BRENTUXIMAB VEDOTIN, NIVOLUMAB, DOXORUBICIN, AND DACARBAZINE FOR EARLY-STAGE CLASSICAL HODGKIN LYMPHOMA (SGN35-027 PART C)

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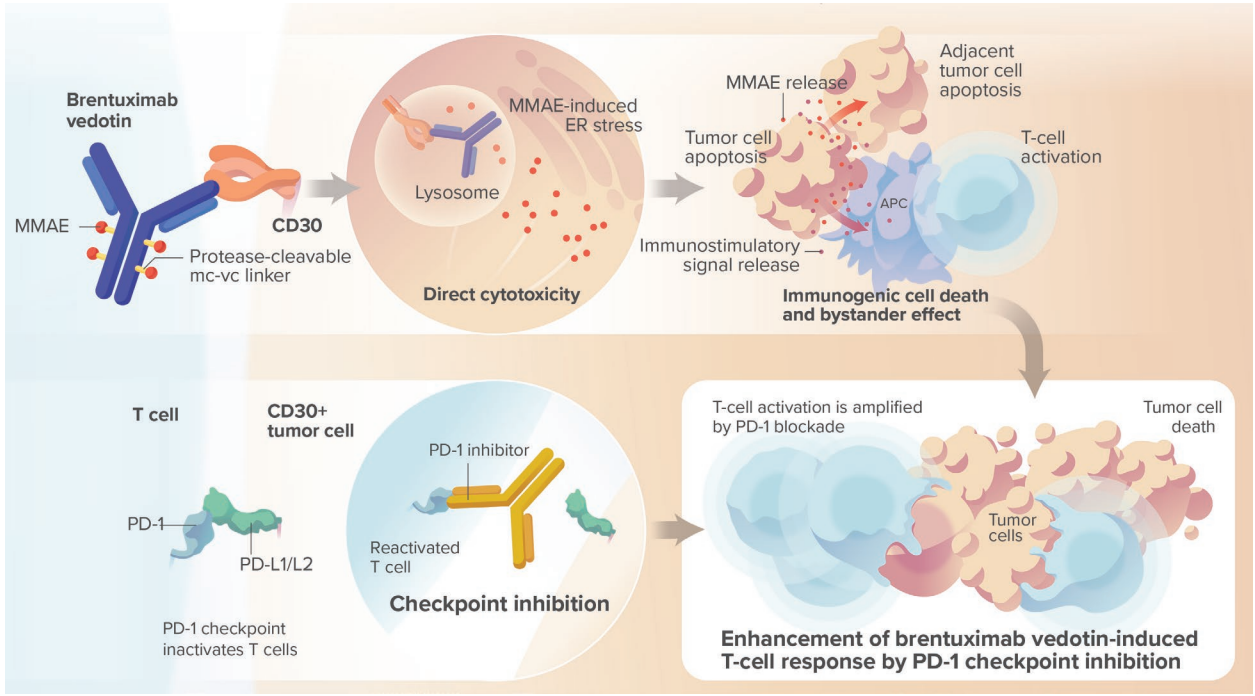
Background

- Brentuximab vedotin (BV) is an antibody-drug conjugate approved for untreated stage III or IV classical Hodgkin Lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD)
- A+AVD has improved overall survival in advanced stage cHL; however, the regimen is associated with increased neuropathy and neutropenia related to overlap of BV with vinblastine[1-4]
- In earlier studies, BV+nivolumab was well tolerated with promising efficacy[5-6]
- It is hypothesized that BV with nivolumab combined with AD (AN+AD) may result in high response rates and a tolerable safety profile, with less toxicity compared with vinblastine-containing regimens

Here, the efficacy and safety results from Part C of this Phase 2 study of patients with early-stage cHL treated with AN+AD are presented

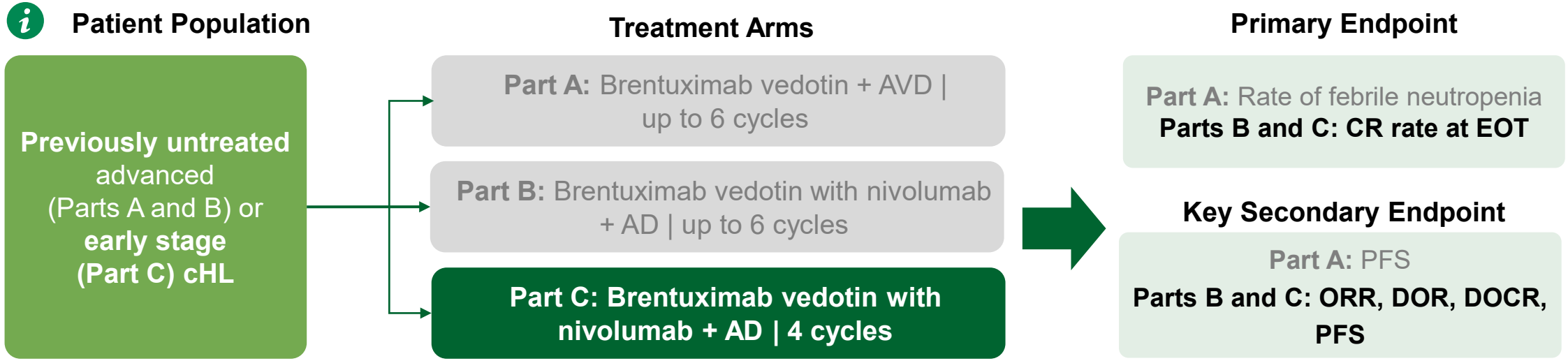


Brentuximab vedotin plus a PD-1 inhibitor is an investigational drug combination; the safety and efficacy of the drug combination has not been established.

1. Connors, J. N Engl J Med. 2018;378:331-344 2. Ansell, S. N Engl J Med. 2022;387:310-320 3. Ramchandren R. J Clin Oncol. 2019;37:1997-2007 4. Abramson, JS. Blood. 2023:7:1130 5. Advani, R. Blood. 2021;138:427-38 6. Yasenchak, CA. Blood. 2020; 136:18-19.

Study Design

NCT03646123 | Active, not recruiting



- SGN35-027 is an open-label, multiple part, multicenter, phase 2 trial
- Part C enrolled patients with stage I/II cHL, without bulky mediastinal disease (<10 cm)
- Patients received 4 cycles of AN+AD (BV 1.2 mg/kg, nivolumab 240 mg, doxorubicin 25 mg/m^2, and dacarbazine 375 mg/m^2)
- Response assessments were taken at Cycle 2 and EOT, including PET and diagnostic-quality CT
  - CR rate at EOT assessed per Lugano[8] with incorporation of LYRIC[9]
- Plasma samples (baseline, C2D1, C4D1, and EOT) from 20 patients were submitted to Foresight Diagnostics for circulating tumor DNA (ctDNA) measurement using PhasED-Seq, an ultrasensitive minimal residual disease (MRD) assay for B-cell lymphomas

Data Cut-off: 05 SEP 2023

[8]Cheson, BD. J Clin Oncol. 2014;32:3058-68, [9]Cheson, BD. Blood. 2016;128:2489-96

Patient Disposition, Demographics, and Disease Characteristics

Most patients had stage IIa disease, and 94% completed intended therapy of 4 cycles

Summary of Disposition, n (%)	Part C N = 156
Patients who received ≥1 dose	154 (99)
Patients on treatment	0
Patients off treatment	154 (99)
Patients in long-term follow-up	143 (92)
Reasons for treatment discontinuation[a]	
Completed treatment	147 (94)
Progressive disease	0
Adverse event[b]	4 (3)
Investigator decision	1 (1)
Patient decision, non-adverse event	2 (1)
Patients off study	13 (8)

Patient Demographics and Disease Characteristics	Part C N = 154
Age, median years (range)	31 (18, 77)
Sex, Female, n (%)	84 (55)
Race, White, n (%)	129 (84)
Disease stage at initial diagnosis, n (%)	
I	17 (11)
II	137 (89)
Extranodal disease present, n (%)	15 (10)
B symptoms present at initial diagnosis, n (%)	35 (23)

[a]Treatment discontinuation includes all study drugs
[b]Adverse events leading to discontinuation: grade 3 alanine aminotransferase increase, grade 3 hepatitis, grade 4 drug-induced liver injury, grade 3 acute pancreatitis

Antitumor Activity

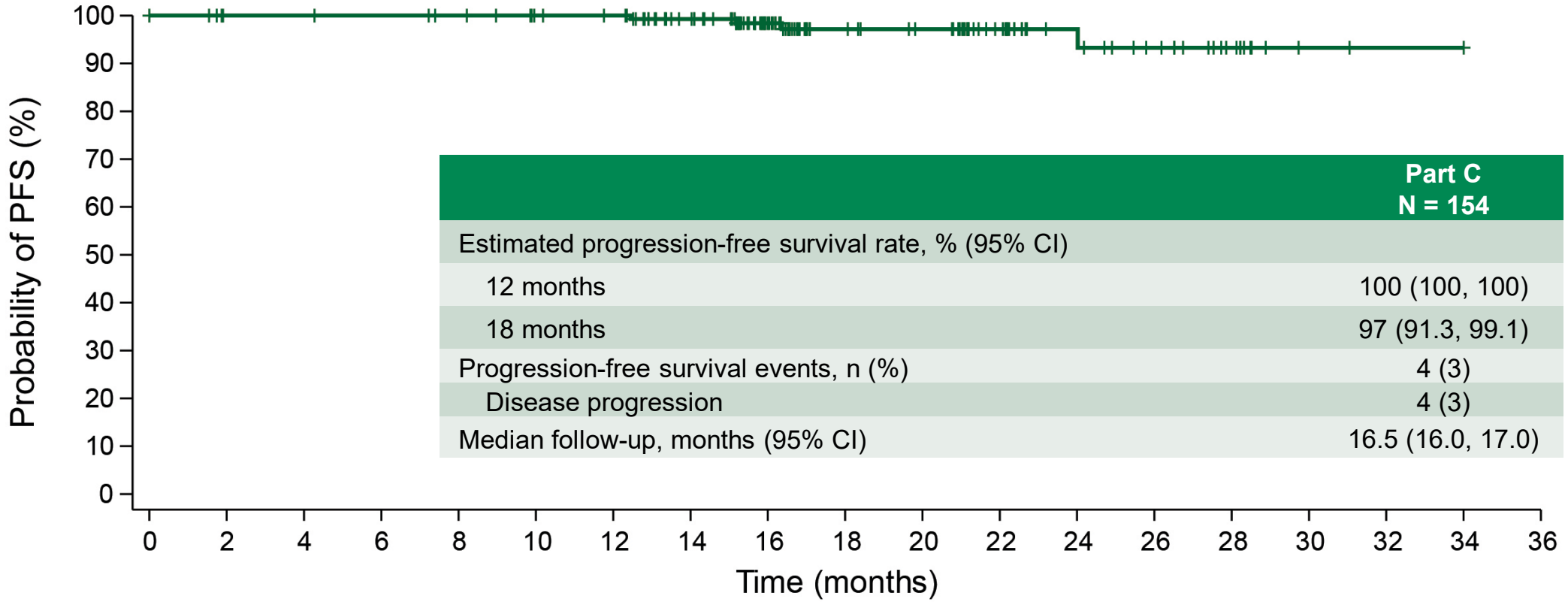
95% of patients experienced a response of CR or PR at EOT; 91% had a CR

Overall Response at EOT per Investigator, n (%)	All treated patients N = 154	Efficacy evaluable patients N = 150[a]
Objective response rate (complete + partial response)	147 (95)	147 (98)
95% CI	(90.9, 98.2)	(94.3, 99.6)
Complete response	140 (91)	140 (93)
95% CI	(85.2, 94.9)	(88.1, 96.8)
Partial response	7 (5)	7 (5)
Stable disease	0	0
Progressive disease	0	0
Indeterminate response[b]	3 (2)	3 (2)
Not evaluable	4 (3)	0

[a]Efficacy evaluable includes patients who completed EOT response assessments
[b]1 patient achieved CR in long-term follow-up, 1 patient achieved partial response in long-term follow-up, 1 patient complete metabolic response at C2 and remained indeterminate response-2 through long-term follow-up

- Best response of CR at any time point on treatment or in long-term follow up was 99% (153/154) in all treated patients
- 99% (N=154) (95% CI, 95.0, 99.9) of patients had a **duration of response** beyond 12 months
- 98% (N=153) (95% CI, 93.7, 99.6) of patients had a **duration of complete response** beyond 12 months

Progression-free Survival



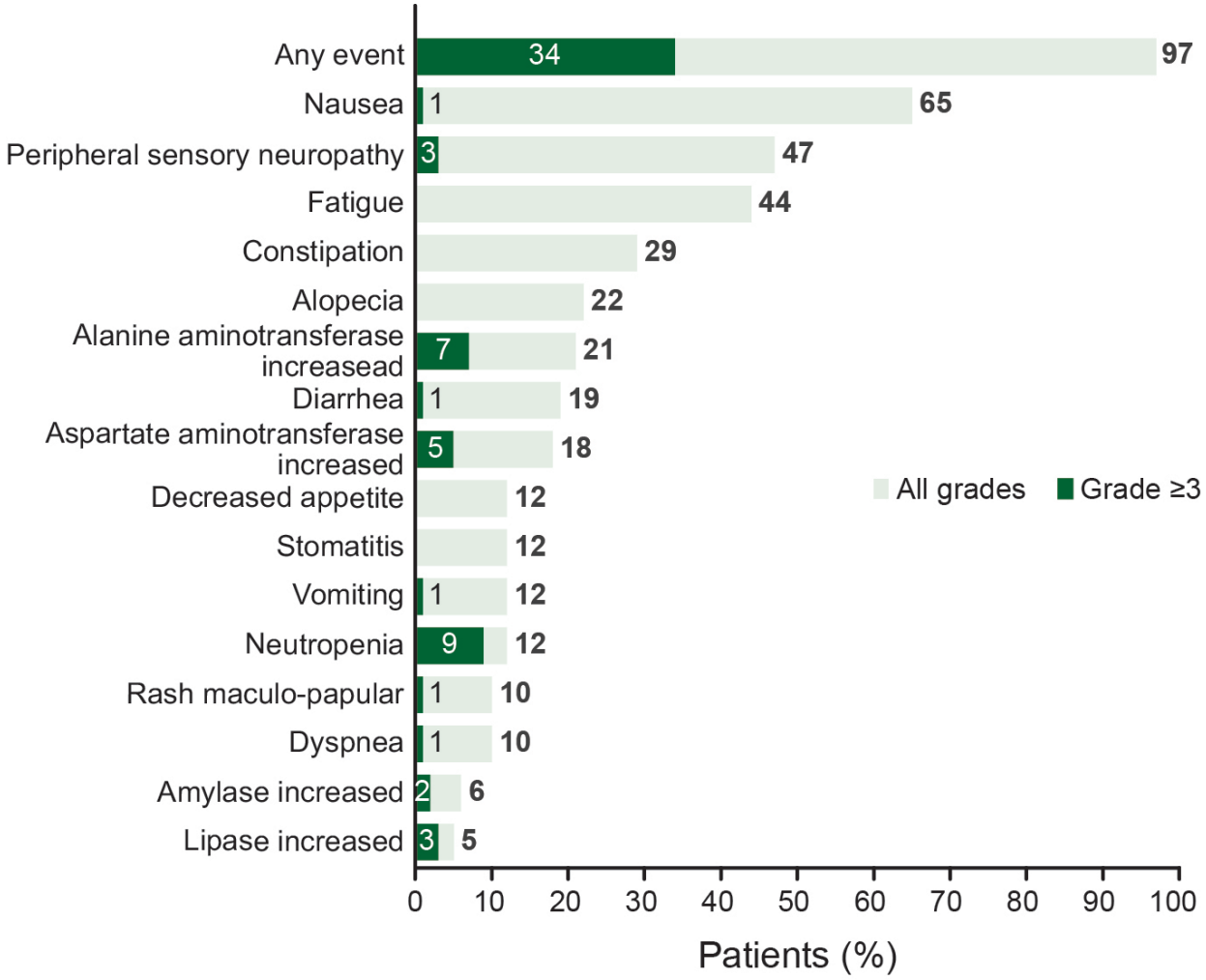
	Part C N = 154
Estimated progression-free survival rate, % (95% CI)	
12 months	100 (100, 100)
18 months	97 (91.3, 99.1)
Progression-free survival events, n (%)	4 (3)
Disease progression	4 (3)
Median follow-up, months (95% CI)	16.5 (16.0, 17.0)

N at risk (events)

Part C	154(0)	150(0)	150(0)	149(0)	147(0)	142(0)	140(0)	124(1)	90(2)	60(3)	55(3)	38(3)	25(3)	18(4)	10(4)	2(4)	1(4)	1(4)	0(4)

Summary of Adverse Events

Most Common Treatment-related TEAEs



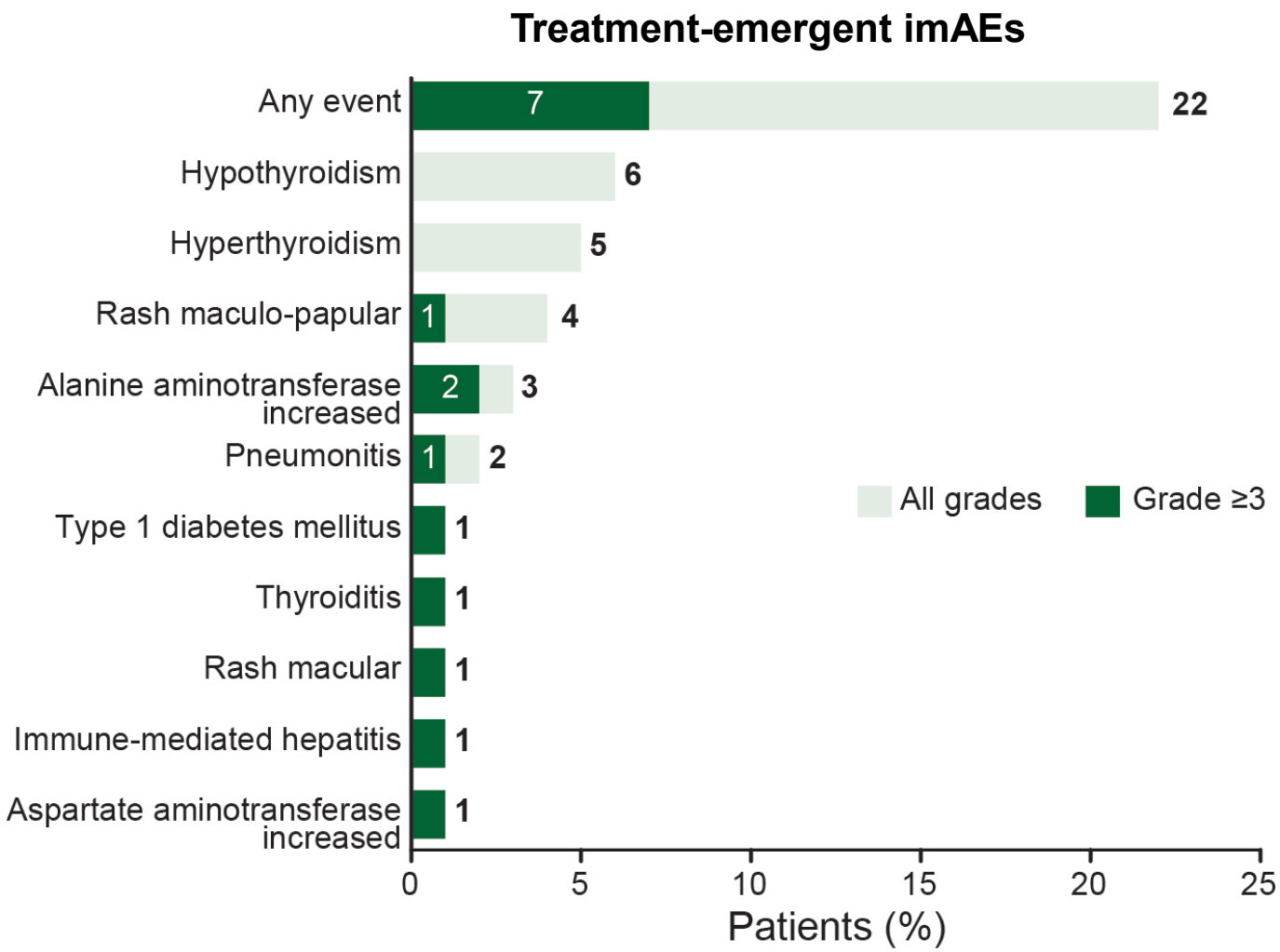
≥10% of patients (all grades) or ≥2% of patients with grade ≥3

Treatment-Emergent Adverse Events (TEAEs)

- No events of febrile neutropenia were reported
  - 67/154 (44%) received G-CSF during treatment, most of which (63/67, 94%) were given as primary prophylaxis
  - G-CSF was not required per protocol
- Peripheral neuropathy[a] (PN) occurred in 86/154 (56%); PN was primarily low grade
  - Grades 1 and 2: 69/154 (45%) and 12/154 (8%), respectively
  - Grade 3: 5/154 (3%)
  - 33/86 (38%) had complete resolution and 5/86 (6%) with improvement of at least one grade at last follow-up. All ongoing PN is ≤ Grade 2
- No grade 5 adverse events were reported
- 4/154 (3%) had TEAEs leading to the discontinuation of BV:
  - PN (n=2), pneumonitis (n=1), drug-induced liver injury (n=1)
- 13/154 (8%) had TEAEs leading to the discontinuation of nivolumab. The most common reason was increased LFTs (n=6)

[a]Events include MedDRA SMQ peripheral neuropathy terms

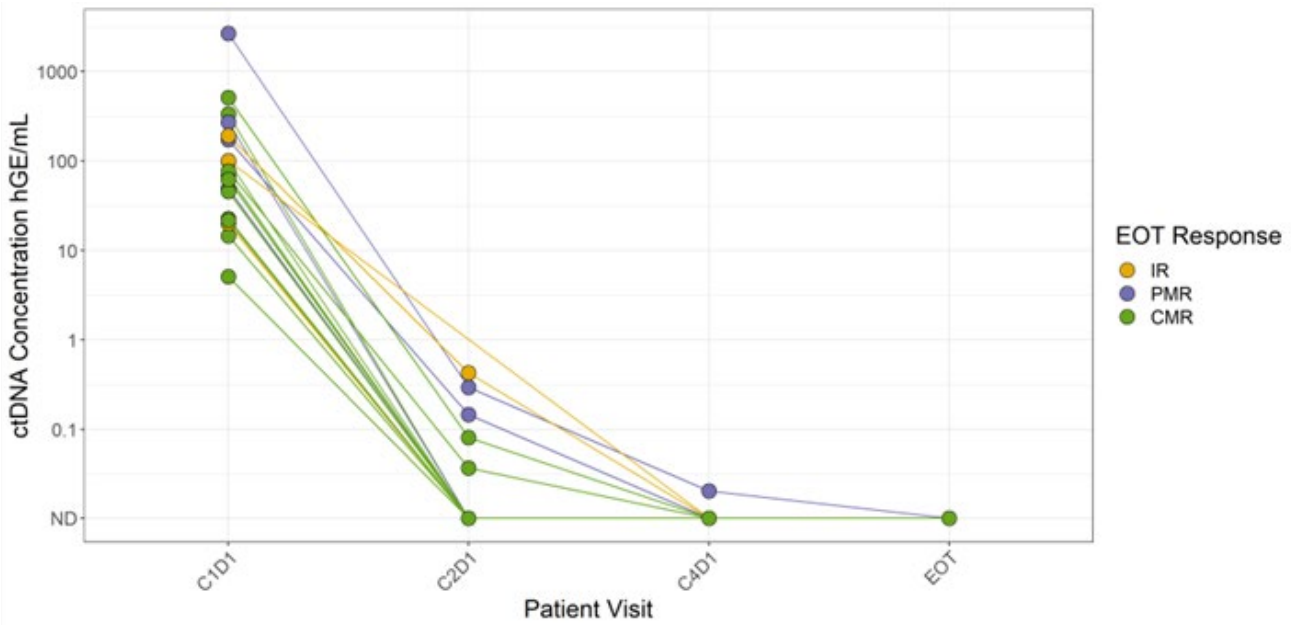
Immune-mediated Adverse Events

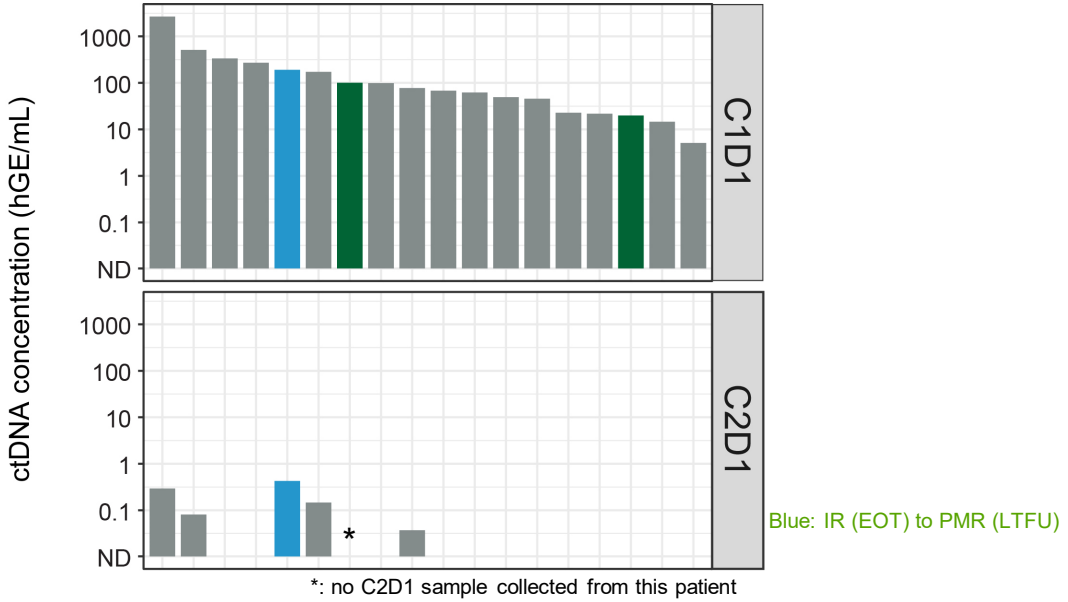


- The maximum grades for immune-mediated adverse events (imAEs) reported were primarily grade 1-2, and were consistent with the safety profile of nivolumab
- 4/154 (3%) had imAEs leading to discontinuation of nivolumab:
  - Pneumonitis (n=2), hepatitis (n=1), thyroiditis (n=1)

Preliminary ctDNA Analysis

ctDNA changes during treatment may complement PET/CT assessment





- As false-positive PET results can occur after treatment with checkpoint inhibitors, ctDNA has the potential to provide a more precise measurement of tumor burden[10]
- Compared to PET, molecular response by ctDNA could be observed earlier than metabolic response by imaging, and rapid decreases were consistent with radiological response

- 18 of the 20 patients analyzed had detectable ctDNA at baseline, with significant decline observed by C2D1. **All 18 patients** had undetectable ctDNA by End of Treatment
- PET/CT showed indeterminate response at End of Treatment for 3 patients, who subsequently achieved responses of complete metabolic response and partial metabolic response in long-term follow-up

Note: Absolute ctDNA concentration was quantified as mutant haploid genome equivalents/mL plasma (hGE/mL). ctDNA levels reported as "Not Detected" were assumed to be 0; for visualization purposes a minimal concentration was added to all samples for all graphs.

10. Lynch R, Blood, 2023 141(21):2576-2586

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Conclusions

- ORR and CR rates at EOT were 95% and 91%, respectively
  - Of the 3 patients with an indeterminate response at EOT, 1 patient subsequently achieved a complete response, and another achieved partial response during long term follow-up
- With a median follow-up of 16.5 months, 12-month PFS was 100%, and 18-month PFS was 97%
- AN + AD was well tolerated
  - No cases of febrile neutropenia
  - Peripheral neuropathy was primarily low grade. 38% of all PN cases completely resolved and 6% improved in grade since last follow-up; all ongoing PN events are grade 2 or lower
  - ImAEs were primarily low-grade
- A pilot study suggested ctDNA changes during treatment might have predictive value and complement PET/CT assessments; further analyses are warranted
- Follow-up of Part C is ongoing with 92% of patients in long-term follow-up
- AN + AD shows promising efficacy and tolerability in patients with 1L early stage cHL

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