WEEKLY LADIRATUZUMAB VEDOTIN MONOTHERAPY FOR METASTATIC TRIPLE NEGATIVE BREAST CANCER

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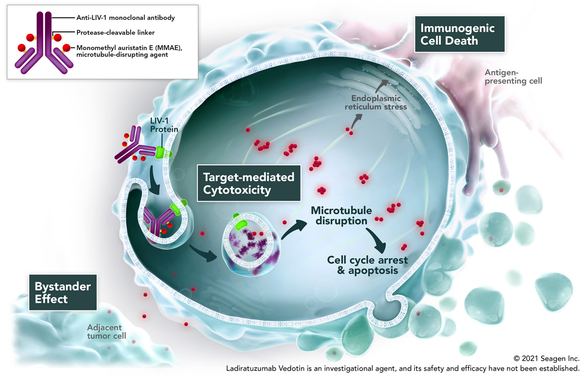
Background

- Breast cancer is the most common malignancy and the leading cause of cancer-related death in women worldwide[1]
  - Approximately 30% of patients with breast cancer will develop recurrent or metastatic breast cancer (mBC)[2]
- Ladiratuzumab vedotin (LV) monotherapy administered every 3 weeks (Q3w) in clinical trials has encouraging activity in late-line metastatic triple negative disease (mTNBC)[3]
- Pharmacokinetic (PK) modeling suggested Q1w dosing may improve efficacy and mitigate certain toxicities
  - Q1w dosing is hypothesized to reduce peak-to-trough fluctuations and to decrease maximum drug concentration resulting in improved efficacy and a differentiated safety profile
- Part E of the ongoing SGNLVA-001 trial (NCT01969643) was designed to evaluate the activity, tolerability, and pharmacologic characteristics of Q1w LV dosing

Ladiratuzumab Vedotin Proposed Mechanism of Action

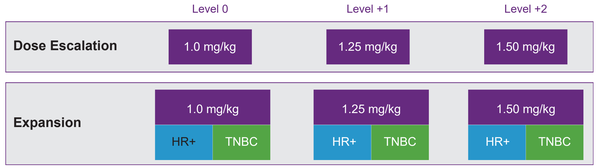
- LV[4]:
  - Investigational humanized IgG1 antibody-drug conjugate (ADC)
  - Selectively binds to cells expressing LIV-1
  - Conjugated to monomethyl auristatin E (MMAE)
- LV mediated delivery of MMAE drives antitumor activity through:
  - Cytotoxic cell killing
  - Inducing immunogenic cell death[5]



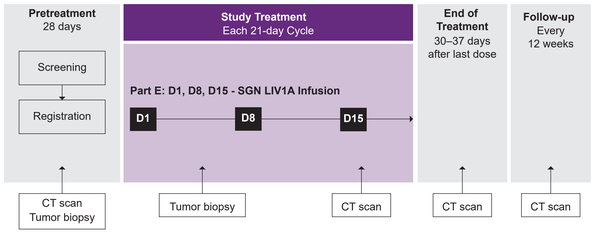
Ladiratuzumab Vedotin is an investigational agent, and its safety and efficacy have not been established.

Study Design

- SGNLVA-001 is an ongoing, multi-part, open label study investigating the safety and efficacy of LV in patients with mBC
- Population: patients with first (1L) or second line (2L) endocrine therapy refractory hormone receptor-positive (HR+)/HER2-negative (HER2-) mBC or 2L mTNBC
- There is no LIV-expression requirement to be eligible for the study
- Part E evaluated LV in escalation and expansion phases
  - Starting dose of LV 1.0 mg/kg Q1w
  - Dose escalation used the modified toxicity probability interval method, with each dose escalation cohort enrolling 2 HR+/HER2- patients
  - Dose-expansion cohorts may be opened at any dose level that has cleared dose limiting toxicities (DLT) evaluation (DLT evaluation period is 3 weeks)
  - Approximately 82 patients to be enrolled: 40 in mTNBC and 42 in HR+/HER2-
- Tumor assessments occurred every 6 weeks per RECIST v1.1



Treatment and Evaluation Schema



Key Eligibility Criteria

- Pathologically confirmed breast cancer with radiographic evidence of incurable, unresectable, locally advanced or metastatic disease
- HER2- disease (per 2019 ASCO/CAP guidelines)
- Patients were considered to have HR+ disease if biopsies show >1% of cells expressing estrogen or progesterone receptors (per 2018 ASCO/CAP guidelines)
- Prior Therapy:
  - HR+/HER2-: chemotherapy-eligible and not considered a candidate for hormonal therapy
    - Must have progressed on or relapsed after receiving endocrine or hormonally directed therapy with cyclin-dependent kinases inhibitors
    - ≤1 prior cytotoxic regimen for incurable unresectable locally advanced or mBC (LA/mBC)
  - mTNBC: must have received exactly one prior cytotoxic regimen for incurable, unresectable LA/mBC
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group (ECOG) = 0 or 1
- Able to provide tissue samples for biomarker analysis
- Neuropathy ≤ Grade 2
- Adequately-treated central nervous system metastases and off corticosteroids

Patient and Disease Characteristics

- Data cut off date: 19 March 2021
- 81 patients enrolled across dose escalation and expansion cohorts
  - 20 patients at 1.0 mg/kg Q1w dose: 10 TNBC and 10 HR+/HER2-
  - 52 patients at 1.25 mg/kg Q1w dose: 29 TNBC and 23 HR+/HER2-
  - 9 patients at 1.5 mg/kg Q1w dose: 1 TNBC and 8 HR+/HER2-
- Demographic and disease characteristics of patients were generally consistent across cohorts

	TNBC (n=40)	HR+ (n=41)	Total (n=81)
Female	40 (100%)	41 (100%)	81 (100%)
Median age, years (range)	54 (32–78)	58 (37–77)	55 (32–78)
Median weight, kg (range)	70.7 (48.3–114.4)	73.1 (43.9–111.4)	72.4 (43.9–114.4)
De novo metastatic/Stage IV at diagnosis, n (%)	7 (18%)	6 (15%)	13 (16%)
Histology at diagnosis, n (%)			
HR+/HER2-	0	41 (100%)	41 (51%)
TNBC	40 (100%)	0	40 (49%)
ECOG Performance Status, n (%)			
0	24 (60%)	26 (63%)	50 (62%)
1	16 (40%)	15 (37%)	31 (38%)
Median number of systemic cytotoxic prior therapies for LA/MBC (range)	1 (1–2)	1 (1–3)	1 (1–3)

Dose Limiting Toxicity and Dose Evaluation

- No DLTs were observed at any dose
- Enrollment focused on 1.25 mg/kg Q1w dosing
  - Anti-tumor activity observed at both 1.25 mg/kg and 1.5 mg/kg Q1w
  - Neutropenia was observed in a higher proportion of patients at 1.5 mg/kg Q1w versus 1.25 mg/kg Q1w

Treatment Emergent Adverse Events

- The most frequently reported AEs across the LV dose groups were fatigue, nausea, and peripheral sensory neuropathy
- Most AEs were mild to moderate (Grade 1–2) in severity (data not shown)
- The most frequently reported SAEs across the LV dose groups were dyspnea, febrile neutropenia, and nausea (5% each) (data not shown)

	LV Dose			
Preferred Term	1.0 mg/kg (n=20)	1.25 mg/kg (n=52)	1.5 mg/kg (n=9)	Total (n=81)
Fatigue	12 (60%)	30 (58%)	7 (78%)	49 (61%)
Nausea	10 (50%)	31 (60%)	4 (44%)	45 (56%)
Peripheral sensory neuropathy	3 (15%)	28 (54%)	5 (56%)	36 (44%)
Constipation	8 (40%)	20 (39%)	6 (67%)	34 (42%)
Decreased appetite	6 (30%)	23 (44%)	2 (22%)	31 (38%)
Diarrhea	9 (45%)	16 (31%)	4 (44%)	29 (36%)
Vomiting	10 (50%)	16 (31%)	2 (22%)	28 (35%)
Myalgia	4 (20%)	16 (31%)	4 (44%)	24 (30%)
Neutropenia	4 (20%)	14 (27%)	6 (67%)	24 (30%)
Abdominal pain	5 (25%)	16 (31%)	1 (11%)	22 (27%)

Treatment Emergent Grade ≥3 Adverse Events

- In general, severe AEs were uncommon across the LV dose groups

	LV Dose			
Preferred Term	1.0 mg/kg (n=20)	1.25 mg/kg (n=52)	1.5 mg/kg (n=9)	Total (n=81)
Neutropenia	2 (10%)	11 (21%)	4 (44%)	17 (21%)
Fatigue	3 (15%)	7 (14%)	2 (22%)	12 (15%)
Hyperglycemia	3 (15%)	6 (12%)	0	9 (11%)
Neutrophil count decreased	2 (10%)	5 (10%)	2 (22%)	9 (11%)
Hypokalemia	0	6 (12%)	2 (22%)	8 (10%)
Hypophosphataemia	1 (5%)	6 (12%)	1 (11%)	8 (10%)
Nausea	2 (10%)	4 (8%)	1 (11%)	7 (9%)
Anemia	1 (5%)	4 (8%)	1 (11%)	6 (7%)
Hypertension	1 (5%)	4 (8%)	1 (11%)	6 (7%)
Abdominal pain	0	4 (8%)	1 (11%)	5 (6%)

Dose Modifications

- Dose delays, reductions, and discontinuations were most commonly due to peripheral sensory neuropathy

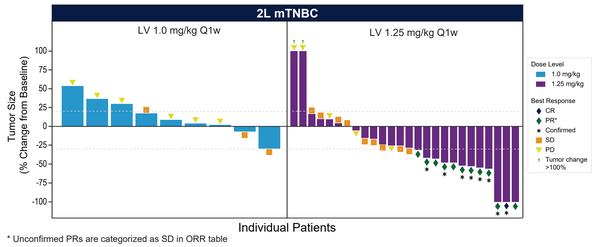
	LV Dose			
Preferred Term	1.0 mg/kg (n=20)	1.25 mg/kg (n=52)	1.5 mg/kg (n=9)	Total (n=81)
Delay	2 (10%)	6 (12%)	1 (11%)	9 (11%)
Reduction	4 (20%)	27 (52%)	5 (56%)	36 (44%)
Discontinuation	3 (15%)	8 (15%)	3 (33%)	14 (17%)

Response by LV Dose in 2L mTNBC

	LV Dose[a]	
Endpoint	1.0 mg/kg (n=10)	1.25 mg/kg (n=29)
Confirmed Complete Response	0	0
Confirmed Partial Response	0	8 (28%)
Stable Disease	3 (30%)	13 (45%)
Progressive Disease	6 (60%)	7 (24%)
Not Evaluable	1 (10%)	1 (3%)
ORR % (95% CI)	0 (0–31%)	28% (13–47%)
Duration of response, months (95% CI)	0	2.9 (2.2–7.0)

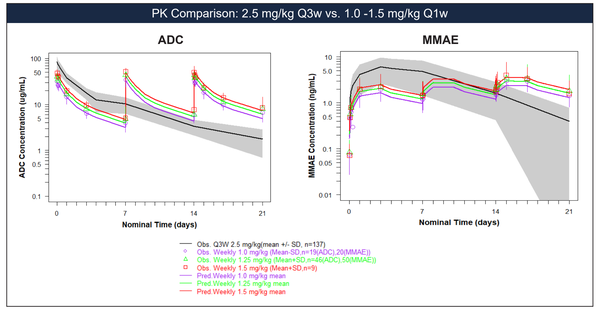
Unconfirmed PRs are categorized as SD
[a] LV 1.5 mg/kg Q1w, only 1 mTNBC subject accrued and has PD as best response

Maximum Change in Tumor Burden



* Unconfirmed PRs are categorized as SD in ORR table

Q1w Dosing Reduces Peak-to-trough Fluctuations and Maintains Lower C_{max} and Higher C_{trough} Compared to Q3w Dosing



Conclusions

- LV, an investigational humanized IgG1 ADC, is a manageable and well-tolerated regimen when administered every week to patients with TNBC
- LV Q1w PK data were consistent with model predictions:
  - Q1w dosing reduced peak-to-trough fluctuations and maintained lower maximum concentration and higher trough concentration
  - Despite a higher cumulative dose, maximum MMAE concentration was lower compared to 2.5 mg/kg Q3w
- LV 1.25 mg/kg Q1w selected for expansion as it offered an appropriate balance of safety and efficacy
  - In 2L mTNBC cohort, the LV 1.25 mg/kg Q1w regimen achieved an ORR 28%
- LV has demonstrated activity in TNBC
  - This study showed the potential of LV to be a novel treatment option for TNBC
  - Improved efficacy observed with LV 1.5 mg/kg Q1w compared to lower doses in HR+/HER2- patients (data not shown) supports exploration of higher dose
  - Subsequent evaluations will be conducted to refine the dosing regimen to maximize clinical efficacy while balancing safety

References

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