Flat-dose nivolumab (NIVO) as second-line (2L) treatment (tx) in Asian patients (pts) with advanced non-small cell lung cancer (NSCLC): CheckMate 870 long-term results

Shun Lu[1]*, Ying Cheng[2], Jianying Zhou[3], Mengzhao Wang[4], Jun Zhao[5], Baocheng Wang[6], Gongyan Chen[7], Jifeng Feng[8], Zhiyong Ma[9], Lin Wu[10], Changli Wang[11], Kewei Ma[12], Shucai Zhang[13], Jun Liang[14], Yong Song[15], Jie Wang[16], Yi-Long Wu[17], Ang Li[18], Yizhi Huang[19], Jianhua Chang[20]

[1]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai China; [2]Jilin Cancer Hospital, Changchun, China; [3]The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; [4]Peking Union Medical College Hospital, Beijing, China; [5]Beijing Cancer Hospital, Beijing, China; [6]Jinan Military General Hospital, Jinan, China; [7]Affiliated Cancer Hospital of Harbin Medical University, Harbin, China; [8]Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China; [9]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [10]Hunan Cancer Hospital (The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University), Changsha, China; [11]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [12]The First Hospital of Jilin University, Changchun, China; [13]Beijing Chest Hospital, Beijing, China; [14]Peking University International Hospital, Beijing, China; [15]Nanjing General Hospital, Nanjing, China; [16]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing China; [17]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; [18]Bristol Myers Squibb Company, Princeton, NJ, USA; [19]Bristol-Myers Squibb, Shanghai, China; [20]Shanghai Cancer Center Fudan University, Shanghai, China

Introduction

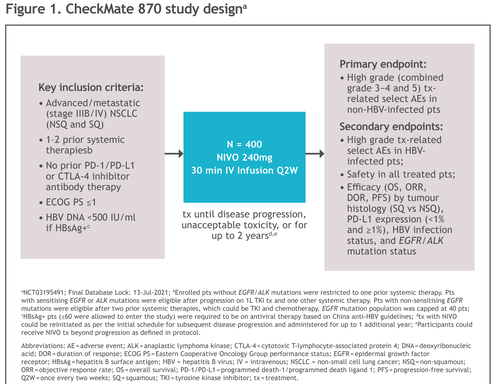
- Lung cancer is one of the most common causes of cancer-related deaths both globally and in China[1,2]. Moreover, NSCLC is the dominant form of lung cancer (approximately 85% of cases)[3]
- NIVO, a first-in-human programmed death (PD-1) immune checkpoint inhibitor antibody, was approved in China as 2L tx for advanced NSCLC via weight-based 60-minute infusion based on the CheckMate 078 study, a randomised, open-label, phase 3 trial in a predominantly Chinese population[4]
- NIVO significantly improved overall survival (OS) versus docetaxel (median [95% CI] 12.0 [10.4 - 14.0] vs 9.6 [7.6 - 11.2] months) in the CheckMate 078 study[4]. However, *EGFR*/*ALK*-positive and HBV-positive pts were excluded
  - Moreover, the more convenient flat dosing of NIVO over a 30-minute infusion is yet to be evaluated in this pt population
- Here, we present long-term results from the CheckMate 870 study, a single-arm, open-label, phase 3 trial, investigating the safety and efficacy of flat-dose NIVO via the more convenient 30-minute infusion in pts with previously treated advanced or metastatic NSCLC, including those with hepatitis B virus and *EGFR* mutation/*ALK* translocation

Methods

Study Design

- In CheckMate 870 (NCT03195491), Asian (mostly Chinese) adult pts with advanced/metastatic NSCLC previously treated with one or two systemic therapies, ECOG performance status ≤1, and HBV DNA titre <500 IU/ml (if HBsAg+) were enrolled (**Figure 1**)
  - Eligible pts received NIVO 240 mg via intravenous (IV) infusion over 30 minutes every 2 weeks (Q2W) for 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurred first
- Pts with non-squamous histology were tested for *EGFR* mutation and *ALK* rearrangement

Figure 1. CheckMate 870 study design[a]



[a]NCT03195491; Final Database Lock: 13-Jul-2021; [b]Enrolled pts without *EGFR*/*ALK* mutations were restricted to one prior systemic therapy. Pts with sensitising EGFR or *ALK* mutations were eligible after progression on 1L TKI tx and one other systemic therapy. Pts with non-sensitising *EGFR* mutations were eligible after two prior systemic therapies, which could be TKI and chemotherapy. *EGFR* mutation population was capped at 40 pts; [c]HBsAg+ pts (≤60 were allowed to enter the study) were required to be on antiviral therapy based on China anti-HBV guidelines; [d]tx with NIVO could be reinitiated as per the initial schedule for subsequent disease progression and administered for up to 1 additional year; [e]Participants could receive NIVO tx beyond progression as defined in protocol.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; DNA = deoxyribonucleic acid; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IV = intravenous; NSCLC = non-small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; PD-1/PD-L1 = programmed death-1/programmed death ligand 1; PFS = progression-free survival; Q2W = once every two weeks; SQ = squamous; TKI = tyrosine kinase inhibitor; tx = treatment.

Assessments

- Safety, laboratory, and efficacy assessments were performed at Cycle 1 Day 1, at each subsequent cycle (Q2W) and at follow-up visits (Day 35 +/- 7 days and Day 100 +/-7 days after last dose)
- Pts were followed for at least 100 days after the last dose of nivolumab, and survival follow-up occurred every 12 weeks (+/-14 days) for 2 years
- PROs were assessed on Day 1 (+/-5 days) and every 4 weeks for the first 6 months, then every 6 weeks for the remainder of the study. PROs were assessed using EQ-5D-3L, EQ-VAS and lung cancer symptom score (LCSS)
- Tumour response was evaluated by investigators using RECIST v1.1

Results

Patients and disposition

- Overall, 400 pts received study tx; baseline characteristics are presented in **Table 1**
- *EGFR* mutation positive and negative status was reported in 34 (8.5%) and 263 (65.8%) patients, respectively, while 103 (25.8%) patients were not evaluable; *ALK* translocation positive, negative, and not evaluable status was reported in 10 (2.5%), 281 (70.3%), and 109 (27.3%) patients, respectively; there were 168 (42.0%), 174 (43.5%) patients with PD-L1 expression ≥1%, <1%, respectively, and 58 (14.5%) were not evaluable
- At database lock (July 13, 2021), median (range) duration of therapy was 3.24 (2.60 - 3.45) months overall, 3.25 (2.60 - 3.45) months for non-HBV infected pts, and 1.54 (0.95 - 12.68) for HBV infected pts; 18.8% of pts overall, 18.3% of non-HBV infected pts, and 29.4% of HBV infected pts received tx for >12 months
- All pts had discontinued the study drug at data cut-off; The most common reasons were disease progression (n = 274, 68.5%), completion of tx (n = 38, 9.5%), study drug toxicity (n=28, 7.0%), and adverse events unrelated to study drug (n = 21, 5.3%)

Table 1. Baseline patients demographics and characteristics

	Non-HBV N = 383	HBV N = 17	All treated N = 400
Age (years), mean (SD)	60.6 (8.72)	59.1 (7.86)	60.5 (8.68)
Male	301 (78.6)	13 (76.5)	314 (78.5)
Race Chinese Asian other	377 (98.4) 6 (1.6)	17 (100.0) 0	394 (98.5) 6 (1.5)
Baseline ECOG PS 0 1	53 (13.8) 328 (85.6)	5 (29.4) 12 (70.6)	58 (14.5) 340 (85.0)
Tobacco use status Non-smoker Smoker Current Former	125 (32.6) 258 (67.4) 24 (6.3) 234 (61.1)	7 (41.2) 10 (58.8) 0 10 (58.8)	132 (33.0) 268 (67.0) 24 (6.0) 244 (61.0)
Number of prior systemic regimens[b] 1 2 3	336 (87.7) 40 (10.4) 6 (1.6)	15 (88.2) 2 (11.8) 0	351 (87.8) 42 (10.5) 6 (1.5)
Histology Non-squamous Squamous	253 (66.0) 129 (33.7)	10 (58.8) 7 (41.2)	263 (65.8) 136 (34.0)
CNS metastases Yes No	7 (1.8) 376 (98.2)	0 17 (100.0)	7 (1.8) 393 (98.3)

Data are presented as n (%). [a]In the non-HBV population, 1 pt (0.3%) had ECOG PS 2 and ECOG PS was not reported for 1 patient (0.3%); [b]In the non-HBV population, 6 pts (1.6%) had ≥3 prior systemic regimens; 3 pts (0.8%) had no prior systemic regimens. Abbreviations: CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus.

Tx-related select AEs

- A summary of tx-related select AEs by HBV infection status is presented in **Table 2**
- Grade 3 - 4 tx-related select AEs occurred with low frequency (0.0 - 2.1%) in non-HBV infected pts (**primary endpoint**), and the most common were hepatic (2.1%), skin (1.8%), and pulmonary (1.3%). There were no Grade 5 tx-related select AEs
- Except for endocrine and skin AEs experienced by 1 (5.9%) pt each, there was no other Grade 3 - 4 tx-related select AEs in HBV-infected pts
- The majority of tx-related select AEs were manageable with supportive care

Table 2. Tx-related select AEs by HBV infection status

Tx-related select AEs[a]	Non-HBV N = 383		HBV N = 17		All treated N = 400	
	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4
Endocrine Thyroid disorder Diabetes Adrenal disorder	79 (20.6) 77 (20.1) 2 (0.5) 1 (0.3)	3 (0.8) 1 (0.3) 2 (0.5) 0	1(5.9) NR NR NR	1(5.9) NR NR NR	80 (20) NR NR NR	4 (1) NR NR NR
Hepatic	73 (19.1)	8 (2.1)	4 (23.5)	0	77 (19.3)	8 (2.0)
Skin	72 (18.8)	7 (1.8)	5 (29.4)	1 (5.9)	77 (19.3)	8 (2.0)
Renal	19 (5.0)	2 (0.5)	0	0	19 (4.8)	2 (0.5)
Pulmonary	17 (4.4)	5 (1.3)	1 (5.9)	0	18 (4.5)	5 (1.3)
Gastrointestinal	13 (3.4)	2 (0.5)	0	0	13 (3.3)	2 (0.5)
Hypersensitivity/Infusion reaction	0	0	0	0	0	0

Data are presented as n (%). [a]Includes events reported between the first dose and 30 days after last dose of study therapy; AEs of special interest were events with a potential immunological cause. Abbreviations: AE = adverse events; HBV = hepatitis B virus; NR = not reported.

Overall safety summary

- Tx-related AEs of any grade occurred in 301 (75.3%) pts, including 288 (75.2%) non-HBV pts and 13 (76.5%) HBV-infected pts (Table 3)
- Grade 3 - 4 tx-related AEs occurred in 60 (15%) pts, including 55 (14.4%) non-HBV pts and 5 (29.4%) HBV-infected pts
- Grade 5 tx-related AEs occurred in 9 (2.3%) pts, including 6 (1.6%) non-HBV subjects and 3 (17.6%) HBV-infected subjects
- The reported causes of death were malignant neoplasm progression and pneumonia in 2 patients each, and immune mediated myocarditis, myocarditis, ventricular fibrillation, sudden death and death in 1 patient each

Table 3. Overall safety summary in all treated pts

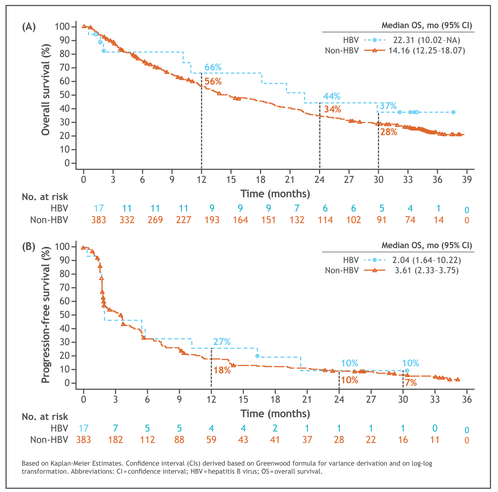
Tx-related select AEs[a]	Non-HBV N = 383		HBV N = 17		All treated N = 400	
	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4	Any Grade	Grade 3 - 4
TRAEs	288 (75.2)	55 (14.4)	13 (76.5)	5 (29.4)	301 (75.3)	60 (15.0)
Treatment-related serious AEs	61 (15.9)	27 (7.0)	7 (41.2)	3 (17.6)	68 (17.0)	30 (7.5)
TRAEs leading to discontinuation	23 (6.0)	8 (2.1)	3 (17.6)	1 (5.9)	26 (6.5)	9 (2.3)
TRAEs cause of death	6 (1.6)		3 (17.6)		9 (2.3)	

Data are presented as n (%). a)Includes events reported between the first dose and 30 days after last dose of study therapy; AEs of special interest were events with a potential immunological cause. Abbreviations: AE = adverse events; HBV = hepatitis B virus; TRAE = tx-related adverse event.

Efficacy

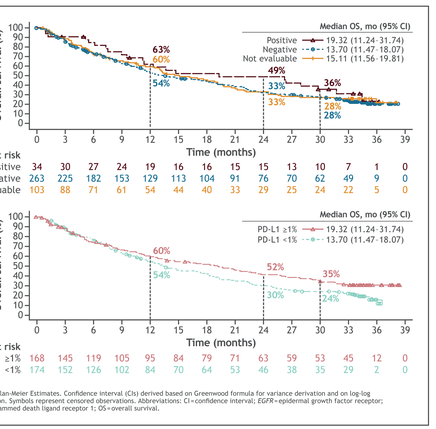
- After a minimum follow-up of 35.4 months and a median follow-up of 37.6 months, 12- and 24-month OS rates in all treated patients were 56% and 34%, respectively
- Median OS and median PFS for all treated, non-HBV and HBV-infected pts are shown in **Figure 2**
- Median OS for *EGFR* and PD-L1 pt subgroups are shown in **Figure 3**
- OS rates among HBV, *EGFR*, *ALK* and PD-L1 pt subgroups are shown in **Table 4**
- The ORR and DOR in all treated pts and pt subgroups are shown in **Table 5**
  - Median duration of response (DOR) in all treated pts was 19.38 months

Figure 2. (A) OS and (B) PFS in total, HBV, and non-HBV pts



Based on Kaplan-Meier Estimates. Confidence interval (CIs) derived based on Greenwood formula for variance derivation and on log-log transformation. Abbreviations: CI = confidence interval; HBV = hepatitis B virus; OS = overall survival.

Figure 3. OS by (A) EGFR mutation and (B) PD-L1 expression



Based on Kaplan-Meier Estimates. Confidence interval (CIs) derived based on Greenwood formula for variance derivation and on log-log transformation. Symbols represent censored observations. Abbreviations: CI = confidence interval; *EGFR* = epidermal growth factor receptor; PD-L1 = programmed death ligand receptor 1; OS = overall survival.

- Median (95% CI) PFS in EGFR positive, negative and not evaluable subgroups was 1.87 (1.71, 4.73) months, 3.25 (2.07, 3.68) months and 5.36 (3.42, 6.01) months, respectively
- Median (95% CI) PFS was 4.73 (3.68, 5.65) months and 2.33 (1.94, 3.68) months in patients with PD-L1 ≥1% and PD L1 <1%, respectively

Table 4. OS rates by patient subgroups

Patient subgroups	N	Overall survival rates, % (95% CI)	
		12-months	24-months
Total	400	56 (51 - 61)	34 (29 - 39)
HBV infection status			
Non-HBV-infected	383	56 (50 - 61)	34 (29 - 39)
HBV-infected	17	66 (37 - 85)	44 (19 - 67)
Histology			
Squamous	136	57 (48 - 65)	32 (24 - 40)
Non-squamous	264	56 (49 - 62)	35 (29 - 41)
PD-L1 expression			
≥1%	168	60 (52 - 67)	52 (44 - 59)
<1%	174	54 (46 - 62)	30 (23 - 38)
Molecular type			
EGFR mutation			
Positive	34	63 (44 - 77)	49 (31 - 65)
Negative	263	54 (48 - 60)	33 (27 - 39)
Not evaluable	103	60 (49 - 69)	33 (24 - 43)
ALK translocation			
Positive	10	60 (25 - 83)	40 (12 - 67)
Negative	281	56 (49 - 61)	33 (27 - 39)

Based on Kaplan-Meier estimates. Confidence interval (CIs) derived based on Greenwood formula for variance derivation and on log-log transformation. Not assessable if minimum follow-up of 10 months was not reached. Abbreviations: *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; HBV = hepatitis B virus; PD-L1 = programmed death ligand 1.

Table 5. DOR and ORR by patient subgroups

Patient subgroups	N	ORR n (%)	DOR median (95% CI), months
All treated	400	60 (15)	19.38 (11.04 - 24.97)
HBV infection status			NA (8.15 - NA)
Non-HBV-infected	383	57 (14.88)	19.38 (11.04 - 24.97)
HBV-infected	17	3 (17.65)	NA (8.15 - NA)
***EGFR* mutation status**			
Positive	34	6 (17.65)	12.57 (5.59 - NA)
Negative	263	34 (12.93)	19.61 (9.49 - 17.60)
PD-L1 expression			
≥1%	168	43 (25.60)	16.11 (9.43 - 27.60)
<1%	174	11 (6.32)	19.38 (8.11 - 24.97)

ORR = CR + PR. Median computed using Kaplan-Meier method. DOR was defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Abbreviations: CI = confidence interval, DOR = duration of response; *EGFR* = epidermal growth factor receptor; HBV = hepatitis B virus; NA = not assessable, ORR = objective response rate, PD-L1 = programmed cell death ligand 1.

Table 6. Patient-reported outcomes (PROs) in HBV subgroups

	Baseline		6 months (Tx cycle 13)		Change from baseline	12 months (Tx cycle 25)		Change from baseline
	N[a]	Mean (SD)	N[a]	Mean (SD)	Mean (SD)	N[a]	Mean (SD)	Mean (SD)
EQ-5D-3L								
Non-HBV	381	0.81 (0.14)	127	0.86 (0.15)	0.03 (0.15)	73	**0.89 (0.07)**	0.04 (0.11)
HBV	17	0.77 (0.14)	7	0.77 (0.19)	0.04 (0.13)	4	**0.90 (0.08)**	0.11 (0.11)
Total	398	0.81 (0.14)	134	0.85 (0.15)	0.03 (0.15)	77	**0.89 (0.08)**	0.04 (0.11)
EQ-VAS[b]								
Non-HBV	381	77.8 (15.04)	127	85.5 (15.92)	NR	73	87.7 (10.44)	NR
HBV	17	70.2 (21.07)	7	80.1 (14.96)	NR	4	94.8 (6.85)	NR
Total	398	77.5 (15.38)	134	85.2 (15.86)	NR	77	88.1 (10.37)	NR
EQ-VAS[b]								
Non-HBV	381	18.72 (15.17)	127	9.77 (11.81)	-6.26 (12.85)	73	8.43 (16.83)	-5.84 (17.31)
HBV	17	17.44 (13.06)	7	16.57 (17.35)	-5.33 (21.03)	4	2.58 (3.90)	-17.21 (21.07)
Total	398	18.66 (15.08)	134	10.13 (12.17)	-6.21 (13.28)	77	8.13 (16.45)	-6.43 (17.54)

[a]Number of subjects who filled the questionnaire at study assessment and with baseline value. bEQ-VAS ranges from 0 to 100, with 0 representing the worst health, 100 the best health. Abbreviations: HBV = hepatitis B virus; LCSS = lung cancer symptom score; NR = not reported; PRO = patient-reported outcome.

HBV reactivation

- The HBV reactivation rate was 17.6% (3/17)

Conclusions

- At a median follow-up of 37.6 months, NIVO 240 mg flat dose, 30-minute infusion, Q2W, appeared to show similar efficacy and safety to weight-based NIVO dosing (3 mg/kg, Q2W, 60-minute infusion) in Chinese pts with advanced NSCLC who progressed during or after ≥1 prior systemic therapy, including pts with HBV infection and/or *EGFR* mutation
- The occurrence of high-grade tx-related select AEs was low, and the safety profile of NIVO was similar in non-HBV and HBV-infected pts; Data should be interpreted with caution due to the small number of HBV-infected pts (n = 17); No new safety signals were observed in this long-term follow-up
- NIVO tx resulted in a numerical improvement in OS in pts with EGFR mutation and in a numerically higher ORR in pts with higher PD-L1 expression. Durable response across all subgroups that was consistent with results from pivotal trials
- Overall, long-term results from CheckMate 870 demonstrated that NIVO 240 mg, 30-minute infusion, Q2W is well tolerated, efficacious, and maintains health status and quality of life in Asian pts with advanced NSCLC, regardless of HBV, EGFR and PD-L1 status

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