A Phase II Study of Perioperative Ivonescimab Alone or Combined with Chemotherapy in Resectable Non-Small Cell Lung Cancer

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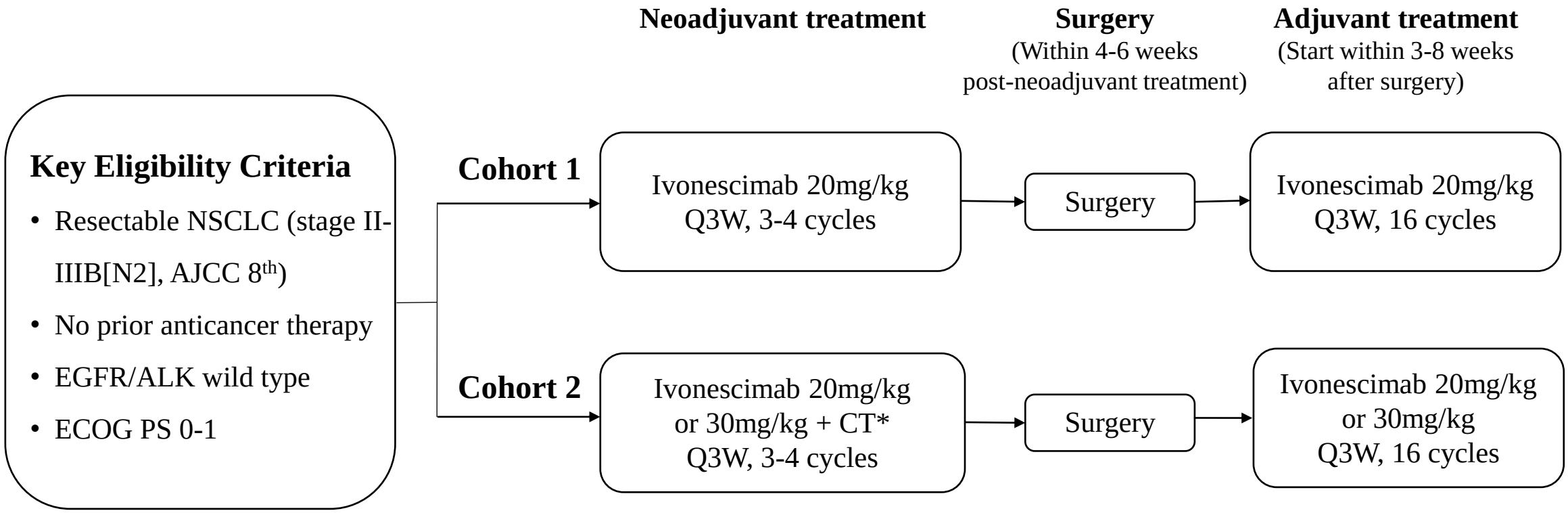
Background

- Recent phase III trials have demonstrated the efficacy of neoadjuvant PD-(L)1 inhibitors combined with chemotherapy followed by surgery and adjuvant PD-(L)1 inhibitors for resectable non-small cell lung cancer (NSCLC), including KEYNOTE 671[1], CheckMate 77T[2], AEGEAN[3], Neotorch[4], and RATIONALE 315[5].
- Ivonescimab is a first-in-class anti-PD-1/VEGF bispecific antibody. Ivonescimab, both as monotherapy and in combination with chemotherapy, showed promising antitumor activity and manageable safety profile in patients with advanced NSCLC[6,7].
- Here we report the efficacy and safety of a phase II study of perioperative ivonescimab alone or combined with chemotherapy in resectable NSCLC (NCT05247684).

[1]Wakelee H, et al. N Engl J Med. 2023 Aug 10;389(6):491-503. [2]Cascone T, et al. N Engl J Med. 2024 May 16;390(19):1756-1769. [3]Heymach JV, et al. N Engl J Med. 2023 Nov 2;389(18):1672-1684.
[4]Lu S, et al. JAMA. 2024 Jan 16;331(3):201-211. [5]D. Yue, et al. 2023 ESMO LBA58. [6]Fang W, et al. JAMA. 2024 Aug 20;332(7):561-570. [7]Wang L, et al. J Thorac Oncol. 2024 Mar;19(3):465-475.

Study Design

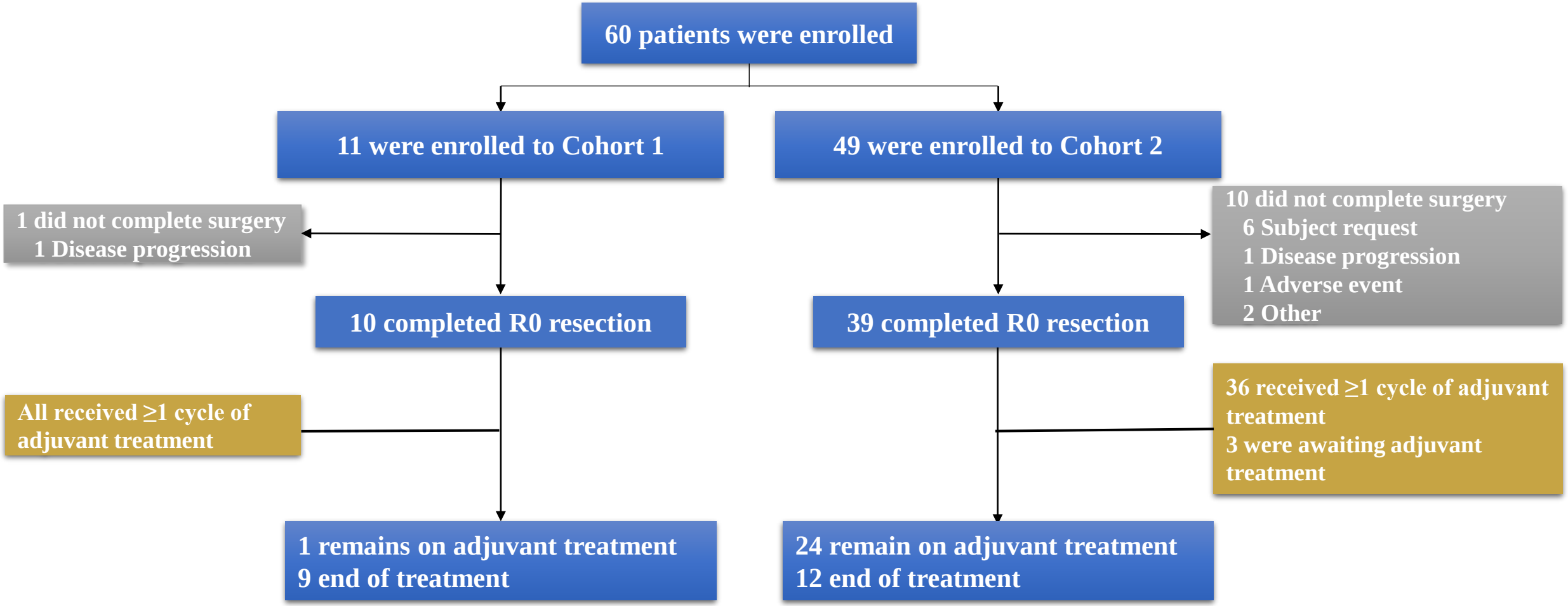


*Chemotherapy: Cisplatin/Carboplatin + Paclitaxel

- **Primary Endpoints: MPR, Safety**
- **Secondary Endpoints: pCR, EFS, OS, ORR, the rate of R0 resection and downstaging**

Data cutoff date: Feb 01, 2024. As of Feb 01, 2024, 60 patients were enrolled in the study.
NSCLC, non-small cell lung cancer; AJCC, American Joint Committeon cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q3W, every 3 weeks; MPR, major pathological response; pCR, pathological complete response; EFS, event-free survival; OS, overall survival; ORR, objective response rate.

Patient Disposition

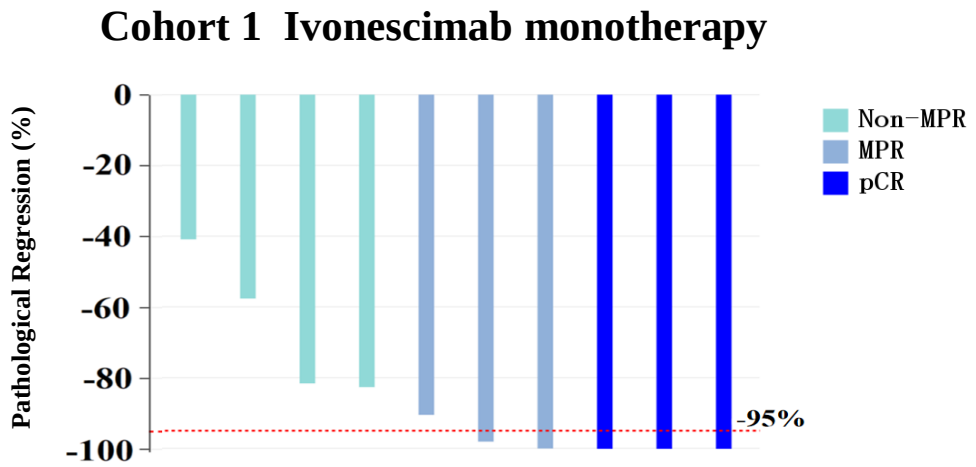


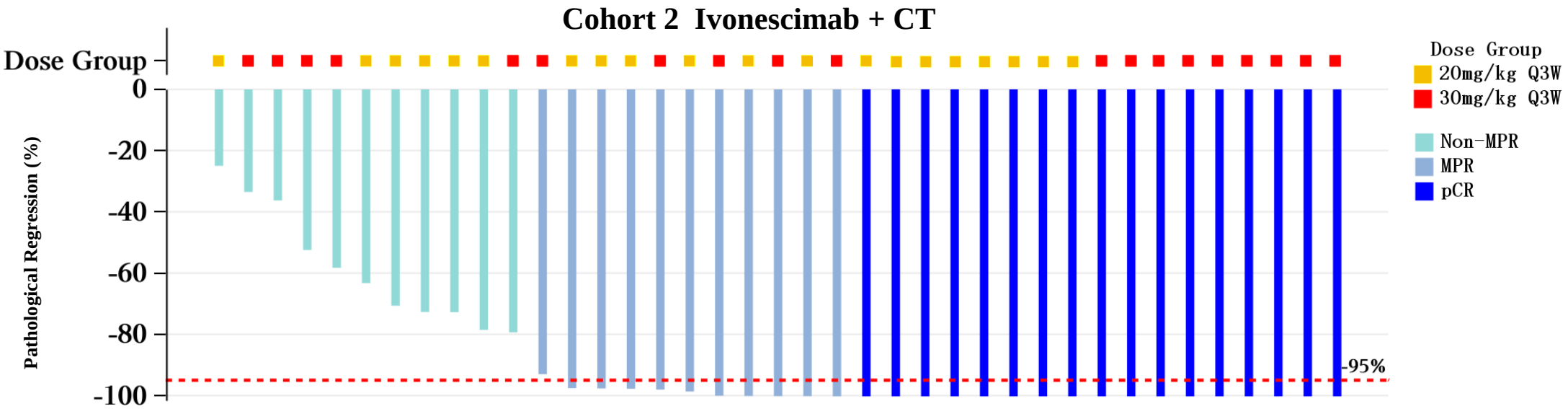
Baseline Characteristics

Characteristics		Cohort 1 Ivonescimab monotherapy (N=11)	Cohort 2 Ivonescimab + CT (N=49)	Total (N=60)
Dose level of Ivonescimab, n(%)	20mg/kg	11 (100.0)	24 (49.0)	35 (58.3)
	30mg/kg	0	25 (51.0)	25 (41.7)
Age, years	Median (range)	64 (50, 70)	64 (30, 74)	64 (30, 74)
Sex, n(%)	Male	9 (81.8)	42 (85.7)	51 (85.0)
ECOG, n(%)	PS=0	11 (100)	48 (98.0)	59 (98.3)
Smoking status, n(%)	Never	1 (9.1)	10 (20.4)	11 (18.3)
	Current or former	10 (90.9)	39 (79.6)	49 (81.7)
Histology, n(%)	Squamous	8 (72.7)	37 (75.5)	45 (75.0)
	Non-squamous	3 (27.3)	12 (24.5)	15 (25.0)
PD-L1 expression, n(%)	<1%	2 (18.2)	12 (24.5)	14 (23.3)
	≥1%	9 (81.8)	33 (67.3)	42 (70.0)
	Unknown	0	4 (8.2)	4 (6.7)
Clinical stage, n(%)	II	3 (27.3)	10 (20.4)	13 (21.7)
	III	8 (72.7)	39 (79.6)	47 (78.3)
N stage, n(%)	N0	3 (27.3)	3 (6.1)	6 (10.0)
	N1/2	8 (72.7)	46 (93.9)	54 (90.0)
	N1	0	12 (24.5)	12 (20.0)
	N2	8 (72.7)	34 (69.4)	42 (70.0)

Pathological Response

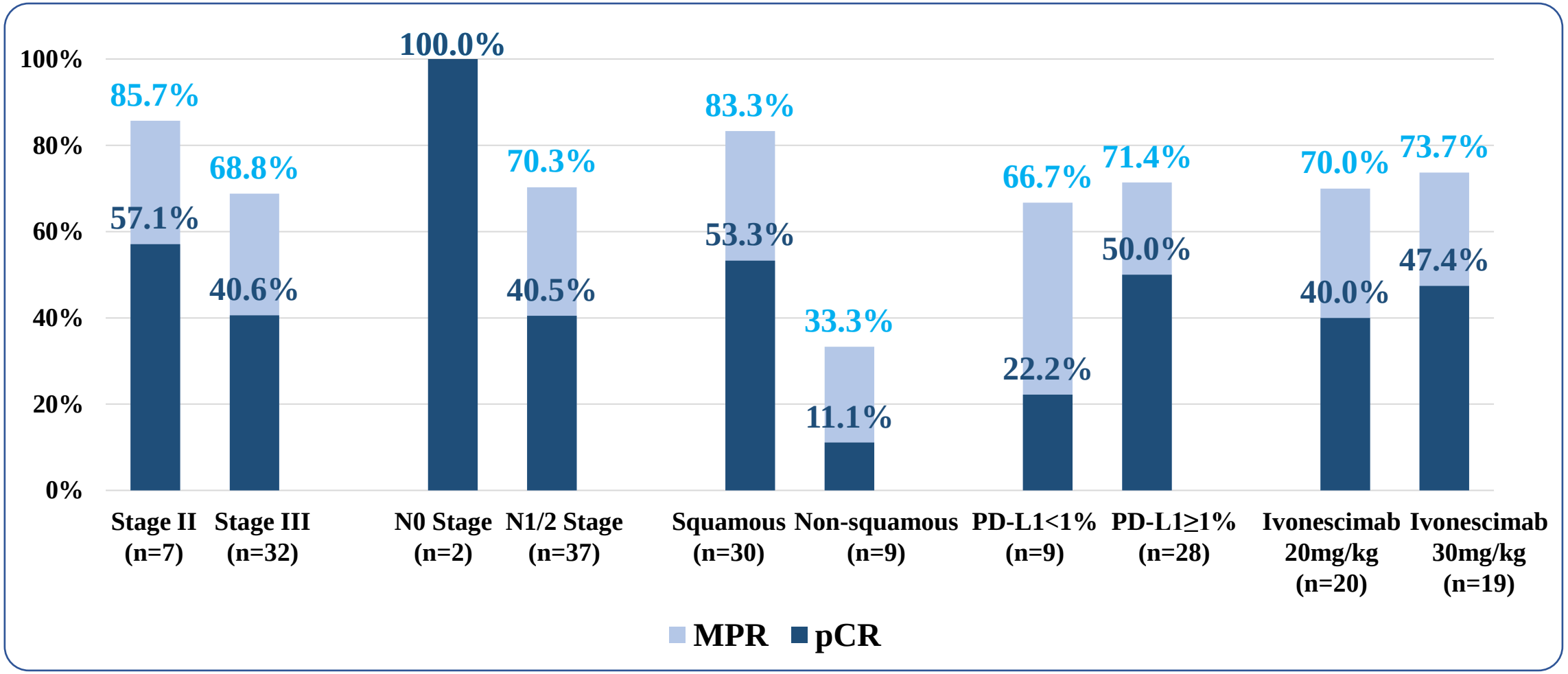
	Cohort 1 (N=10)	Cohort 2 (N=39)
MPR	60.0%	71.8%
- RVT*＜5%	50.0%	69.2%
pCR	30.0%	43.6%





*RVT: residual viable tumor cells in both primary tumor and lymph nodes.

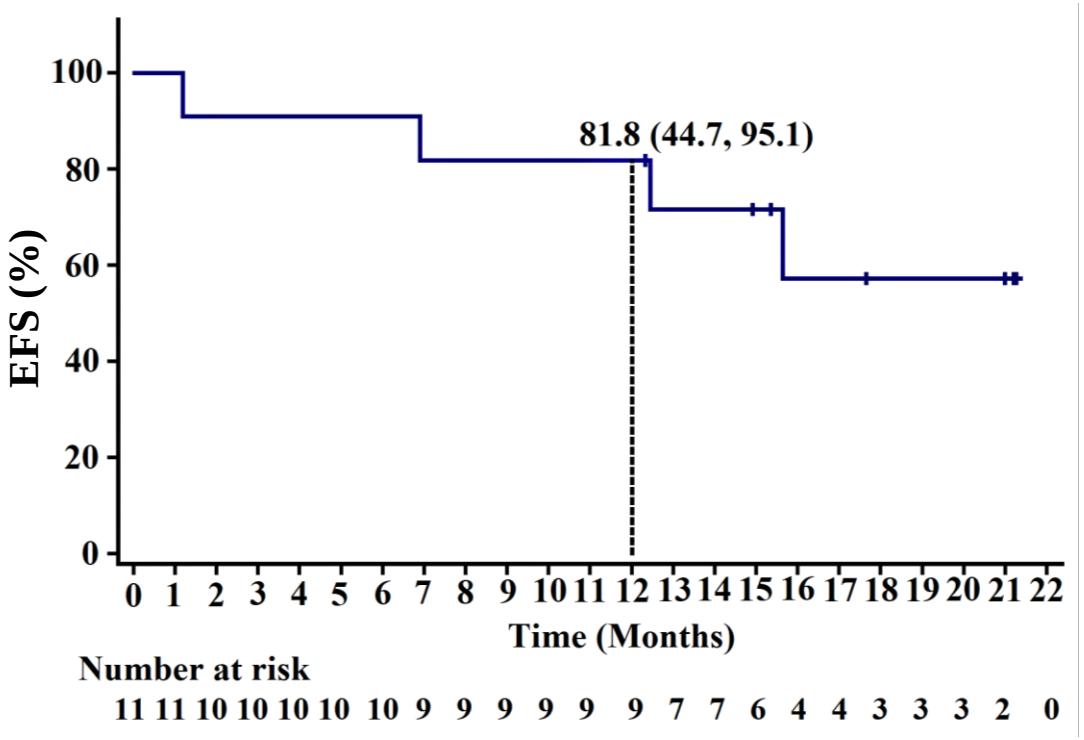
MPR and pCR by Subgroups in Cohort 2



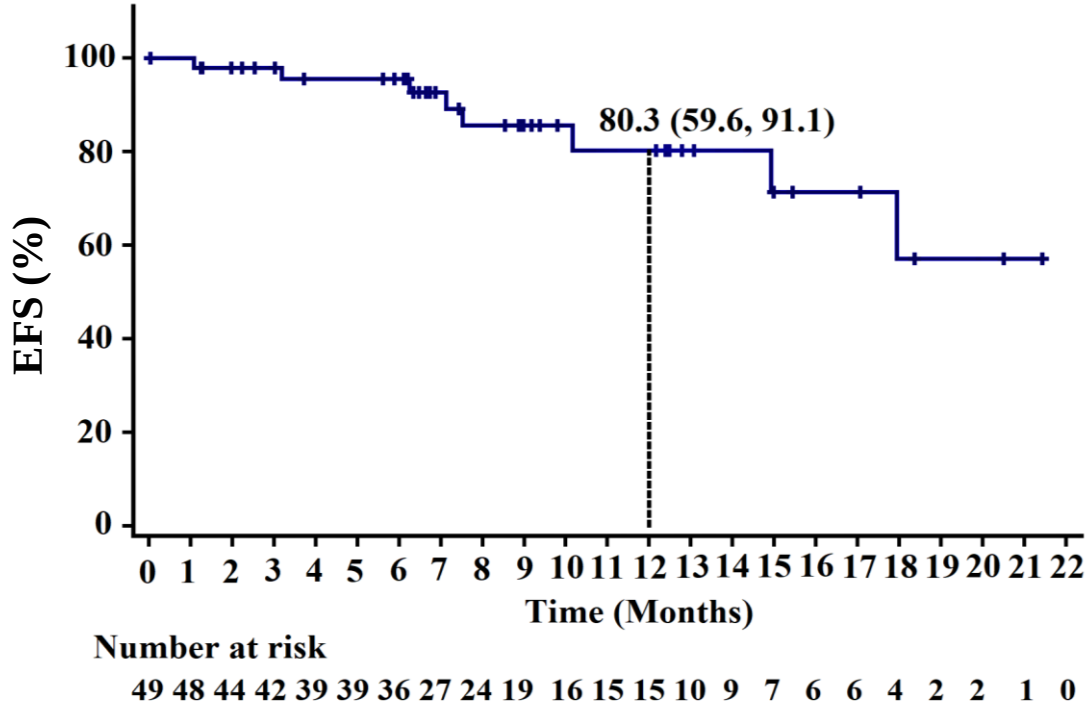
The expression of PD-L1 was unknown in two patients.

EFS

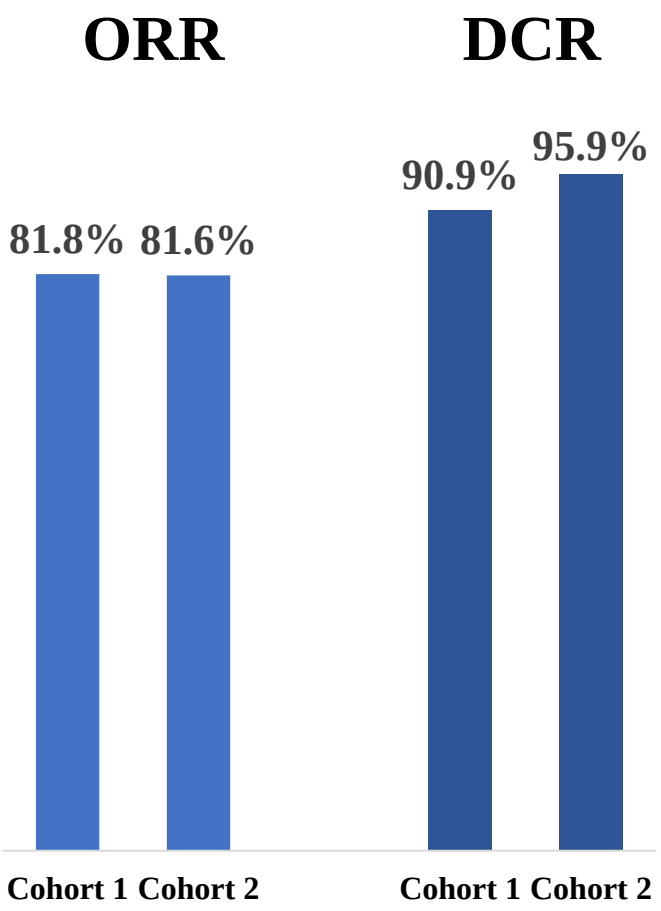
Cohort 1 Ivonescimab monotherapy (n=11)	
Median Follow-up (95% CI)	17.64 (12.3, 21.2)
No. of Events/No. of Patients (%)	4/11 (36.4%)
Median EFS (95% CI)	NR (6.9, NE)

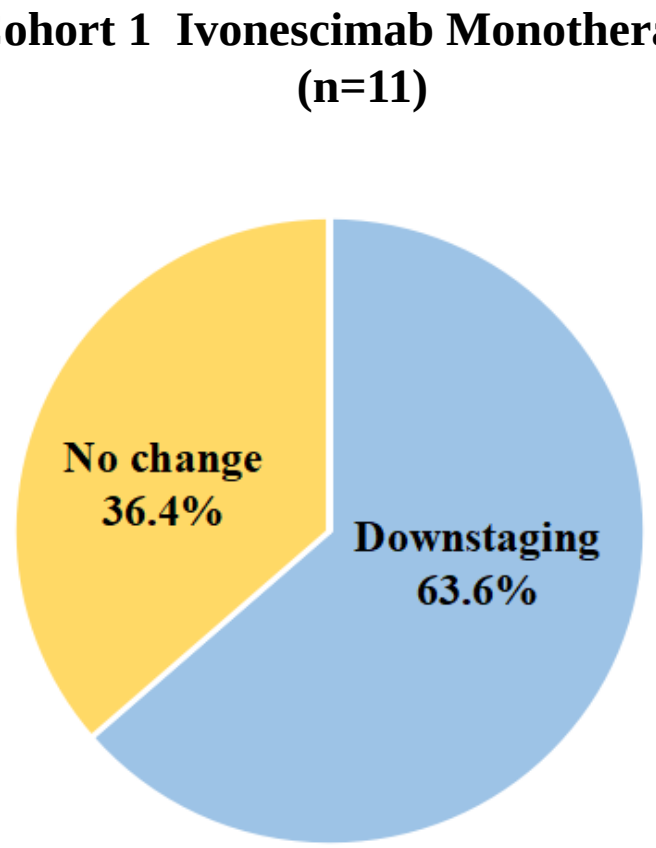


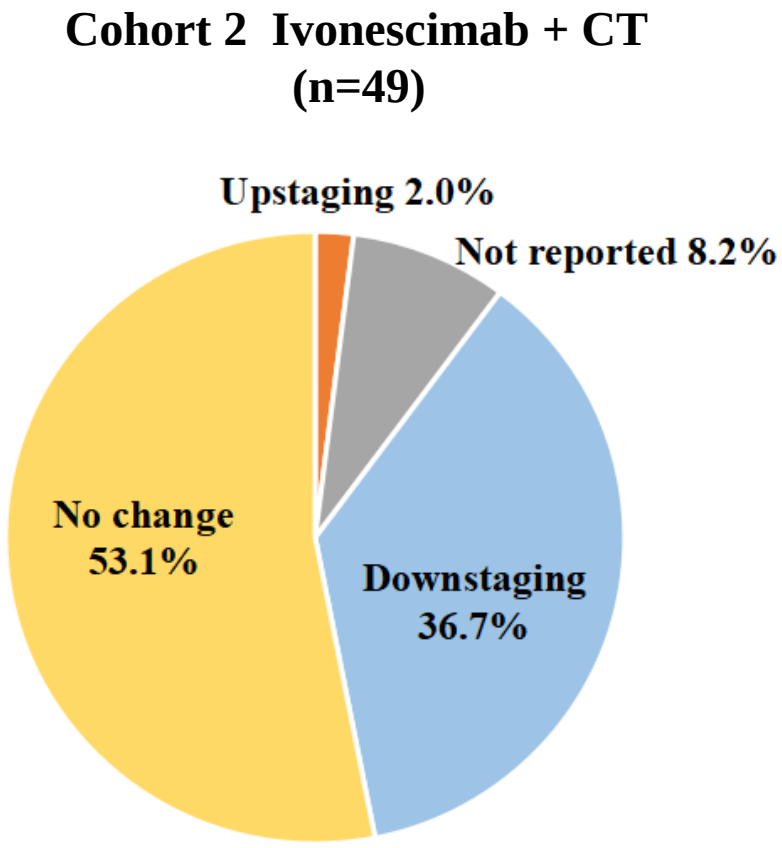
Cohort 2 Ivonescimab + CT (n=49)	
Median Follow-up (95% CI)	8.94 (6.6, 12.2)
No. of Events/No. of Patients (%)	8/49 (16.3%)
Median EFS (95% CI)	NR (14.9, NE)



Tumor Response and Stage Change in Neoadjuvant Phase







ORR, objective response rate; DCR, disease control rate.

Safety Profile

TRAEs, n (%)	Cohort 1 Ivonescimab monotherapy (N=11)	Cohort 2 Ivonescimab + CT (N=49)	Total (N=60)
Any grade	9 (81.8)	42 (85.7)	51 (85.0)
Grade≥3	4 (36.4)	16 (32.7)	20 (33.3)
SAE	2 (18.2)	1 (2.0)	3 (5.0)
Leading to treatment delay of ivonescimab	3 (27.3)	6 (12.2)	9 (15.0)
Leading to discontinuation of ivonescimab	4 (36.4)	1 (2.0)	5 (8.3)
Leading to death	0	0	0
Leading to delayed or cancelled surgery	0	0	0
Surgery related TRAE	1 (10.0)	7 (17.9)	8 (16.3)
Grade≥3 irAE	4 (36.4)	1 (2.0)	5 (8.3)

The median follow-up time was 17.64 months in cohort 1 and 8.94 months in cohort 2.
TRAE, treatment-related adverse event (related to ivonescimab); irAEs were evaluated by investigators.
The TRAEs leading to discontinuation of ivonescimab and grade≥3 irAEs were the same events.
Surgery related TRAE defined as TRAE reported within 90 days after surgery or until the start of adjuvant treatment, whichever occurred first (in patients who completed the surgery).

Conclusions

- Perioperative ivonescimab monotherapy or combined with chemotherapy for resectable NSCLC demonstrated high rates of pCR and MPR in this phase II study.

- Compared with ivonescimab monotherapy, rates of MPR and pCR in ivonescimab combined with chemotherapy were numerically higher, and across tumor stage and PD-L1 expression subgroups.
  - Ivonescimab + chemotherapy: pCR rate was 43.6%, MPR rate was 71.8%
    -As of Aug 30, 2024, 55 patients in cohort 2 completed surgery, pCR and MPR rates were improved to 52.7% and 72.7%, respectively. For squamous NSCLC, pCR and MPR rates were 63.6% and 84.1%, respectively.
  - Ivonescimab monotherapy: pCR rate was 30.0%, MPR rate was 60.0%

- Although EFS is not mature yet, higher pCR rates relative to historic studies[1-3] may predict longer EFS. Additional follow-up studies are planned to confirm these results.

- The safety profile was manageable. There were no TRAEs that led to cancelled or delayed surgery or wound healing complications.

[1]Wakelee H, et al. N Engl J Med. 2023 Aug 10;389(6):491-503. [2]Cascone T, et al. N Engl J Med. 2024 May 16;390(19):1756-1769. [3]Lu S, et al. JAMA. 2024 Jan 16;331(3):201-211.

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