Current Oncology Reports (2020) 22: 28
https://doi.org/10.1007/s11912-020-0888-x

GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Management of Stage IIB Cervical Cancer: an Overview of the Current Evidence

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Published online: 12 February 2020

Abstract

Purpose of Review To review and discuss the present evidence of surgery- and radiation-based treatment strategies for stage IIB cervical cancer.

Recent Findings Recently, two randomized controlled trials compared the efficacy of neoadjuvant chemotherapy followed by radical hysterectomy (NACT + RH) with that of concurrent chemoradiotherapy (CCRT) for stage IB3–IIB cervical cancer. When these studies were combined ($N = 1259$), NACT + RH was associated with a shorter disease-free survival [hazard ratio (HR) 1.36, 95% confidence interval (CI) 1.13–1.64], but with a similar overall survival (HR 1.11, 95% CI 0.90–1.36) when compared with the findings for CCRT. Stage-specific analysis for stage IIB cervical cancer demonstrated that disease-free survival was significantly worse with NACT + RH than with CCRT (HR 1.90, 95% CI 1.25–2.89); however, no significant difference was observed for stage IB3–IIA cervical cancer.

Summary Based on the results of recent level I evidence, the standard treatment for stage IIB cervical cancer remains CCRT.

Keywords Cervical cancer · Stage II · Concurrent chemoradiotherapy · Neoadjuvant chemotherapy · Radical hysterectomy · Survival

This article is part of the Topical Collection on *Gynecologic Cancers*.

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Introduction

General Overview of Stage IIB Cervical Cancer

Cervical cancer is the most frequently occurring gynecological malignancy globally, and it has been estimated that over 570,000 new cases are diagnosed annually worldwide, with 311,000 deaths being reported in 2018 [1]. In the present review, cervical cancer staging was based on the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system [2, 3•]. It has been shown that the rate of recurrence is higher and survival outcomes are worse in patients with advanced cervical cancer (stage IB3–IVB) than in patients with early-stage cervical cancer (stage IA-IB2) [4]. Stage II cervical cancer is divided into stages IIA and IIB, and stage IIB cancer is defined as a tumor that invades the parametrium but does not extend into the pelvic sidewall. The 5-year survival rate in patients with stage IIB cervical cancer is approximately 80% [5].

Guidelines for the Treatment of Stage IIB Cervical Cancer

Concurrent chemoradiotherapy (CCRT) is the recommended approach for treating locally advanced cervical cancer (LACC) in guidelines from the USA, Europe, and other developed countries [4, 6, 7]. The specific guidelines are summarized in Table 1 [4, 7–10]. For the treatment of patients with stage IIB cervical cancer, CCRT is recommended in USA, China, and Korea. Neoadjuvant chemotherapy (NACT) followed by radical hysterectomy (RH) is mentioned as a treatment option in the European guidelines [7]. In Japan, RH and CCRT are recommended for patients with stage IIB cervical cancer, and approximately 40% of institutions perform RH [11–13•].

The reasons for these national differences are unclear. In our opinion, there are three possibilities; first, the differences may have resulted from the diverse perceptions regarding RH [14–16]. A secondary factor is that some clinicians prefer to perform NACT to avoid potential long-term radiotherapy (RT) and related complications [17]. Lastly, there is a concern regarding increased complications associated with RT, with the common occurrence of underweight patients [18].

Some clinicians have a concern about severe side effects of CCRT due to the difference in body habitus. A retrospective study involving 401 patients with stage IB–IV cervical cancer who were treated with CCRT illustrated that underweight patients (body mass index < 18.5 kg/m^2) had worse overall survival (hazard ratio [HR] 2.37, 95% confidence interval [CI] 1.28–4.38) and more frequent complications (radiation enteritis 16.7% vs. 13.6%, $P = 0.03$; fistula 11.1% vs. 8.8%, $P = 0.05$; bowel obstruction 33.3% vs. 4.4%, $P < 0.001$; and lymphedema 5.6% vs. 1.2%, $P = 0.02$) when compared with the findings in normal weight or obese patients [19]. The mean body mass index of women has been shown to vary by country [18], and thus the side effects of CCRT might differ among countries.

Problems in the Surgical Treatment of Stage IIB Cervical Cancer

Primary surgery for stage IIB cervical cancer has been reported to have a low complete resection rate, and patients often require adjuvant treatment [20••]. Postoperative RT, particularly CCRT,

Table 1 Guidelines for the treatment of stage IIB cervical cancer

Region	Organization	Classification	Recommended treatment
USA	NCCN [4]	No evidence of metastasis	P-CCRT + ICBT
		Pelvic LN metastasis	P-CCRT + ICBT ± PALN EBRT
		PALN metastasis	Extended field of EBRT + p-CT + ICBT
		Distant metastasis	Systematic therapy
Europe	ESMO [7]	Not specified	P-CCRT
			NACT + RH or NACT + RT
China	NHC [8]	Not specified	C-CCRT + ICBT
Japan	JSGO [9]	Squamous cell carcinoma	RH (+ adjuvant therapy) or CCRT
		Adenocarcinoma	RH (+ adjuvant therapy)
Korea	KGOG [10]	No PALN metastasis	C-CCRT
		PALN metastasis	Extended field of EBRT + c-CT

CCRT, chemoradiotherapy; *c-CCRT*, cisplatin-based chemoradiotherapy; *c-CT*, cisplatin-based chemotherapy; *EBRT*, external beam radiation therapy; *ICBT*, intra-cervical brachytherapy; *LN*, lymph node; *NACT*, neoadjuvant chemotherapy; *p-CCRT*, platinum-based chemoradiation; *p-CT*, platinum-based chemotherapy; *RT*, radiotherapy; *RH*, radical hysterectomy; *PALN*, para-aortic lymph node; *NHC*, National Health Commission of the People's Republic of China; and *PET-CT*, positron emission tomography with computed tomography

is associated with an increased risk of treatment-related complications, thereby adding RT to the surgery-related morbidity [21–23]. It is unknown whether these multimodality treatments truly improve overall survival (OS) and disease-free survival (DFS) when compared with the outcomes for primary CCRT alone.

Mabuchi et al. found that the frequency of grade 3–4 late toxicities was higher with RH plus adjuvant CCRT than with primary CCRT (24.1% vs. 10.6%, $P = 0.048$) in patients with stage IIB cervical cancer, and this was without improvements in OS (66.4% vs. 68.3%, $P = 0.25$) [24]. A similar investigation for stage IIB cervical cancer was performed in other studies, and these studies showed that RH plus adjuvant CCRT was associated with a higher frequency of grade 3–4 late treatment-related complications without improvements in OS and PFS [25, 26]. Although these were only small retrospective studies, the findings indicate that RH plus adjuvant CCRT is more harmful than primary CCRT without any survival benefit.

Prognostic Factors for Stage IIB Cervical Cancer

Our 2019 report investigated the prognostic factors for stage IIB cervical cancer [27•]. In this study, we found that nearly half of the patients (44.0%) diagnosed with clinical stage IIB cervical cancer did not have pathological stage IIB cervical cancer. Therefore, to determine the prognostic factors for stage IIB cervical cancer, only cases of pathologically confirmed stage IIB cervical cancer were analyzed. A multivariate analysis revealed that nonsquamous cell carcinoma histology (adjusted HR 2.139, 95% CI 1.446–3.163, $P < 0.001$), metastases to multiple pelvic lymph nodes (adjusted HR 2.725, 95% CI 1.686–4.404, $P < 0.001$), and metastases to multiple paraaortic lymph nodes (adjusted HR 2.466, 95% CI 1.163–5.228, $P = 0.019$) were significantly associated with a poor cause specific survival for stage IIB cervical cancer.

Recent Topics of NACT Followed by RH

A 2012 meta-analysis including six randomized controlled trials (RCTs) with a total of 1078 patients with IB1-IIIB cervical cancer (all histological types) reported that OS was better with NACT followed by RH (NACT + RH) than with RH alone (HR 0.77, 95% CI 0.62–0.96) [28]. Following the publication of this meta-analysis, several subsequent studies were conducted to investigate whether NACT + RH for LACC improves OS and DFS [29–31]. Although several guidelines recommend performing CCRT for LACC, there was a possibility that NACT + RH is superior to CCRT for LACC in terms of OS and DFS, providing the rationale for two RCTs comparing NACT + RH with CCRT [32••, 33••].

Purpose of this Review

We focused on the two recent RCTs [32••, 33••] (NACT + RH vs. CCRT) to investigate whether NACT + RH or CCRT is superior for the treatment of LACC. LACC has been reviewed in other studies [34, 35]; however, most of these studies did not focus on stage IIB cervical cancer or account for the various treatments utilized in different countries (Table 1). Therefore, in this article, we review the recent studies and latest developments regarding stage IIB cervical cancer and discuss the current treatment modalities.

Radiation-Based Approach for Stage IIB Cancer

Primary CCRT

Conventional RT (RT without chemotherapy) has been recognized as an efficient therapy for cervical cancer [36]. Platinum-based CCRT has been reported as a superior treatment for patients with LACC and those with advanced high-risk cervical cancer (III-IVA) [22, 37–39], with demonstrated improvements in both OS and DFS when compared with the findings for conventional RT alone. Following the 1999 National Cancer Institute clinical alert, CCRT has been recommended in cases of advanced cervical cancer and LACC [40]. A Cochrane systematic review reported that the mortality risk was lower with CCRT than with conventional RT (HR 0.81, 95% CI 0.71–0.91) in cases of advanced cervical cancer [41], and there was a 6% improvement (from 60 to 66%) in the 5-year OS rate with CCRT.

No RCT has focused on stage IIB cervical cancer with a protocol comparing surgery-based treatment with RT-based treatment. Few small retrospective studies reported that RH plus adjuvant RT and primary CCRT showed equivalent OS rates (RH 78% vs. CCRT 77%, $P = 0.97$) in patients with stage IIB cervical cancer [42, 43]. However, most patients (90.5–100%) required adjuvant therapy due to the presence of unfavorable prognostic factors. Several studies have reported that the combination of RH and adjuvant RT or CCRT has a high risk of chronic morbidities, such as small bowel obstruction, lower limb lymphedema, and chronic neurological bladder [20••, 24, 26, 43, 44].

Based on these results, several guidelines now recommend primary CCRT and not primary surgery for the treatment of LACC, regardless of the histological type [4, 8, 12]. Primary surgery appears to have a low complete resection rate, and patients often require adjuvant treatment.

Primary CCRT for Cervical Adenocarcinoma

According to the National Comprehensive Cancer Network guidelines, the management of locally advanced cervical adenocarcinoma (ADC) is similar to that of squamous cell carcinoma (SCC) with some minor modifications [4]. Most guidelines do not subclassify treatment recommendations according to the LACC histological type. This is because of limited information on less frequent histological types, such as ADC making performing RCTs on these entities a difficult task [4, 8, 10].

A 2014 retrospective study involving 1489 SCC patients and 182 ADC patients compared the efficacy of RT and CCRT for SCC and ADC [46]. The authors divided patients into SCC treated with RT (SCC-RT), ADC treated with RT (ADC-RT), SCC treated with CCRT, and ADC treated with CCRT groups. When the SCC-RT ($n = 647$) and ADC-RT ($n = 70$) groups were compared, the ADC-RT group showed a statistically slightly worse OS ($P = 0.049$) [46]. However, when cisplatin-based CCRT was administered, the OS of ADC patients ($n = 112$) drastically improved [22] and was similar to that of SCC patients ($n = 842$, $P = 0.46$) [46].

The findings of these studies suggest that radiosensitivity is poor in ADC patients and that chemotherapy additional to RT as a radiosensitizer holds greater promise for the treatment of ADC [47]. However, a small retrospective study involving 249 patients with FIGO stage IIB–IVA cervical cancer (SCC: 225 patients, ADC: 24 patients) reported that OS with CCRT was poorer in patients with ADC than in those with SCC (58.6% vs. 26.7%, $P = 0.004$) [47]. The authors performed a multivariate analysis and found that ADC histology was an independent predictor of poor PFS (HR 1.94, 95% CI 1.07–3.35). Further investigation is required to determine the differences in radiosensitivity between SCC and ADC.

Future Perspectives for CCRT

Chemotherapy Regimen

Platinum-based CCRT has been shown to successfully improve survival outcomes in patients with LACC, and additional trials have continued to demonstrate further improvements [48–50]. Currently, chemotherapy usually involves single-agent cisplatin or a combination of cisplatin plus fluorouracil [38, 51]. Several chemotherapy regimens, along with changes in dosage and timing, have been investigated.

Duenas-Gonzalez et al. performed a RCT involving 515 patients with stage IIB–IVA cervical cancer. The patients were randomly assigned to a group weekly of cisplatin and gemcitabine for 6 weeks (CDDP + GM CCRT) with CCRT, and then, two consecutive 21-day cycles of cisplatin and gemcitabine and a standard platinum-based CCRT group (no adjuvant therapy) [48]. The CDDP + GM CCRT group showed improved PFS at 3 years (74.4% vs. 65.0%, $P = 0.029$) and improved OS (HR 0.68, 95% CI 0.49–0.95, $P = 0.022$) when compared with the findings in the standard platinum-based CCRT group; however, there was a significantly increased frequency of grade 3–4 neutropenia (51.2% vs. 5.9%), and it resulted in an increased rate of grade 3–4 hematologic toxicity (71.9% vs. 23.9%, $P < 0.001$) [20••, 48]. The other major complication was diarrhea (17.7% vs. 4.7%).

Despite the improvements in PFS and OS, CDDP + GM CCRT is not currently recommended because of not only severe treatment-related toxicities but also limited information on which therapy (additional gemcitabine during CCRT, adjuvant chemotherapy [ACT] of cisplatin and gemcitabine, or both) actually improves OS [20••, 52]. Studies involving chemotherapy regimens with RT are expected to improve OS with tolerable treatment-related toxicities [41, 49, 50].

Adjuvant Chemotherapy after CCRT

A two-arm RCT was performed to investigate whether CCRT followed by ACT improves PFS and OS [53]. This RCT compared OS and PFS in 259 patients with stage IIB–IVA cervical cancer who had been randomly assigned to a standard CCRT alone group and a CCRT followed by ACT (CCRT + adjuvant; paclitaxel plus carboplatin every 4 weeks for 3 cycles) group [53]. The 3-year PFS (HR 1.26, 95% CI 0.82–1.96, $P = 0.293$) and 3-year OS (HR 1.42, 95% CI 0.81–2.49, $P = 0.221$) were not significantly different between the CCRT + adjuvant group and CCRT alone group.

With regard to investigation of the efficacy of these approaches, an international RCT, the OUTBACK study, is currently ongoing. This trial is assessing whether treatment involving 4 cycles of carboplatin and paclitaxel chemotherapy following standard cisplatin-based CCRT improves OS [54, 55].

NACT Prior to CCRT

A systematic review was conducted in 2016 to evaluate the available data regarding NACT followed by CCRT. This review identified only two published phase II studies, two unpublished phase II studies, and three retrospective studies with a total of 323 participants [56]. Due to limited data, the authors could not investigate the OS or PFS benefit; however, they could determine the grade 3–4 treatment toxicity rate (approximately 25%) and the response rate (approximately 70%). The most frequent grade 3–4 toxicity was neutropenia, followed by anemia, and then diarrhea. The INTERLACE trial is currently investigating the efficacy of the addition of chemotherapy prior to CCRT and will hopefully clarify whether this treatment strategy can improve OS [57].

Surgery-Based Approach for Stage IIB Cervical Cancer

NACT + RH Versus RH Alone

A Cochrane analysis involving six RCTs with 1078 cases reported that OS was better with NACT + RH than with surgery alone [28]. The six RCTs randomized between 107 and 291 women with stage IB–IIIB cervical cancer (FIGO 1994) [58–62]. In this meta-analysis, patients treated with NACT + RH showed significantly better PFS (HR 0.75, 95% CI 0.61–0.93, $P = 0.008$) and OS (HR 0.77, 95% CI 0.62–0.96, $P = 0.02$) when compared with the findings in those treated with surgery alone.

Despite the positive results of this Cochrane analysis, Kim et al. performed another meta-analysis in 2013 to assess the efficacy of NACT + RH at an earlier stage of cervical cancer compared with that of Cochrane review. The meta-analysis involved patients with stage IB1–IIA cervical cancer from five RCTs and three observational studies [63], and they reported that NACT + RH reduced the need for adjuvant RT according to the postoperative pathological analysis including intermediate- or high-risk factor in all studies (odds ratio [OR] 0.57, 95% CI 0.33–0.98). However, it did not significantly improve OS (HR 1.12, 95% CI 0.88–1.36) or PFS (HR 1.12, 95% CI 0.85–1.46) when compared with the findings for RH alone in patients with stage IB1–IIA2 cervical cancer.

The conflicting results between the Cochrane review and the review by Kim et al. might have been associated with differences in the inclusion criteria. The disease stage was more advanced in the Cochrane review (stage IB–IIIB) than in the review by Kim et al. (stage IB1–IIA2) [28, 63]. These findings suggest that the target population of NACT + RH should be carefully considered. Some experts consider NACT + RH to be beneficial in only select high-risk cases (e.g., cases involving bulky tumors greater than 4 cm in size; histopathological documented risk factors such as grade 3, lymphovascular involvement, and vascular involvement; and suspected lymph node metastasis) [64]. However, at present, there is no high-quality evidence indicating which patients could benefit the most from NACT + RH.

In order to summarize the RCTs comparing NACT + RH and RH alone, we performed a systematic literature review and identified seven studies (Table 2). In all studies, cisplatin (not carboplatin) chemotherapy was utilized. In four of the seven studies, one or 2 cycles were administered, and in the remaining three studies, 3 cycles were used prior to surgery. Three studies showed significantly better OS with NACT + RH than with RH alone, whereas the remaining four studies showed no difference. The complete response (CR) and partial

Table 2 Randomized controlled trials comparing NACT followed by RH versus RH alone

Authors	Year	No.	FIGO stage	Stage IIB cases	Histology	Neoadjuvant regimen	Interval (weeks)	Cycles	CR + PR	Adjuvant cases	OS	PFS or DFS
NACT + RH superior												
Chen [62]	2008	144	IB3-IIB	20/72 (28%)	SCC, ADC, ADS	P + M + 5-FU	2–3	2	50/72 (69%)	NA	↑ 4-year OS	NA
Cai [60]	2006	106	IB1-IB3	0	SCC, ADC	P + 5-FU	3	2	44/52 (85%)	32/52 (62%)	↑ 5-year OS	↑ 5-year PFS
Sardi [58]	1997	210	IB1-IB3	0	SCC	P + V +B	1.5	3	88/102 (86%)	102/102 (100%)	↑ 8-year OS	NA
No difference												
Yang [87]	2016	217	IB3-IIB	72/109 (66%)	SCC, ADC, ADS	I + P, T + P	3	1–2	77/107 (72%)	44/107 (41%)	3-year OS	3-year DFS
Katsumata [98]	2013	134	IB3-IIB	38/67 (57%)	SCC	B + V + M + P	3	2–4	44/67 (66%)	48/67 (72%)	5-year OS	5-year DFS
Eddy [61]	2007	288	IB3	0	SCC, ADC, ADS	V + P	1.5	3	75/145 (52%)	65/145 (45%)	5-year OS	5-year PFS
Napolitano [59]	2003	192	IB-IIIB	16/106 (15%)	SCC	P + V +B	3	3	84/106 (79%)	NA	5-year OS	5-year DFS*

Data presented as No. (%)

* Significant difference was observed in stage IB–IIA (77.1% vs 64.3%, $P < 0.05$) and no difference was observed in stage IIB (56.2% vs 57.1%, $P > 0.05$)

5-FU, 5-fluorouracil; *B*, bleomycin; *C*, carboplatin; *T*, paclitaxel; *P*, cisplatin; *I*, irinotecan; *M*, mitomycin; *V*, vincristine

SCC, squamous cell carcinoma; *ADC*, adenocarcinoma; *ADS*, adenosquamous carcinoma; *CR*, complete response; *DFS*, disease free survival; *FIGO*, International Federation of Gynecology and Obstetrics; *NA*, not available; *NACT*, neoadjuvant chemotherapy; *N.S.*, not significant; *OP*, operation alone; *OS*; overall survival; *PFS*, progression free survival; *PR*, partial response; *RCT*, randomized controlled trial; *RH*, radical hysterectomy; vs, versus

response (PR) rates for NACT were 52–86%. The reason for the difference in the results may be the heterogeneity of the included patients. In our view, the group of studies that showed no difference had more stage IIB cases, and the response rate (CR + PR) appeared to be lower in this group of studies than in the group of studies that showed NACT + RH superiority (Table 2).

Based on our literature review, it appears controversial whether NACT + RH or RH alone is better for stage IB–IIB cervical cancer. Moreover, these analyses were not specific to stage IIB cervical cancer; thus, according to the current evidence, we could not assess whether NACT + RH is better than RH alone for improving OS and PFS in patients with stage IIB cervical cancer.

NACT + RH Versus Conventional Radiotherapy

As CCRT has been used for LACC recently, available studies that compared NACT + RH and conventional RT are relatively old. One 2002 RCT included 441 patients with stage IB3–III cervical cancer and randomized the patients 1:1 to NACT + RH or conventional RT. The study found that the 5-year OS and 5-year PFS rates were significantly better with NACT + RH than with conventional RT alone (56.5% vs. 44.4%, $P < 0.05$ and 55.4% vs. 41.3%, $P < 0.05$, respectively) [65]. Additionally, when the authors investigated stage IB3–IIB cases, the 5-year OS and 5-year PFS rates remained significantly better with NACT + RH than with conventional RT alone (64.7% vs. 56.5%, $P < 0.05$ and 59.7% vs. 46.7%, $P < 0.05$, respectively).

A 2003 meta-analysis involving patients with stage IB3–IVA cervical cancer revealed a highly significant 35% decrease in the risk of death in the NACT + RH group when compared with the risk in the conventional RT alone group (HR 0.65, $P = 0.0004$), with an absolute improvement in the 5-year survival rate from 50 to 64% [66]. Therefore, NACT + RH is expected to be superior to conventional RT for stage IIB cervical cancer. Conventional RT alone is usually not performed in LACC cases currently. Therefore, it is essential to determine whether NACT + RH or CCRT is better for the treatment of LACC.

NACT + RH Versus CCRT

Gupta et al. performed a phase III RCT (ClinicalTrials.gov Identifier: NCT00193739) to determine whether NACT + RH is superior to CCRT for LACC. The study involved 635 patients with stage IB3, IIA, and IIB cervical cancer and compared NACT followed by RH (NACT + RH group) with platinum-based CCRT (CCRT group) [32••]. The authors found that the 5-year DFS was lower in the NACT + RH group than in the CCRT group (HR 1.38, 95% CI 1.02–1.87, $P = 0.038$) and that there was no significant difference in the 5-year OS between the groups (HR 1.025, 95% CI 0.752–1.398, $P = 0.87$). These findings raise concerns regarding the number of NACT cycles (three), the choice of carboplatin, the inclusion of patients with stage IIA1 disease, and the omission of brachytherapy in the study [20••, 67].

Zou et al. listed two points pertinent to the discussion of the study by Gupta et al. The first is regarding the number of chemotherapy cycles. A previous study found that one to two courses of NACT are suitable for patients with LACC [68, 69]. The second is the choice of platinum drugs. A phase III trial compared the conventional paclitaxel plus cisplatin regimen with the paclitaxel plus carboplatin regimen in patients with metastatic or recurrent cervical cancer [70]. Subanalyses in this study found that among patients who had not received prior cisplatin-based chemotherapy, OS was shorter in the paclitaxel plus carboplatin group than in the paclitaxel plus cisplatin group (13.0 vs. 23.2 months; HR 1.571, 95% CI 1.06–2.32) [70]. Therefore, Zou et al. considered that it might be possible to improve the outcome of NACT + RH by using cisplatin for chemotherapy.

Another RCT (ClinicalTrials.gov Identifier: NCT00039338) included 626 patients with LACC (stages IB2, IIA2, and IIB) and compared NACT + RH, and CCRT was reported by Kenter et al. [33••]. Several concerns were raised regarding the study reported by Gupta et al., and this second study resolved some of these concerns [32••]. Although Kenter et al. excluded IIA1 cases and utilized a cisplatin-based chemotherapy regimen (planned total cisplatin dose of at least 225 mg/m^2), their results were similar to the findings in the study by Gupta et al. with decreased DFS (HR 1.35, 95% CI 1.07–1.70) and no significant change in OS (HR 1.18, 95% CI 0.89–1.55) [33••]. These two RCTs are the only studies that are currently available to discuss NACT + RH and CCRT. They had a similar study design; however, several points (e.g., primary outcome (OS or PFS), presence/absence of stage IIA1 and ADC, and difference in NACT regimen) are different. Therefore, we have summarized these RCTs in Table 3 to help understand the differences between them.

Regarding treatment-related complications with NACT + RH and CCRT, short-term complications, particularly hematologic complications, were significantly more frequent in the NACT + RH group than in the CCRT group (Table 3). Conversely, long-term complications, such as small bowel and vaginal complications, were more frequent in the CCRT group than in the NACT + RH group. Although the pattern of complications was different in the NACT + RH and CCRT groups, in both studies, the rate of complications in both groups was generally well tolerated. In our viewpoint, the toxicity of both treatments was similar. Based on these results, we believe that NACT + RH is not superior to CCRT for the treatment of LACC (Table 3).

NACT + RH for Stage IIB Cervical Cancer

As shown in Table 3, a subgroup analysis with various stages of cervical cancer in the study by Gupta et al. found that DFS was significantly shorter in the NACT + RH group than in the CCRT group among patients with stage IIB cancer (67.2% in the NACT group vs. 79.3% in the CCRT group [HR 1.90, 95% CI 1.25–2.89]) [32••]. However, there were no significant differences in patients with stage IB3 and IIA cervical cancer. A subgroup analysis for the 5-year OS rate was not performed in this study. Kenter et al. performed a subgroup analysis of the 5-year OS rate in patients with stage IIB cervical cancer and found no significant difference between the NACT and CCRT groups (68.0% in the NACT group vs. 76.0% in the CCRT group [HR 1.32, 95% CI 0.93–1.88]) [33••].

In the subanalysis of stage IIB cervical cancer in these two recent RCTs, DFS was shorter with NACT + RH than with CCRT, but there was no significant difference in OS. However, these RCTs did not focus on stage IIB cervical cancer, and no RCT comparing NACT + RH with CCRT

Table 3 A comparison of two randomized controlled studies comparing NACT followed by RH versus CCRT

	Gupta S et al. (2018) [32••]		Kenter G. et al. (2019) [33••]	
Study design	RCT		RCT	
Study size	$n = 633$		$n = 626$	
	NACT + RH	CCRT	NACT + RH	CCRT
	$n = 316$	$n = 317$	$n = 314$	$n = 312$
2018 FIGO stage				
IB3	18%	18%	26%	28%
IIA	25%	25%	15%	15%
IIB	57%	58%	57%	57%
Histology				
SCC	100%	100%	85%	85%
ADC/ADS	–	–	15%	15%
Median follow-up	5 years		8 years	
NACT regimen	Single regimen§		Various regimens**	
Operable cases‡	227/316 (72.2%)		240/314 (76.4%)	
Adjuvant therapy	73/227 (32.2%)		80/240 (33.3%)	
Acute toxicity#	$n = 316$	$n = 317$	$n = 299$	$n = 292$
Hematologic	25 (8.0%)*	6 (1.8%)*	36 (12.0)*	15 (5.1%)*
Gastrointestinal	11 (3.5%)	12 (3.8%)	34 (11.4)	20 (6.8%)
Renal	0	0	16 (5.4)	4 (1.4%)
Chronic toxicity	$n = 316$	$n = 317$	$n = 293$	$n = 290$
Small bowel	NA	NA	5 (1.7%)*	21 (7.2%)*
Rectal	7 (2.2%)	11 (3.5%)	4 (1.4%)	5 (1.7%)
Bladder	5 (1.6%)	11 (3.5%)	13 (4.4%)	11 (3.8%)
Vaginal$	38 (12.0%)*	81 (25.6%)*	6 (2.0%)	14 (4.8%)
Overall survival				
5-year (%)‡	75.4%	74.7%	71.7%	75.5%
IB-IIB	HR 1.03 (0.75–1.40)		HR 1.18 (0.89–1.55)	
IB	NA		HR 0.89 (0.48–1.65)	
IIA	NA		HR 1.21 (0.59–2.49)	
IIB	NA		HR 1.32 (0.93–1.88)	
Disease-free survival				
5-year (%)‡	69.3%	76.7%	56.9%	65.6%
IB-IIB	HR 1.38 (1.02–1.87)*		HR 1.35 (1.07–1.70)*	
IB	HR 1.03 (0.51–2.08)		NA	
IIA	HR 0.90 (0.50–1.62)		NA	
IIB	HR 1.90 (1.25–2.89)*		NA	

Number and percentage per column is shown

‡ Indicates the rate of possible surgery cases. Surgery was impossible in the cases with inadequate efficacy of neoadjuvant chemotherapy or intraoperative unresectable disease

$ Indicates the rate of required adjuvant therapy after RH

Only grade 3–4 toxicities

* $P < 0.05$

$ Kenter's study investigated the uterus-vagina-vulva complications

‡ Whole cohort

§ carboplatin and paclitaxel

**Cisplatin alone, cisplatin + paclitaxel, cisplatin + paclitaxel + irinotecan, and cisplatin and others

SCC, squamous cell carcinoma; *ADC*, adenocarcinoma; *ADS*, adenosquamous carcinoma; *FIGO*, the 2018 International Federation of Gynecology and Obstetrics; *HR*, hazard ratio with 95% confidence interval; *NA*, not available; *NACT*, neoadjuvant chemotherapy; *RCT*, randomized controlled trial; *RH*, radical hysterectomy

in patients with stage IIB cervical cancer has been published. To overcome this issue, an open-labeled phase III RCT (SYSGO002) comparing NACT + RH with platinum-based CCRT in patients with stage IIB cervical cancer is currently ongoing [71].

Systematic Review of NACT + RH

To identify other RCTs evaluating NACT + RH, we performed a systematic search and meta-analysis for determining the impact of NACT + RH compared with CCRT on LACC. We also conducted a systematic search of articles published until July 31, 2019, with some modifications of our study [72]. We searched three publicly available searching engines, PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), using various keywords associated with this topic, and confirmed that the only currently available RCTs were the studies by Gupta et al. and Kenter et al. [32••, 33••].

The meta-analysis and production of all graphics were performed using Cochrane Collaboration's RevMan 5.3 software [73]. For consistency, data from all outcomes (continuous and bivariate) were entered into RevMan 5.3 in such a way that negative effect sizes or relative risks less than one favored active intervention. Some missing values were estimated by RevMan 5.3, using the available data of HR, 95% CI, and *P* value. All statistical analyses were based on a two-sided hypothesis, and a *P* value < 0.05 was considered statistically significant. All analyses were performed using Statistical Package for Social Sciences software (version 25.0, IBM Corp., Armonk, NY, USA).

The results of our meta-analysis are shown in Figs. 1 and 2. There is no heterogeneity between these studies ($I^2 = 0\%$). Our meta-analysis revealed no significant difference in OS (HR 1.11, 95% CI 0.90–1.36, $P = 0.34$), but a significantly shorter DFS with NACT + RH than with CCRT (HR 1.36, 95% CI 1.13–1.64, $P = 0.001$). As shown in Fig. 2, our subanalysis found no significant differences in OS and DFS between NACT + RH and CCRT among patients with stage IB3 and IIA cervical cancer. However, DFS was significantly worse with NACT + RH than with CCRT among patients with stage IIB cervical cancer (HR 1.90, 95% CI 1.25–2.89, $P = 0.04$).

Based on these results, CCRT appears to be the best treatment approach for stage IIB cervical cancer. However, considering the pitfalls in the clinical diagnosis of stage IIB cervical cancer, which will be discussed below, there is no clear consensus on the optimal treatment for clinically diagnosed stage IIB cervical cancer.

Accuracy of the Clinical Diagnosis of Stage IIB Cervical Cancer

The accuracy rate of the preoperative diagnosis of parametrial involvement has been reported to be approximately 50% [27•, 74]. This implies that approximately 50% of all clinically diagnosed cases of stage IIB cervical

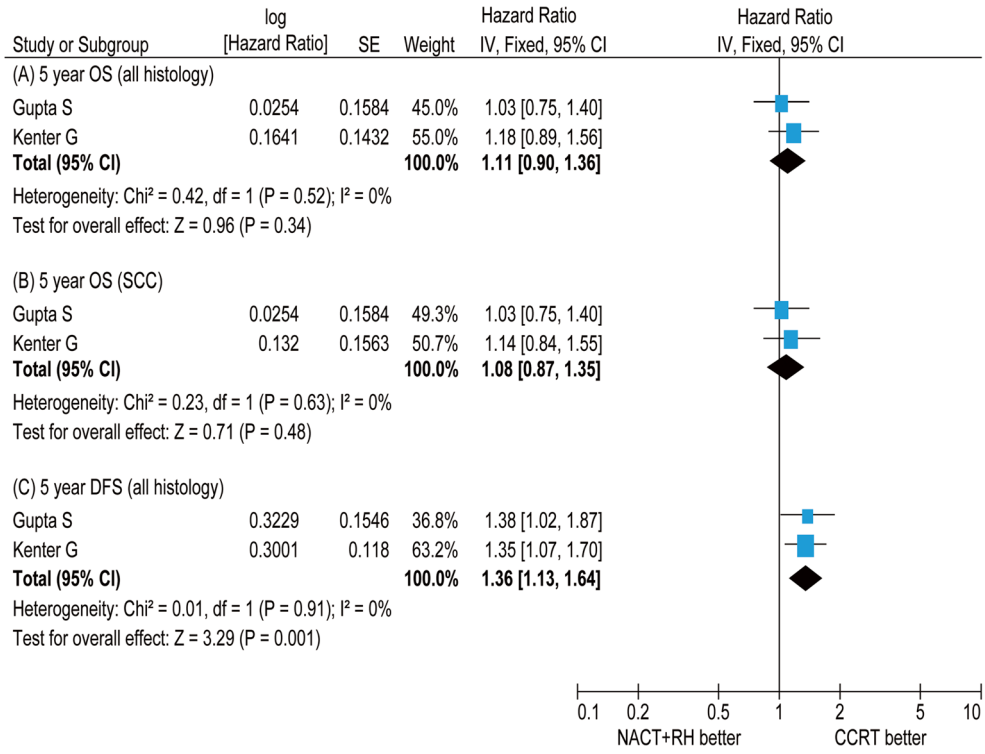

Fig. 1 Forest plots for NACT + RH versus chemoradiotherapy. Forest plots for OS (**A**), for OS (SCC) (**B**), and for DFS (**C**). NACT + RH showed significantly lower DFS and non-significant lower OS compared to chemoradiotherapy alone. I^2 was 0% in both studies; thus, a fixed analysis was performed. Abbreviations; NACT, neoadjuvant chemotherapy, RH, radical hysterectomy; OS, overall survival; DFS, disease-free survival. Some values listed above might be slightly different from the original values because of calculating by Revman 5.3

cancer are overdiagnosed cases. To improve the accuracy of the diagnosis, various studies have been published. Magnetic resonance imaging (MRI) is considered effective for improving diagnostic accuracy in select cases. The positive predictive value of MRI for the assessment of parametrial involvement has been reported to be approximately 80–90% [75, 76]. The negative-predictive value of MRI for the exclusion of parametrial invasion has been reported to be 94%; thus, it is important to accurately select patients who are suitable candidates for RH [77].

Transrectal ultrasonography (TRUS) has been reported to be a useful tool for the assessment of parametrial invasion. A previous study involving 95 patients with cervical cancer showed that the positive predictive value of parametrial invasion detection by TRUS was 98.9% and the negative predictive value was 83.3% [78]. We consider that these tools might be beneficial for identifying stage IIB cases that are clinically suspected but not pathologically confirmed.

In settings where appropriate imaging is available, patients with clinical stage IIB cervical cancer (< 4 cm) are good candidates for preoperative assessment by MRI or TRUS if pathological IB1–2 cervical cancer is indicated, and more than half of patients are able to avoid RT [44, 79]. If a patient wants to avoid RT owing to concerns regarding long-term side effects (ovarian conservation, sexual dysfunction, etc.), an accurate diagnosis is essential. Sexual dysfunction has been reported to be less in patients treated with RH and lymph node dissection than in those treated with RT [23, 80]. Therefore, MRI or TRUS might be considered in selected patients with clinical stage IIB cervical cancer.

NACT + RH for Stage IIB Cervical Adenocarcinoma

The two key RCTs, which compared OS and DFS between NACT + RH and CCRT, had similar study designs, but there were differences in the included histological types. All cases were SCC in the study by Gupta et al., whereas the cases were SCC, ADC, and adenosquamous carcinoma in the study by Kenter et al. As presented in Fig. 2, the NACT + RH group ($n = 31$) showed no significant OS when compared with the finding in the CCRT group ($n = 35$; HR 2.03, 95% CI 0.90–4.57) [33••]. As subanalysis of each stage of ADC was not performed, we could not investigate stage IIB cervical adenocarcinoma from the data in these two recent RCTs.

A 2013 Cochrane review identified a preference for primary surgery in the treatment of early-stage ADC when surgery was compared with RT or CCRT [81]. The authors could find only one RCT from 1997, and they investigated OS and DFS. The RCT involved 343 patients with stage IB1–IIA2 cervical cancer (14% ADC) who were randomly assigned to primary surgery or conventional RT [44]. In the subanalysis of ADC, there was a significant advantage for patients who underwent surgery compared with those who underwent conventional RT in terms of 5-year OS (70% vs. 59%, $P = 0.05$) and DFS (66% vs. 47%, $P = 0.02$). However, surgery was not compared with CCRT, and the subanalysis of stage IIB cervical adenocarcinoma was not performed in this study.

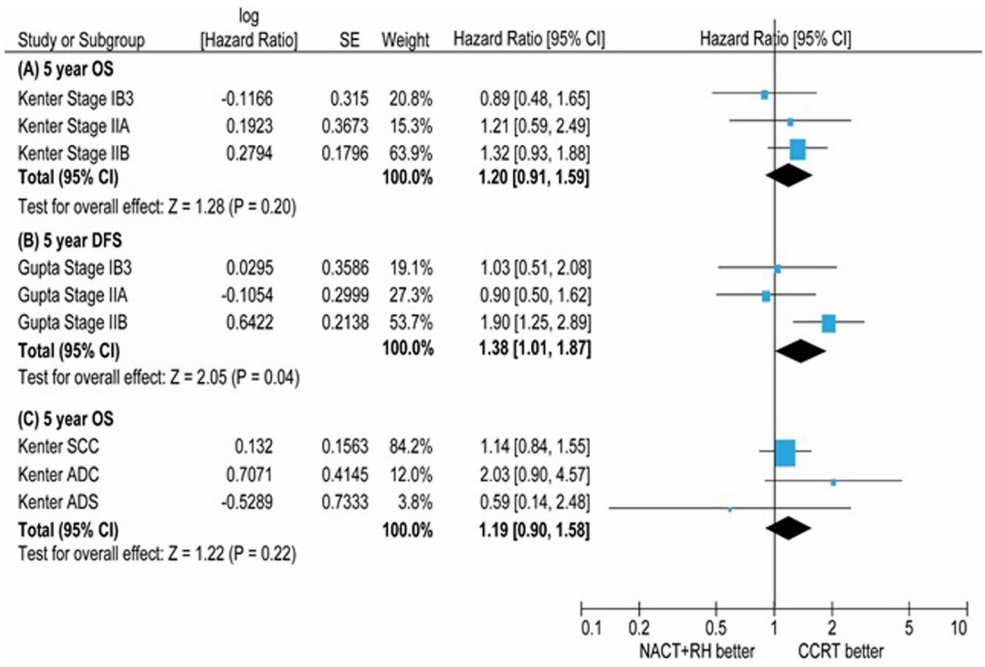

Fig. 2 Subanalysis of the OS and DFS from the NACT + RH versus CCRT trials. Stage-specific subanalyses for OS (**A**), for DFS (**B**), and for OS stratified for histology (**C**). A significantly worse DFS was observed for stage IIB cervical cancer for the NACT + RH group (**B**). NACT, neoadjuvant chemotherapy; RH, radical hysterectomy; OS, overall survival; DFS, disease-free survival; SCC, squamous cell carcinoma; ADC, advanced cervical adenocarcinoma; ADS, adenosquamous carcinoma. Some values listed above might be slightly different form original values because of calculating by Revman 5.3

Chemotherapy Regimen for NACT

Although various studies have been reported regarding the performance of NACT prior to surgery for stage IB3–IIB cervical cancer [82], the ideal regimen, dosage, and number of courses remain unclear. A previous report showed that NACT yields CR and PR rates ranging from approximately 10–20% and 10–40%, respectively [83, 84]. However, in about 10% of patients, there was an insufficient response to chemotherapy, resulting in a delay in the administration of effective local therapy.

In order to evaluate various NACT regimens utilized in conjunction with RH, we performed a systematic literature review on studies published during the previous 5 years (August 1, 2014 to July 31, 2019), wherein NACT was performed prior to surgery. This approach was compared with RH alone for LACC (stage IB–IIB). We selected studies that included more than 50 cases in the NACT group, and the efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [85]. We identified seven studies and summarized the chemotherapy regimen and response rates in Table 4 [29, 86–91]. Platinum-based chemotherapy was administered in all of these studies. Multiple other chemotherapeutic agents, including irinotecan, paclitaxel, and docetaxel, were used with cisplatin or carboplatin. Of the seven studies, one involved one to 2 cycles, three involved one to 3 cycles, two involved two to 3 cycles, and one involved 3 cycles before the surgery. CR rate was approximately 1.9–27.8%, and PR rate was approximately 58.3–83.0%. Progressive disease was noted in 1.4–6.5% of cases. The efficacy appeared to be similar among the regimens.

Treatment for Cervical Adenocarcinoma

Compared with SCC, ADC is associated with a worse prognosis [92, 93], a greater distant metastasis rate [93, 94], and a higher resistance to RT [95]. Thus, surgery is preferred to CCRT in patients with cervical ADC, particularly in those with node-negative cervical disease, unless NACT is warranted to permit less difficult surgical resection. Therefore, it is imperative to determine whether NACT is effective in cases of ADC. On the other hand, chemosensitivity difference between ADC and SCC is controversial as only limited studies are available on this topic.

A 2014 meta-analysis analyzed the impact of NACT on clinical outcomes in patients with various histological types of advanced cervical cancer [96]. They examined 11 studies (two RCTs and nine observational studies) that investigated OS and the response rate to chemotherapy in patients who received NACT+RH to determine whether the efficacy of

Table 4 NACT regimens reported in previous studies

Author	Year	No.	Study design	FIGO stage	Histology	Regimen	Interval (weeks)	Cycles	Operable cases	CR + PR	PD
He [29]	2018	61	NACT (IAI) + RH vs	IB3, IIA2	SCC, ADC, ADS	T + P (IAI)	2	1–3	61/61 (100%)	56/61 (91.8%)	0/61 (0%)
			NACT (IV) + RH			T + C (IV)	3–4	1–3			
Shimada [99]	2016	52	NACT + RH	IB3-IIB	ADC, ADS, Other	D + C	3	1–3	50/52 (96.2%)	36/52 (69.2%)	1/52 (1.9%)
Yang [87]	2016	109	NACT (IP or TP)	IB3-IIB	SCC, ADC, ADS	I + P	3	1–2	107/109 (98.2%)	33/49 (67.3%)	0/49 (0%)
			+ RH vs RH			T + P	3	1–2		45/58 (77.6%)	0/49 (0%)
Li [88]	2015	72	NACT + RH vs RH	IB3-IIB	SCC, ADC, ADS	L + P	3	2–3	NA	62/72 (86.1%)	1/72 (1.4%)
Scandurra [89]	2015	152	NACT + RH	IB3-IVA	SCC, ADC	If + T + P	3	1–3	139/152 (91.4%)	128/152 (84.2%)	3/152 (2.0%)
Gui [90]	2014	211	NACT (IAI) + RH vs	IB3-IIB	SCC, ADC	5-FU + P (IAI)	3	3	96/118 (81.4%)	104/118 (88.1%)	5/118 (4.2%)
			NACT (IV) + RH			5-FU + P (IV)	3	3	72/93 (77.4%)	79/93 (84.9%)	6/93 (6.5%)
Liu [91]	2014	103	NACT + RH vs RH	IB3IIA2	SCC, ADC	5-F + P	3	2–3	98/103 (95.1%)	63/103 (61.2%)	0/103 (0%)

5-FU, 5-fluorouracil; *B*, bleomycin; *C*, carboplatin; *T*, paclitaxel; *P*, cisplatin; *I*, irinotecan; *If*, ifosfamide; *M*, mitomycin; *V*, vincristine. *SCC*, squamous cell carcinoma; *ADC*, adenocarcinoma; *ADS*, adenosquamous carcinoma; *NACT*, neoadjuvant chemotherapy; *RH*, radical hysterectomy *FIGO*, International Federation of Gynecology and Obstetrics; *IV*, intravenous; *IAI*, intra-arterial injection; *NA*, not available; *No.*, number; *N.S.*, not significant; *P CR*, complete response; *R*, partial response; *RCT*, randomized controlled trial

NACT varies among cervical cancer types. These studies involved cases of SCC and non-SCC, including ADC and adenosquamous carcinoma. The 5-year OS was significantly better in patients with SCC than in those with non-SCC (HR 1.47, 95% CI 1.06–2.06). This meta-analysis suggested that ADC is less chemosensitive than SCC.

Our nation-wide retrospective cohort study determined the efficacy of NACT for various histological types of LACC [13]. We divided the patients into SCC and non-SCC groups and further subdivided them into taxane/platinum NACT and non-taxane/platinum NACT groups. Among women who received NACT + RH, DFS tended to be worse in those from the non-SCC group than in those from the SCC group. This included both the taxane/platinum NACT group (HR 1.44, 95% CI 0.90–2.30, $P = 0.12$) and the non-taxane/platinum NACT group (HR 1.38, 95% CI 0.93–2.04, $P = 0.11$). Based on these results, we consider that the ideal chemotherapy regimen for ADC is yet to be determined and that the prognosis should be recognized as being worse in patients with ADC than in those with SCC.

Discussion

Based on our literature review, we consider that the recommended treatment for stage IIB cervical cancer is CCRT. Although no significant difference was observed in OS [32••, 33••], it appears that DFS is better with CCRT than with NACT + RH in patients with stage IIB cervical cancer [32••]. Our review also found that a RCT comparing NACT + RH with CCRT focused specifically on stage IIB has not been published. Moreover, only limited information on stage IIB ADC is available. Thus, further studies are required in this area.

When selecting a treatment for stage IIB cervical cancer, clinicians should consider several possible pitfalls. First, the clinical diagnosis of parametrial involvement is difficult, and the addition of MRI or TRUS may be helpful. Overdiagnosis of stage IB1–2 might lead to overtreatment with CCRT. Second, there is a lack of well-designed studies focused on stage IIB ADC. Based on the current evidence, CCRT is recommended for this disease; however, it is essential to take into consideration the poor sensitivity of ADC to RT [44, 47]. It would be of clinical interest to conduct a study comparing NACT + RH with primary CCRT for patients with stage IIB ADC.

Unlike the negative outcomes of NACT + RH observed in patients with stage IIB cervical cancer, we consider those with stage IB3 or IIA cervical cancer to be good candidates for NACT + RH, as a subanalysis of two RCTs showed comparable outcomes [32••, 33••]. Although OS and DFS did not significantly change between the NACT + RH and CCRT groups in the two RCTs, NACT therapy decreased the need for adjuvant RT [63]. A meta-analysis investigated the efficacy of NACT + RH for stage IB–IIA cervical cancer and found that the need for adjuvant RT was lower in the NACT + RH group than in the RH alone group (34% vs. 53%; OR 0.57, 95% CI 0.33–0.98) [63, 83, 97].

Conclusion

Although there is a possibility that NACT + RH is superior to CCRT for the treatment of LACC, recent studies have failed to demonstrate this hypothesis. Based on the current level I evidence, primary CCRT is recommended for the treatment of stage IIB cervical cancer. The ideal chemotherapy regimen (NACT or CCRT) for improving survival in patients with LACC is yet to be determined.

Funding Information This study is supported by Ensign Endowment for Gynecologic Cancer Research (K.M.).

Compliance with Ethical Standards

Conflict of Interest Shinya Matsuzaki has received research funding from MSD.

Maximilian Klar has served on advisory boards for Tesaro and GlaxoSmithKline.

Mikio Mikami declares that he has no conflict of interest.

Muneaki Shimada declares that he has no conflict of interest.

Brendan H. Grubbs declares that he has no conflict of interest.

Keiichi Fujiwara has received research funding from Kaken, Shionogi, AstraZeneca, Pfizer, Eisai, MSD, Taiho Oncology, Zeria, Chugai, GlaxoSmithKline, Eli Lilly, ImmunoGen, OncoTherapy Science, Regeneron, and Genmab; and has received compensation from AstraZeneca, Pfizer, Eisai, MSD, Taiho Oncology, Zeria, Chugai, Nihon Kayaku, Novartis, Kyowa Hakko Kirin, Janssen, Daiichi Sankyo, Mochida, and Genmab for service as a consultant.

Lynda D. Roman has received compensation from Tempus and Quantgene for service as a consultant.

Koji Matsuo has received honoraria from Chugai; a textbook editorial expense from Springer; and reimbursement for investigator meeting attendance expenses from VBL Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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