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Drug Discovery and Development of Recently Approved Drugs: Tisotumab Vedotin

Hongzhu Long[1, a), †], Boxuan Ma[2, *,b), †], Mingyu Shi[3, c), †] and Xuetong Zeng[4, d), †]

[1] Cheltenham Ladies' College, Bayshill Rd, Cheltenham, United Kingdom
[2] University of California, Santa Cruz, Santa Cruz, CA, United States
[3] St George's School Cologne, Duisburg, Germany
[4]Shenzhen Foreign Language School, Shenzhen, China

[a)]hongzhu.long6@outlook.com,
[b)] *bma79@ucsc.edu
[c)]Steven20031231@gmail.com,
[d)]zengxuetong9@gmail.com
[†]These authors contributed equally to this paper

Abstract. Recurrent or metastatic cervical cancer is the primary reason for dying in the female population. Although advanced research in immunization may provide a potential treatment for cervical cancer, it is still one of the usual fetal female cancers globally. Previous studies on bevacizumab and chemotherapy provided efficient treatments with a survival benefit for women, but different strategies are needed to increase the overall survival rate of this cancer. Tisotumab vedotin is an investigative and pioneering immunoglobulin-medicine combination that targets tissue factor (TF), a protein in high concentrations in various solid tumours. Tisotumab vedotin bonds to tissue factor on aimed cells and then releases monomethyl auristatin E (MMAE). In addition, Tisotumab vedotin's direct cytotoxicity may increase nearby tumour cells' spectator toxicity and various immune-linked effects. This paper will discuss previous studies on Tisotumab vedotin, and their data will be analyzed further. The improvement toward this treatment will be proposed as well. This paper aimed to establish a thorough understanding and further analysis of the previous clinical trials and findings on Tisotumab vedotin.

Keywords: Cervical Cancer, Tisotumab vedotin, clinical trials

1. Introduction

1.1. Overview of disease and the need for medication

Cervical cancer is a very common style of cancer among female population, with the highest occurrence and death rates, often affecting countries with low human development indices. HPV vaccination and screening for precancerous lesions can be very effective in helping to prevent cervical cancer. Cervical cancer is highly treatable and curable when detected in its early stages. Although largely preventable through screening and vaccination, cervical cancer remains a fatal disease and is particularly ineffective if diagnosed as advanced or recurrent cervical cancer. Once cervical cancer has

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recurred or metastasised, the cure rate becomes very low, with a five-year survival rate of 17 per cent [1].

Bevacizumab and duplex chemotherapy is used as the s general first-line therapy for repeated or metastasizing cervical cancer. But almost all patients will experience recurrence after 1L therapy. In addition, a single institution's experience shows that only 30%-70% of patients receive second-line treatment. This is because plenty of patients pass away ahead of receiving a cure [2]. Treatment visits from a single institution have shown a poor prognosis for women who relapse after platinum/bevacizumab treatment and studies have shown that retreatment with a platinum/bevacizumab regimen can only provide modest improvement [3]. Significantly higher incidences of gastrointestinal fistulas (3%) and thromboembolic events (8%) have also been reported in patients treated with bevacizumab [4]. Primary treatment exposure to radiotherapy and chemotherapy is considered to alter the biological characteristics of the disease and recurrent foci in previously irradiated areas are likely to result in limited delivery of cytotoxic drugs due to effects on blood supply and relative hypoxia.

The response rate of the existing 2L+ therapy is very low. One report shows that the response rate of bevacizumab plus chemotherapy to 2L is 0%-6%, which is because the previous inhibition of vascular endothelial growth factor may have a negative impact on the subsequent treatment response [5]. Initial treatment of cervical cancer exposed to radiotherapy and chemotherapy is considered to change the biological characteristics of the disease. Recurrent cancer foci in previously irradiated areas may affect blood provision and relative hypoxemia, which limits the distribution of cytotoxic medicine to common or metastasizing cervical cancer. The data leading to this third-line treatment are very few. About sixty per cent of patients did not receive third-line therapy, and the response rate of patients who received 3L treatment was shallow [6]. These data show that the clinical needs of this patient group have not been met, which is conducive to exploring new treatment methods.

1.2. Introduction of research drug products

Tisotumab Vedotin is the outset human immunoglobulin-drug conjugate contrary to tissue factors signalled on the cell surface that provides a toxic burden to tumour cells. Tisotumab Vedotin consists of a human monoclonal immunoglobulin G1 (subtype κ) that targets tissue factors (TF) and binds to the drug monomethyl olstatin E(MMAE) [7].

TF serves as the primary cell initiator of blood coagulation under physiologically ordinary situations. Following vascular damage, the TF: FV IIA complex initiates the thrombin cascade, which results in the deposition of fibrin and the activation of platelets. 2 TF helps promote tumour development, angiogenesis, metastasis, and thrombosis in cancer patients during carcinogenesis. In many tumours, TF expresses itself inappropriately [8]. By raising cell survival rates or by utilising tissue factor procoagulant activity and protease to trigger the receptor-2(PAR-2) signal, it may accelerate tumour development.

The immunohistochemistry average value of TF expression in cervical cancer tissues was shown to be substantially greater than that in healthy tissues next to the malignancy, according to the data analysis report. Tisotumab bedouin can effectively stop the invasion and spread of cervical cancer cells because it can target tumour cells that express tissue factors without compromising their function in coagulation.

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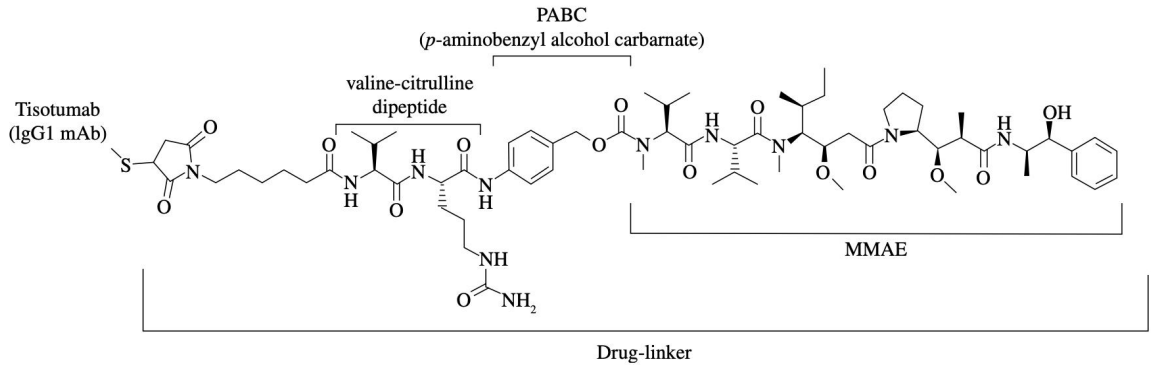


Figure 1. Chemical structure of tisotumab vedotin [7].

1.3. Mechanism of tisotumab vedotin

Tisotumab Vedotin-tftv is an autoantibodies-drug conjugate guided by tissue factor (TF-011). The antibody is a human IgG 1 against TF on the cell surface, which is a protein found on cancer cells, especially cervical cancer cells. In vitro coagulation network is mainly started by TF. Tisotumab Vedotin produces cytotoxic effects on tumours expressing TF mainly through effective binding to TF expressed on cervical tumours. Tisotumab Vedotin rapidly internalizes into tumour cells, where it undergoes lysosomal degradation, releasing a cytotoxic payload. This leads to the internalization of TF complex of antibody-drug conjugates. Once internalized, the MMAE in the drug-target complex is released by hydrolysis of protein. MMAE is a microtubule-disrupting agent that destroys the microtubule network of the active splinter cell, driving to cell cycle detention and upregulation. [9]

In vitro studies have shown that Tisotumab Vedotin can induce immune cell demise, attract immune cells, induce immune cell death, and promote tumour cell demise through Fcγ receptor-negotiated actuation function. In addition, the factor VII(FVIIa)-dependent intracellular signalling of TF activation by Tisotumab Vedotin slightly impacted procoagulant action.

1.4. Metabolism and route of elimination

Small peptides, amino acids, unbound MMAEs, and decomposition products related to unbound MMAEs were formed upon decomposition of Tisotumab Vedotin-tftv. Tisotumab Vedotin-tftv releases unbound MMAE by protein decomposition and is metabolized in vitro primarily by CYP3A4. The elimination of Tisotumab Vedotin-tftv has never been completely established. However, data show that 17% of the total dose was regained in faecal matter and 6% in urine, primarily as an unchanged drug, within one week after one amount of another antibody-drug conjugate containment MMAEs. Therefore, after the administration of Tisotumab Vedotin-tftv, the excretion of MMAE is expected to be similar [10].

2. Summary of non-clinical trials

Tisotumab vedotin therapy has resulted in effective and durable tumour regression in various solid cancer xenografts models expressing TF, including patient-derived xenografts models with heterogeneous TF expression. Effective tumour regression has also been observed in xenotransplantation models of bladder, lung, cervical, and ovarian cancer previously treated with paclitaxel. [11]

The effect of Tisotumab Vedotin on TF coagulation was evaluated. In eFax generation assays and thromboelastography studies, Tisotumab vedotin had little effect on coagulation (only 19% inhibition). The effect of high-dose treatment with the naked antibody Tisotumab on coagulation parameters in vivo was studied in cynomolgus monkeys. At a dose of 100 mg/kg, Tisotumab had no effect on coagulation parameters or functional bleeding time, and at repeated doses of 5 mg/kg had no effect on coagulation parameters in cynomolgus monkeys.[8]

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The safety profile of Tisotumab Vedotin in the cynomolgus monkey study was as expected for MMAE/tubulin disruptors. It was therefore approved for entry into clinical trials. [12]

3. Summary of clinical trials

Tisotumab vedotin is being studied in two clinical trials; GEN701 and GEN702. Each trial had two parts; I) dose escalation component and II) cohort expansion component.

GEN701: This is the first human trial of tisotumab vedotin every three weeks(1Q3W). It is indicated for ovarian, cervix, endometrial, bladder, castration-resistant prostate cancer, esophageal cancer, non-small cell lung cancer and head and neck squamous cell carcinoma.

Part I) The dose escalation part has been completed.

Part II) The expansion of GEN701 is a work in progress.

GEN702: Treatment with tisotumab vedotin was weekly for 3 weeks and then discontinued for 1 week(3Q4W). Suitable for ovarian, cervix, endometrium, bladder, castration resistance to prostate cancer, esophageal cancer and non-small cell lung cancer.

Part I) The dose escalation part has been completed.

Part II) Patients enrolled in the GEN702 expansion cohort were initially treated with a frequent regimen of tisotumab vedotin 1.2mg/kg 3Q4W, but the regimen was discontinued because of severe ocular adverse effects. Patients in GEN702 were switched to tisotumab vedotin 2.0 mg/kg 1Q3W, which was found to be potentially effective and well tolerated in GEN701. The GEN702 extension is complete.

4. Scientific summary

4.1. Pharmacodynamics

MMAE-negotiated cell cycling disruption plus death for cancer plus spectator cells as promotion for immunostimulatory cell damage are two of the avenues by which tisotumab vedotin improves tissue factor-dependent anticancer effectiveness in several preclinical studies. Additionally, tumour and bystander cell arrest and apoptosis, stimulation of immunostimulatory cellular damage, antigen-attachment fragment-negotiated suppression of PAR-2-reliant signal, and Fc kinase effector functions are also covered. Furthermore, TF-011 decreased tissue component: Following antibody attachment to cells, stimulation with FVIIa resulted in the release of IL-8 from MDA-MB-231 cells with an IC50 of one point four g/ml and ERK phosphorylation from an IC50 of 0.12 g/milliliter, indicating disruption of PAR-2 intracellular signalling [1-3]. The cytotoxic of tisotumab vedotin contrary to A431 and HPAF-II cells was dose-dependent for an EC50 of 4–10 ng/ml, but it had little impact on cell lines that did not express tissue factors. Tisotumab vedotin was not hazardous to A549 monocultures but was toxic to both TF-positive and detrimental types of cells in mixed cultures, suggesting bystander cytotoxicity. Furthermore, it was shown that co-culturing tumour cells killed by Tisotumab vedotin with heterologous normal PBMCs led to the activation of innate immune cells and T cell proliferation [2-4].

4.2. Pharmacokinetics

MMAE's pharmacokinetics are related to metabolites. The conjugated form of MMAE is metabolised mainly in vitro by CYP3A4 after being released from the conjugation by proteolytic cleavage. After only one dosage of another antibody medication cocktail, including MMAE, 17 percent and 6 per cent, respectively, of the entire given MMAE was recovered in faecal matter over a week, mainly intact. Following the injection of tisotumab vedotin, a similar MMAE excretion profile is predicted. It is uncertain what effect liver transplantation or mild, moderate, or severe liver illness will have on the pharmacokinetic contour of nivolumab vedotin or unconjugated MMAE. Similar results are predicted with concurrent use of nivolumab vedotin and these medicines. MMAE failed to substantially enhance the levels of any CYP450 enzyme in human hepatocytes during in vitro experiments or to inhibit the CYP1A2 series enzymes [5].

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4.3. Therapeutic trials

The median response duration was 8.3 months, with a consistent, verified response in situ for 62% of patients for six months or longer [12]. Patients with recurrence or advanced cervical cancer had outstanding anticancer activity in response towards first tisotumab vedotin with carboplatin and 2nd- and 3rd with pembrolizumab, according to a report of stage Ib/II Innovative 205 investigation. Patients in the initial therapy group obtained tisotumab vedotin at the advisable dose together with carboplatin AUC 5 every three weeks. Those in the 2nd or 3rd therapy group got tisotumab vedotin at the advised dose and pembrolizumab two IV once per three weeks.

In the primary-string group, patients achieved an objective action, including four complete and fourteen partial responses. Four people answered for more than eight months, with a 4.2-month average. In the dosage escalation stage of this trial, participants with tumour cells were included throughout eight dose groups using the usual 3+3 dosage escalation technique. All dose cohorts together included 11 patients with stable disease [1,6].

4.4. Adverse events

In innovaTV 204, the incidence of adverse reactions in patients treated with Tisotumab vedocin was ≥ 10%. Adverse reactions included with fatigue (50% , 7%), fever (16%, 1%), pruritus (13% all grades, 1% grade three or four), nausea(41% all grades, 0% grade three or four), diarrhoea (25% all grades, 2% grade three or four), constipation(23% all grades, 2% grade three or four), abdominal pain (23% all grades, 1% grade three or four), vomiting(17% all grades, 2% grade three or four), peripheral neuropathy (39% all grades, 7% grade three or four), alopecia(39% all grades, 0% grade three or four), rash (25% all grades, 0% grade three or four), epistaxis (39% all grades, 0% grade three or four), haemorrhage (32% all grades, 6% grade three or four) , conjunctival adverse reactions (37% all grades, 0% grade three or four), dry eye (29% all grades, 0% grade three or four), corneal adverse reactions (21% all grades, 3% grade three or four), periorbital adverse reactons (16% all grades, 0% grade three or four), myalgia (21% all grades, 0% grade three or four), arthralgia (16% all grades, 0% grade three or four), pain in limbs (13% , 1%), inappetence (16% all grades, 1% grade three or four), urinary infection (14% , 2%) and weight lose (12% all grades, 0% grade three or four). The proportion of patients with clinically relevant adverse reactions was less than 10%. These include phlebothrombosis (3%), Thrombosis-pulmonary (3%) and pneumonia (2%).[5] There were also some serious adverse effects, which 43% of patients have this condition. Common serious adverse events were intestinal obstruction (6%), hemorrhage (5%), pneumonia (4%), peripheral neuropathy (3%), septicemia (3%), astriction (3%), and fever (3%). Fatal adverse effects, such as multiple system organ failure (1%), septic shock (1%), sudden death (1%) and pneumonia (1%), occurred in 4% of patients.[5] 13% of patients accepting Tisotumab vedotin had adverse effects that led to permanent stop. Peripheral neuropathy (5%) and corneal adverse reactions (4%) were the most common adverse reactions. The remaining 47% of patients had adverse effects that led to dose interruption. Hemorrhage (4%) conjunctival adverse reactions (4%) and peripheral neuropathy (8%) were the most common adverse events. Dose reduction adverse events 23% of patients have this symptom, the most common being conjunctival adverse reactions (9%) and corneal adverse events (8%).[5] Laboratory abnormalities (≥10%) worsened from baseline in patients treated with tisotumab vedotin in innovaTV 204. Including lower hemoglobin (52% , 7%), lymphopenia (42% , 8%), leukopenia (30% all grades, 0% grade three or four) and neutropenia (21% all grades, 3% grade three or four), creatinine (29% all grades,4.1 % grade three or four), alanine aminotransferase (24% all grades, 0% grade three or four), lactate dehydrogenase (22% all grades, 0% grade three or four) and higher uric acid salt (20% all grades, 0% grade three or four), glucose decreased (19% all grades, 0% grade three or four), aspartate aminotransferase increased (18% all grades, 0% grade three or four), reduced sodium (20% all grades, 0% grade three or four), elevated alkaline phosphatase (17% all grades, 0% grade three or four), creatinine kinase increased (16% all grades, 2.1% grade three or four), magnesium reduction (17% all grades, 2.1% grade three or four), albumin is reduced (16% all grades, 0% grade three or four), The

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international standardized ratio of prothrombin was increased (26% all grades, 0% grade three or four) and the activated partial thromboplastin time was prolonged (26% all grades, 2% grade three or four.

5. Improvement and prediction

5.1. Ways that tisotumab vedotin technology can be improved

Tisotumab vedotin has been approved as an efficient drug for cervical cancer, yet there are several challenges in using this technology in therapeutic settings. The next step for researchers is to make potential advancements in Tisotumab vedotin technology, enhancing pharmacokinetics and pharmacodynamics first. Clinical pharmacology is the study of how medications interact with the body. The two main subspecialties of clinical pharmacology are pharmacokinetics and pharmacodynamics. Pharmacodynamics refers to how biological functions in the body react to or are impacted by medications, and pharmacokinetics refers to the absorption, distribution, metabolism, and excretion of drugs. In a nutshell, pharmacokinetics is the way that medications affect the body, and pharmacodynamics is how drugs affect the body.

Furthermore, tisotumab vedotin internalises target cells and releases monomethyl auristatin E when it binds to tissue factor on object cells (MMAE). Cell cycle arrest and apoptotic cell death are brought on by this microtubule-disrupting chemical. The direct cytotoxicity caused by tisotumab vedotin may be increased by the bystander cytotoxicity of surrounding tumour cells and different immune-related effects. The dosage directly relates to the increase in tisotumab vedotin and free monomethyl auristatin E exposure. While the concentration of free MMAE reaches its peak one week after the infusion, that of tisotumab vedotin reaches its peak immediately after injection. According to data from phase 2, where 102 patients were evaluated, the total response rates were 7% for complete responses and 17% for partial responses. Compared to previous treatments and data, this drug had significantly increased the survival and mitigation of cancer. In order to prove that this drug improves the overall response rate, more trials worldwide were needed. Randomized, open-label research comparing tisotumab vedotin to the researcher's choice chemotherapy in recurrent or metastatic cervical cancer is also underway, with an overall survival rate enhancement as the primary goal. Further research on novel treatment methods remains precedent.

5.2. The predicted improvement in the next 5-10 years

Tisotumab vedotin is an antibody-drug conjugate with a unique mechanism of action, which targets tissue-factor to treat cervical cancer after one or more courses of chemotherapy are performed. Various therapeutic options are open, but patients' responses and survival rates remain insufficient. There is no standard of treatment for patients who suffer disease progression while receiving platinum-based chemotherapy. Since tisotumab vedotin is the new antibody-drug conjugate for cervical cancer, it showed a novel pathway in treating cancer–tissue factors with enhanced pharmacology effect when compared to previous treatments, which have a low response and survival rates. Tisotumab vedotin displaces fair response rates and amenable toxicities and adverse effects. Tisotumab vedotin offers clinicians a suitable therapeutic option for handling cervical cancer. However, because of its clinical potential and recent clinical success in cancer immunotherapy, tisotumab vedotin is still being studied extensively in preclinical and clinical studies. Various pharmacological and formulation engineering strategies are used to reduce toxicity while maintaining or improving treatment response. Tisotumab vedotin is expected to become increasingly successful and widely used in clinical therapy.

6. Conclusion

Cervical cancer is generally a prevalent malignancy in the female population and has a high mortality rate. Cervical cancer is a terrible disease, and the prognosis is particularly poor after a diagnosis of advanced or recurrent cervical cancer, although it can be greatly avoided through screening and immunisation. If cervical cancer has recurred or metastasised, the cure rate is reduced.

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To deliver a toxic burden to tumour cells, tisotumab vedotin targets tissue factors expressed on the cell surface. TF has a role in tumour development, angiogenesis, metastasis, and thrombosis in cancer patients during tumorigenesis. By boosting cell survival or by boosting angiogenesis with the aid of tissue factor procoagulants, it might encourage tumour development. High TF expression in cervical cancer tissue may facilitate cervical cancer cell invasion and metastasis. Tissue factor-expressing tumour cells are the target of tisotumab vedotin, which does not interfere with their function in blood coagulation. The main way that tisotumab vedotin works is by successfully binding the TF expressed on cervical cancer tumours and causing cytotoxic effects on such tumours.

References

[1] McLachlan, J. *et al.* The Impact of Systemic Therapy Beyond First-line Treatment for Advanced Cervical Cancer. *Clin. Oncol.* **29**, 153–160 (2017).

[2] Hong, D. S. *et al.* Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer. *Clin. Cancer Res.* **26**, 1220–1228 (2020).

[3] Boussios, S. *et al.* Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: Where do we stand? A literature review. *Crit. Rev. Oncol. Hematol.* **108**, 164–174 (2016).

[4] Improved Survival with Bevacizumab in Advanced Cervical Cancer - PMC. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4010094/

[5] Zamorano, A. S., Wan, L., Powell, M. A. & Massad, L. S. Repeating platinum/bevacizumab in recurrent or progressive cervical cancer yields marginal survival benefits. *Gynecol. Oncol. Rep.* **22**, 48–51 (2017).

[6] Eskander, R. N. & Tewari, K. S. Targeting angiogenesis in advanced cervical cancer. *Ther. Adv. Med. Oncol.* **6**, 280–292 (2014).

[7] Seagen Inc. *A Single Arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer*. https://clinicaltrials.gov/ct2/show/NCT03438396 (2022).

[8] de Bono, J. S., Concin, N., Hong, D. S., Thistlethwaite, F. C., Machiels, J.-P., Arkenau, H.-T., Plummer, R., Jones, R. H., Nielsen, D., Windfeld, K., Ghatta, S., Slomovitz, B. M., Spicer, J. F., Yachnin, J., Ang, J. E., Mau-Sørensen, P. M., Forster, M. D., Collins, D., Dean, E., … Lassen, U. (2019). TISOTUMAB vedotin in patients with advanced or metastatic solid tumours (innovatv 201): A first-in-human, multicentre, phase 1–2 trial. *The Lancet Oncology*, *20*(3), 383–393.

[9] X, Z. *et al.* Expression of tissue factor in human cervical carcinoma tissue. *Exp. Ther. Med.* **16**, (2018).

[10] Tisotumab vedotin.*Browsing drugs: Drugbank online*. Browsing Drugs | DrugBank Online. (n.d.). Retrieved August 24, 2022, from https://go.drugbank.com/drugs

[11] Breij, E. C. W., de Goeij, B. E. C. G., Verploegen, S., Schuurhuis, D. H., Amirkhosravi, A., Francis, J., Miller, V. B., Houtkamp, M., Bleeker, W. K., Satijn, D., & Parren, P. W. H. I. (2014). An antibody–drug conjugate that targets tissue factor exhibits potent therapeutic activity against a broad range of solid tumors. *Cancer Research*, *74*(4), 1214–1226.

[12] Coleman, R. L., Lorusso, D., Gennigens, C., González-Martín, A., Randall, L., Cibula, D., Lund, B., Woelber, L., Pignata, S., Forget, F., Redondo, A., Vindeløv, S. D., Chen, M., Harris, J. R., Smith, M., Nicacio, L. V., Teng, M. S., Laenen, A., Rangwala, R., … Bhatia, S. (2021). Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovatv 204/GOG-3023/ENGOT-CX6): A multicentre, open-label, single-ARM, phase 2 study. The Lancet Oncology, 22(5), 609–619. https://doi.org/10.1016/s1470-2045(21)00056-5