A phase 1 dose-escalation study of lirilumab (IPH2102, BMS-986015, LIRI), a fully human anti-KIR monoclonal antibody in patients with various hematologic (HEM) or solid (SOL) malignancies

N. Rey1, L. Karlin2, A. Gonçalves1, S. Sadot-Lebouvier3, F. Broussais3, D. Marie4, D. Berton-Rigaud3, P. André4, R. Zerbib4, R. Buffet4, T. Prebet1, A. Charbonnier1, J. Rey1, A. Pigneux5, J. Bennouna3, N. Boissel6 and G. Salles2

1 Institut Paoli-Calmettes, Marseille, France; 2 HU de LYON Sud, Pierre Baille, France; 3 COO – Site René Gauduchaud, St Herblain, France; 4 Inivate Pharma, Marseille, France; 5 Centre Francois Magendie, H. Tard-Léopold, Pessac, France; 6 H. Hôtel Dieu, CIC, Paris, France

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Background
Lirilumab (LIRI) is a fully human IgG4 monoclonal antibody (CHO manufacturing) which binds specifically and with high affinity to the main human inhibitory killer cell immunoglobulin-like receptor (KIR), KIR2DL1 and KIR2DL2/3, expressed by NK cells. This binding blocks the interaction of the KIR2DL receptors with HLA-C allotypes, their natural ligands, and prevents the inhibitory signals usually triggered by this interaction. The blockade of KIR by LIRI fosters the activation of NK cells, selectively enhancing the cytotoxicity of NK cells against tumor cells without affecting healthy tissues. Experimental and clinical data suggest that enhancement of NK cell activity, notably by an exchange between NA1 and patient KIR ligand HLA-C, i.e. by a surrogate of KIR blockade, is a susceptible to improve the prognosis of cancers after a reduction of tumor burden by previously administered treatments. We previously reported the safety and efficacy of LIRI, an anti-KIR monoclonal antibody using PH1T1014 (hydromorphic manufacturing).

Study Design
The study was designed to evaluate the safety of single agent LIRI and to identify the dose levels resulting, after a single administration, in either sustained full occupancy of KIR at least 4 consecutive weeks or an interrupted full occupancy of KIR for less than 3 consecutive weeks.

This was an open label, dose-escalation multi-center phase 1 trial in patients with solid tumors (SOL) or hematologic malignancies (HEM). To allow prolonged observation and full pharmacology assessment of LIRI, patients had to have disease in complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) in the dose escalation 3+3 part (sequential inclusions), six dose levels of LIRI were evaluated: 0.015, 0.3, 1, 3, 6, and 10 mg/kg; for dose escalation part of the study, 2 additional cohorts of 8 patients each were entered and treated monthly at 0.015 or 3 mg/kg.

Results

KIR Occupancy and pharmacokinetics

Full KIR occupancy was sustained during ≥4 weeks for dose levels ≥0.3 mg/kg.

LIRI concentration versus time profile showed an initial distribution phase followed by a long terminal elimination phase classical for mAb, and suggests dose dependent linear PK at high doses (from 0.3 mg/kg), with low to moderate interpatient variability.

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Exploratory covariate analysis showed potential effect of body weight, sex, baseline NK and T cell number, %KIR on T cell number on PK.

Only one patient at 0.015 mg/kg in the extension phase became significantly positive (titer=3) for HAHA from cycle 2.

References

(3) Vey et al. Blood 2012;120(1): 1137-43
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