Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally advanced cervical cancer (GCIG INTERLACE): an international, multicentre, randomised phase 3 trial

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Summary

Background Locally advanced cervical cancer is treated with chemoradiotherapy (standard of care), but many patients still relapse and die from metastatic disease. We investigated chemoradiotherapy with or without induction chemotherapy to determine whether induction chemotherapy improves both progression-free survival and overall survival.

Methods The INTERLACE trial was a multicentre, randomised phase 3 trial done at 32 medical centres in Brazil, India, Italy, Mexico, and the UK. Adults (aged ≥18 years) with locally advanced cervical cancer (FIGO 2008 stage IB1 disease with nodal involvement, or stage IB2, IIA, IIB, IIIB, or IVA disease) were randomly assigned (1:1), by minimisation, using a central electronic system, to standard cisplatin-based chemoradiotherapy (once-a-week intravenous cisplatin 40 mg/m² for 5 weeks with 45·0–50·4 Gy external beam radiotherapy delivered in 20–28 fractions plus brachytherapy to achieve a minimum total 2 Gy equivalent dose of 78–86 Gy) alone or induction chemotherapy (once-a-week intravenous carboplatin area under the receiver operator curve 2 and paclitaxel 80 mg/m² for 6 weeks) followed by standard cisplatin-based chemoradiotherapy. Stratification factors were recruiting site, stage, nodal status, three-dimensional conformal radiotherapy or intensity modulated radiotherapy, age, tumour size, and histology (squamous *vs* non-squamous). Primary endpoints were progression-free survival and overall survival within the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT01566240, and EUDRACT, 2011-001300-35.

Findings Between Nov 8, 2012, and Nov 17, 2022, 500 eligible patients were enrolled and randomly assigned to the chemoradiotherapy alone group (n=250) or the induction chemotherapy with chemoradiotherapy group. Of 500 patients, 354 (70%) had stage IIB disease and 56 (11%) stage IIIB disease. Pelvic lymph nodes were positive in 215 (43%) patients. 230 (92%) patients who received induction chemotherapy had at least five cycles. Median interval between induction chemotherapy and chemoradiotherapy was 7 days. Four or more cycles of cisplatin were given to 212 (85%) participants in the induction chemotherapy with chemoradiotherapy group and to 224 (90%) of participants in the chemoradiotherapy alone group. 462 (92%) participants received external beam radiotherapy and brachytherapy with a median overall treatment time of 45 days. After a median follow-up of 67 months, 5-year progression-free survival rates were 72% in the induction chemotherapy with chemoradiotherapy group and 64% in the chemoradiotherapy alone group with a hazard ratio (HR) of 0·65 (95% CI 0·46–0·91, p=0·013). 5-year overall survival rates were 80% in the induction chemotherapy with chemoradiotherapy group and 72% in the chemoradiotherapy alone group, with an HR of 0·60 (95% CI 0·40–0·91, p=0·015). Grade 3 or greater adverse events were reported in 147 (59%) of 250 individuals in the induction chemotherapy with chemoradiotherapy group versus 120 (48%) of 250 individuals in the chemoradiotherapy alone group.

Interpretation Short-course induction chemotherapy followed by chemoradiotherapy significantly improves survival of patients with locally advanced cervical cancer.

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*A complete list of the INTERLACE investigators is provided in the appendix

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical trials and systematic reviews published in English between Jan 1, 2003, and March 1, 2024, that assessed induction chemotherapy in patients with cervical cancer, using the terms "cervical or cervix cancer", "induction chemotherapy", or "neoadjuvant chemotherapy". Induction chemotherapy was associated with variable efficacy in locally advanced cervical cancer, which was influenced by study design. Two large trials evaluating neoadjuvant chemotherapy before surgery and standard chemoradiotherapy did not show improvements in survival. Many previous studies did not minimise the time interval between finishing neoadjuvant chemotherapy and definitive radiation, chemoradiotherapy, or surgery. Overall, chemotherapy regimens with shorter cycle duration and higher platinum dose intensity were associated with improved outcomes. We had conducted a single arm multicentre phase 2 trial (CXII study) which showed a high tumour response rate using neoadjuvant short-course once-a-week carboplatin and paclitaxel, and this was used to help design the INTERLACE trial.

Added value of this study

The results of INTERLACE show that a short course of chemotherapy using 6 weeks of carboplatin and paclitaxel immediately before standard chemoradiotherapy provided a clinically meaningful and statistically significant improvement in both progression-free survival and overall survival in women with locally advanced cervical cancer. The drugs are cheap and widely available and therefore this approach can be readily adopted in all health-care settings. This is the first randomised phase 3 study to show a significant survival advantage with the addition of induction chemotherapy before chemoradiotherapy in locally advanced cervical cancer. Although chemoradiotherapy is curative treatment for about 75% of patients (80% in INTERLACE), increasing this by 7–10% (at 3–5 years) represents a clinically meaningful improvement and at a relatively low cost.

Implications of all the available evidence

Induction chemotherapy delivered according to the INTERLACE protocol should be included in clinical guidelines as an option to improve outcomes in patients with locally advanced cervical cancer. This approach could be included in the design of future clinical trials of immunotherapy or other targeted drugs in the front-line setting. The study findings presented here also refute the perception that chemotherapy administered before radiotherapy or chemoradiotherapy is detrimental to outcome.

Introduction

Globally, there were 660 000 new cases and 350 000 deaths due to cervical cancer in 2022.[1] Although the incidence has decreased in high-income countries due to the implementation of successful screening and HPV vaccination programmes, cervical cancer is the most common cancer type in 23 countries and the leading cause of cancer death in 36 low-income countries. Even in high-income countries health inequalities exist where, for example, the US cervical cancer death rate is 2-fold higher in the most versus least deprived areas.[2] Patients often present with locally advanced disease for which chemoradiotherapy has been the standard treatment for nearly 25 years.[3–5] Improvements in local control have been driven by the delivery of high-quality radiotherapy,[6] but still up to 30% of patients will relapse and die within 5 years.[7] Adjuvant carboplatin and paclitaxel chemotherapy after chemoradiotherapy did not improve progression-free survival or overall survival in the international phase 3 OUTBACK trial.[8]

The aim of short-course induction chemotherapy before definitive radiotherapy or chemoradiotherapy is to reduce tumour volume and micrometastatic disease. In a meta-analysis of 18 trials, neoadjuvant chemotherapy based on a shorter platinum-based chemotherapy cycle length (≤14 days) and increased cisplatin dose density (>25 mg/m² per week) improved overall survival, but there was substantial heterogeneity in the design and outcome of these trials.[9] A single arm multicentre phase 2 trial was conducted to investigate neoadjuvant short-course weekly carboplatin and paclitaxel (CXII study) before chemoradiotherapy and showed a high tumour response rate.[10] The CXII results led to the INTERLACE trial, a multicentre international randomised trial, to evaluate whether the addition of the same short-course induction chemotherapy (induction chemotherapy) before chemoradiotherapy is more effective than chemoradiotherapy alone.

Methods

Study design and participants

INTERLACE is a randomised phase 3 trial conducted in 32 centres in Brazil, India, Italy, Mexico, and the UK. Adults (aged ≥18 years) with newly diagnosed histologically confirmed locally advanced cervical cancer were eligible. Eligible patients had stage IB1 disease with nodal involvement, or stage IB2, IIA, IIB, IIIB, or IVA disease (International Federation of Gynecology and Obstetrics [FIGO] staging system, 2008); squamous, adenocarcinoma, or adenosquamous histology; fit for radical treatment; and with no positive lymph nodes above the aortic bifurcation. Positive lymph nodes were defined as either histologically positive or PET-positive, or at least 15 mm (short axis measurement) on CT or MRI. Key exclusion criteria were FIGO 2008 stage IIIA disease and presence of para-aortic nodes. This reason for exclusion was due to the uncertainty at the time of trial conception that these patients were truly being treated curatively. Full eligibility criteria are provided in the protocol (appendix pp 20–21). Of note, vaginal

bleeding was not an exclusion criterion and transfusion was permitted and recommended to maintain the haemoglobin of at least 11 g/dL.

The trial adhered to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulatory requirements including all local ethics approvals. All patients provided written informed consent before enrolment. The trial was funded by Cancer Research UK with additional support from the University College London–University College London Hospitals Biomedical Research Centre. It was designed by the Trial Management Group, with oversight by a Trial Steering Committee and an Independent Data Monitoring Committee (IDMC). The IDMC had oversight of treatment and radiotherapy compliance but did not review all treatment protocol variations.

Randomisation

Patients were approached to consider the trial soon after diagnosis at their local cancer centre. Patients were randomly assigned 1:1 to receive standard chemo-radiotherapy alone or induction chemotherapy followed immediately by standard chemoradiotherapy. Allocation was done by minimisation, using a central electronic system, with stratification factors: recruiting site, FIGO stage, positive or negative nodal status, three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiation therapy (IMRT), age, tumour size, and squamous or non-squamous histology. No blinding or masking was performed.

Procedures

The induction chemotherapy regimen was carboplatin area under the receiver operator curve 2 and paclitaxel 80 mg/m² given once a week for 6 weeks followed by chemoradiotherapy starting in week 7. In both groups, chemoradiotherapy comprised external beam radiation therapy (EBRT) with once-a-week cisplatin 40 mg/m² for 5 weeks and brachytherapy. The EBRT dose was 40·0–50·4 Gy delivered in 20–28 fractions to a planned pelvic volume using 3DCRT or IMRT. Brachytherapy was delivered using a two-dimensional (2D) or three-dimensional (3D) approach with full 3D image-guided adaptive brachytherapy (IGABT) recommended.[6,11] The minimum total 2 Gy equivalent dose from combined EBRT and brachytherapy was 78 Gy to point A. Overall radiation treatment time was 50 days maximum (per protocol) or up to 56 days with the Trial Management Group's approval. All centres underwent radiotherapy quality assurance assessment before and during participation (conducted externally by the National Radiotherapy Trials Quality Assurance assessment centre based at Mount Vernon Hospital, Northwood, UK, and overseen by the Trial Management Group). Guidelines for chemotherapy modifications and managing delays in radiotherapy are outlined in the protocol (appendix pp 3–112).

Patients had baseline imaging (CT chest or abdomen or PET-CT, MRI, or CT pelvis) within 50 days of randomisation and physical examination within 14 days of starting treatment. Positive nodes were defined as CT or MRI of at least 15 mm short axis or PET avid. Physical examinations were performed once a week during chemoradiotherapy and induction chemotherapy, then at weeks 4 and 12 after completing chemoradiotherapy, and then once every 3 months for years 1 and 2 and once every 6 months for years 3, 4, and 5. Pelvic MRI or CT was performed 12 weeks after completing chemoradiotherapy to define treatment response and, thereafter, at the clinician's discretion and at disease progression to document sites of relapse. This follow-up was in accordance with standard real-world practice. Quality of life (QoL) assessments were self-reported at baseline, weeks 1 and 3 of chemoradiotherapy, then at clinical reviews thereafter. Induction chemotherapy patients had an additional QoL assessment at week 4 of induction chemotherapy.

Outcomes

The primary endpoints were overall survival and investigator-assessed progression-free survival, defined as time from randomisation to date of progression or death, whichever occurred first. Overall survival was defined as time from randomisation to date of death from any cause. Patients who did not have an event were censored at the date they were last known to be alive for each endpoint.

Secondary endpoints included adverse events, pattern of first relapse, time to next anticancer therapy, and health-related QoL using the EORTC questionnaire (QLQ-C30) and the cervical cancer module (QLQ-CX24).

Statistical analysis

The initial target accrual was 700 patients but, given the slower than expected accrual, this was reduced to 500 patients on the recommendation of the Independent Data Monitoring Committee. Recruitment of 500 patients could detect a hazard ratio (HR) for overall survival between 0·65 and 0·70 after at least 192 deaths (two-sided 5% significance level with 70–84% power), assuming a 5-year overall survival rate of 60% in the chemoradiotherapy alone group.[7] Overall survival and progression-free survival were used in a fixed sequence hierarchical testing approach to maintain an overall error rate of 5%, with progression-free survival as the first ranked endpoint then overall survival (progression-free survival would need to have $p<0·05$ to allow formal testing for overall survival). The sample size was based on overall survival only, as this would require more events than progression-free survival. The target HR for progression-free survival was 0·65, requiring 132–168 events (for 70–80% power; appendix p 3). The Independent Data Monitoring Committee recommended reporting and release of progression-free survival after reaching at least 132 progression-free survival events when they confidentially examined efficacy and they

considered a clear effect to have been observed that would not change much with more events. The database was locked on March 1, 2024, for the analyses presented here.

Analyses were by intention-to-treat (ITT). Progression-free survival and overall survival were analysed using Kaplan–Meier plots and Cox proportional hazards regression to obtain HRs adjusted for the randomisation stratification factors. The absolute risk differences at 3 years and 5 years were obtained by applying the HR to the progression-free survival or overall survival rate in the chemoradiotherapy alone group. A post-hoc sensitivity analysis using regression standardisation[12] was used to estimate the risk difference at 3 years and 5 years. For each patient, the highest grade for each type of adverse event was used. QoL was analysed using repeated measures analysis.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

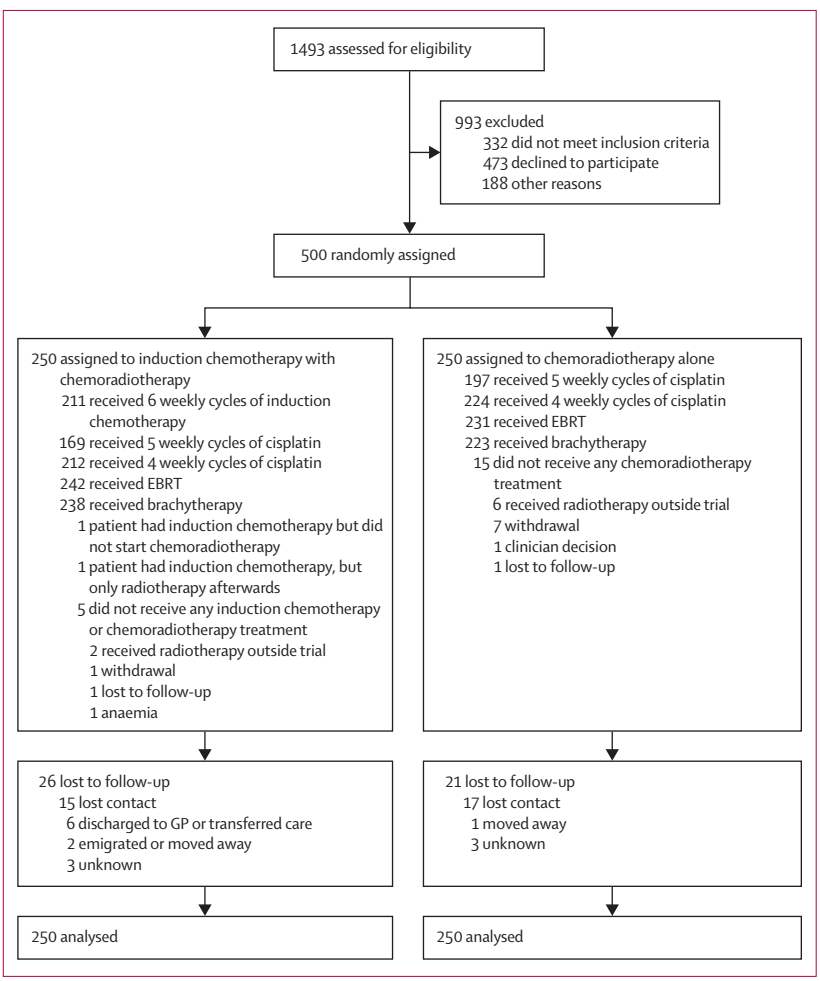

Figure 1: **Trial profile**
EBRT=external beam radiation therapy. GP=general practitioner.

Results

Between Nov 8, 2012, and Nov 17, 2022, 500 patients were recruited from 32 centres in Brazil, India, Italy, Mexico, and the UK (figure 1), with most patients recruited in the UK (380 [76%] of 500) and Mexico (100 [20%] of 500). The median age was 46 (range 24–78) years and all disease stages were represented (with 354 [71%] of 500 patients with FIGO 2008 stage IIB disease and 215 [43%] with pelvic nodal involvement). PET was used in at least 25% of patients for staging purposes. The groups were well balanced (table 1).

In the induction chemotherapy with chemoradiotherapy group, of 250 patients, 211 (84%) completed 6 weeks of induction chemotherapy and 230 (92%) completed 5 weeks (table 2). Reasons for not completing six cycles were neutropenia, hypersensitivity reactions, patient or clinician decisions, renal toxicity, or withdrawal. The median interval from induction chemotherapy completion to chemoradiotherapy start in 242 patients in this group was 7 (range 5–54) days, with an interval of 7 or fewer days in 189 (78%), 8–14 days in 42 (17%), and 15 or more days in 11 (5%).

Adherence to chemoradiotherapy was high in both groups; 212 (85%) of 250 patients in the induction chemotherapy with chemoradiotherapy group and 224 (90%) of 250 patients in the chemoradiotherapy alone group completed at least four cycles of cisplatin, with 169 (68%) of 250 and 197 (79%) of 250, respectively, completing five cycles (table 3). EBRT was delivered to 242 (97%) of 250 patients in the induction chemotherapy with chemoradiotherapy group and 231 (92%) of 250 patients in the chemoradiotherapy alone group, of whom 238 (98%) of 242 and 224 (97%) of 231, respectively, also received brachytherapy (table 3). An additional four (2%) patients in the induction chemotherapy with chemoradiotherapy group and eight (3%) patients in the chemoradiotherapy alone group received EBRT outside the trial. Therefore, within the ITT population, 246 (98%) of 250 patients in the induction chemotherapy with chemoradiotherapy group and 239 (96%) of 250 patients in the chemoradiotherapy alone group received EBRT on or off trial. Median overall radiation treatment time (which incorporates radiotherapy interruptions) was 45 days in both groups (minimum 36 days and maximum 88 days) with 452 (96%) of 473 patients completing radiotherapy in 56 days or sooner. The overall radiation treatment time exceeded the 56 days for nine (4%) of 242 patients in the induction chemotherapy with chemoradiotherapy group and seven (3%) of 231 patients in the chemoradiotherapy alone group, and the main reasons for exceeding the maximum 56 days were radiotherapy and brachytherapy scheduling problems (nine of 16) and adverse events (five of 16).

140 (58%) of 242 patients in the induction chemotherapy with chemoradiotherapy group and 138 (60%) of 231 patients in the chemoradiotherapy alone group received EBRT delivered using 3DCRT, whereas the

remainder were treated using IMRT. Four patients received a biological effective dose lower than 45 Gy in 25 fractions for their EBRT. Brachytherapy dose was prescribed to point A in 70% (322 of 462) in both groups, 49% (227 of 462) using 3D imaging and 21% (95 of 462) using 2D. In the remaining 30% (140 of 462), 3D IGABT was used with dose prescribed to the high-risk clinical target volume (HRCTV). Median total 2 Gy equivalent dose for all patients was 79·4 Gy (range 44·3–120·9 Gy) and for patients treated with IGABT 87 Gy (56·3–120·9 Gy). Overall, 22 (9%) of 242 patients in the induction chemotherapy with chemoradiotherapy group and 20 (9%) of 231 patients in the chemoradiotherapy alone group received extended field EBRT. All participating centres had, as a minimum, the first three patients prospectively reviewed for both contouring and planning, with any variations corrected before treatment. Retrospective review of contouring and planning was carried out in a subset of patients thereafter, with at least one patient per centre assessed. Variations from protocol in this subset were equally distributed across both groups (appendix p 158).

Median interval from baseline imaging to randomisation was 14 (range 0–49) days. Median time from randomisation to treatment start was 7 (0–46) days in the induction chemotherapy with chemoradiotherapy group and 19 (5–67) days in the chemoradiotherapy alone group (with an interval of <19 days in 112 [48%], 19–30 days in 121 [52%], 31–45 days in one [<1%], and >45 days in one [<1%] of 235 patients in the chemoradiotherapy alone group). There was no correlation between the time to start treatment and subsequent relapse in the chemoradiotherapy alone group.

At the time of analysis, the median follow-up was 67 months, with 151 progression-free survival events (131 first relapses and 20 deaths without previous record of relapse) and 114 deaths. The progression-free survival and overall survival Kaplan–Meier curves are shown in figure 2. The HR for progression-free survival was 0·65 (95% CI 0·46–0·91, p=0·013), representing a 35% relative reduction in the hazard of progression or death among patients who had induction chemotherapy with chemoradiotherapy. The 3-year progression-free survival rates were 75% for the induction chemotherapy with chemoradiotherapy group and 72% for the chemoradiotherapy alone group and corresponding 5-year rates were 72% and 64%, respectively. The absolute risk difference at 3 years (using the HR) is 8·7 percentage points (95% CI 2·2–13·9), and 10·8 percentage points (2·6–17·4) at 5 years. Using regression standardisation, the risk difference at 3 years is 8·8 percentage points (95% CI 1·6–15·9), and 9·9 percentage points (1·9–18·0) at 5 years.

The HR for overall survival was 0·60 (95% CI 0·40–0·91, p=0·015), representing a 40% relative reduction in the hazard (risk) of dying. The 3-year overall survival rates were 85% for the induction chemotherapy with chemoradiotherapy group and 80% for the

	Induction chemotherapy with chemoradiotherapy (n=250)	Chemoradiotherapy alone (n=250)
Age, years*	46 (26–78)	46 (24–78)
ECOG status		
0	214 (86%)	221 (88%)
1	36 (14%)	29 (12%)
Country		
UK	190 (76%)	190 (76%)
Mexico	49 (20%)	51 (20%)
Italy	5 (2%)	3 (1%)
India	5 (2%)	5 (2%)
Brazil	1 (<1%)	1 (<1%)
FIGO stage (2008)		
IB1	2 (1%)	2 (1%)
IB2	19 (8%)	23 (9%)
IIA	17 (7%)	14 (6%)
IIB	178 (71%)	176 (70%)
IIIB	26 (10%)	30 (12%)
IVA	8 (3%)	5 (2%)
Cell stage		
Non-squamous	44 (18%)	45 (18%)
Squamous	206 (82%)	205 (82%)
Nodal status		
Negative	144 (58%)	141 (56%)
Positive	106 (42%)	109 (44%)
FIGO stage (2018)		
I and II	128 (51%)	126 (50%)
IIIB and IVA	22 (9%)	16 (6%)
IIIC	100 (40%)	108 (43%)
Longest tumour diameter, cm†	4·8 (1·3–13·5)	4·9 (1·8–12·8)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. FIGO=International Federation of Gynecology and Obstetrics. *25–75 percentiles 27–75 for chemoradiotherapy with induction chemotherapy and 26–73 for chemoradiotherapy alone. †25–75 percentiles 2·0–9·1 for chemoradiotherapy with induction chemotherapy and 2·0–8·3 for chemoradiotherapy alone.

Table 1: **Baseline characteristics**

	Induction chemotherapy (n=250)
Paclitaxel with carboplatin cycles completed	
Six cycles	211 (84%)
At least five cycles	230 (92%)
Main reasons for fewer than six cycles	
Adverse events	29 (12%)
Haematological	9
Non-haematological	17
Both	3
Withdrawal or other reasons not due to toxicity	10 (4%)
Median interval from induction chemotherapy to radiotherapy, days	7 (5–54)

Table 2: **Adherence to induction chemotherapy among patients randomly assigned to this group**

	Induction chemotherapy with chemoradiotherapy (n=250)	Chemoradiotherapy alone (n=250)
Cisplatin cycles completed		
Five cycles	169 (68%)	197 (79%)
At least four cycles*	212 (85%)	224 (90%)
Main reasons for fewer than five cycles		
Adverse events leading to discontinuation	68 (27%)	33 (13%)
Haematological	34	4
Non-haematological	20	25
Both	14	4
Other reasons not due to toxicity	13 (5%)	20 (8%)
Radiotherapy		
Received definitive EBRT on or off trial†	246 (98%)	239 (96%)
Received EBRT on trial	242 (97%)	231 (92%)
IMRT	102 (42%)	93 (40%)
3DCRT	140 (58%)	138 (60%)
Received extended field EBRT	22 (9%)	20 (9%)
Received brachytherapy	238 (98%)	224 (97%)
2D point A	46 (19%)	49 (22%)
3D point A	120 (50%)	107 (48%)
3D HRCTV D90	72 (30%)	68 (30%)
Did not receive brachytherapy on trial	4 (2%)	7 (3·0%)
Received EBRT boost	3 (1%)	6 (2·6%)
No boost	1 (<1%)	1 (<1%)
Did not receive EBRT on trial	8 (3%)	19 (8%)
Had radiotherapy outside trial	4 (50%)	8 (42%)
Ineligible or discontinued	1 (13%)	5 (26%)
No EBRT	1 (13%)	1 (5%)
Unknown	2 (25%)	5 (26%)
Median overall treatment time, days	45 (36–70)	45 (37–88)
Median total EQD2, Gy (% ≥78 Gy)‡	79·4 (69·8)	80·0 (71·4)
Median total HRCTV D90 EQD2 (IGABT), Gy‡	86·6	86·8

Data are n (%) or median (range), unless otherwise indicated. 2D=two-dimensional. 3DCRT=three-dimensional conformal radiotherapy. D90=the total dose to 90%. EBRT=external beam radiotherapy. EQD2=2 Gy equivalent dose. HRCTV=high-risk clinical target volume. IGABT=image-guided adaptive brachytherapy. IMRT=intensity modulated radiation therapy. *38 patients in the chemoradiotherapy with induction chemotherapy group and 26 patients in the chemoradiotherapy alone group completed fewer than four cycles, which is not significant (Fisher's exact test p=0·14). †2% of patients in the chemoradiotherapy with induction chemotherapy group and 4% of patients in the chemoradiotherapy alone group did not have EBRT, which is not significant (Fisher's exact test p=0·11). ‡The total EQD2 is the dose to Point A for all patients including those where the dose was prescribed to the HRCTV whereas total HRCTV D90 refers only to patients who received IGABT.

Table 3: **Adherence to cisplatin and radiation during chemoradiotherapy**

chemoradiotherapy alone group and corresponding 5-year rates were 80% and 72%, respectively. The estimated absolute risk difference at 3 years is 7·4 percentage points (95% CI 1·6–11·3), and 10·2 percentage points (2·2–15·9) at 5 years. Using regression standardisation, the risk difference at 3 years is 7·0 percentage points (1·0–13·0), and 9·0 percentage points (1·3–16·7) at 5 years. The overall survival results were based on 114 deaths, which is 59% of the expected number of at least 192 deaths. Of 114 deaths (66 in the chemoradiotherapy alone group and 48 in the induction chemotherapy with chemoradiotherapy group), 52 (21%) in the chemoradiotherapy alone group and 42 (17%) in the induction chemotherapy with chemoradiotherapy group were due to disease progression (appendix p 147). Further overall survival data will be published when more events have occurred.

Progression-free survival and overall survival subgroup analyses showed that the benefit of induction chemotherapy was consistent across the patient and disease factors (appendix pp 144–45), and neither of the statistical tests for subgroup effects were met (all 95% CIs included the overall treatment HRs for both progression-free survival of 0·65 and overall survival of 0·60).[13]

27 (11%) of 250 patients in the induction chemotherapy with chemoradiotherapy group and 22 (9%) of 250 patients in the chemoradiotherapy alone group had local or pelvic relapse (appendix p 148). However, fewer patients had distant only relapses in the induction chemotherapy with chemoradiotherapy group (17 [7%] 250) compared with the chemoradiotherapy alone group (30 [12%] of 250; p=0·015).

Most patients in both groups had an adverse event at any time during treatment (table 4, appendix pp 149–56). Grade 3–4 events were seen in 147 (59%) of 250 patients in the induction chemotherapy with chemoradiotherapy group and 120 (48%) of 250 patients in the chemoradiotherapy alone group. More patients had grade 3–4 haematological adverse events in the induction chemotherapy with chemoradiotherapy group (74 [30%] of 250 *vs* 32 [13%] of 250), largely neutropenia (48 [19%] of 250 *vs* 13 [5%] of 250). Non-haematological grade 3–4 events were similar in both groups. Grade 3–4 vaginal toxicity was only seen in two patients during induction chemotherapy and there was no difference in all grade vaginal bleeding between the two groups. Blood transfusion rates were not recorded. Anaemia of grade 2 or greater was seen in 71 (28%) and 43 (17%) of the induction chemotherapy with chemoradiotherapy and chemoradiotherapy group, respectively.

Of 250 patients in the induction chemotherapy with chemoradiotherapy group, 54 (22%) had a grade 3–4 adverse event during the induction phase. Neutropenia was the most common (in 18 [7%]), and all others had a frequency of less than 3%, including anaemia (in four [2%]). Infection was reported in six (2%) patients. Hair loss was reported as grade 1 in 39 (16%) and grade 2 in 106 (42%). Although we do not have a record of how often it was used, scalp cooling was permitted. Grade 1–2 peripheral neuropathy, fatigue, constipation, and dyspnoea were more common in the induction chemotherapy with chemoradiotherapy group (appendix pp 154–56), but they were all transient. No G3 thrombocytopenia was seen during induction chemotherapy, with only nine (4%) patients experiencing grade 1–2 thrombocytopenia.

There were three deaths within 30 days of completing treatment, one (respiratory failure) in the induction

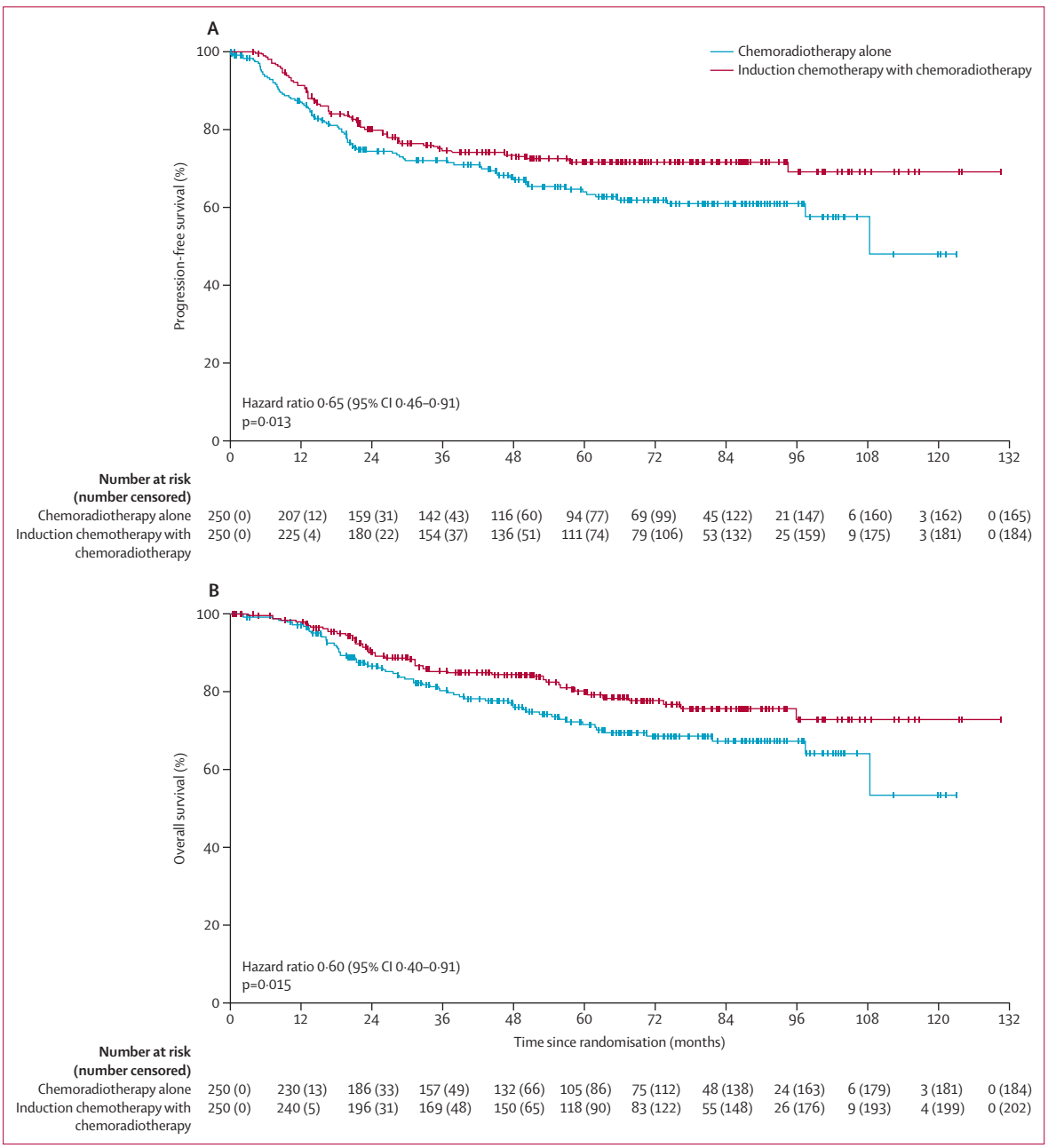

***Figure 2*: Kaplan–Meier estimates of progression-free survival (A) and overall survival (B)**

chemotherapy with chemoradiotherapy group, and two in the chemoradiotherapy alone group (sepsis and pulmonary embolism); none were considered treatment-related.

Time to next anticancer therapy (systematic therapies, surgery, or radiotherapy) is shown in the appendix (p 146), and was improved in the induction chemotherapy with chemoradiotherapy group. When the event was next treatment or death, the HR for induction chemotherapy with chemoradiotherapy versus chemoradiotherapy alone was 0·54 (95% CI 0·38–0·77), p=0·0010. When the event was next treatment only and death was counted as a competing risk, the HR was 0·56 (95% CI 0·34–0·91), p=0·019.

In the induction chemotherapy with chemoradiotherapy group, QoL slightly worsened during the induction chemotherapy treatment, with mean change from baseline generally of less than 5 units, which is not a clinically relevant effect on the scale 0–100 (appendix p 157). The mean difference in QoL scores between the trial groups over the whole treatment period were also indicative of worse symptoms in the induction

chemotherapy with chemoradiotherapy group but again, the differences were less than 5 units and not clinically important. In addition, any differences between the groups were not clinically meaningful by 12 months after treatment. QoL will be reported in more detail separately.

Discussion

Short-course once-a-week induction dose-dense carboplatin and paclitaxel delivered immediately before chemoradiotherapy resulted in an 11 percentage point improvement in the progression-free survival rate and a 10 percentage point improvement in the overall survival rate at 5 years, which were clinically meaningful and statistically significant. This represents the first published substantial overall survival improvement among patients with locally advanced cervical cancer since concomitant cisplatin over two decades ago. As expected, haematological toxicity (mainly neutropenia) was more common with induction chemotherapy with chemoradiotherapy, particularly during chemoradiotherapy. Granulocyte-colony stimulating factor (GCSF) was permitted as per standard clinical practice but we do not have a record of how often this was used. Careful monitoring of blood counts during the entire course of treatment and early intervention with GCSF are recommended. Importantly, infection rates were similar in both groups. Although the increase in haematological toxicity reduced the number of patients who received five cycles of cisplatin during radiation this was a modest difference that was even smaller when considering patients who received four cycles or more. In the seminal study of Rose and colleagues,[5] 17% received four cycles or fewer of cisplatin and there are no clear data regarding the minimum number of cisplatin cycles that is required in this setting. However, if having less cisplatin does matter for the induction chemotherapy with chemoradiotherapy cohort, it would have diluted the progression-free survival and overall survival advantage provided by induction chemotherapy, and the benefits would have been even larger than we report.

The frequency of low-grade thrombocytopenia in the induction chemotherapy treatment period was low and no differences in vaginal symptoms or bleeding in the two groups were reported. We therefore do not believe vaginal bleeding should be a contraindication for this treatment approach.

Progression-free survival and overall survival analysis showed that all subgroups benefited from induction chemotherapy. However, we acknowledge that FIGO 2008 IIIB disease and IVA disease were a small proportion of patients (14%) and those with para-aortic nodal involvement were excluded and therefore some of the highest risk patients are not included. However, by categorising patients using FIGO 2018 staging, 49% would be stage III or IV. Importantly FIGO 2008 stage IB1 patients were only eligible if they had nodal involvement and overall accounted for less than 10% of patients recruited. Furthermore, 40% of patients in the induction chemotherapy with chemoradiotherapy group and 43% of those in the chemoradiotherapy groups had FIGO 2018 stage IIIC 1 disease. Translational work will seek to identify biomarkers for response.

This is likely to represent true clinical practice and the difference between groups is unlikely to account for any substantial progression rates before treatment.

The impact of induction chemotherapy depends on successful delivery of chemoradiotherapy. Adherence to chemoradiotherapy was high and similar between the two trial groups. When considering the ITT population, 98% of patients in the induction chemotherapy with chemoradiotherapy group and 96% in chemoradiotherapy group received EBRT on or off trial. This 3% difference could not account for the reported 8% overall survival difference. Although comparison between trials is difficult, the 5-year progression-free survival and overall survival in the chemoradiotherapy alone group (64% and 72%, respectively) were similar to those reported in other major locally advanced cervical cancer studies, such as OUTBACK (62% and 71%),[8] and the more recent EMBRACE-I (68% and 74%)[6] and RetroEMBRACE (overall survival 65%).[11] When comparing INTERLACE with EMBRACE-I it is important to acknowledge that the EMBRACE cohort had a wider range of FIGO stages with 18% stage IB (*vs* 9% in INTERLACE) and 25% stage III or IV (*vs* 14% in INTERLACE). New dose objectives, leading to improved local control, have been established based on these publications.

One long-standing concern with the use of induction chemotherapy in locally advanced cervical cancer is the

	Induction chemotherapy with chemoradiotherapy (n=250)		Chemoradiotherapy alone (n=250)
	Occurred at any time	Occurred after induction chemotherapy	
Any grade 3–4 event during induction chemotherapy	54 (22%)	NA	NA
Any adverse event	247 (99%)	243 (97%)	237 (95%)
Any grade 3–4 event	147 (59%)	131 (52%)	120 (48%)
Any haematological grade 3–4 event	74 (30%)	60 (24%)	32 (13%)
Neutropenia	48 (19%)	37 (15%)	13 (5%)
Anaemia	13 (5%)	9 (4%)	9 (4%)
Thrombocytopenia	13 (5%)	13 (5%)	5 (2%)
Any non-haematological grade 3–4 event	109 (44%)	98 (39%)	107 (43%)
Abdominal or pelvic pain	13 (5%)	11 (4%)	18 (7%)
Diarrhoea	20 (8%)	19 (8%)	31 (12%)
Fatigue, muscle weakness, or joint pain	28 (11%)	25 (10%)	14 (6%)
Infection	14 (6%)	12 (5%)	13 (5%)

There were three deaths within 30 days of completing treatment, one (respiratory failure) in the induction chemotherapy with chemoradiotherapy group, and two in the chemoradiotherapy alone group (sepsis and pulmonary embolism); none were considered treatment-related. NA=not applicable.

Table 4: **Adverse events**

delay in the delivery of definitive chemoradiotherapy, with historical data suggesting a detrimental effect on outcome. The results presented should allay these concerns when using this specific weekly platinum dense regimen, especially as they are in keeping with findings of the first systematic review of neoadjuvant chemotherapy in locally advanced cervical cancer and a subsequent updated review.[9, 14] Further recent trials[15–18] have also shown improved tumour response rates and overall survival with neoadjuvant chemotherapy but other studies using 3-weekly chemotherapy cycles[19,20] continue to report no improvement. Two notable large phase 3 trials comparing neoadjuvant chemotherapy before surgery and chemoradiotherapy alone also demonstrate no overall survival benefit and a detrimental progression-free survival effect with neoadjuvant chemotherapy.[21,22] Many previous neoadjuvant chemotherapy studies failed to control the interval between chemotherapy completion and definitive radiation, chemoradiotherapy, or surgery with the interval varying from 15 days[19] to 6 weeks.[21] Accelerated repopulation during this period could potentially account for the absence of benefit of neoadjuvant chemotherapy.[23] This factor was considered in the design of INTERLACE and the interval from completion of induction chemotherapy to chemoradiotherapy start was 7 days or less for 78% of patients and 14 days or less in 93%. No difference in rates of relapse or death was seen in patients where the interval to start chemoradiotherapy was 7 days or less or 14 days or less (26% for both). A strict timeframe is still important and a combination of a dose-dense chemotherapy schedule and a short gap between the induction chemotherapy and start of chemoradiotherapy limits the potential for repopulation before definitive chemoradiotherapy. It is therefore vital that this treatment should not be used to compensate for delays in the radiotherapy pathway. In centres with substantial waiting time for radiotherapy the induction chemotherapy should be scheduled once the radiotherapy dates have been confirmed so there is no gap between chemoradiotherapy and induction chemotherapy. This relies on effective multidisciplinary work but we acknowledge that this can present challenges in some settings. It is also important to note that 20% of patients within INTERLACE were treated in Mexico, a middle-income country, as per protocol, showing the likely feasibility of this strategy globally but caution is needed when generalising.

A higher tumour control probability is seen when the applied radiation dose is increased or the overall radiation treatment time is less than 56 days.[24] In INTERLACE, the median overall radiation treatment time in both groups was 45 days with 97% of patients in the chemoradiotherapy alone group and 96% of those in the induction chemotherapy with chemoradiotherapy group completing radiotherapy within 56 days.

Distant only relapses were more frequent in the chemoradiotherapy alone group (12% *vs* 7% in the induction radiotherapy with chemoradiotherapy group) suggesting that induction chemotherapy with chemoradiotherapy was more effective in controlling distant micrometastatic disease. According to FIGO 2018, 49% of the INTERLACE patient population were stage III or IV with an expectation that about 30% would die from metastatic disease, highlighting the importance of introducing additional therapy. Only one patient in the induction chemotherapy with chemoradiotherapy group and three patients in the chemoradiotherapy alone group had isolated para-aortic nodal recurrences showing that most distant relapses were not salvageable.

The INTERLACE trial took 10 years to recruit, similar to some other large trials of locally advanced cervical cancer.[21,22] This was partly due to strict radiotherapy quality assurance requirements, and clinician and patient-related factors such as concern about delaying definitive treatment and hair loss. This long recruitment duration is not likely to account for the survival difference seen. During the past decade IMRT and IGABT were adopted as standard of care but only 40% of both groups were treated with IMRT and 30% had IGABT within the INTERLACE trial. However, the techniques applied and dose delivered were well balanced across both treatment groups. In addition, the survival and pelvic control rates in the chemoradiotherapy alone group were similar to those reported for RetroEmbrace, where 3DCRT and MR-guided brachytherapy were used.[11] Furthermore, the primary benefits of IMRT are to reduce toxicity and allow for nodal boosts, but there is no clear evidence that IMRT per se improves overall survival. It is important to note that in EMBRACE-I[6] only 21% of patients had dose escalation from the standard point A plan and therefore many patients who receive brachytherapy prescribed to point A will receive a much higher dose to the HRCTV. In addition, 41% in EMBRACE-I[6] would have received a higher dose to the HRCTV if the dose had been prescribed to point A. For patients who received IGABT, the total dose to 90% HRCTV of 2 Gy equivalent dose was 87 Gy which is within current EMBRACE guidance.

Patients with para-aortic lymph-node involvement and lower vaginal involvement were excluded from INTERLACE because, at the time of trial design, there was uncertainty regarding whether chemoradiotherapy represented curative treatment. However, a single centre retrospective review of para-aortic node-positive patients treated with INTERLACE protocol induction chemotherapy and extended field chemoradiotherapy confirmed 3-year overall survival and progression-free survival rates (83% and 78%.)[25] We therefore anticipate that these patients would also benefit from induction chemotherapy with chemoradiotherapy.

Checkpoint inhibitors have been evaluated in locally advanced cervical cancer with mixed findings. Durvalumab given alongside and following chemoradiotherapy did not improve progression-free survival.[26] However, pembrolizumab administered with and following chemoradiotherapy did improve progression-free survival

(HR 0·70, p=0·0020).[27] The progression-free survival HR estimate was 0·59 (95% CI 0·43–0·82) for patients with FIGO 2014 stage III–IVA disease compared with 0·91 (95% CI 0·63–1·31) for patients with node-positive stage IB2–IIB disease. On this basis the Food and Drug Administration has restricted approval of pembrolizumab to patients with stage III disease or IVA disease only.[28] Overall survival data were not mature at the time of progression-free survival analysis. Following a protocol specified second interim analysis, the authors have now reported a statistically significant improvement in overall survival with pembrolizumab (HR death 0·67; 95% CI 0·50–0·90, p=0·0004).[29] The data in favour of immunotherapy as well as the positive results for induction chemotherapy presented here support the need for further investigation of a combination approach in patients with locally advanced cervical cancer.

Recommendations on neoadjuvant therapy vary between country-specific guidelines without any clear steer when to use it.[30] Globally, 37% of patients diagnosed with cervical cancer have locally advanced disease,[31] representing many patients who could benefit from two affordable, effective, and readily available drugs given before chemoradiotherapy.

In conclusion, this short-course induction chemotherapy regimen followed within 7 days by chemoradiotherapy improves survival of patients with locally advanced cervical cancer. It should now be considered a standard of care and be included in the design of future trials that explore the incorporation of new agents for the treatment of locally advanced cervical cancer.

Contributors

MM conceptualised the trial. MM, JAL, AH, GE, and PD developed the trial design. AH and SV did the statistical analysis. MM wrote the first draft of the manuscript with input from GE, AH, and JAL and all authors contributed to subsequent drafting of the manuscript and agreed to be accountable for all aspects of the manuscript. AH, SV, MM, GE, and PD analysed the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AH and SV have directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

GE reports consulting fees from MSD and Eisai; payment or honoraria from Eisai and GSK; support for attending meeting from MSD; and participation on Data Safety Monitoring Board or Advisory Board for GSK, MSD, and Eisai, outside the submitted work. JAL reports grants from AstraZeneca and Merck/MSD; consulting fees from AstraZeneca, Clovis Oncology, GSK, Artios Pharma, Merck/MSD, VBL Therapeutics, Bristol Myers Squibb, Nuvation, Immagene, Incyte, Immunogen/AbbVie, and Novocure; payment or honoraria from AstraZeneca, MSD/Merck, Clovis Oncology, and GSK; participation on Data Safety Monitoring Board or Advisory Board for Mersana and SutroBio; and leadership role on the European Society for Medical Oncology's Clinical Practice Guidelines—Gynaecological Cancer—until December, 2023, past Vice President role for the European Society of Gynaecological Oncology, until 2021, and Chair for National Ovarian Cancer Audit Committee, outside the submitted work. MM reports payment or honoraria from MSD, Eisai, GSK, Roche, and Medscape; support for attending meetings or travel from Daiichi Sanko; and past role as a Chair of Cervical Cancer Research Network (until September 2021), outside the submitted work. AM reports participation on data safety monitoring board or advisory board for Cannariabio (on an ovarian cancer trial, since 2023) and executive committee member role with the Gynecologic Cancer Intergroup (since 2024), outside the submitted work. AH reports honoraria for educational activities from AbbVie, Almirall, Boehringer Ingelheim, Clovis Oncology, Ipsen, Takeda, AstraZeneca, Daiichi Sankyo, Merck Serono, MSD, UCB, Kyowa Kirin, Servier, Sobi, Pfizer, and Roche, outside the submitted work. All other authors declare no competing interests.

Data sharing

Requests to access de-identified participant data can be made to ctc.interlace@ucl.ac.uk. Proposals will be reviewed by members of the INTERLACE Trial Management Group, and if accepted, a data sharing agreement will be put in place. Data would include efficacy, toxicity, and adherence variables that have formed the results in this paper.

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