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Evidence Mapping of Immunotherapy in the Treatment of Locally Advanced Cervical Cancer

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ADMINISTRATIVE INFORMATION

Support - MSD China.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - Yirong Yin, Binqi Zhang and Liang Ding are employed by MSD China. Other authors have no conflicts of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 July 2026 and was last updated on 23 July 2026.

INTRODUCTION

Review question / Objective The purpose of this study is as follows:
1.To systematically identify, map and characterize prospective clinical studies evaluating immunotherapy (IO) in patients with locally advanced cervical cancer (LACC) by patient population, intervention strategy, study design and outcome classification.
2. To describe and classify immunotherapy intervention strategies used in LACC, focusing on the integration of immunotherapy into chemoradiotherapy-based or surgery-based treatments, with respect to timing, sequencing and duration.
3. To map immunotherapy strategies across different LACC patient subgroups, such as disease stage, biomarkers, and other study-defined features.
4. To visualize immunotherapy trials for LACC according to the direction of efficacy results (favors intervention arm, no difference, favors control arm, or inconclusive), stratified by study phase.
5. To identify evidence gaps and unmet research needs in immunotherapy for LACC and to inform future research directions, with particular attention to underexplored clinical areas (e.g., fertility preservation) and considerations relevant to clinical practice in China.

Background China bears the heaviest global burden of cervical cancer, with 151,000 new cases and 56,000 deaths annually[1]. Locally advanced cervical cancer (LACC; FIGO 2018 IB3–IVA) accounts for 67.7 % of cases in clinical practice in China[2]—almost double the worldwide median of 37%[3]. LACC is associated with 5-year overall survival rates of only 24–76 % with traditional treatment modalities, and the prognosis worsens markedly as the disease progresses[4].
Concurrent chemoradiotherapy (CCRT) remains the guideline-recommended cornerstone of treatment for most patients with LACC. However, in real-world clinical practice in China, adherence to guideline-recommended CCRT remains suboptimal. This gap stems from limited radiotherapy access, institutional variability, and

provider/patient preferences, leading many patients to receive surgery-based regimens. In a national physician survey, surgery-based regimens were reported to be used in 67.1%, 42.0%, and 26.6% of patients with FIGO 2018 stage IB3–IIA2, IIB, and III–IVA disease, respectively in China[2].

LACC primarily driven by persistent high-risk HPV infection, exhibits an immunosuppressive tumor microenvironment (TME) characterized by PD-L1 overexpression and impaired T-cell activity. Immunotherapy (predominantly anti-PD-1/PD-L1 checkpoint inhibitors) exerts antitumor effects by reversing T-cell suppression and activating systemic immune responses. Radiotherapy and chemotherapy both create a favorable milieu for PD-1/PD-L1 blockade. For surgery, neoadjuvant ICIs aim to eradicate micrometastases early and prime systemic immunity, though this remains investigational.

The KEYNOTE-A18 trial established pembrolizumab plus CCRT as a new standard of care for high-risk LACC[5]. In China, domestic immunotherapeutic agents are also being actively explored. A randomized controlled trial demonstrated that adding tislelizumab to CCRT significantly increased the complete response rate from 19.2% to 44.4% (P=0.035), with an objective response rate of 100%[6]. Real-world studies of camrelizumab or sintilimab plus CCRT confirm favorable efficacy and manageable safety[7].

Chinese researchers have shown strong interest in immunotherapy integrated into surgery-based treatment pathways for LACC. Several trials have reported encouraging results. The NACI study (camrelizumab-based immunotherapy plus chemotherapy) achieved an objective response rate of 98% and a pathological complete response (pCR) rate of 38%[8]. The NATIC trial (tislelizumab-based immunotherapy plus chemotherapy) reported a pCR rate of 66.7% and an 18-month disease-free survival rate of 90.0%[9]. The NICE-CC trial is investigating bispecific antibodies (iparomlimab and tuvonralimab)[10]; a case report showed pCR in a PD-L1-negative patient[11].

Collectively, existing studies provide important insights into immunotherapy strategies for LACC. However, evidence generated from heterogeneous study designs and treatment paradigms has not been systematically synthesized. Rapidly accumulating data have made the evidence base increasingly diverse and, in some areas, inconsistent.

A key unresolved issue is how distinct patient populations should be aligned with different immunotherapy strategies, such as IO+CCRT versus IO+surgery. Uncertainty remains regarding how disease stage, nodal status, tumor burden, and biomarker profiles should inform selection between different approaches.

Additional uncertainties relate to the optimal timing, sequencing, and duration of immunotherapy within multimodal treatment pathways. Investigated strategies include neoadjuvant, concurrent, and maintenance immunotherapy added to definitive treatment. Reported maintenance durations vary widely across studies (e.g., 1 or 2 years)—with limited evidence to guide optimal treatment length. Differences among immunotherapeutic agents and their integration with chemoradiotherapy-based or surgery-based backbones further add to this complexity.

Given the substantial heterogeneity across study populations, interventions, study designs, endpoints, and follow-up, direct comparison or pooling of treatment efficacy is inherently limited and may introduce bias. Accordingly, this evidence synthesis adopts a descriptive mapping approach to systematically characterize differences across studies, identify where evidence is robust or exploratory, and clarify the applicability of immunotherapy strategies to specific patient populations and treatment pathways. This approach aims to support clinical decision-making and highlight critical research gaps, with particular relevance to the Chinese clinical context.

Rationale High disease burden, together with rapidly evolving yet heterogeneous immunotherapy (IO) evidence in LACC, and complex multimodal treatment decision-making—particularly within the Chinese clinical context where both CCRT and surgery-based pathways are used, has created substantial uncertainty for physicians in translating emerging data into a coherent and actionable clinical decision framework, while potentially contributing to suboptimal patient outcomes in routine practice.

This evidence mapping focuses on LACC (primarily FIGO 2018 stage IB3–IVA). Capturing the full LACC stage range and stage-restricted subgroups enables structured characterization of how immunotherapy strategies have been investigated across clinically relevant scenarios.

Given the heterogeneity in study design, treatment backbones, and outcome reporting, conventional quantitative synthesis is not appropriate and may risk misleading interpretation. Accordingly, this study adopts a descriptive evidence mapping approach to systematically characterize and compare immunotherapy intervention strategies with respect to treatment backbone, timing, sequencing, and duration. By organizing the evidence using structured tables and visual mapping techniques, this study aims to clarify the

current landscape, distinguish mature from exploratory evidence, classify outcomes based on primary efficacy results, and identify key knowledge gaps to inform future research and clinical decision-making, with particular relevance to China. Furthermore, the data will provide inputs to the medical strategy for the implementation of KEYNOTE-A18.

METHODS

Strategy of data synthesis For published studies and conference abstracts, searches will be conducted in three English-language databases (Medline via PubMed, EMBASE, and the Cochrane Library) and two Chinese-language databases (CNKI and VIP). The database search will be limited to studies published within the predefined time frame (e.g. 2016–2026). In addition, a targeted search of major clinical trial registries will be conducted to identify ongoing, completed, and unpublished trials, including ClinicalTrials.gov and Chinese Clinical Trial Registry (ChiCTR). Additional relevant studies may be identified through expert input to supplement these searches, particularly for recently reported data not yet indexed in databases or registries.

An example of the preliminary search strategy for one database (PubMed) is provided below.

#1. "Uterine Cervical Neoplasms"[Mesh] OR ((cervicis[tw] OR cervical[tw] OR cervix[tw]) AND (Carcinoma*[tw] OR cancer*[tw] OR adenocarcinoma*[tw] OR neoplasm*[tw] OR malignan*[tw] OR tumor*[tw] OR tumour*[tw]))

#2. locally advanced[tw] OR locoregional advanced[tw] OR locoregionally advanced[tw] OR "stage IB2"[tw] OR "stage IB3"[tw] OR "stage II"[tw] OR "stage IIA"[tw] OR "stage IIB"[tw] OR "stage III"[tw] OR "stage IIIA"[tw] OR "stage IIIB"[tw] OR "stage IIIC"[tw] OR "stage IVA"[tw]

#3. #1 AND (#2 OR LACC[tw])

#4. "Immunotherapy"[Mesh] OR Immunotherap*[tw] OR immunolog* therap*[tw] OR "CAR T-Cell Therap*"[tw] OR immune checkpoint inhibitor*[tw] OR ICIs[tw] OR ICI[tw] OR immune checkpoint blockade*[tw] OR immunocheckpoint inhibitor*[tw] OR immunocheckpoint blockade*[tw] OR immune suppressor*[tw] OR immune checkpoint suppressor*[tw] OR check-point inhibitor*[tw] OR CPIs[tw] OR CPI[tw] OR "Programmed Cell Death 1 Receptor"[Mesh] OR "Programmed Cell Death 1 Ligand 2 Protein"[Mesh] OR "B7-H1 Antigen"[Mesh] OR "programmed cell death protein-1"[tw] OR "programmed cell death-ligand 1"[tw] OR "PD-1"[tw] OR "PD-L1"[tw] OR "PD1"[tw] OR "PDL1"[tw] OR "Nivolumab"[Mesh] OR Nivolumab[tw] OR Opdivo[tw] OR "ONO-4538"[tw] OR ONO4538[tw] OR "MDX-1106"[tw] OR MDX1106[tw] OR "BMS-936558"[tw] OR BMS936558[tw] OR "atezolizumab" [Supplementary Concept] OR atezolizumab[tw] OR "anti-PDL1"[tw] OR MPDL3280A[tw] OR "MPDL-3280A"[tw] OR Tecentriq[tw] OR "RG-7446"[tw] OR RG7446[tw] OR "camrelizumab" [Supplementary Concept] OR camrelizumab[tw] OR "SHR-1210"[tw] OR SHR1210[tw] OR "sintilimab" [Supplementary Concept] OR sintilimab[tw] OR IBI308[tw] OR "pembrolizumab" [Supplementary Concept] OR pembrolizumab[tw] OR "SCH-900475"[tw] OR Keytruda[tw] OR "MK-3475"[tw] OR lambrolizumab[tw] OR mk3475[tw] OR tislelizumab[tw] OR "bgb a317"[tw] OR bgba317[tw] OR "toripalimab" [Supplementary Concept] OR toripalimab[tw] OR "js 001"[tw] OR js001[tw] OR "cemiplimab" [Supplementary Concept] OR cemiplimab[tw] OR REGN2810[tw] OR "cemiplimab rwlc"[tw] OR libtayo[tw] OR "avelumab" [Supplementary Concept] OR avelumab[tw] OR MSB0010682[tw] OR bavencio[tw] OR MSB0010718C[tw] OR "MSB-0010718C"[tw] OR "durvalumab" [Supplementary Concept] OR durvalumab[tw] OR "MEDI-4736"[tw] OR MEDI4736[tw] OR Imfinzi[tw] OR Envafolimab[tw] OR kn035[tw] OR Sugemalimab[tw] OR "cs 1001"[tw] OR cs1001[tw] OR GB226[tw] OR "GLS-010"[tw] OR Penpulimab[tw] OR "ak 105"[tw] OR Rosnilimab[tw] OR "anb 030"[tw] OR ANB030[tw] OR GenSci120[tw] OR Adebrelimab[tw] OR Cosibelimab[tw] OR "ck 301"[tw] OR unloxcyt[tw] OR Nofazinlimab[tw] OR "cs 1003"[tw] OR "MAX-10181"[tw] OR BAT7104[tw] OR HLX43[tw] OR "SHR-1701"[tw] OR PM8002[tw]

#5. "CTLA-4 Antigen"[Mesh] OR "cytotoxic T lymphocyte-associated protein-4"[tw] OR "CTLA-4"[tw] OR CTLA4[tw] OR CD152[tw] OR "Ipilimumab"[Mesh] OR Ipilimumab[tw] OR Yervoy[tw] OR "MDX 010"[tw] OR MDX010[tw] OR "MDX-CTLA-4"[tw] OR "tremelimumab" [Supplementary Concept] OR tremelimumab[tw] OR ticilimumab[tw] OR "CP 675"[tw] OR CP675[tw] OR "CP-675206"[tw] OR CP675206[tw] OR BAT4706[tw] OR Erfonrilimab[tw] OR KN046[tw] OR "Iparomlimab-Tuvonralimab"[tw] OR QL1706[tw] OR Cadonilimab[tw] OR AK104[tw] OR "ak 104"[tw] OR Volrustomig[tw] OR "medi 5752"[tw] OR MEDI5752[tw]

#3 AND (#4 OR #5) AND ("2016/01/01"[Date - Publication] : "3000"[Date - Publication]).

Eligibility criteria Population: Adult patients with locally advanced cervical cancer (LACC) are included, defined as FIGO 2018 stage IB3–IVA, FIGO 2014 or 2009 stage IB2–IVA, or equivalent stages from other or unspecified FIGO

classification systems. For studies without explicit FIGO version or staging, eligibility will be determined based on reported patient characteristics. (Note: Studies covering the entire stage range or only a subset (e.g., stage III–IVA only) are both eligible for inclusion.)
Interventions: Studies evaluating immunotherapy as part of an interventional treatment strategy for LACC.
Immunotherapy is defined as immune checkpoint inhibitors (PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, dual-pathway agents, etc.) or other immunotherapeutic approaches. (Note: Studies evaluating immunotherapy as neoadjuvant / induction, concurrent, adjuvant / maintenance / consolidation were all eligible for inclusion.)
Comparisons: No limitation, single-arm studies can be included.
Outcomes: The primary endpoint(s) of the studies must evaluate at least one of the following efficacy endpoints:
Response Endpoints:
(1)Objective response rate (ORR);
(2)Pathological complete response (pCR);
(3)Complete response (CR);
Survival Endpoints:
(4)Progression-free survival (PFS);
(5)Disease-free survival (DFS);
(6)Event-free survival (EFS);
(7)Overall survival (OS);
Local-related Endpoints: including locoregional recurrence-free survival (LRFS), local/locoregional control rate, local progression/recurrence/failure events, time to local recurrence;
Distant-related Endpoints: including metastasis-free survival (MFS/DMFS), distant progression/ metastasis/failure events, time to distant metastasis
Study Design: Prospective trials from published articles, conference abstracts and clinical trial registries: Randomized controlled trials, non-randomized comparative studies, single-arm phase I–III interventional trials.
Time: Studies published or publicly reported within the last 10 years (2016–2026), regardless of trial completion status.

Source of evidence screening and selection Two independent reviewers will screen studies by reading titles and abstracts (or registry/conference records where applicable) of the search results as 1st level screening. All potentially relevant citations will be requested and inspected in detail using the full-text version as 2nd level screening. Disagreements between reviewers will be resolved by discussion, with assistance from a third party if necessary. If the number of eligible trials is excessive, we will prioritize summarizing information from the most recently published, largest, and comparator-controlled trials, as they provide a higher level of evidence. This approach will ensure that our synthesis reflects the most robust and up-to-date evidence while maintaining methodological rigor and transparency throughout the selection process. Reasons for exclusion of sources of evidence that do not meet the inclusion criteria will be recorded and reported in the final review.

Data management Data management Software and Hardware: All data will be backed-up in two separate hardware to avoid data loss.
Description of Data Preparation and Methods for Data Retrieval and Collection: Data from published literature, conference abstracts, and trial registries will be used for this evidence mapping. We will manage citations using EndNote X7. For study selection, all potential publications identified from the searches will be screened using Rayyan (https://www.rayyan.ai/). The data from included studies will be accurately collected and recorded electronically, utilizing Microsoft Word and/or Excel file.
All data collected for the study should be recorded accurately, promptly, and legibly. The investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance of data has been assessed to meet the minimum requirements for all study objectives.

Language restriction English and Chinese.

Country(ies) involved China.

Keywords Locally Advanced Cervical Cancer; Immunotherapy; Evidence Mapping.

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