Publication Number: 3072
Submission ID: 172537

Strategies to Develop anti-KIR3DL2 mAb Lacutamab in Patients with Peripheral T-Cell Lymphoma: Preliminary Monotherapy Clinical Data and Pre-Clinical Combinability Data

Swaminathan Iyer[1], Sabarish Ayyappan[2], I. Brian Greenwell[3], Won Seog Kim[4], Seung Tae Lee[5], Won Sik Lee[6], Jin Seok Kim[7], Youngwoo Jeon[8], William Johnson[9], Utpal Dave[10], Sung-Soo Yoon[11], Ka-Won Kang[12], Florent Carrette[13], Julien Viotti[13], Al Jose Leyco[13], Marianna Muller[13], Steven Horwitz[9]

1. MD Anderson Cancer Center, USA; 2. University of Iowa, USA; 3. Medical University of South Carolina, USA ; 4. Samsung Medical Center, South Korea; 5. University of Maryland, USA; 6. Inje University Busan Paik Hospital, South Korea; 7. Severance Hospital Yonsei University Health System, South Korea; 8. The Catholic University of Korea, Yeouido St. Mary`s Hospital, South Korea; 9. Memorial Sloan Kettering Cancer Center, USA; 10. Indiana University, South Korea; 11. Seoul National University Hospital, South Korea; 12. Korea University Anam Hospital, South Korea; 13. Innate Pharma S.A., France

Disease overview & lacutamab clinical development

Unmet medical need in PTCL

- Peripheral T-cell Lymphoma (PTCL) is a heterogeneous group of mature T-cell lymphomas associated with poor prognosis with a 5-year survival rate of approximately 30% to 40%[1].
- No universally accepted standard of care, especially in the relapse/refractory (R/R) setting [2-3]. Therefore, there is an urgent and significant need for innovative treatment strategies.
- KIR3DL2 is a killer immunoglobulin-like receptor that is expressed across different subtypes of T-cell lymphomas including approximately 50% of PTCL patients [4-6].
- Lacutamab is a first-in-class Fc-optimized monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells through antibody-dependent cell-cytotoxicity (ADCC) and antibody-dependent cell-phagocytosis (ADCP) (Figure 1).

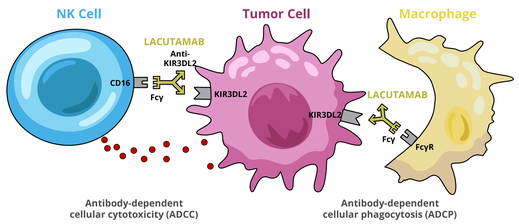

Figure 1: IPH4102/Lacutamab Mechanisms of Action

Lacutamab Clinical Development

- Lacutamab is in development in Cutaneous T-cell lymphoma (CTCL) and Peripheral T-cell Lymphoma (PTCL). Ongoing trials include:
  - CTCL: Phase 2 monotherapy in Sézary Syndrome and Mycosis Fungoides patients (NCT03902184; TELLOMAK)[7-10].
  - R/R PTCL: Phase 1b (NCT05321147, IPH4102-102) monotherapy and Phase 2 combination with GemOx (NCT04984837; KILT IST) are ongoing.
- Previous trials in patients with R/R CTCL demonstrated lacutamab had an acceptable safety profile and promising activity [11].
- Here, we present preliminary safety data from an ongoing Phase 1b study in PTCL (NCT05321147) evaluating the safety and efficacy of lacutamab monotherapy in patients with KIR3DL2-expressing R/R PTCL who have received at least one prior line of systemic therapy.
- The combinability of lacutamab with various therapies used in PTCL was tested. Here we provide preclinical combination data supporting anti-tumor activity and rationale for the exploration of lacutamab in combination with therapies used in frontline or R/R PTCL.

Clinical study design and preliminary safety results

- IPH4102-102: A multi-center, open label Phase 1b clinical trial evaluating safety and efficacy of lacutamab monotherapy in R/R PTCL that express KIR3DL2 (NCT05321147)

R/R PTCL
KIR3DL2-expressing
≥ 1 prior line of systemic therapy
N = 20 + 20

→

Lacutamab
750 mg iv weekly x 5 wks, every 2 wks x 10 then every 4 wks until disease progression or unacceptable toxicity

Primary Objective:
To assess safety and tolerability of lacutamab in R/R PTCL

Secondary Objective:
To assess antitumor activity: ORR, CR rate, DoR, TTNT, EFS, OS, and to characterize the pharmacokinetics and immunogenicity

CR: Complete response; DoR: Duration of response; EFS: Event free survival; ORR: Objective response rate; OS: Overall survival; TTNT: Time to next treatment

- At the data cut-off 10 patients were treated with lacutamab. Median age 71.0 years (range: 61-77), 60% male, median prior lines of therapies was 3 (range: 1-5), and median follow-up was 1.9 months (m) (range: 0.5-8.8 m).
- The majority (90%) of treatment-emergent adverse events (TEAEs) were of grade 1-2 severity. The most frequent related TEAEs observed in more than one patient were diarrhea, fatigue and platelet count decrease (20% each). Grade ≥3 related TEAEs were observed in 2 (20%) patients: 1 patient with serum sickness, and 1 patient with aspartate aminotransferase elevation.
- No serious TEAEs were reported. There were no TEAEs leading to treatment discontinuation nor death.

Preclinical combinations (continued)

Lacutamab combination with bendamustine improves *in vivo* antitumor response and survival

Bendamustine is an alkylating agent inducing tumor cell death, with promising activity in R/R PTCL[13]. It is also demonstrated to improve ADCC[14].

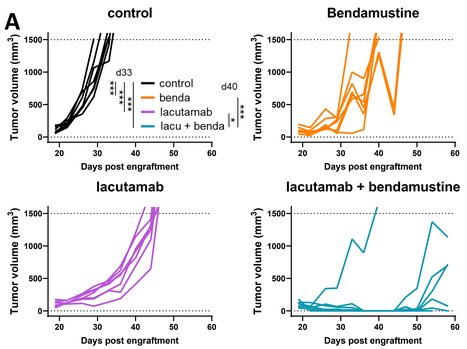

Figure 4: In vivo combination of lacutamab and bendamustine
CCRF-CEM T lymphoblast tumor cells expressing endogenous levels of KIR3DL2 were subcutaneously injected in CB17 SCID mice. Mice were treated from the day of randomization (day 19, ~100mm³) and throughout the experiment with 15mg/kg lacutamab or isotype control (QW, i.p) and with 25mg/kg bendamustine or vehicle (QW, i.v). **(A)** Tumor growth curves of each individual mouse (n=7 per group). **(B)** Kaplan Meyer curves for survival. Benda: bendamustine.
* p<0.05, ** p<0.01, *** p<0.001.

Preclinical combinations

Lacutamab combination with CHOP improves in vivo antitumor response

CHOP-based chemotherapy is a frontline treatment option in PTCL[2].

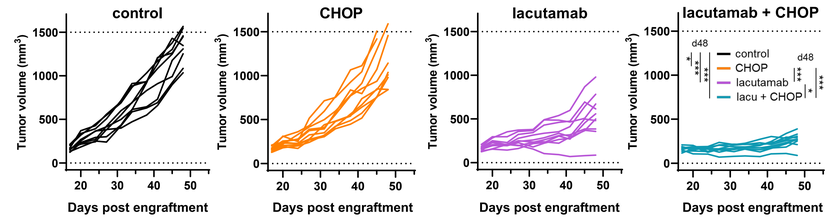

Figure 2: In vivo combination of lacutamab with CHOP
KIR3DL2-expressing Raji cells were subcutaneously injected in CB17 SCID mice. Mice were treated from the day of randomization (day 17, ~160 mm³) and throughout the experiment with 15mg/kg lacutamab or isotype control (QW, i.v) and with one cycle of CHOP (30mg/kg cyclophosphamide i.v once, 2.475mg/kg doxorubicin i.v once, 0.375mg/kg vincristine i.v once, 0.15mg/kg prednisone p.o daily, 5 days). Tumor growth curves of each individual mouse are shown (n=10 per group). * p<0.05, ** p<0.01, *** p<0.001.

Lacutamab combination with pralatrexate improves in vivo antitumor response and survival

Pralatrexate is a folate analog blocking DNA synthesis approved for the treatment of R/R PTCL[12].

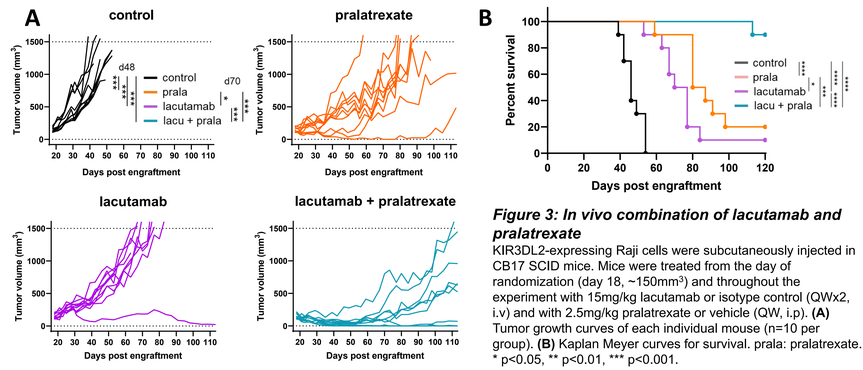

Figure 3: In vivo combination of lacutamab and pralatrexate
KIR3DL2-expressing Raji cells were subcutaneously injected in CB17 SCID mice. Mice were treated from the day of randomization (day 18, ~150mm³) and throughout the experiment with 15mg/kg lacutamab or isotype control (QWx2, i.v) and with 2.5mg/kg pralatrexate or vehicle (QW, i.p). **(A)** Tumor growth curves of each individual mouse (n=10 per group). **(B)** Kaplan Meyer curves for survival. prala: pralatrexate.
* p<0.05, ** p<0.01, *** p<0.001.

Conclusion

- Preliminary Phase 1b data in patients with R/R PTCL confirm the acceptable safety profile of lacutamab monotherapy.
- Preclinical evaluations demonstrate combinations of lacutamab that CHOP, pralatrexate and bendamustine greatly improve antitumor activity in vivo and inform the future development of lacutamab to provide additional therapeutic options that may improve outcomes for PTCL patients.

Bibliography

1. Khan et al. Cancers (Basel) 2021, 13:5627; **2.** Horwitz SM, et al. 2022, J Natl Compr Canc Netw. 2022 Mar;20(3):285-308; **3.** Foss, F. M., P. L. Zinzani, et al. 2011, Blood Jun 23;117(25):6756-67; **4.** Bagot, M., A. Moretta, et al. 2001 Blood 97(5): 1388-1391; **5.** Decroos et al. Haematologica 2023 Oct 1;108(10):2830-2836; **6.** Cheminant et al. Blood 2023 Sep 29;140(13):1522-1532; **7** Porcu P. et al, ASH 2022; **8.** Bagot, M., et al, EORTC 2022; **9.** Porcu P. et al, ICML 2023; **10.** Bagot, M., et al, EORTC-CLTG 2023; **11.** Bagot, M., P. L Porcu, et al. 2019; Lancet oncol. Aug;20(8):1160-1170; **12.** O'Connor, et al. 2011 J Clin. Oncol. Mar 20;29(9):1182-9; **13.** Rebrousiere E et al. 2016 Oncotarget Dec 20;7(51):85573-85583; **14.** Kawasaki, et al. 2022 Jun;49(6):4421-4433

Acknowledgments

- The patients and families that participated in this trial;
- The clinical study teams who made this trial possible;
- The pharmacology team who generated preclinical data.

SCAN ME

Study sponsored by Innate Pharma