system[3]
- The programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) axis plays a central role in suppressing antitumor immunity; dysregulation of the PD-1/PD-L1 axis can be used by cancer cells to evade the immune system[4,5]
  - Compared with standard chemotherapy, PD-1 inhibitors have demonstrated clinically meaningful survival benefit and an improved safety profile in patients with previously treated NSCLC[3]
- Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1
  - Tislelizumab shows higher affinity to PD-1 than pembrolizumab and nivolumab, with an ~100- and 50-fold slower off-rate, respectively[6]
- Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy
- Previous reports from this first-in-human (FIH), phase 1A/1B study (NCT02407990) have shown single-agent tislelizumab was generally well tolerated and demonstrated antitumor activity in patients with solid tumors[7,8]
  - The recommended dose of 200-mg tislelizumab administered intravenously (IV) every 3 weeks (Q3W) was established[8]
  - When given for >12 months, treatment with tislelizumab remained generally well tolerated and durable responses were observed, regardless of PD-L1 status[9]
- Here we present the clinical effects of tislelizumab observed in patients with NSCLC enrolled in the 1B portion of this study

METHODS

Overall Design

- This FIH study was a dose-finding/indication-expansion study of tislelizumab in patients with advanced tumors
  - In phase 1A, 10 mg/kg IV Q2W was the maximum administered dose; maximum tolerated dose was not reached
    - Fixed-dose tislelizumab (200 mg Q3W) was evaluated in phase 1A, Part 3
  - All patients in phase 1B received tislelizumab as a 5-mg/kg IV infusion Q3W
  - Radiographic assessment was performed approximately every 9 weeks

Key Eligibility Criteria of the NSCLC Subset

- Adult patients (aged ≥18 years) with histologically or cytologically confirmed advanced or metastatic NSCLC for which no effective standard therapy was available were eligible
  - Patients must have had at least one measurable lesion, as defined per RECIST v1.1, and have received standard therapy but no prior anti-PD-1 or PD-L1 treatment
  - An Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 was required
- Patients were excluded if they had a history of severe hypersensitivity reactions to other monoclonal antibodies or a history of interstitial lung disease or non-infectious pneumonitis, except for those induced by radiation therapies
- Patients who had prior malignancy active within the previous 2 years, except for NSCLC, and locally curable cancers that have apparently been cured—such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast—were excluded
  - In phase 1B, patients with NSCLC who had a documented *EGFR* mutation or *ALK* rearrangement were excluded

Study Assessments

- Safety/tolerability of tislelizumab was the primary endpoint of phase 1A and was assessed by monitoring the incidence and severity of adverse events (AEs; NCI-CTCAE v4.03) and by evaluating results from physical examinations, ophthalmologic examinations, electrocardiograms, and laboratory investigations
- Objective response rate (ORR), based on RECIST v1.1, was the primary endpoint of phase 1B
  - ORR was defined as complete response (CR) + partial response (PR)
- Other efficacy endpoints, across both phases, included disease control rate (DCR, defined as CR+PR+stable disease [SD]), clinical benefit rate (CBR, defined as CR+PR+SD with a duration of ≥24 weeks), progression-free survival (PFS), and overall survival (OS)
- PD-L1 expression was an exploratory endpoint and retrospectively assessed with the VENTANA™ PD-L1 (SP263) assay
  - Tumors were considered PD-L1 positive (PD-L1+) if ≥25% of tumor cells exhibited PD-L1 membrane staining, otherwise they were considered PD-L1 negative (PD-L1–)
- Exploratory analyses of ORR, PFS, and OS in Asian and non-Asian subpopulations were also conducted

RESULTS

Patient Disposition

- A total of 49 patients with NSCLC were enrolled in phase 1B of the study and received tislelizumab 5mg/kg Q3W (Table 1)
  - Most of the enrolled patients were either Caucasian (n=23) or Asian (n=21)
  - The majority of patients were male (n=27), current/former smokers (n=34), and had received ≥1 prior systemic treatments (n=44) or radiotherapy (n=21)
- Most patients (n=29) had adenocarcinoma; 14 patients had squamous cell carcinoma
  - Two patients with *EGFR* ex19del mutations were enrolled
- The median study follow-up duration was 11.2 months (range: 0.5-34.5)
- As of 20 May 2019, seven patients remained on treatment and 42 had discontinued tislelizumab
  - Reasons for treatment discontinuation included disease progression (n=30), AEs (n=9), and patient withdrawal from the study (n=3)

Table 1: Patient Demographics and Disease Characteristics in Non-small Cell Lung Cancer

		NSCLC (N=49)*
Median age, years (range)		62.0 (39-78)
Sex, n (%)	Male	27 (55.1)
	Female	22 (44.9)
Race, n (%)	Caucasian	23 (46.9)
	Asian	21 (42.9)
	Other	5 (10.2)
Number of prior systemic treatments, n (%)	0	3 (6.4)†
	1	24 (51.1)
	2	10 (21.3)
	≥3	10 (21.3)
Patients with any prior anticancer radiotherapy, n (%)		21 (42.9)
Histology, n (%)	Adenocarcinoma	29 (59.2)
	Squamous	14 (28.6)
	Mucinous	1 (2.0)
	Other	5 (10.2)
Nicotine use, n (%)	Never	15 (30.6)
	Former	27 (55.1)
	Current	7 (14.3)
Active on treatment, n (%)		7 (14.3)
Median study follow-up, months (range)		11.2 (0.5-34.5)

*Two patients were *EGFR* ex19del mutation positive.
†Patients may have received adjuvant and/or neoadjuvant therapies.
Abbreviation: NSCLC, non-small cell lung cancer.

Antitumor Activity

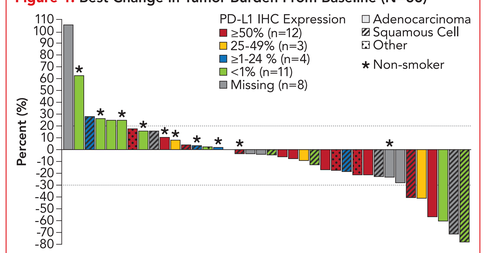
- A total of 46 (94%) patients with NSCLC were evaluable, defined as any patient who had measurable disease at baseline and at least one post-baseline tumor assessment
- Clinical response observed with tislelizumab is summarized in Table 2 and presented in Figures 1-3 with reference to baseline characteristics, including histology, nicotine use, and PD-L1 expression
- Overall, six patients achieved a confirmed PR and 23 patients achieved SD
  - Objective response rate for the efficacy-evaluable population was 13.0% (95% CI: 4.9, 26.3)
  - Disease control and clinical benefit rates were 63.0% (95% CI: 47.6, 76.8) and 37.0% (95% CI: 23.2, 52. 5), respectively
  - Median time to response was ~3 months (91 days; range: 62-189)
- Across the 46 efficacy-evaluable patients, clinical benefit was observed regardless of PD-L1 expression (Table 2)
- As of 20 May 2019, of the six patients who achieved a partial response per RECIST v1.1, only one PD-L1+ patient had their disease progress
  - Duration of response has not yet been reached

Table 2: Confirmed Best Overall Response in the Efficacy Evaluable Population and by PD-L1 Status (N=46)

Best Overall Response, Confirmed	Total (N=46)	PD-L1+ (n=16)	PD-L1– (n=19)	PD-L1 Unknown (n=11)
CR, n (%)	0	0	0	0
PR, n (%)	6 (13.0)	3 (18.8)	2 (10.5)	1 (9.1)
SD, n (%)	23 (50.0)	11 (68.8)	8 (42.1)	4 (36.4)
PD, n (%)	13 (28.3)	1 (6.3)*	8 (42.1)	4 (36.4)
Missing, n (%)	4 (8.7)	1 (6.3)	1 (5.3)*	2 (18.2)
ORR, % (95% CI)	**13.0 (4.9, 26.3)**	**18.8 (4.1, 45.7)**	**10.5 (1.3, 33.1)**	**9.1 (0.2, 41.3)**

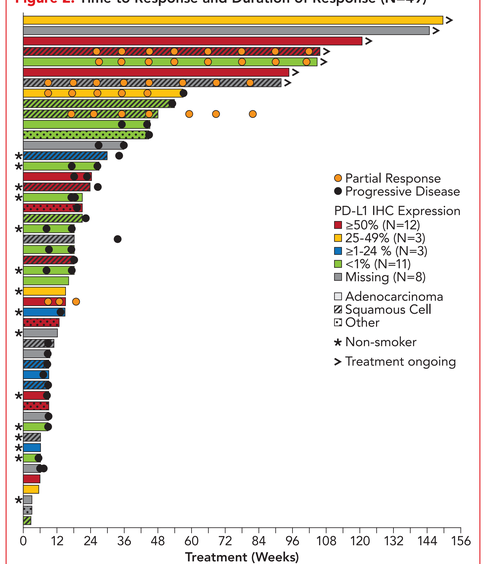
ORR=CR+PR. *Patient carries *EGFR* mutation.
Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PD-L1; programmed cell death ligand-1; PR, partial response; SD stable disease.

Figure 1: Best Change in Tumor Burden From Baseline (N=38)†



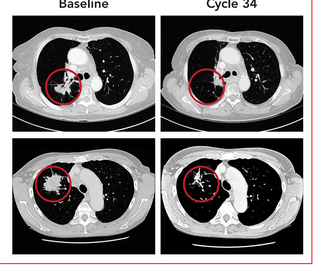
†Patients with evaluable, post-baseline target lesion assessment.
If not indicated by an *, patient was a current/former smoker.
Abbreviations: IHC, immunohistochemistry; PD-L1, programmed cell death ligand-1.

Figure 2: Time to Response and Duration of Response (N=49)



If not indicated by an *, patient was a current/former smoker.
Two patients were *EGFR* ex19del mutation positive.
Abbreviations: IHC, immunohistochemistry; PD-L1, programmed cell death ligand-1.

Figure 3: Radiographic Images of a Patients with PD-L1 Negative (A) and PD-L1 Positive (B) NSCLC

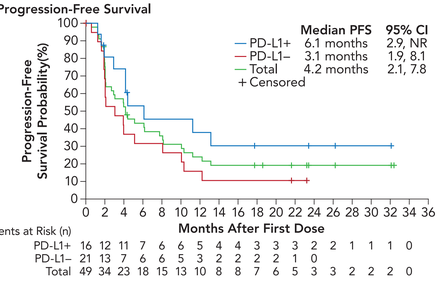


A. 65-year old, female, current smoker with PD-L1-negative (<25% of tumor cells with PD-L1 membrane staining) Stage IIIa adenocarcinoma NSCLC who received prior radiotherapy and 2 prior chemotherapy regimens

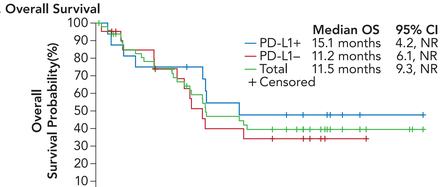
B. 69-year old, female, former smoker with PD-L1-positive (≥25% of tumor cells with PD-L1 membrane staining) Stage IV squamous cell NSCLC who received 1 prior chemotherapy regimen

Figure 4: Survival Estimates With Tislelizumab 5mg/kg Q3W (N=49)

A. Progression-Free Survival



B. Overall Survival



Two patients were *EGFR* ex19del mutation positive.
Abbreviations: CI, confidence interval; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

Progression-Free and Overall Survival

- As of 20 May 2019, 23 of the 49 (46.9%) patients with NSCLC were still alive
- Across all 49 patients, the median PFS and OS (Figure 4) were 4.2 months (95% CI: 2.1, 7.8) and 11.5 months (95% CI: 9.3, not reached [NR]), respectively
- Overall survival at 1 year was 46.9% (95% CI: 31.4, 60.9) in the overall NSCLC patient population

Asian and Non-Asian Subpopulation Analyses

- Overall, there was generally consistent clinical activity for tislelizumab in Asian (n=21) and non-Asian patients (n=28) (Table 3), although interpretations are limited due to small sample size
  - Differences in ORR could in part be attributed to a greater proportion of Asian patients having ≥3 prior treatments (n=9/21) vs non-Asian patients (n=1/28); additionally, the Asian cohort had a greater proportion of never-smokers (n=14/21) than the non-Asian cohort (n=1/28)

Table 3: Clinical Activity for Single-Agent Tislelizumab in Patients With Non-small Cell Lung Cancer

	Patients With NSCLC		
	Asian	Non-Asian	Overall
ORR, % (95% CI)*	10.5 (1.3, 33.1)	14.8 (4.2, 33.7)	13.0 (4.9, 26.3)
Median PFS, months (95% CI)	3.9 (1.9, 8.1)	5.1 (2.1, 11.2)	4.2 (2.1, 7.8)
Median OS, months (95% CI)	11.5 (8.5, NR)	11.5 (6.1, NR)	11.5 (9.3, NR)
Overall survival at 1 year, % (95% CI)	49 (23.0, 70.7)	45 (26.4, 62.6)	47 (31.4, 60.9)

Data presented from the overall population (N=49), unless otherwise indicated.
*Efficacy evaluable data set (N=46).
Abbreviations: CI, confidence interval; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Safety and Tolerability

- Adverse events considered related to tislelizumab by the investigator were reported in 53.1% (n=26/49) of patients with NSCLC
  - Seven (14.3%) patients experienced a total of eight treatment-related AEs (TRAEs) that led to treatment discontinuation (pneumonitis, n=4; elevated ALT, elevated AST, immune-mediated enterocolitis, and vomiting, n=1 each)
- The most commonly reported TRAEs were hyperthyroidism and hypothyroidism (n=6 each); the majority of reported TRAEs were grade ≤2 in severity (Table 4)
  - Six patients (12.2%) experienced a total of eight grade ≥3 TRAEs (pneumonitis, n=3; elevated ALT, elevated AST, immune-mediated enterocolitis, macular rash, and vomiting, n=1 each)

CONCLUSIONS

- Treatment with tislelizumab was generally well tolerated and demonstrated antitumor activity in patients with advanced NSCLC
  - Median follow-up was 11.2 months and seven (14%) patients remain on treatment
  - As of 20 May 2019, 23 (47%) of patients were alive
- Adverse events reported in these patients were consistent with the overall safety profile of tislelizumab observed in previous studies, were generally of low severity and, with exception of the fatal events, were manageable and reversible
  - The rate of treatment discontinuation due to tislelizumab-related AEs was low (n=7/49, 14.3%)
- Overall, 29 patients achieved confirmed PR (n=6) or SD (n=23)
  - In the efficacy-evaluable population, ORR was 13% and DCR was 63%
  - In the overall NSCLC population, the median PFS and OS were 4.2 and 11.5 months, respectively
  - Clinical benefit was observed regardless of PD-L1 expression and regardless of ethnicity in Asian and non-Asian patients
- The safety and efficacy of tislelizumab as a single agent or in combination with chemotherapy are currently being evaluated in phase 3 studies in patients with NSCLC (NCT03358875, NCT03594747, NCT03663205)

- A total of 18 patients (36.7%) experienced ≥1 immune-related AEs (irAEs), the most commonly reported irAEs (defined as ≥5% patients) were hypothyroidism (n=6), hyperthyroidism (n=6), pneumonitis (n=5), rash (n=4), and generalized pruritus (n=4)
- Serious AEs considered related to tislelizumab were reported in four patients (pneumonitis, n=3; vomiting, n=1)
- Two patients experienced a fatal AE (pneumonia, n=1; pneumonitis, n=1); only pneumonitis was considered related to treatment
  - While pneumonitis was considered to be at least possibly related to tislelizumab, the event occurred in a patient with severely compromised pulmonary capacity and confounding factors at baseline

Table 4: Treatment-Related Adverse Events Occurring in at Least 3 (≥5%) Patients With NSCLC

	Total NSCLC (N=49)	
	All Grades	Grade ≥3
Hyperthyroidism	6 (12.2)	0
Hypothyroidism	6 (12.2)	0
Fatigue	5 (10.2)	0
Pneumonitis	5 (10.2)	3 (6.1)
Generalised pruritus	4 (8.2)	0
Rash	4 (8.2)	0
Alopecia	3 (6.1)	0
Vomiting	3 (6.1)	1 (2.0)

Abbreviation: NSCLC, non-small cell lung cancer.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. D'Addario G, Fruh M, Reck M, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v116-119.
3. Liu Y, Zhou S, Du Y, et al. Efficacy and safety of programmed death 1 inhibitors in patients with advanced non-small cell lung cancer: a meta-analysis. *Cancer Manag Res*. 2019;11:4619-4630.
4. Dahan R, Sega E, Engelhardt J, Selby M, Korman AJ, Ravetch JV. FcγRs modulate the anti-tumor activity of antibodies targeting the PD-1/PD-L1 axis. *Cancer Cell*. 2015;28:285-295.
5. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther*. 2015;37:764-782.
6. Feng Y HY, Sun H, Zhang B, et al. The molecular binding mechanism of tislelizumab, an investigational anti-PD-1 antibody, is differentiated from pembrolizumab and nivolumab. In: *Proceedings of the 110th Annual Meeting of the American Association for Cancer Research*. March 29-April 3, 2019; Atlanta, GA.
7. Deva S, Lee J-S, Lin C-C, et al. A phase 1A/1B trial of tislelizumab, an anti-PD-1 antibody, in patients with advanced solid tumors. Presented at the ESMO Immuno Oncology meeting. December 13-16, 2018; Geneva, Switzerland.
8. Wu Y, Zhao J, Zhang Q, Pan H, Wang J, Bai Y, et al. Preliminary results with tislelizumab in Chinese patients with non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2018;13(10):S741-S742.
9. Desai J, Markman B, Gan H, et al. Long-Term Exposure (LTE) to Tislelizumab, an Investigational Anti-PD-1 Antibody, in a First-in-Human Phase 1 Study. In: *Proceedings of the 110th Annual Meeting of the American Association for Cancer Research*. March 29-April 3, 2019; Atlanta, GA.

ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative center study staff and study patients, and to recognize those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. PD-L1 IHC data was generated by Roche Tissue Diagnostics and overseen by Chunyan Liu MD. This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Regina Switzer, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com