

A phase 2, multicenter study to evaluate the efficacy and safety of using autologous tumor infiltrating lymphocytes (LN-145) in patients with recurrent, metastatic, or persistent cervical carcinoma

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BACKGROUND

- Cervical cancer is a leading cause of cancer-related death in women with over 12,000 new cases and 4,000 deaths in the US alone^{1,2,3}
- Advanced recurrent/persistent and metastatic forms of cervical cancer have poor outcomes with mean progression free survival (PFS) rates less than 6 months following standard platinum-based chemotherapy⁴⁻⁶
- ORR remains below 11% and PFS of 6 months of less than 24% in patients who have failed at least 1 systemic therapy for their recurrent, metastatic, or persistent cervical carcinoma⁷
- The presence of tumor-infiltrating lymphocytes (TIL) have been well documented in patients with HPV-associated cancers, including cervical carcinoma⁸, and have been positively correlated with improved patient outcomes^{9,10}
- Several early studies have demonstrated the feasibility of isolation and culture of TIL from cervical tumors^{11,12}
- A pilot study of TIL therapy in 9 patients with previously treated cervical carcinoma demonstrated an ORR of 33% that included 2 durable long-term (46 and 54 mos) responses^{8,13}
- This study was designed to evaluate the efficacy and safety of LN-145, an autologous investigational TIL therapy for the treatment of patients with recurrent, metastatic, or persistent cervical carcinoma

References

- Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J., and Jemal, A. 2015. Global cancer statistics, 2012. *CA Cancer J Clin* 65:87-108.
- Zsiros, E., Tsuji, T., and Odunsi, K. 2015. Adoptive T-cell therapy is a promising salvage approach for advanced or recurrent metastatic cervical cancer. *J Clin Oncol* 33:1521-1522.
- Tewari, K.S., and Monk, B.J. 2012. Invasive cervical cancer. In *Clinical gynecologic oncology*. P. DiSaia, and W.T. Creasman, editors. Philadelphia: Mosby.
- Long, H.J., 3rd. 2007. Management of metastatic cervical cancer: review of the literature. *J Clin Oncol* 25:2966-2974.
- Long, H.J., 3rd, Bundy, B.N., Grendys, E.C., Jr., Benda, J.A., McMeekin, D.S., Sorosky, J., Miller, D.S., Eaton, L.A., and Fiorica, J.V. 2005. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A Gynecologic Oncology Group Study. *J Clin Oncol* 23:4626-4633.
- Monk, B.J., Sill, M.W., McMeekin, D.S., Cohn, D.E., Ramondetta, L.M., Boardman, C.H., Benda, J., and Cella, D. 2009. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 27:4649-4655.
- Monk, B.J., Sill, M.W., Burger, R.A., Gray, H.J., Buekers, T.E., and Roman, L.D. 2009. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol* 27(7):1069-74.
- Stevanovic, S., Draper, L.M., Langhan, M.M., Campbell, T.E., Kwong, M.L., Wunderlich, J.R., Dudley, M.E., Yang, J.C., Sherry, R.M., Kammula, U.S., et al. 2015. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J Clin Oncol* 33:1543-1550.
- Shah, V.V., Yan, X., Jing, L., Zhou, Y., Chen, H., and Wang, Y. 2011. A reversed CD4/CD8 ratio of tumor-infiltrating lymphocytes and a high percentage of CD4(+)FOXP3(+) regulatory T cells are significantly associated with clinical outcome in squamous cell carcinoma of the cervix. *Cell Mol Immunol* 8:59-66.
- de Vos van Steenwijk, P.J., Ramwadhoebe, T.H., Goedemans, R., Doorduijn, E.M., van Ham, J.J., Gorter, A., van Hall, T., Kuijper, M.L., van Poelgeest, M.L., van der Burg, S.H., et al. 2013. Tumor-infiltrating CD14-positive myeloid cells and CD8-positive T-cells prolong survival in patients with cervical carcinoma. *Int J Cancer* 133:2884-2894.
- Ghosh, A.K., and Moore, M. 1992. Tumour-infiltrating lymphocytes in cervical carcinoma. *Eur J Cancer* 28A:1910-1916.
- Hilders, C.G., Ras, L., van Eendenburg, J.D., Nooyen, Y., and Fleuren, G.J. 1994. Isolation and characterization of tumor-infiltrating lymphocytes from cervical carcinoma. *Int J Cancer* 57:805-813.
- Stevanovic et al. 2017. Landscape of immunogenic tumor antigens in successful immunotherapy of virally induced epithelial cancer. *Science* 356:200-205.

STUDY OVERVIEW

- Phase 2, multicenter prospective, open label, interventional study was designed to evaluate adoptive cell therapy (ACT) with autologous TIL infusion (LN-145) followed by IL-2 after a non-myeloablative (NMA) lymphodepletion preparative regimen for the treatment of patients with recurrent, metastatic, or persistent cervical cancer who were unresponsive to or failing prior therapy
- All squamous cell carcinoma, adenocarcinoma, and adenosquamous pathologies will be enrolled regardless of HPV status
- Up to 40 clinical study sites globally
- The planned sample size, N = 47 treated patients
- Simon's 2-Stage design with fifteen patients included in the first stage

OBJECTIVES

Primary objective:

- To evaluate the efficacy of LN-145 in patients with recurrent, metastatic, or persistent cervical carcinoma using the objective response rate (ORR).

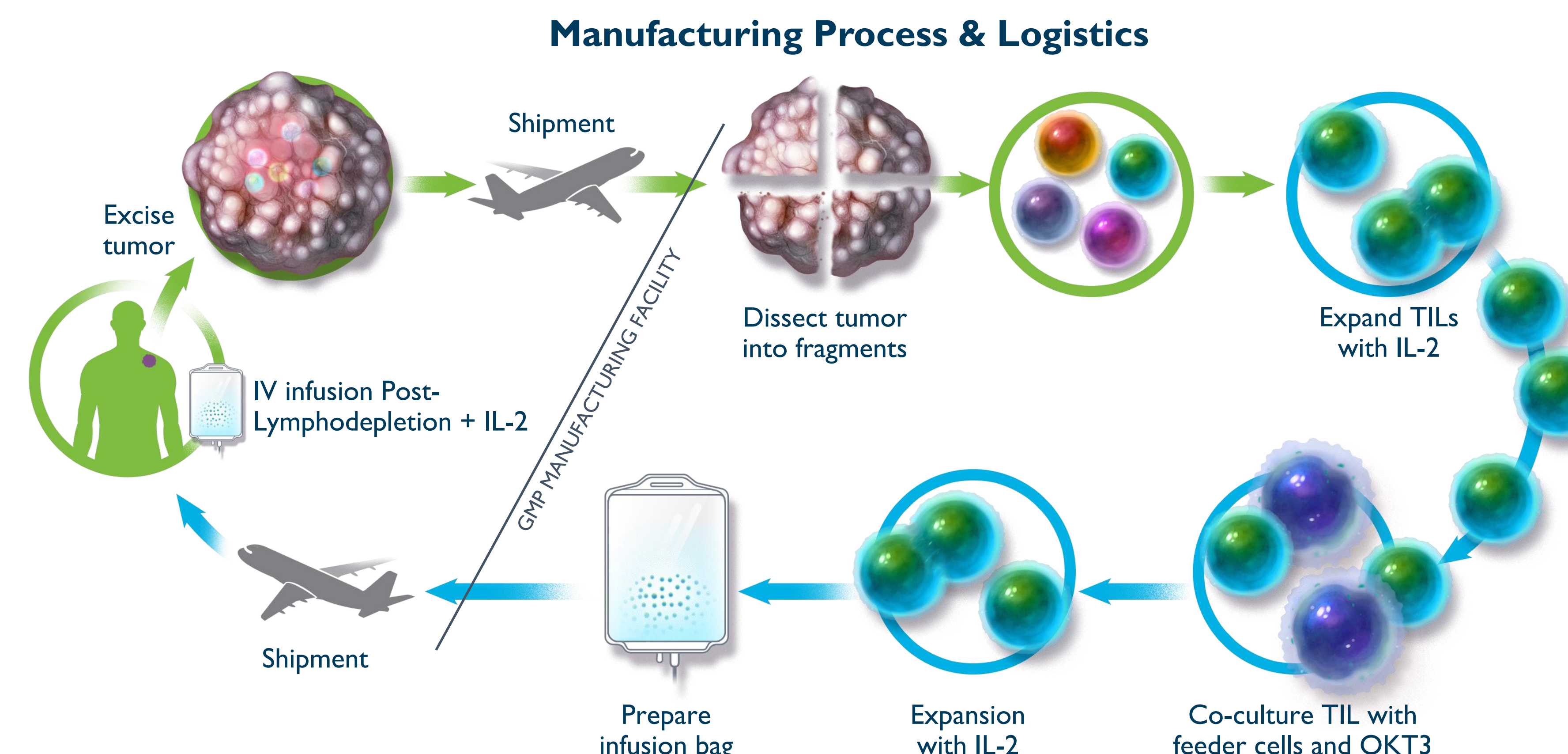
Secondary objective:

- To characterize the safety profile of LN-145 in patients with recurrent, metastatic, or persistent cervical carcinoma
- To evaluate efficacy of LN-145 in patients with recurrent, metastatic, or persistent cervical carcinoma such as complete response (CR) rate, duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS), and overall survival (OS)

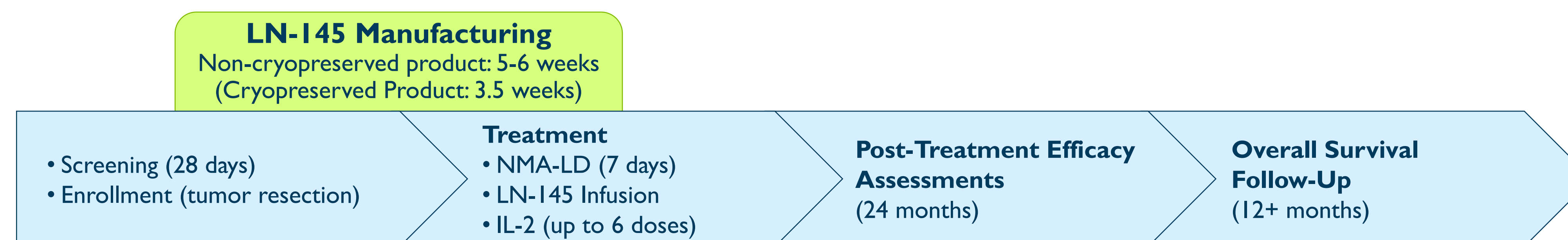
Exploratory objective:

- To explore the persistence of LN-145 and immune correlates of response, survival, toxicity of the treatment
- To explore efficacy based on immune-related RECIST (irRECIST) as assessed by independent review
- To assess health-related quality of life (HRQoL)

PROCESS, LOGISTICS & STAGES OF STUDY



Stages of Study: Linear Flow



NMA-LD: nonmyeloablative lymphodepletion, IL-2: Interleukin-2

MAJOR INCLUSION CRITERIA

- 18 years of age or older;
- Must have metastatic, recurrent, or persistent cervical carcinoma not amenable to curative surgery or radiation;
- Must have at least 1 lesion resectable for TIL generation that yields at least 1.5 cm in diameter of tissue. If previously irradiated, the irradiation must have occurred at least 3 months prior to resection;
- Must have a remaining lesion measurable as per RECIST 1.1 for response assessment. If previously irradiated, the irradiation must have occurred at least 3 months prior to enrollment (tumor resection);
- Must have received at least 1 line of prior systemic therapy for their metastatic, recurrent, or HNSCC;
- Minimum 28 day washout from last dose of tumor-directed therapy to tumor resection;
- ECOG performance status of 0 or 1;
- Adequate bone marrow, liver, and renal function;
- HIV negative;
- Negative or undetectable for Hepatitis B and Hepatitis C;
- Up to 1 year of birth control following completion of study treatment

MAJOR EXCLUSION CRITERIA

- Prior cell transfer therapy;
- Systemic steroid therapy greater than 10mg daily equivalents of prednisone;
- Greater than grade 1 prior treatment-related toxicities except for peripheral neuropathy, alopecia, or vitiligo;
- Active immunotherapy-related grade 2 diarrhea or colitis in the previous 6 months; patients may be included if asymptomatic and demonstrated uninfamed colon by colonoscopy;
- Active systemic infections, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system that, in the opinion of the investigator, would increase the risk of participation;
- Symptomatic and/or untreated brain metastases;
- Primary or acquired immunodeficiency;
- End-stage renal disease requiring dialysis;
- Left ventricular ejection fraction < 45%;
- Forced expiratory volume in one second ≤ 60% predicted;
- Primary malignancy in the previous 3 years requiring treatment in the last year; and
- Pregnant or breastfeeding.

SUMMARY

- Recurrent, metastatic, or persistent cervical carcinoma presents a high unmet medical need with low survival rates and with limited effective treatment options.
- Presence of TIL have been correlated with improved outcomes in cervical carcinoma
- TIL have demonstrated efficacy in other solid tumors including durable long-term responses following progression on checkpoint inhibitors
- Pilot data using TIL therapy for the treatment of cervical carcinoma has demonstrated the potential for long-term durable responses
- This study aims to assess the potential of TIL therapy for the treatment of cervical cancer patients with recurrent, metastatic, or persistent disease