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Nivolumab + Chemotherapy Vs Chemotherapy as NAT in Resectable Stage III A NSCLC: Primary Endpoint Results of pCR from phase II NADIM II trial

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INTRODUCTION

- NSCLC accounts for 80–85% of all lung cancer cases[1]
- Approximately 20% of patients with NSCLC are diagnosed with stage IIIA (N2) disease[1]
- Multimodality treatment is necessary in this group of patients
- Outcomes remain poor for these patients, with a 5-year overall survival of around 36%[2,3]
- Preoperative CT have been shown to significantly improve overall survival in resectable NSCLC (HR for survival, 0.87, 95% CI 0.78–0.96, p=0.007). However, the absolute 5-year survival improvement is 5%[4]
- A strong association between pathological complete response (pCR) and survival following neoadjuvant CT has been shown across studies (HR for survival, 0.49; 95% CI 0.43-0.56)[5]
- However, the median rate of pCR after neoadjuvant CT is low, 4% (range 0–16%)[6]

HR, hazard ratio; NSCLC, non-small cell lung cancer; pCR, pathological complete response

1. Siegel RL, et al. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30; 2. Ramnath N, et al. Chest 2013; 143 (suppl 5): e314S-340S; 3. Goldstraw P, et al. J. Thorac. Oncol. 2016, 11, 39–51; 4. NSCLC Meta-analyses Collaborative Group. Lancet 2014;383:1561–1571; 5. Waser N, et al. Poster presentation at ESMO 2020; Sept 19-21; Virtual; P1243; 6. Hellmann, MD, et al. Lancet Oncol 2014;15:e42–e50.

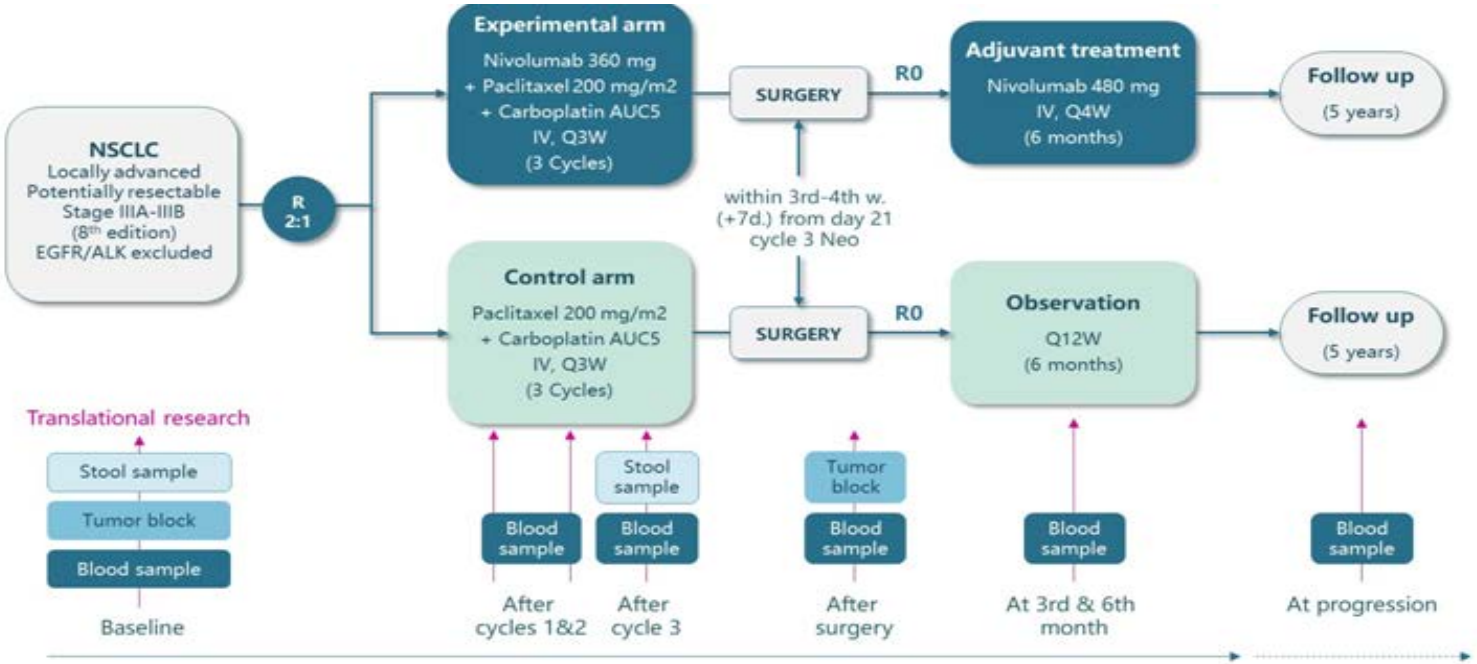
INTRODUCTION

- Neoadjuvant immunotherapy for resectable NSCLC have shown promising activity in several single-arm, phase II studies.
- Phase III CM816, showed a higher rate of pathological complete response (pCR) on tumor resection and improved EFS compared to that seen with neoadjuvant chemotherapy [6]
- NADIM II is a randomized, phase 2, open-label study evaluating nivolumab + CT versus CT as neoadjuvant treatment for resectable stage IIIA-B (AJCC 8th edition) NSCLC. It is an Investigator Sponsored Research Study.
- Here we present the primary endpoint results on pCR, as well as key safety data

DFS, disease-free survival; EFS, event-free survival; OS, overall survival; pCR, pathological complete response

1. Forde PM, et al. N Engl J Med 2018;378:1976–1986; 2. Provencio M, et al. Lancet Oncol 2020;21:1413–1422; 3. Gao S, et al. J Thorac Oncol 2020;15:816–826; 4. Shu C, et al. Lancet Oncol 2020;21:786–795; 5. Cascone T, et al. Nat Med 2021. Epub ahead of print. doi: 10.1038/s41591-020-01224-2; 6. Forde P, et al. NEJM 2022 https://doi.org/10.1056/NEJMoa2202170.

STUDY DESIGN



NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

ENDPOINTS

Primary endpoint

- Pathological complete response in the intention-to-treat population (ITT)

Secondary endpoints

- Major pathological response (MPR)
- Portion of delayed/canceled surgeries, length of hospital stays, surgical approach, incidence of AE/SAE related to surgery
- Safety and tolerability: Adverse events graded according to CTCAE v5.0
- Potential predictive biomarkers (ctDNA, TCR)
- Other: (i) OS at 12, 18 and 24 months; (ii) PFS at 12, 18 and 24 months; (iii) Down-staging; (iv) Mortality at 90 days after surgery; (v) Association between clinical baseline characteristics and ORR, pathological response, AEs, PFS and OS; (vi) Association between pathological response and PFS or OS; (vii) Association between MPR and histology; (viii) Association between histology and PFS at 18 months

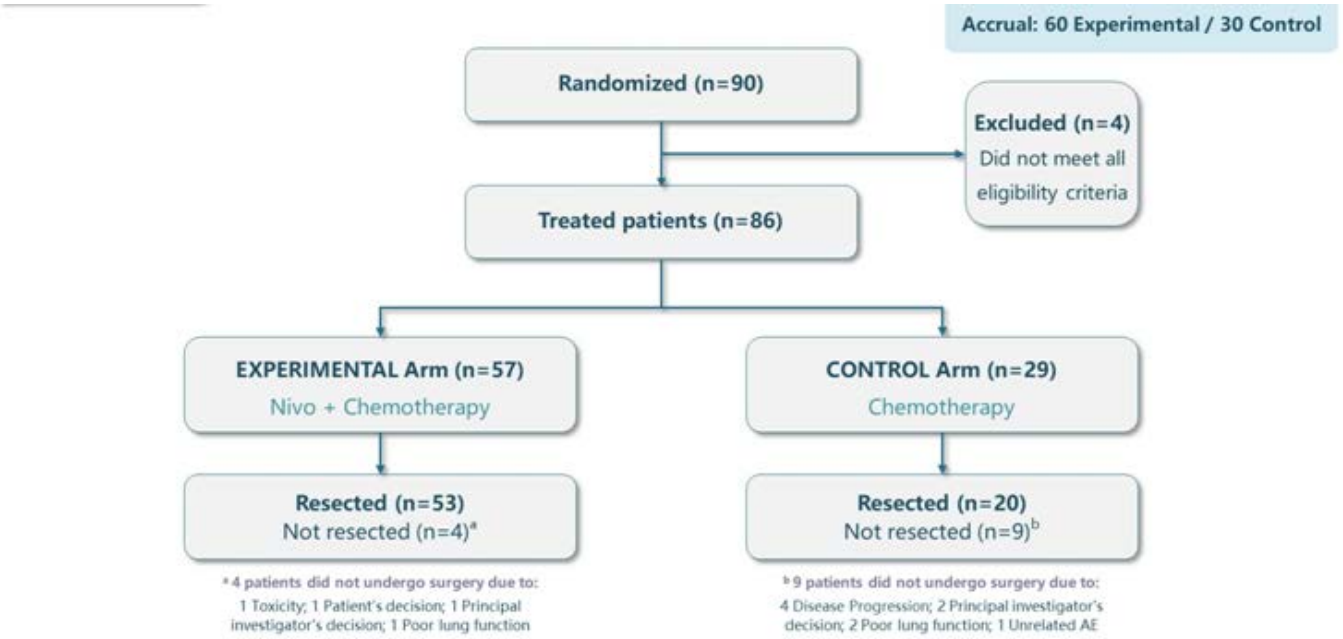
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; EFS, event-free survival; ITT, intention-to-treat; MRP, major pathological response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event

STATISTICAL ANALYSIS

- The analysis was conducted according to the intention-to-treat (ITT) principle[a]
  - → **This population was defined as those** patients that were included in the study and who had received at least one dose of study treatment
- **Pathological complete response** (pCR) was defined as the absence of any viable tumor cell in the resected lung specimen and all regional lymph nodes
- Referring to the results of previous phase 2 NADIM trial (NCT03081689)[1], we assumed a proportion of pCR of 10% in the Control Arm (CT + surgery) and 40% in the Experimental Arm (CT+ immunotherapy + surgery + immunotherapy)
- An alpha level of 5%, a statistical power of 80%, and a drop-out rate of 15% was set
- A sample size of 90 patients (60 in the Experimental Arm and 30 in the Control Arm) was estimated to show the difference between both groups
- An independent data monitoring committee evaluated the superiority of nivolumab + CT vs CT for pCR at the preplanned analysis

[a]ITT principle: patients who did not undergo surgery were considered as non-responders for final analysis
ITT, intention-to-treat; pCR, pathological complete response
1. Provencio M, et al. Lancet Oncol 2020;21:1413–1422;

FLOW DIAGRAM



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BASELINE CHARACTERISTICS

Baseline characteristics - ITT population		
Characteristic	**NIVO + Chemo (n = 57)**	**Chemo (n = 29)**
Age – median (range), years	63 (58-70)	62 (57-66)
Female – No. (%)	21 (36.8)	13 (44.8)
History of tobacco use – No. (%)		
Never smoker	5 (8.7)	0 (0.0)
Former smoker	23 (40.4)	10 (34.5)
Current smoker	29 (50.9)	19 (65.5)
ECOG PS – No. (%)		
0	31 (54.4)	16 (55.2)
1	26 (45.6)	13 (44.8)
Histology – No. (%)		
Adenocarcinoma	25 (43.9)	11 (37.9)
Adenosquamous	1 (1.8)	0 (0.0)
Squamous	21 (36.8)	14 (48.3)
Large Cell Carcinoma	2 (3.5)	1 (3.5)
NOS / Undifferentiated	7 (12.3)	2 (6.9)
Other	1 (1.8)	1 (3.5)

Baseline characteristics - ITT population		
Characteristic	**NIVO + Chemo (n = 57)**	**Chemo (n = 29)**
TNM classification (AJCC 8th edition)		
T1N2M0	12 (21.1)	4 (13.8)
T2N2M0	16 (28.1)	7 (24.1)
T3N1M0	2 (3.5)	1 (3.5)
T3N2M0	13(22.8)	5 (19.3)
T4N0M0	6 (10.5)	9 (31.0)
T4N1M0	8 (14.0)	3 (10.3)
Tumor size – Median (range), mm	43 (29-54)	52 (39-75)
Nodal stage – No. (%)		
N0	6 (10.5)	9 (31.0)
N1	10 (17.5)	4 (13.8)
N2	41 (71.9)	16 (55.2)
N2 multiple station	21(36.8)	10 (34.5)

Chemo, Chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; Nivo, Nivolumab; NOS, not otherwise specified

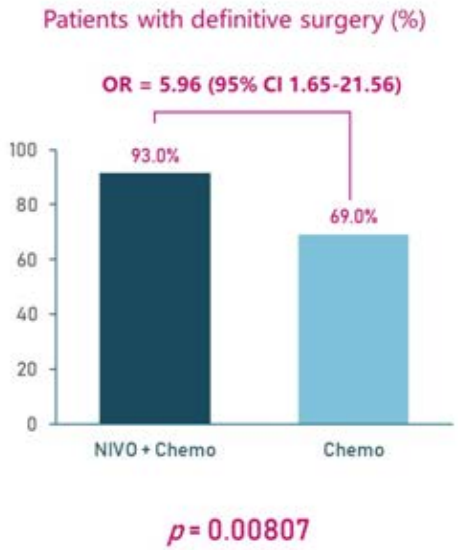
BASELINE CHARACTERISTICS

Baseline characteristics - ITT population		
Comorbidity, %	**NIVOLUMAB + Chemo (n = 57)**	**Chemo (n = 29)**
Yes	7.0	7.1
Asthma	0.0	3.5
Heart disease	8.7	3.5
Diabetes mellitus	12.3	10.3
Dyslipemia	42.1	24.1
Alcoholism	1.8	3.5
Hepatitis	3.5	0.0
Hypercholesterolemia	1.8	6.9
Hypertension	47.4	31.0
Nephropathy	1.8	3.5
Obesity	10.5	3.5
Depressive Syndrome / Anxiety	7.0	20.7
Vasculopathy	3.5	3.5
Autoimmune disease	1.8	0.0
Neurological disease	1.8	0.0
Hypothyroidism	5.3	3.5
Benign prostatic hypertrophy	5.3	10.3
COPD	22.8	6.9
Other	87.7	69.0

Chemo, chemotherapy; COPD, chronic obstructive pulmonary disease; ITT, intention-to-treat

SURGERY SUMMARY

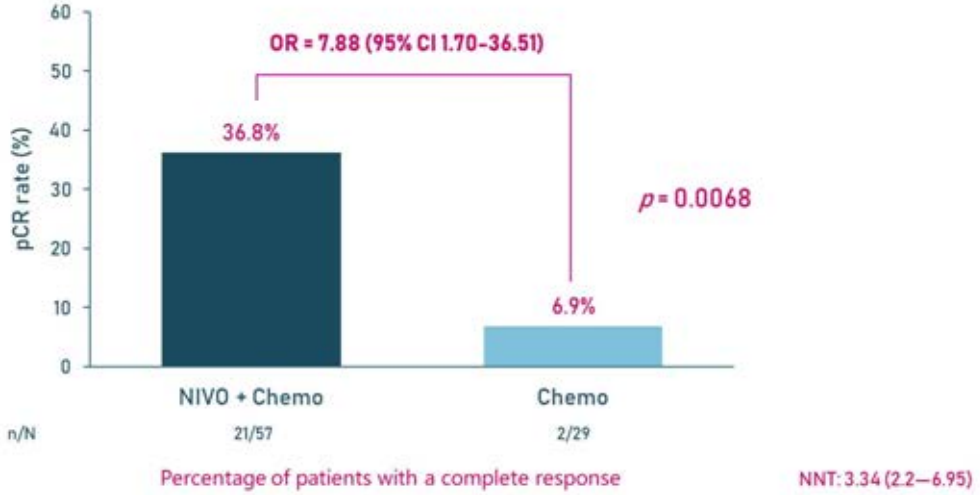
Surgery summary			
Patients, No. (%)	**NIVO + chemo (n = 57)**	**Chemo (n = 29)**	**Total**
Patients with definitive surgery	53 (93.0)	20 (69.0)	73
Patients with cancelled definitive surgery	4 (7.0)	9 (31.0)	13
Due to adverse events	1 (1.7)	0 (0.0)	1
Due to disease progression	0 (0.0)	4 (13.7)	4
Not suitable for surgery	3 (5.2)	5 (17.2)	8



Nivo, nivolumab; Chemo, chemotherapy

PRIMARY ENDPOINT pCR

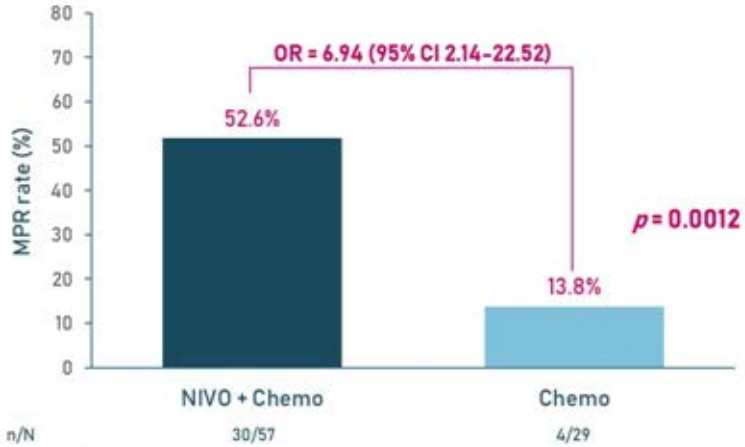
pCR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; pCR, pathological complete response; RR, risk ratio

SECONDARY ENDPOINT MPR

MPR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population [b]

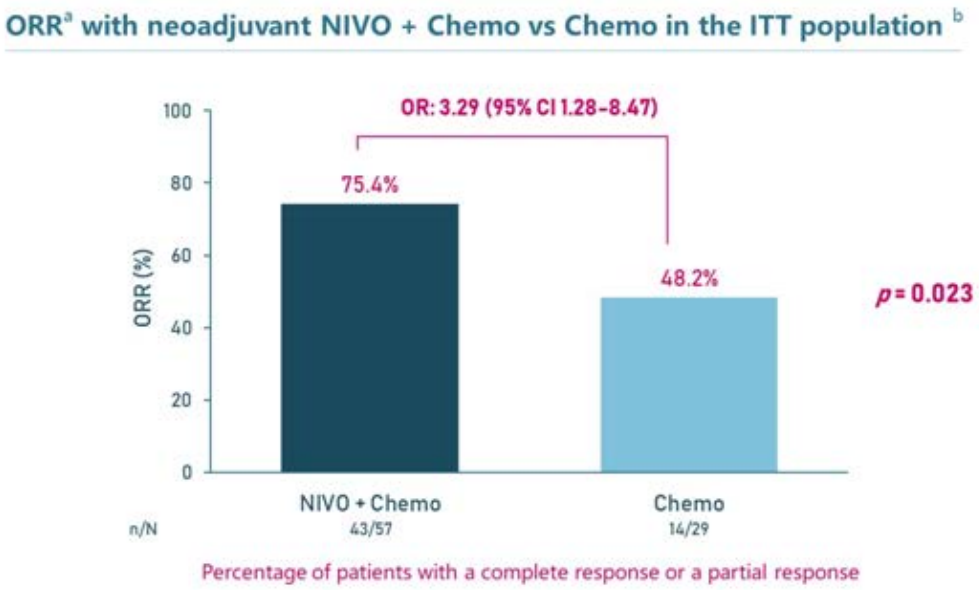


Percentage of patients with a complete response or a major response

NNT: 2.57 (1.76–4.81)

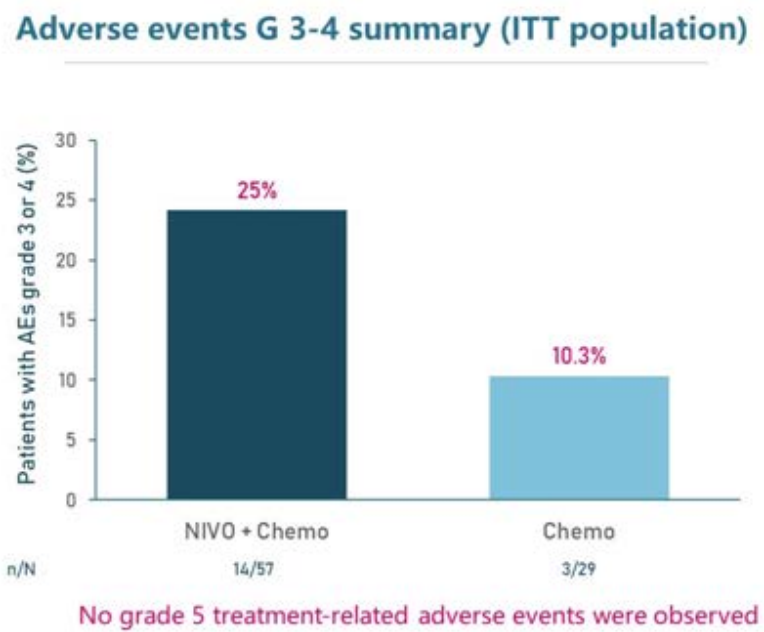
[a]MPR was defined as ≤10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; MPR, major pathological response; Nivo, nivolumab; RR, risk ratio

SECONDARY ENDPOINT ORR



[a]ORR was defined as percentage of patients who had a partial response or complete response to the treatment following RECIST 1.1 criteria; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; ORR, overall response rate.

SECONDARY ENDPOINT SAFETY



AE, adverse event; Chemo, chemotherapy; Nivo, nivolumab; ITT, intention-to-treat

SECONDARY ENDPOINT SAFETY

Treatment-related adverse events in the EXPERIMENTAL arm: NIVOLUMAB + Chemotherapy (n = 57)			
Adverse event, No. (%)	**Grade 1-2**	**Grade 3**	**Grade 4**
Any treatment-related adverse event	**52 (91.2)**	**12 (21.1)**	**2 (3.5)**
Fatigue	32 (56.1)	1 (1.8)	**1 (1.8)**
Alopecia	17 (29.8)	0 (0.0)	0 (0.0)
Arthralgia	17 (29.8)	0 (0.0)	0 (0.0)
Diarrhea	8 (14.0)	2 (3.5)	0 (0.0)
Anemia	8 (14.0)	0 (0.0)	0 (0.0)
Myalgia	11 (19.3)	0 (0.0)	0 (0.0)
Pruritus	7 (12.3)	0 (0.0)	0 (0.0)
Rash acneiform	7 (12.3)	0 (0.0)	0 (0.0)
Anorexia	5 (8.8)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	5 (8.8)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	5 (8.8)	1 (1.8)	0 (0.0)
Hypothyroidism	5 (8.8)	0 (0.0)	0 (0.0)
Nervous system disorders	5 (8.8)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorder	4 (7.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders - Other, specify	3 (5.3)	0 (0.0)	0 (0.0)
Febrile neutropenia	1 (1.8)	3 (5.3)	**1 (1.8)**

Adverse events with an incidence of ≥10% or grade 3–4 severity with incidence of ≥5% are shown

Treatment-related adverse events in the CONTROL arm: Chemotherapy (n = 29)			
Adverse event, No. (%)	**Grade 1-2**	**Grade 3**	**Grade 4**
Any treatment-related adverse event	**26 (89.7)**	**3 (10.3)**	**0 (0.0)**
Alopecia	10 (34.5)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	10 (34.5)	1 (3.4)	0 (0.0)
Arthralgia	8 (27.6)	0 (0.0)	0 (0.0)
Anemia	3 (10.3)	0 (0.0)	0 (0.0)
Mucositis oral	3 (10.3)	0 (0.0)	0 (0.0)
Paresthesia	3 (10.3)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	3 (10.3)	0 (0.0)	0 (0.0)
Peripheral motor neuropathy	3 (10.3)	0 (0.0)	0 (0.0)
Pruritus	2 (6.9)	0 (0.0)	0 (0.0)
Dry skin	2 (6.9)	0 (0.0)	0 (0.0)
Diarrhea	2 (6.9)	0 (0.0)	0 (0.0)
Disgeusia	2 (6.9)	0 (0.0)	0 (0.0)
Hearing impaired	2 (6.9)	0 (0.0)	0 (0.0)
Nervous system disorders	2 (6.9)	0 (0.0)	0 (0.0)

Adverse events with an incidence of ≥10% or grade 3–4 severity with incidence of ≥5% are shown

CONCLUSIONS

- NADIM II confirms superiority of neoadjuvant nivolumab plus chemotherapy combination in patients with resectable stage IIIA-B NSCLC
- The addition of neoadjuvant nivolumab to chemotherapy:
  - → Significantly improved pCR (OR = 7.88 [95% CI 1.70-36.5]) (Chi-squared test: p = 0.0068)
  - → Maintained a tolerable safety profile, with a moderate increase in grade 3-4 toxicity
  - → Did not impede the feasibility of surgery

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