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ORIGINAL ARTICLE

R-GEM-Lenalidomide versus R-GEM-P as second-line treatment of diffuse large B-cell lymphoma: results of the UK NRCI phase II randomised LEGEND trial

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Abstract

Outcome of patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL) remains poor, highlighting the need for novel treatment approaches. The multicentre randomised phase II LEGEND trial evaluated lenalidomide in combination with rituximab, methylprednisolone and gemcitabine (R-GEM-L) vs. standard R-GEM-P as second-line treatment of DLBCL. The study closed early to recruitment after the planned interim analysis failed to demonstrate a complete response (CR) rate of ≥ 40% in either arm. Among 34 evaluable patients, 7/18 (38.9%) achieved CR with R-GEM-L and 3/16 (18.8%) with R-GEM-P. Median event-free and overall survival was 3.5/3.8 months and 10.8/8.3 months for R-GEM-L and R-GEM-P, respectively. The incidence of grade ≥ 3 toxicities was 52% in R-GEM-L and 83% in R-GEM-P. Efficacy and tolerability of R-GEM-L seem comparable with R-GEM-P and other standard salvage therapies, but a stringent design led to early trial closure. Combination of lenalidomide with gemcitabine-based regimens should be further evaluated in r/r DLBCL.

Keywords DLBCL · Second-line therapy · Lenalidomide

Introduction

Outcome of patients with diffuse large B-cell lymphoma (DLBCL) has considerably improved with the addition of rituximab to front-line CHOP chemotherapy [1–3]. However, up to 40–50% of patients still relapse or are primary refractory depending on their clinical risk score. High-dose chemotherapy followed by autologous stem cell transplant (ASCT) is regarded as standard treatment for relapsed/refractory (r/r) DLBCL with disease sensitive to induction therapy [4]. Different platinum-based salvage induction regimens are used in clinical practice, such as R-DHAP, R-ICE and R-GDP/GEM-P, which achieve similar overall response rates (ORR) of around 40–60% [5–8].

Response to second-line therapy is significantly worse in patients with early relapse and in patients with a high international prognostic index (IPI) at the time of relapse [5, 9]. In addition, several studies have demonstrated inferior outcome

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for r/r DLBCL patients who were previously exposed to rituximab, with 3-year progression- and event-free survival rates of only 17–21% [5, 10]. This poor-risk patient group constitutes the vast majority of r/r DLBCL seen in current practice and novel treatment strategies are therefore urgently needed. In contrast to other non-Hodgkin lymphomas, precision medicine approaches have made little progress in DLBCL and no small molecule inhibitors have been approved thus far.

The immunomodulatory drug lenalidomide showed marked activity in DLBCL as single agent [11–13], combined with rituximab, [14, 15] and in combination with immunochemotherapy [16–19] in both first-line and the relapsed setting. The anti-lymphoma activity of lenalidomide is mediated through various immunomodulatory mechanisms for immune modulation such as T-cell activation and antibody-dependent cellular cytotoxicity, but also direct cytotoxicity and anti-angiogenesis [20]. Some effects like B-cell receptor signalling-dependent NFkB activation are specific for the activated B-cell (ABC) subtype of DLBCL, [21] and several retrospective analyses suggested higher efficacy of lenalidomide in non-germinal centre B-cell (GCB) cases [17, 22]. However, other anti-lymphoma effects of lenalidomide seem to be independent of the cell-of-origin (COO) [23].

The present study was conducted to evaluate the efficacy of lenalidomide in combination with rituximab, methylprednisolone and gemcitabine (R-GEM-L) as second-line treatment of DLBCL with the aim to develop a novel ambulatory salvage regimen sparing cisplatin-related toxicities.

Methods

Patients

Patients older than 18 years with histologically confirmed $CD20^+$ DLBCL, relapsed or refractory after one prior line of rituximab- and anthracycline-containing therapy, were eligible. Patients were required to have a WHO performance status (PS) of 0–2, be deemed eligible for multi-agent therapy with or without consolidation ASCT, and have adequate organ function including a calculated creatinine clearance of ≥ 50 ml/min. Key eligibility criteria are provided in the Supplement.

Study design and treatment

In this open-label, multicentre, phase II study, patients were stratified according to IPI (0–1 vs. ≥ 2) and time to relapse (≤ 12 vs. > 12 months) and randomised to receive either 3 cycles of R-GEM-P [rituximab 375 mg/m^2 days 1 and 15, methylprednisolone 1 g days 1–5, gemcitabine 1000 mg/m^2 days 1, 8, 15, cisplatin 100 mg/m^2 day 15; q28 days (arm A)] or 3 cycles of R-GEM-L [rituximab 375 mg/m^2 days 1 and 15, methylprednisolone 1 g days 1–5, gemcitabine 1000 mg/m^2 days 1, 8, 15, lenalidomide 25 mg days 1–21; q28 days (arm B)]. Response was assessed with CT imaging after 1 treatment cycle and only patients showing at least stable disease (SD) received further 2 cycles. After end of induction treatment, response was assessed by FDG-PET scan and contrast-enhanced CT according to the modified IWG 2007 criteria [24].

Patients with complete response (CR) after induction treatment underwent ASCT as indicated. ASCT-eligible patients with only residual localised active disease were allowed to proceed with ASCT after involved field radiotherapy (IFRT) to the residual site. Patients with partial response (PR) but generalised disease, SD or progressive disease (PD) came off study and were treated as per local practice. For patients on arm B, induction treatment +/− ASCT was followed by 12 months lenalidomide maintenance 25 mg days 1–21 of a 28-day cycle. Details on co-medication, dose modifications and trial procedures are provided in the Supplement.

The study was performed in accordance with the declaration of Helsinki and standards of Good Clinical Practice. The LEGEND trial was approved by national authorities and the institutional ethics committee of each participating centre. The study is registered with ClinicalTrials.gov (NCT02060656) and under EudraCT 2012-002620-32.

Statistical considerations

The primary endpoint was the CR rate after end of induction treatment in the evaluable patient population according to modified IWG 2007 criteria prioritising blinded central review by the trial radiologists if available (see Supplement). Secondary endpoints included ORR, event-free survival (EFS), overall survival (OS) and toxicity of treatment.

The trial was designed as two phase II studies running in parallel and not powered to compare arms. Using an Optimal Simon 2-stage design based on a true CR rate of at least 60% (p1) but would want to stop the trial if less than 40% (p0), with 5% alpha, 80% power, a total of 46 patients were planned to be recruited to each arm. An interim analysis was planned after 16 patients were recruited into each arm (stage 1) and required more than 7 CRs in order to recruit further 30 into each arm in stage 2.

Molecular analyses

COO classification was performed by immunohistochemistry (IHC) according to the Hans algorithm in 38/40 cases. In 21/38 cases, tissue was available for IHC review by the trial histopathologist, the remaining were based on local

assessment. In 20 cases, tissue was sufficient for additional NanoString-based COO assessment (Lymph2Cx assay) [25].

Results

Interim analysis and study closure

Results of the planned interim analysis were reviewed by the Independent Data Monitoring Committee (IDMC), which showed a CR in 3/16 patients in each arm as per local assessment. With the pre-defined threshold of > 7/16 CRs in the R-GEM-L arm not being met, the IDMC recommended early closure of the trial. Recruitment to LEGEND was suspended in November 2016 with 40 patients enrolled.

Patient characteristics

Between October 2013 and November 2016, 40 patients from 10 UK centres were enrolled. One patient withdrew consent before starting therapy; the remaining patients received at least 1 cycle of treatment (Fig. 1). Median follow-up of the intent-to-treat (ITT) population was 21.5 months for living patients.

Patients' characteristics are shown in Table 1. The median age of the study population was 59 years. Seventy-eight percent of cases had primary refractory disease or relapse within 12 months of first-line treatment. There was a trend towards worse baseline characteristics of patients in the R-GEM-P arm (more patients with bulky disease, PS 2, high LDH, B-symptoms and non-GCB immunophenotype), but this did not reach statistical significance due to small numbers. Fourteen of the thirty-eight (36·8%) cases were GCB subtype and 24/38 (63·2%) non-GCB according to IHC. Concordance between IHC and NanoString was 68%.

The frequency of dose reductions and delays was similar in both arms (Table 2). Median treatment interval length was 31 (range 27–42) and 36 (range 28–91) days in R-GEM-L and R-GEM-P, respectively. Relative doses achieved were as follows (median): 96.7% rituximab, 100% methylprednisolone, 95.2% gemcitabine, 93.7% lenalidomide (R-GEM-L), and 98.2% rituximab, 100% methylprednisolone, 89.7% gemcitabine, 75.0% cisplatin (R-GEM-P). Of the 21 patients, 14 patients R-GEM-L and 13/19 patients on R-GEM-P completed three cycles of induction treatment. The main reason for early treatment termination was PD in both arms (Table 2). Two patients on R-GEM-P stopped due to toxicity (one died from pulmonary haemorrhage, one had grade 2 acute kidney failure which resolved). Sixteen patients came off study after completion of induction treatment due to insufficient response, eight in each arm (Fig. 1). Ten patients successfully harvested stem cells and proceeded to ASCT, and one patient on R-GEM-P failed to harvest (Table 2). Five patients in arm B received lenalidomide maintenance, one without prior ASCT. Median duration of maintenance was 9 months (IQR 2·3-11·0).

Toxicities

The overall incidence of adverse events was similar in both arms (Table 3). The incidence of grade ≥ 3 toxicities was 11/21 (52·4%) in R-GEM-L and 15/18 (83·3%) in R-GEM-P. Main toxicities were haematological toxicities and infectious complications, with no obvious difference in any particular toxicity between arms. Frequencies of typical cisplatin-associated toxicities are listed in the Supplement. Neuropathy was seen in both treatment arms whereas renal and ototoxicity only occurred in the R-GEM-P arm as expected. There were 19 SAEs reported in 12 patients during 50 cycles of R-GEM-L and 29 SAEs in 13 patients during 44 cycles or R-GEM-P.

Twenty-four deaths have been reported, 11 in the R-GEM-L and 13 in the R-GEM-P arm. Eighteen were due to PD and three were deemed treatment-related. One patient on R-GEM-P died from treatment-related pulmonary haemorrhage during the first cycle. One patient on R-GEM-P died from sepsis with bowel ischemia (treatment-related) < 1 month after study withdrawal for acute kidney failure and one died of unknown cause 5 months after study withdrawal. In R-GEM-L, one patient died from multi-organ failure 6 weeks after finishing induction therapy (treatment-related), one patient died of unknown cause 6 months after study withdrawal, one from cerebral haemorrhage (unrelated).

Efficacy

Response was evaluable in 34 patients (Fig. 1). CR was achieved in 7/18 (38·9%; 95% CI 16·4–61.4) patients in the R-GEM-L arm and 3/16 (18·8%; 95% CI 0–37.9) patients in R-GEM-P (Table 4). ORR was 10/18 (55·6%; 95% CI 32·6–78.5) for R-GEM-L and 6/16 (37·5%; 95% CI 13·8–61.2) for R-GEM-P. Response according to COO subgroups is shown in the Supplement. CR rates were 16.7% (2/12) for GCB and 36.4% (8/22) for non-GCB cases. There was no indication of a differential response of COO groups to either arm, but numbers are small. Interestingly, both GCB cases achieving CR were treated with R-GEM-L.

With a median follow-up of 21.5 months, median EFS was 3.5 months (95% CI: 0.9–unobtainable) and 3.8 months (95% CI: 1.5–9.2) for R-GEM-L and R-GEM-P, respectively [HR 0·85 (95% CI: 0.39–1.86)]. Median OS was 10.8 months (95% CI: 5.9–unobtainable) for R-GEM-L and 8.3

Fig. 1 Consort diagram

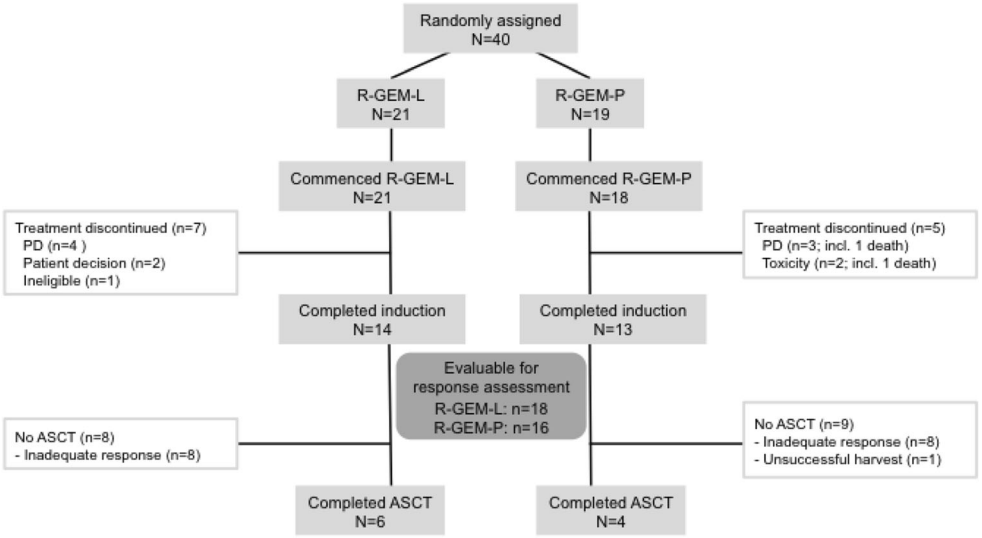

Table 1 Baseline characteristics

Characteristics	R-GEM-L ($N = 21$)	R-GEM-P ($N = 19$)	P
Age, years (median, range)	58 (21–75)	59 (21–77)	
Sex, female	8 (38.1%)	5 (26.3%)	0.51
WHO performance status			0.06
0	14 (66.7%)	9 (47.4%)	
1	7 (33.3%)	5 (26.3%)	
2	0 (0%)	5 (26.3%)	
Stage			0.44
I	3 (14.3%)	4 (21.1%)	
II	5 (23.8%)	1 (5.3%)	
III	2 (9.5%)	2 (10.5%)	
IV	11 (52.4%)	12 (63.2%)	
Bulk (≥ 10 cm)	1/17 (5.9%)	4/17 (23.5%)	0.34
B symptoms	5 (23.8%)	8 (42.1%)	0.31
Elevated LDH	10 (47.6%)	11 (57.9%)	0.55
Extranodal involvement > 1 sites	8/20 (38.2%)	6/19 (32.6%)	0.75
IPI score			0.41
0–1	7 (33.3%)	5 (26.3%)	
2–3	12 (57.1%)	9 (47.4%)	
4–5	2 (9.5%)	5 (26.3%)	
IHC COO subtype ($N = 38$)			0.51
GCB	9 (42.9%)	5 (29.4%)	
Non-GCB	12 (57.1%)	12 (70.6%)	
Time to relapse			1.00
≤ 12 months	16 (76.2%)	15 (78.9%)	
> 12 months	5 (23.8%)	4 (21.1%)	
Response to first-line treatment			0.91
CR	7 (33.3%)	7 (36.8%)	
PR	6 (28.6%)	4 (21.1%)	
SD/PD	5 (23.8%)	6 (31.6%)	
Unknown	3 (14.3)	2 (10.5%)	

Table 2 Treatment characteristics

Characteristics	R-GEM-L ($N = 21$)	R-GEM-P ($N = 19$)
Induction treatment		
Treatment cycles with dose reduction	18/51 (35.3%)	14/44 (31.8%)
Treatment cycles with delays	12/51 (23.5%)	13/44 (29.5%)
Induction cycles completed		
3	14* (66.7%)	13 (68.4%)
2	0 (0%)	0 (0%)
1	7 (33.3%)	5 (26.3%)
0	0 (0%)	1 (5.3%)
Early termination of induction	7 (33.3%)	5 (26.3%)
PD	4	3
Toxicity	0	2
Other	3	0
Stem cell harvest > 2×10^6/kg $CD34^+$	8/8	4/5
ASCT	6 (28.6%)	4 (21.1%)

*1 patient received 4 cycles

months (95% CI: 4.4–13.0) for R-GEM-P [HR 0·63 (95% CI: 0.28–1.45); Fig. 2].

Discussion

New treatment approaches are the key to improve outcome of patient with r/r DLBCL and lenalidomide is among the most promising novel agents in this setting. This is the first study combining lenalidomide with rituximab, methylprednisolone and gemcitabine in the second-line treatment of DLBCL.

The LEGEND trial closed early to recruitment after the planned interim analysis had demonstrated a CR rate of < 40% in the R-GEM-L arm (18.8% based on local response assessment). Of note, final analysis of the primary endpoint in all 34 evaluable patients as per blinded central radiology review resulted in a CR rate of 38.8% in R-GEM-L and 18.8% in R-GEM-P. These results are comparable with two recently published large phase III trials in r/r DLBCL. The ORCHARRD trial with a patient population similar to LEGEND reported CR rates of 15% and 22% after R-DHAP and O-DHAP, respectively [8]. In the randomised NCIC-CTG LY.12 trial evaluating R-GDP and R-DHAP as second-line treatment for aggressive lymphomas (71% de novo r/r DLBCL), CR rates ranged between 13 and 14% [7]. In this context it appears that a CR rate of ≥ 40% as stopping rule for our trial was set unrealistically high. At the time LEGEND was designed, high quality data from comparable patient cohorts (rituximab pre-exposure, PET-based response assessment) were lacking which could have better informed statistical considerations for our trial. Overall, response rates seen with R-GEM-L are indeed encouraging to further evaluate this chemo-sparing combination in r/r DLBCL.

We did not find evidence for a differential response of COO subtypes to R-GEM-L, but numbers were small and we only had full COO assessment available by IHC. The hypothesis that efficacy of lenalidomide is largely restricted to non-GCB subtypes primarily came from in vitro models of NFkB-dependent effects of the agent [21, 26], as well as retrospective clinical analyses showing that the supposedly poor prognosis of non-GCB r/r DLBCL can be "overcome" by lenalidomide [17, 22]. A prospective trial comparing single-agent

Table 3 Most common grade ≥ 3 toxicities. Adverse events that occurred in more than one patient of either arm at grade ≥ 3 are shown

	R-GEM-L ($N = 21$)		R-GEM-P ($N = 18$)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
All toxicities	21 (100%)	11 (52%)	18 (100%)	15 (83%)
Neutropenia	11 (52.4%)	6 (29.0%)	7 (27.7%)	4 (22.2%)
Thrombocytopenia	16 (72.7%)	3 (14.3%)	10 (55.5%)	7 (38.9%)
Anaemia	14 (66.7%)	1 (4.8%)	13 (72.2%)	3 (16.7%)
Infection	6 (28.6%)	3 (14.3%)	8 (44.4%)	5 (29.4%)
Fever	5 (23.8%)	3* (14.3%)	6 (33.3%)	1# (5.9%)
Thromboembolism	1 (4.8%)	1 (4.8%)	4 (22.2%)	3 (16.7%)
Fatigue	17 (81.0%)	0 (0%)	11 (61.1%)	2 (11.1%)

*incl. 1 febrile neutropenia, # neutropenic sepsis

Table 4 Response to induction treatment. Response was assessed by blinded central review according to IWG 2007 criteria. In 7 patients with clinical PD no further images were performed

	Evaluable patients ($N = 34$)		Enrolled patients ($N = 40$)	
End of treatment response*	R-GEM-L ($N = 18$) *n* (%)	R-GEM-P ($N = 16$) *n* (%)	R-GEM-L ($N = 21$) *n* (%)	R-GEM-P ($N = 19$) *n* (%)
Complete response	7 (38.9)	3 (18.8)	7 (33.3)	3 (15.8)
Partial response	3 (16.7)	3 (12.5)	3 (14.3)	3 (15.8)
Stable disease	1 (5.6)	1 (6.3)	1 (4.8)	1 (5.3)
Progressive disease	7 (38.9)	9 (62.5)	7 (33.3)	9 (47.4)
Clinically assessed	4	3	4	3
Not done/evaluable	na	na	3 (14.3)	3 (15.8)
Overall response rate	10 (55.6)	6 (37.5)	10 (47.6)	6 (31.6)

*3 cases on R-GEM-L and 3 cases on R-GEM-P not evaluable for end of treatment response; 5 cases had only local response assessment available

lenalidomide vs. investigator's choice demonstrated superior response rates for lenalidomide in both subtypes, but a significant effect on progression-free survival (PFS) was only seen in non-GCB cases [13]. However, differential response of non-GCB DLBCL to lenalidomide could not be demonstrated in two recent prospective trials in the first-line setting [23, 27]. Therefore, further evaluation of R-GEM-L and other lenalidomide combinations should be considered across all molecular subtypes of DLBCL.

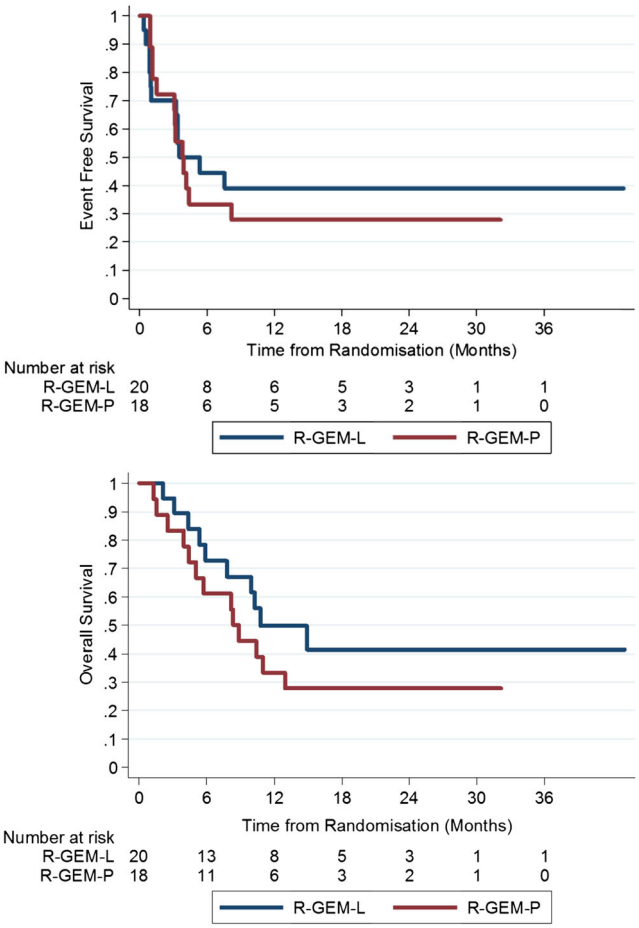

Fig. 2 Kaplan-Meier curves of survival in arm A and B. **a** EFS. **b** OS in the R-GEM-L and R-GEM-P arms

With only 28.6% and 21.1% of patients proceeding to ASCT after induction treatment, median OS was expectedly short with 10.8 and 8 months in R-GEM-L and R-GEM-P, respectively. In ORCHARRD, 35% of patients underwent ASCT with a median survival of around 13 months [8]. In the LEGEND trial, only patients in CR or radiotherapy to residual localised disease were allowed to proceed to ASCT, whereas in ORCHARRD, all patients with PR were eligible for ASCT. This might have accounted for the lower rate of transplants performed in our trial. Some patients in ORCHARRD converted from PR to CR after ASCT; however, subgroup analyses confirmed that achievement of PET negativity before ASCT is associated with a significantly better prognosis [8, 28, 29].

R-GEM-L was well tolerated and no unexpected toxicities occurred. There was a trend towards fewer grade ≥ 3 toxicities and toxicity-related treatment discontinuations in R-GEM-L compared with R-GEM-P, but numbers were small and the trial was not powered for this comparison. Gemcitabine/platinum-based salvage therapies have been widely adopted after the NCIC-CTG LY.12 trial has demonstrated equal efficacy and better tolerability of R-GDP compared with R-DHAP [7]. Given the good tolerability of R-GEM-L, addition of lenalidomide at lower doses to the full R-GEM-P or R-GDP regimen could also be an attractive approach to further improve efficacy. Reduced dosing schedules of lenalidomide have been used in combination with R-ICE (25 mg D1-7) and R-ESHAP (10 mg D1-14) with acceptable toxicity profiles [18, 19].

In conclusion, this is the first study evaluating efficacy and tolerability of lenalidomide with gemcitabine-based salvage treatment in r/r DLBCL. Although data are limited due to the early closure of the trial, our results are

encouraging and provide a basis for taking this combination forward in r/r DLBCL or other lymphomas.

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Author contributions A.K.: trial physician, contributed to the conduct of the study, analysed and interpreted data, and wrote the report. C.P.: trial statistician, designed the study, analysed data and contributed to writing of the report. B.P.: trial coordinator, gathered, entered and coordinated data. K.M.A, M.P.M, J.R., R.J., S.P: co-investigators, gathered and interpreted data. S.B.: contributed to the study design. I.C.: contributed to the study conduct. R.B.: trial specimen coordinator, gathered tissue for central review. N.V.: performed NanoString analyses. A.W.: trial histopathologist, performed central histopathology review. Y.D., I.Z.: trial radiologists, performed central radiology review. D.C.: chief investigator, responsible for the study conduct and final report. All authors reviewed and approved the final version of the report.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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