XON7, a new emerging multitarget immunotherapy against metastatic soft tissue sarcomas

Ciron Carine, Gwenaelle Evanno, Pierre-Joseph Royer, Odile Duvaux, Firas Bassissi

Context

Soft tissue sarcomas (STS) are rare and heterogeneous malignancies originating from mesenchymal tissues, comprising over 50 subtypes. While surgery and radiotherapy are effective for localized disease, advanced and metastatic STS have poor outcomes due to limited efficacy of standard treatments like doxorubicin and frequent therapeutic resistance. Advances in molecular profiling have enabled targeted therapies, such as PARP inhibitors, but their effectiveness remains limited by the diversity of STS and resistance mechanisms. In this study, we evaluate the safety and efficacy of XON7, a first-in-class glyco-humanized polyclonal antibody (GH-pAb), as a novel therapeutic approach to address these challenges.

Methods

XON7's antitumor efficacy was tested in a panel of primary patient-derived sarcoma tumors and established sarcoma cell lines using CellTiter-Glo assay. Mechanisms of action assessed included complement-dependent cytotoxicity (CDC), apoptosis, antibody-dependent cell cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Apoptotic pathways were explored via caspase 8/9 activation, reactive oxygen species (ROS) production, and mitochondrial membrane potential. In vitro 3D cultures, XON7's impact on tumor growth, spheroid formation, and metastasis was evaluated. In vivo XON7 efficacy was evaluated in patient-derived xenograft (PDX) models of STS, with tri-weekly treatments initiated at tumor volumes of 150–200 mm^3.

Results

XON7 acts via plural MOA (CDC, apoptosis and ADCP), it demonstrated a potent anti-tumor activity in a panel of soft tissue sarcoma cells, with cytotoxicity ranging from 60% to 100% at a concentration of 300 µg/ml. Apoptotic induction involved both intrinsic and extrinsic pathways as evidenced by caspase 8/9 activation, ROS generation and loss of mitochondrial membrane potential. In 3D culture, repeated exposure to XON7 at a concentration of 300µg/ml significantly reduced the surface and viability of spheroids (liposarcoma SW872 cell line). XON7 also demonstrated its ability to reduce tumorogenicity and metastasis in a transwell invasion assay. In a PDX mice model of dedifferentiated liposarcoma, XON7 inhibited tumor growth by 50% over 48 days.

Conclusion

XON7 characterized by its plurality of action and potent antitumor efficacy, currently under clinical evaluation, XON7 emerges as a promising immunotherapy for soft tissue sarcomas.

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Abstract 3421

INTRODUCTION

Soft tissue sarcomas (STS) are rare and heterogeneous malignancies originating from mesenchymal tissues, comprising over 50 subtypes. While surgery and radiotherapy are effective for localized disease, advanced and metastatic STS have poor outcomes due to limited efficacy of standard treatments like doxorubicin and frequent therapeutic resistance. Advances in molecular profiling have enabled targeted therapies, such as PARP inhibitors, but their effectiveness remains limited by the diversity of STS and resistance mechanisms.

In this study, we evaluate the safety and efficacy of **XON7**, a first-in-class glyco-humanized polyclonal antibody (GH-pAb), as a novel therapeutic approach to address these challenges.

MATERIAL AND METHODS

XON7 was obtained by hyperimmunizing pigs genetically modified to lack Neu5GC and α1,3-Gal epitopes, using tumor-associated antigens.

In Vitro Assays

- Complement-dependent cytotoxicity (CDC) was evaluated on primary tumor cells and established cell lines using rabbit complement (1:12) and serial dilutions of XON7
- 3D tumor spheroid models were used to assess the impact of repeated XON7 administrations.

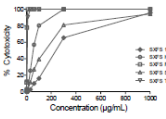
In Vivo Studies

Low Passage Champions TumorGraft® Models of Human Sarcoma in Immunocompromised Mice (in the Champions Sarcoma PDX Screen).

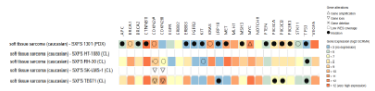
Mice were randomized into treatment groups when tumor volumes reached 150–200 mm^3. Three mice were included per group. XON7 was administered three times per week at a dose of 40 mg/kg in the treatment group. Tumor growth was monitored twice weekly. The final endpoint was defined as a tumor volume reaching 2000 mm^3, at which point mice were euthanized. Survival curves were generated based on these criteria.

RESULTS

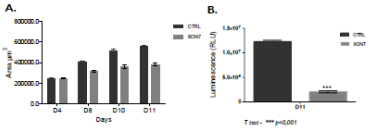
XON7 induces a potent anti tumoral activity against a panel of sarcoma cancer cell lines (CellTiter-Glo 24h)



After 24 hours incubation with serial dilutions of XON7 and in the presence of rabbit complement, XON7 induced cytotoxic activity ranging from 94% to 100% at the highest concentration

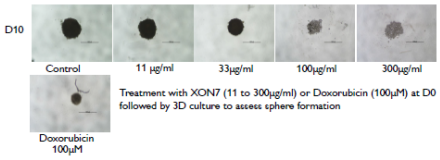


Evaluation of XON7 anti-tumor activity in 3D cultures



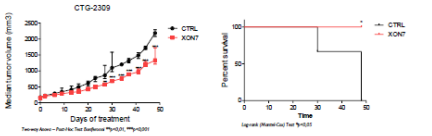
Spheroids were treated on day 3 (D3) with 300 µg/mL of XON7 in the presence of rabbit complement (1:6 dilution). This treatment led to a tumor growth inhibition of over 30% (**A**). However, cell viability analysis on day 11 (D11) revealed a loss exceeding 84%, indicating that the spheroid core was completely necrotic and that the remaining structure resembled an empty shell (**B**).

XON7 reduces the tumorogenicity of SW872 cells , unlike doxorubicin, by blocking tumorsphere formation (measurment D10)

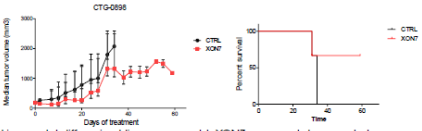


Treatment with XON7 (11 to 300µg/ml) or Doxorubicin (100µM) at D0 followed by 3D culture to assess sphere formation

XON7 is effective and well tolerated in pdx model of soft tissue liposarcomas.



In this dedifferentiated liposarcoma model, the XON7 treatment group showed a significant reduction in tumor growth after 3 weeks of treatment. By day 48, all mice in the control group had reached the endpoint, whereas all mice in the XON7 group were still alive.



In this second dedifferentiated liposarcoma model, XON7 treatment led to a marked tumor growth arrest starting after 3 weeks. No mice survived beyond day 34 in the control group, whereas 2 out of 3 mice in the XON7 group were still alive at day 60.

REFERENCE

To learn more about polyclonal antibodies in oncology:
Ciron et al. JCI Insight 2024 Feb 8;9(3)

Poster high resolution

CONCLUSION

- XON7 shows potent cytotoxic against soft tissue sarcoma cells via complement-dependent cytotoxicity and apoptosis
- XON7 reduces tumor-initiating capacity by preventing spheroid formation
- XON7 reduces tumor growth in pdx model of soft tissue liposarcoma after 3 weeks of treatment with no associated toxicity

XON7 can provide a novel and promising therapy against metastatic soft tissue sarcoma

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