Evaluating Biomarkers of JTX-8064 (anti-LILRB2/ILT4 monoclonal antibody) in an Ex Vivo Human Tumor Histoculture System to Inform Clinical Development

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Abstract

Background: Leukocyte Immunoglobulin-like receptor B2 (LILRB2); ILT4) is an immunoinhibitory protein expressed on the surface of macrophages that has been increasingly recognized as a therapeutic target of interest in immune-oncology (IO). Upon binding its ligands, MHC molecules in e.g. HLA-A,B,C,LILRB2 inhibits myeloid cell activation; this has been linked to the activation of tyrosine phosphatases providing a potential target for therapeutic interventions. While JTX-8064 is a LILRB2/ILT4 antagonist, this efficacy profile was the first target prioritized from a macrophage discovery effort leading to the development of JTX-8064, a LILRB2/ILT4 monoclonal antibody specifically designed to target and inhibit LILRB2. JTX-8064 has been shown to induce anti-CD163+ macrophage polarization in vitro and in vivo. Since blocking of LILRB2 has been shown to enhance anti-tumor activity, in this study, LILRB2 immunoreceptor tyrosine inhibitor (ILT4) antagonism was assessed in a multi-assay high-throughput screen to identify potential predictive biomarkers for the clinical development of JTX-8064.

Methods: More than 1000 fresh tissue samples from 10 different tumor types were treated with JTX-8064 or isotype control antibody for 24hrs in the histoculture system. A subset was also treated with anti-CD163 or JTX-8064 antibodies. RNA was isolated from tumors prior to any treatment as well as from treated samples and gene expression was analyzed using the NanoString® and qPCR assays. Additional IHC analyses were performed on baseline untreated tumor samples.

Results: JTX-8064 was shown to induce pharmacodynamic responses to JTX-8064 in untreated samples that do not have a histoculture system. A subset was also treated with anti-CD163 or JTX-8064 antibodies. RNA was isolated from tumors prior to any treatment as well as from treated samples. Gene expression was analyzed using the NanoString® and qPCR assays. Additional IHC analyses were performed on baseline untreated tumor samples.

Discussion: Three gene signatures were assessed: macrophage polarization (ILR3, Tnf, and Il4), T cell activation (Ccr7, Gzmb, and Pdcd1), and cytokine-stimulated (Il12b, Il6, and Gadd45g) to identify predictive biomarkers of pharmacodynamic responses to JTX-8064. Microarray analysis was performed on NanoString® and qPCR assays. Additional IHC analyses were performed on baseline untreated tumor samples.

Conclusions: These histoculture data will inform indication selection and combination strategies for JTX-8064 to maximize potential therapeutic benefit for patients with solid tumor malignancies.

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1. Introduction

2. Methods

3. Results

4. Discussion

5. Conclusions

6. Abbreviations

7. References

8. Acknowledgments

9. Conflict of Interest

10. Funding

11. Clinical Trials

12. Ethics Approval

13. Consent for Publication

14. Data Availability

15. Figures

16. Tables

17. Supplementary Material

18. Appendix

19. References

20. Funding

21. Ethics Approval

22. Consent for Publication

23. Data Availability

24. Figures

25. Tables

26. Supplementary Material

27. Appendix

28. References

29. Funding

30. Ethics Approval

31. Consent for Publication

32. Data Availability

33. Figures

34. Tables

35. Supplementary Material

36. Appendix

37. References

38. Funding

39. Ethics Approval

40. Consent for Publication

41. Data Availability

42. Figures

43. Tables

44. Supplementary Material

45. Appendix

46. References