SGNLVA-002: Single Arm, Open Label Phase 1b/2 Study of Ladiratuzumab Vedotin (LV) in Combination With Pembrolizumab for First-Line Treatment of Patients with Unresectable Locally-Advanced or Metastatic Triple-Negative Breast Cancer (Trial in Progress)

Javier Cortes, MD[1], Sami Diab, MD[2], Reva Basho, MD[3], Mafalda Oliveira, MD[4], Timothy Pluard, MD[5], Carlos Alemany, MD[6], Ursa Brown Glaberman, MD[7], Jane Meisel, MD[8], Valentina Boni, MD[9], Rajni Sinha, MD[10], Laura Estevez, MD[11], Johannes Ettl, MD[12], Sherko Kümmel, MD[13], Luis Manso, MD[14], Yong Wha Moon, MD[15], Rafael Villanueva, MD[16], Rachel Wuerstlein, MD[17], Yinghui Wang, PhD[18], Zejing Wang, MD, PhD[18], Hyo Han, MD[19]

[1]IOB Institute of Oncology, Quiron Group, Madrid & Barcelona, Spain; Vall d´Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Rocky Mountain Cancer Centers, Aurora, CO; [3] Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA; [4]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [5]Saint Luke's Cancer Institute, Kansas City, MO; [6]Advent Health Cancer Institute, Orlando, FL; [7]University of New Mexico Cancer Center, Albuquerque, NM; [8]Winship Cancer Institute, Atlanta, GA; [9]HM Centro Integral Oncologico Clara Campal, Madrid, Spain; [10]Piedmont Cancer Institute, Atlanta, GA; [11]Centro Oncologico MD Anderson, Madrid, Spain; [12]Klinikum Rechts der Isar der Technischen Universitat Munchen, Munich, Germany; [13]Kliniken Essen Mitte Evang. Huyssens Stiftung, Essen, Germany; [14]Hospital Universitario 12 de Octubre, Madrid, Spain; [15]CHA Bundang Medical Center, Seongnam, South Korea; [16]Institut Català d'Oncologia L'Hospitalet, Barcelona, Spain; [17]Klinikum der Universitat Munchen, Munich, Germany; [18]Seattle Genetics, Inc., Bothell, WA; [19]H.Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background

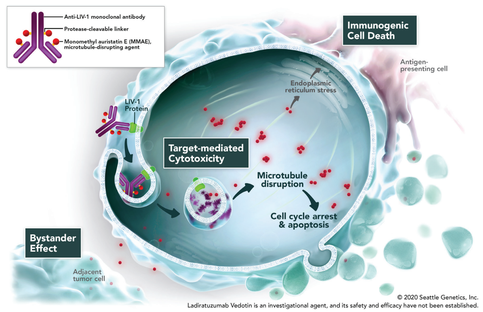
- Breast cancer is the most common malignancy and the leading cause of cancer death for women worldwide[1]
- About 1/3 of patients with breast cancer will develop recurrent or metastatic breast cancer (mBC), which has a 5-year relative survival rate of 27%²
- Patients with metastatic triple-negative breast cancer (mTNBC) have particularly poor outcomes with a median overall survival of approximately 1 year[3,4]
- Traditional chemotherapy for mTNBC is only palliative. Recent approval of a checkpoint inhibitor in combination with chemotherapy shows promise[5-7]
- This ongoing phase 1b/2 study is testing the safety and efficacy of ladiratuzumab vedotin (LV) in combination with pembrolizumab in unresectable locally-advanced or metastatic (LA/M) TNBC (NCT03310957, 2017-002289-35, KEYNOTE 721)

LIV-1 Target

- LIV-1 is a transmembrane protein involved in the signaling pathway leading to epithelialmesenchymal transition (EMT)[8,9]
- LIV-1 is expressed in ≥90% of all clinical subtypes of mBC tumors with low expression in normal tissues[10-11]
- Approximately 70% of mTNBC patients had moderate to high expression of LIV-1 (H-score ≥100)[11]
- LIV-1 expression has been linked with malignant progression to metastasis in breast cancer[9,12]
- Treatment with LV is associated with mitotic arrest, infiltration of macrophages, and upregulation of cytokine signaling[13] which is in line with preclinical reports demonstrating LV monotherapy causes immunogenic cell death (ICD)[14]

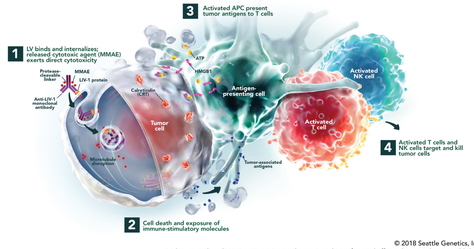
Proposed Mechanism of Ladiratuzumab Vedotin

- Ladiratuzumab vedotin
  - Humanized IgG1 antibody-drug conjugate (ADC)
  - Selectively binds to cells expressing LIV-1
  - Conjugated to monomethyl auristatin E (MMAE)
- LV mediated delivery of MMAE drives antitumor activity through
  - Cytotoxic cell killing
  - Inducing ICD[14]



Ladiratuzumab Vedotin is an investigational agent, and its safety and efficacy have not been established.

Rationale for Combining LV With Pembrolizumab



Ladiratuzumab vedotin is an investigational agents, and its safety and efficacy have not been established.

- LV and pembrolizumab act through distinct and complementary mechanisms
- LV-induced ICD elicits an inflammatory response, leading to enhanced anti-tumor immunity
  - Increased antigen presentation
  - Increased tumor immune cell infiltration[14]
- LV induced ICD creates a microenvironment favorable for enhanced pembrolizumab activity

SeattleGenetics®

Abstract No. P-2075
European Society of Medical Oncology; Virtual Congress 2020; September 19–21, 2020

LV Every 3 Weeks in Combination With Pembrolizumab – Safety & Efficacy Results[11]

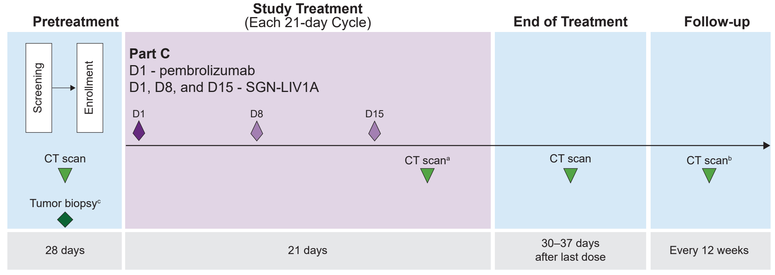
- LV plus pembrolizumab appears tolerable with a manageable safety profile to date
- Preliminary efficacy data show encouraging clinical activity as first-line therapy in patients with unresectable LA/M TNBC
- Two out of 12 patients experienced dose-limiting toxicities (DLTs; colitis and diarrhea) with LV at 2.5 mg/kg every 3 weeks (q3wk) and no DLTs were observed at 2.0 mg/kg q3wk
- The most common treatment-emergent adverse events (TEAEs) were nausea, fatigue, diarrhea, alopecia, constipation, hypokalemia, vomiting, decreased appetite, abdominal pain, decreased weight, neutropenia, and peripheral sensory neuropathy

Rationale for Weekly Dosing

- More frequent, fractionated dosing has improved the activity and/or safety of other ADCs
- Preliminary observations of LV delivered once every week in breast cancer have been well tolerated to date[15]

Study Design – Weekly LV Treatment

- Ongoing single-arm, open label, phase 1b/2 combination LV + pembrolizumab study (NCT03310957, 2017-002289-35)
- Currently enrolling patients with unresectable LA/M TNBC who have not received cytotoxic therapy for treatment of their advanced disease in Part C to evalulate the safety and efficacy of LV at 1.00 or 1.25 mg/kg/week plus pembrolizumab



a Response assessments to be performed every 6 weeks (±3 days) for the first 12 months and every 12 weeks (±7 days) thereafter, regardless of dose delays. For first objective response (CR or PR), a scan will be performed at least 4 weeks after first documentation of response.
b Patients who discontinue study treatment in the absence of disease progression will continue to be evaluated for response every 6 weeks for the first 12 months on study and every 12 weeks thereafter until progression or initiation of a new anticancer treatment. Patients will be followed for OS every 12 weeks.
c Archival or newly obtained core or excisional tumor biopsy.

CT= computed tomography; D=day; CR= complete response; PR= partial response; OS= overall survival

Eligibility

Key Inclusion Criteria

- Unresectable locally-advanced or metastatic, histologically documented TNBC (absence of human epidermal growth factor receptor 2 [HER2] overexpression or amplification, estrogen receptor, and progesterone receptor expression)
- No prior cytotoxic therapy for the treatment of unresectable locally-advanced or mBC
- At least 6 months since prior treatment with curative intent
- Measurable disease per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)
- An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
- Adequate hematologic, kidney, and liver function

Key Exclusion Criteria

- Prior immune-oncology therapy
- Pre-existing neuropathy of at least Grade 2
- Active central nervous system (CNS) metastases
- Active autoimmune disease requiring systemic treatment within the past 2 years

Objectives

Primary Objectives

- Evaluate safety and tolerability of LV + pembrolizumab
- Identify recommended dose of LV + pembrolizumab
- Evaluate confirmed overall response rate of LV + pembrolizumab

Secondary Objectives

- Evaluate duration of response
- Evaluate disease control rate
- Evaluate progression free survival
- Evaluate overall survival

Additional Objectives

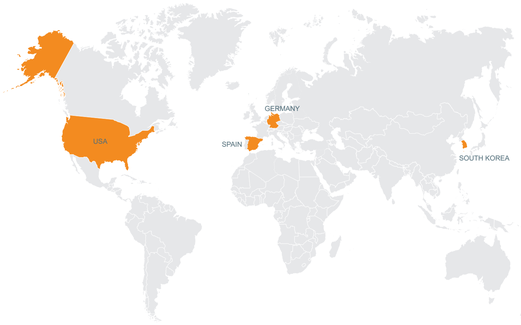
- Assess PD-L1 and LIV-1 expression-response relationship

Primary Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Incidence of DLT
- Confirmed objective response rate (ORR) as determined by the investigator according to RECIST v1.1

Study Sites and Completion Dates

- Sites enrolling in the US, Spain, Germany, and South Korea
- Study Start: Feb 27, 2018
- Estimated Primary Completion: Apr 2021
- Estimated Study Completion: May 2022



Acknowledgments

The authors would like to thank all of the SGNLVA-002 principal investigators:
- Kathy Albain, Cardinal Bernardin Cancer Center/Loyola University Medical Center
- Joan Albanell, Hospital del Mar
- Eleni Andreopoulou, Weill Cornell Medicine
- Silvia Antolin Novoa, Complejo Hospitalario Universitario La Coruna
- Michelina Cairo, Texas Oncology - Houston Memorial City
- Young jin Choi, Pusan National University Hospital
- Patrick Dillon, University of Virginia
- Peter Fasching, Universitatsklinikum Erlangen
- Michael Guarino, Helen F. Graham Cancer Center/Christiana Care Health Systems
- Claus Hanusch, Rotkreuzklinikum Munich
- Seock-Ah Im, Seoul National University Hospital
- Young-Hyuck Im, Samsung Medical Center
- Hyun-Ah Kim, Korea Cancer Center Hospital
- Hans Christian Kolberg, Marien Hospital Bottrop
- Christian Kurbacher, Gynakologisches Zentrum Bonn Friedensplatz
- Joyce O'Shaughnessy, Texas Oncology - Baylor Sammons Cancer Center
- Steven Papish, Summit Medical Group
- Ritesh Parajuli, University of California Irvine
- Pedro Sanchez Rovira, Complejo Hospitalario de Jaen
- Joo Hyuk Sohn, Severance Hospital, Yonsei University Health System
- Danielle Sterrenberg, Ingalls Cancer Care/Ingalls Memorial Hospital
- Erica Stringer-Reasor, University of Alabama at Birmingham
- Katherine H. R. Tkaczuk, University of Maryland
- Michaela Tsai, Virginia Piper Cancer Institute
- Linda Vahdat, The Whittingham Cancer Center/Norwalk Hospital
- Hermann Voss, Stadtisches Klinikum Dessau
- Grace Wang, Miami Cancer Institute at Baptist Health, Inc.
- Sharon Wilks, Texas Oncology - San Antonio Medical Center Northeast

References

1. Bray, et al., CA Cancer J Clin. 2018; 68(6): 394-424
2. SEER Stat Fact Sheets: Female Breast Cancer. 2019
3. den Brok et al., Breast Cancer Res Treat. 2017; 161(3): 549-56
4. Rodler et al., Breast Dis. 2010; 32(1-2): 99-122
5. Isakoff et al., J Clin Oncol. 2015; 33(17): 1902-09
6. Rugo et al., J Clin Oncol. 2015; 33(21): 2361-9
7. Schmid et al., N Engl J Med. 2018; 379(22): 2108-21
8. Lue et al., PLOS One. 2011; 6(11)
9. Hogstrand et al., Biochem J. 2013; 455: 229-37
10. Sussman et al., Mol Cancer Ther. 2014; 13: 2991-3000
11. Han et al., Proceedings of the 2019 San Antonio Breast Cancer Symposium. 2019; Abstract PD1-06
12. Manning et al, Eur J Cancer. 1994; 30A(5): 675-8
13. Specht et al. Ann Oncol. 2018; 29(Suppl 8): viii92
14. Cao et al. Cancer Res. 2018; (13 Suppl): Abstract 2742
15. Seattle Genetics, Data on File

Disclosures

Cortes: AstraZeneca, Athenex, Baxalta GHBN/Servier Affaires, Bayer, Bioasis, Biothere Pharma, Boehringer Ingelheim, Celgene, Cellestia, Clovis, Daiichi Sankyo, Eisai, Erytech, FHoffman-La Roche, GSK, Guardant Health, Leuko, Lilly, Merck, Merus, MSD, Novartis, Pfizer, Piqur Thera, Polyphor, Puma, Queen Mary University of London, Roche, Seattle Genetics, Servier, Ariad Pharma, Daiichi, MedSIR. Diab: Agendia, Amgen, Genentech, Immunomedics, Lilly, Novartis, Pfizer, Puma Biotechnology, Seattle Genetics, Inc. Basho: Genentech, Genomic Health, Seattle Genetics. Oliveira: AstraZeneca, GlaxoSmithKline, PUMA Biotech, Roche, Seattle Genetics, Novartis, Boehringer Ingelheim, Epigenetics, Genentech, Immunomedics, Philips Healthcare, Zenith, Eisai, GP Pharma, Gruenthal, Pierre Fabre. Pluard: Genentech/Roche, Macrogenics, Novartis, Pfizer, Tempus, Seattle Genetics, Inc. Alemany: BMS, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Seattle Genetics, Takeda. Brown-Glaberman: Biotheranostics, Eisai, Halozyme, Novartis, Syndax. Meisel: Lilly, Pfizer, Puma Biotechnology, Seattle Genetics, Inc. Boni: None. Sinha: None. Estevez: None. Ettl: AstraZeneca, Celgene, Daiichi Sankyo, Lilly, Novartis, Pfizer, PfizerRoche, PierreFabre, Roche, Tesaro, Teva. Kümmel: AGO (Arbeitsgemeinschaft Gynäkologische Onkologie), Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Genomic Health, Lilly, MSD, Novartis, Pfizer, PFM Medical, Roche, Sankyo, Somatex, Sonoscape, Sonoscare, WSG (Westdeutsche Studiengruppe). Manso: AstraZeneca, Novartis, Pfizer, Roche, Tesaro. Moon: AstraZeneca, Cellitrion, Chon Kun Dang, Dong-A ST, Eisai. Villanueva: Eisai, Lilly, Novartis, Pfizer. Wuerstlein: None. Y. Wang and Z. Wang: Employees and equity ownership in Seattle Genetics, Inc. Han: Abbvie, Prescient Therapeutics, TapImmune Inc., Seattle Genetics, Inc., G1 Therapeutics, Bristol-Myers Squibb, Pfizer, Novartis.