

from 2 months (estimated from published clinical data in various types of patients with STS who were previously treated with one active agent and based on clinical assessment) to 3 months; in other words, per the Study design, a 4-week improvement is considered successful. The combination of olaratumab plus doxorubicin showed a 12-week improvement in PFS; the combination *tripled* the Study requirement under which the Study is considered successful. This illustrates an unexpected benefit over the anticipated Study outcome that is based on the standard of care, and the prior art when the Study was designed and initiated. When PFS and OS are compared to the currently available and recently investigated treatments referenced *supra*, the results are noteworthy and illustrate a clear unexpected benefit.

In one aspect of the present disclosure, there is provided olaratumab, doxorubicin and dexrazoxane for use in combination with each other in the treatment of soft tissue sarcoma wherein, following a fourth administration of doxorubicin to a patient, dexrazoxane is to be administered to the patient and wherein dexrazoxane is to be administered following administration of olaratumab to the patient and prior to administration of doxorubicin to the patient, wherein dexrazoxane is to be administered at a dose of about 600 mg/m² to about 750 mg/m², or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

In another aspect of the present disclosure, there is provided a use of olaratumab in the manufacture of a medicament for the treatment of soft tissue sarcoma, wherein the medicament is to be administered in combination with doxorubicin, wherein following the fourth administration of doxorubicin to a patient, a cardioprotective agent is to be administered to the patient, wherein the cardioprotective agent is to be administered following administration of olaratumab to the patient and prior to administration of doxorubicin to the patient, and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 600 mg/m² to about 750 mg/m², or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising olaratumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, a pharmaceutical composition of doxorubicin with one or more pharmaceutically acceptable carriers, diluents, or excipients, and a pharmaceutical

composition of a cardioprotective agent with one or more pharmaceutically acceptable carriers, diluents, or excipients, for use in combination with each other in the treatment of soft tissue sarcoma, wherein following the fourth administration of doxorubicin to a patient, the cardioprotective agent is to be administered to the patient after the olaratumab is administered and before the doxorubicin is administered, and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 600 mg/m² to about 750 mg/m², or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

In another aspect of the present disclosure, there is provided a medicament comprising olaratumab, doxorubicin and dexrazoxane for use in the treatment of soft tissue sarcoma, wherein:

- i) olaratumab is to be administered to a patient, wherein the patient has soft tissue sarcoma; and
- ii) doxorubicin is to be administered to the patient,

wherein following a fourth administration of doxorubicin to the patient dexrazoxane is to be administered to the patient, wherein dexrazoxane is to be administered following administration of olaratumab to the patient and prior to administration of doxorubicin to the patient, and wherein dexrazoxane is to be administered at a dose of about 600 mg/m² to about 750 mg/m², or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

The present disclosure also provides a method of treating a patient having soft tissue sarcoma, comprising administering to the patient in need thereof olaratumab and doxorubicin. In a preferred embodiment of the present disclosure, the olaratumab is administered at a dose of about 15 mg/kg. In another embodiment of the present disclosure, the doxorubicin is administered at a dose of about 60 mg/m² or about 75 mg/m². In a preferred embodiment of the present disclosure, the doxorubicin is administered at a dose of about 75 mg/m². In yet another preferred embodiment of the present disclosure, the olaratumab is administered before the doxorubicin is administered. In a preferred embodiment of the present disclosure, the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides a kit comprising olaratumab and doxorubicin, wherein the olaratumab and the doxorubicin are to be administered simultaneously, separately or sequentially.

The present disclosure further provides a kit comprising a pharmaceutical composition comprising olaratumab, with one or more pharmaceutically acceptable carriers, diluents, or excipients, and a pharmaceutical composition comprising doxorubicin, with one or more pharmaceutically acceptable carriers, diluents, or excipients, wherein the olaratumab and the doxorubicin are to be administered simultaneously, separately or sequentially.

The present disclosure also provides a pharmaceutical composition comprising olaratumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, in combination with a pharmaceutical composition of doxorubicin with one or more

pharmaceutically acceptable carriers, diluents, or excipients, wherein the olaratumab and the doxorubicin are to be administered simultaneously, separately or sequentially for use in the treatment of soft tissue sarcoma.

The present disclosure also provides the use of olaratumab in the manufacture of a medicament for the treatment of soft tissue sarcoma, wherein the medicament is to be administered simultaneously, separately or sequentially with doxorubicin.

The present disclosure also relates to a combination of olaratumab and doxorubicin for simultaneously, separately or sequentially use in the treatment of soft tissue sarcoma.

The present disclosure further provides olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma.

In a preferred embodiment of the present disclosure relating to the pharmaceutical composition disclosed above, the use disclosed above, a combination disclosed above and/or olaratumab for a use disclosed above, the olaratumab is administered at a dose of about 15 mg/kg.

In another embodiment of the present disclosure relating to the pharmaceutical composition disclosed above, the use disclosed above, a combination disclosed above and/or olaratumab for a use disclosed above, the doxorubicin is administered at a dose of about 60 mg/m² or about 75 mg/m².

In a preferred embodiment of the present disclosure relating to the pharmaceutical composition disclosed above, the use disclosed above, a combination disclosed above and/or olaratumab for a use disclosed above, the doxorubicin is administered at a dose of about 75 mg/m².

In yet another preferred embodiment of the present disclosure relating to the pharmaceutical composition disclosed above, the use disclosed above, a combination disclosed above and/or olaratumab for a use disclosed above, the olaratumab is administered before the doxorubicin is administered.

In yet another preferred embodiment of the present disclosure relating to the pharmaceutical composition disclosed above, the use disclosed above, a combination disclosed above and/or olaratumab for a use disclosed above, the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also contemplates the following non-limiting list of embodiments, which are further described elsewhere herein:

In reference to the various embodiments disclosed above, soft tissue sarcoma is disease consisting of but not limited to: leiomyosarcoma, alveolar soft part sarcoma, chondroblastic osteosarcoma, chondrosarcoma, clear cell sarcoma, endometrial stromal sarcoma, epithelial sarcoma, epithelioid, extraskeletal myxoid chondrosarcoma, fibromyxoid sarcoma, fibrosarcoma, fibrosarcomatous transformation in a recurrent dermatofibrosarcoma, hemangiopericytoma, high grade undifferentiated sarcoma, liposarcoma, malignant fibrous histiocytoma, malignant glomus tumor, malignant peripheral nerve sheath tumor, malignant solitary fibrous tumor, malignant spindle cell sarcoma, malignant spindle cell tumor with rhabdoid features, myxofibrosarcoma, myxoid chondrosarcoma, myxoid liposarcoma, myxoid sarcoma, neurofibrosarcoma, osteosarcoma, pleomorphic sarcoma (including: high grade spindle and pleomorphic sarcoma of left thigh, poorly differentiated, round cell sarcoma, sarcoma, smooth muscle tumor, solitary fibrous tumor, spindle cell sarcoma, undifferentiated), rhabdomyosarcoma, synovial sarcoma, undifferentiated sarcoma, and undifferentiated uterine sarcoma. The soft tissue sarcoma may also be selected from the group consisting of leiomyosarcoma and other soft tissue sarcomas. The soft tissue sarcoma may be at an advanced stage.

According to a preferred embodiment of the present disclosure, there is provided a combination or a pharmaceutical composition comprising olaratumab and doxorubicin for separate, simultaneous or sequential use in therapy wherein the combination or pharmaceutical composition is administered parenterally.

According to a preferred embodiment of the present disclosure, there is provided a combination olaratumab and doxorubicin for separate, simultaneous or sequential use in therapy wherein the olaratumab is administered on a 21-day cycle on day one and day eight, wherein each dose of olaratumab falls within the range of about 10 mg/kg to about 18 mg/kg. Preferably, the dose is in the range of about 13.5 mg/kg to about 16.5 mg/kg and most preferably is about 15 mg/kg. Preferably, patients should be treated in cycles of 21 days until evidence of confirmed disease progression.

According to another preferred embodiment of the present disclosure, there is provided a combination of olaratumab and doxorubicin for separate, simultaneous or sequential use in therapy wherein the doxorubicin is administered on a 21-day cycle on day one and day eight, wherein each dose of doxorubicin falls within the range of about

60 mg/m² to about 75 mg/m². Preferably, the dose is about 60 mg/m² and most preferably is about 75 mg/m².

According to a further preferred embodiment of the present disclosure, there is provided a combination comprising olaratumab and doxorubicin for sequential use in therapy, wherein the doxorubicin is administered after the administration of the olaratumab.

According to another embodiment of the present disclosure, there is provided a combination comprising olaratumab and doxorubicin for sequential use in therapy, wherein the doxorubicin is administered one hour after the administration of the olaratumab.

The present disclosure also provides for administering olaratumab at repeated intervals. Preferably, where olaratumab is administered at repeated intervals, the doxorubicin will be administered after the administration of olaratumab. In another embodiment, when the olaratumab is administered at repeated intervals, the doxorubicin will be administered one hour after the administration of the olaratumab.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and the olaratumab is administered before the doxorubicin is administered.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and the doxorubicin is administered at a dose of about 60 mg/m² or about 75 mg/m².

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg, the doxorubicin is administered at a dose of about 60 mg/m² or about 75 mg/m², and the olaratumab is administered before the doxorubicin is administered.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein doxorubicin is administered at a dose of about 75 mg/m² and the olaratumab is administered before the doxorubicin is administered.

Preferably, the present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and the doxorubicin is administered at a dose of about 75 mg/m².

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg, the doxorubicin is administered at a dose of about 75 mg/m², and the olaratumab is administered before the doxorubicin is administered.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab and the doxorubicin are dosed on an a 21-day cycle, the olaratumab is administered at a dose of about 15 mg/kg, the doxorubicin is administered at a dose of about 75 mg/m², and the olaratumab is administered before the doxorubicin is administered.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and the olaratumab is administered before the doxorubicin is administered and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and the doxorubicin

is administered at a dose of about 60 mg/m² or about 75 mg/m² and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg, the doxorubicin is administered at a dose of about 60 mg/m² or about 75 mg/m², and the olaratumab is administered before the doxorubicin is administered and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein doxorubicin is administered at a dose of about 75 mg/m² and the olaratumab is administered before the doxorubicin is administered and wherein the soft tissue sarcoma is leiomyosarcoma.

Preferably, the present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg and the doxorubicin is administered at a dose of about 75 mg/m² and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab is administered at a dose of about 15 mg/kg, the doxorubicin is administered at a dose of about 75 mg/m², and the olaratumab is administered before the doxorubicin is administered and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure also provides for olaratumab for simultaneous, separate or sequential use in combination with doxorubicin in the treatment of soft tissue sarcoma, wherein the olaratumab and the doxorubicin are dosed on an a 21-day cycle, the olaratumab is administered at a dose of about 15 mg/kg, the doxorubicin is administered at a dose of about 75 mg/m², and the olaratumab is administered before the doxorubicin is administered and wherein the soft tissue sarcoma is leiomyosarcoma.

The present disclosure provides for the combination of olaratumab and doxorubicin providing a median OS of approximately 98.9 weeks (at 90%

Confidence Interval [CI]: 89.6, NE [wherein NE denotes that the limit was not reached]) (at 95% CI: 70.9, NE), or at least 70.9 weeks. The invention also provides for the combination of olaratumab and doxorubicin providing a median PFS of approximately 29.9 weeks (at 90% CI: 23.7, 36.0) (at 95% CI: 22.3, 36.7), or at least 22.3 weeks. The present disclosure also provides for the combination of olaratumab and doxorubicin providing approximately a 40-week improvement in OS as compared to doxorubicin alone (the standard of care). The present disclosure also provides for the combination of olaratumab and doxorubicin providing approximately a 12-week improvement in PFS of as compared to doxorubicin alone (the standard of care). The present disclosure also provides for combinations of the aforementioned unexpected benefits.

The present disclosure provides for olaratumab in various aspects disclosed herein. Olaratumab is an antibody specific for human PDGFR α and comprising the sequences disclosed in TABLE 1: (1) the 6 CDR amino acid sequences (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, CDRL3); (2) the heavy chain variable region (VH) and the light chain variable region (VL); (3) the a heavy chain and the light chain; or (4) two heavy chains and two light chains.

The term “soft tissue sarcoma” or “STS,” as used herein, is a malignancy that originates in soft or connective tissue like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues; all of mesenchymal origin. More than 50 histological subtypes of STS have been identified. Subtypes included in the Study included: leiomyosarcoma and “other sarcomas.” Due to low population prevalence, non-leiomyosarcoma soft tissue sarcoma subtypes were represented in the Study collectively as “other sarcoma” for statistical purposes as discussed *infra*. As referred herein, “soft tissue sarcoma” or “STS” is defined as: alveolar soft part sarcoma, chondroblastic osteosarcoma, chondrosarcoma, clear cell sarcoma, endometrial stromal sarcoma, epithelial sarcoma, epithelioid, extraskeletal myxoid chondrosarcoma, fibromyxoid sarcoma, fibrosarcoma, fibrosarcomatous transformation in a recurrent dermatofibrosarcoma, hemangiopericytoma, high grade undifferentiated sarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant glomus tumor, malignant peripheral nerve sheath tumor, malignant solitary fibrous tumor, malignant spindle cell sarcoma, malignant spindle cell tumor with rhabdoid features,

WE CLAIM:

1. Olaratumab, doxorubicin and dexrazoxane for use in combination with each other in the treatment of soft tissue sarcoma wherein, following a fourth administration of doxorubicin to a patient, dexrazoxane is to be administered to the patient and wherein dexrazoxane is to be administered following administration of olaratumab to the patient and prior to administration of doxorubicin to the patient, wherein dexrazoxane is to be administered at a dose of about 600 mg/m^2 to about 750 mg/m^2 , or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.
2. Olaratumab, doxorubicin, and dexrazoxane for use according to Claim 1, wherein the olaratumab is to be administered at a dose of about 15 mg/kg.
3. Olaratumab, doxorubicin, and dexrazoxane for use according to any one of Claims 1 to 2, wherein the doxorubicin is to be administered at a dose of about 60 mg/m^2 or about 75 mg/m^2 .
4. Olaratumab, doxorubicin, and dexrazoxane for use according to Claim 3, wherein the doxorubicin is to be administered at a dose of about 75 mg/m^2 .
5. Olaratumab, doxorubicin, and dexrazoxane for use according to any one of the preceding Claims, wherein the olaratumab is to be administered at a dose of about 15 mg/kg, wherein the doxorubicin is to be administered at a dose of about 75 mg/m^2 , and wherein dexrazoxane is to be administered at a dose of about 750 mg/m^2 .
6. Olaratumab, doxorubicin, and dexrazoxane for use according to any one of the preceding Claims, wherein the soft tissue sarcoma is leiomyosarcoma.
7. Use of olaratumab in the manufacture of a medicament for the treatment of soft tissue sarcoma, wherein the medicament is to be administered in combination with doxorubicin, wherein following the fourth administration of doxorubicin to a

patient, a cardioprotective agent is to be administered to the patient, wherein the cardioprotective agent is to be administered following administration of olaratumab to the patient and prior to administration of doxorubicin to the patient, and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 600 mg/m^2 to about 750 mg/m^2 , or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

8. The use according to Claim 7, wherein the olaratumab is to be administered at a dose of about 15 mg/kg .
9. The use according to any one of Claims 7 to 8 wherein the doxorubicin is to be administered at a dose of about 60 mg/m^2 or about 75 mg/m^2 .
10. The use according to Claim 9, wherein the doxorubicin is to be administered at a dose of about 75 mg/m^2 .
11. The use according to any one of Claims 7 to 10, wherein the olaratumab is to be administered at a dose of about 15 mg/kg , wherein the doxorubicin is to be administered at a dose of about 75 mg/m^2 , and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 750 mg/m^2 .
12. The use according to any one of Claims 7 to 11, wherein the soft tissue sarcoma is leiomyosarcoma.
13. A pharmaceutical composition comprising olaratumab with one or more pharmaceutically acceptable carriers, diluents, or excipients, a pharmaceutical composition of doxorubicin with one or more pharmaceutically acceptable carriers, diluents, or excipients, and a pharmaceutical composition of a cardioprotective agent with one or more pharmaceutically acceptable carriers, diluents, or excipients, for use in combination with each other in the treatment of soft tissue sarcoma, wherein following the fourth administration of doxorubicin to a patient, the cardioprotective agent is to be administered to the patient after the

olaratumab is administered and before the doxorubicin is administered, and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 600 mg/m^2 to about 750 mg/m^2 , or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

14. The pharmaceutical compositions for use according to Claim 13, wherein the olaratumab is to be administered at a dose of about 15 mg/kg.
15. The pharmaceutical compositions for use according to Claim 13 or Claim 14, wherein the doxorubicin is to be administered at a dose of about 60 mg/m^2 or about 75 mg/m^2 .
16. The pharmaceutical compositions for use according to Claim 15, wherein the doxorubicin is to be administered at a dose of about 75 mg/m^2 .
17. The pharmaceutical compositions for use according to any one of claims 13 to 16, wherein the olaratumab is to be administered at a dose of about 15 mg/kg, wherein the doxorubicin is to be administered at a dose of about 75 mg/m^2 , and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 750 mg/m^2 .
18. The pharmaceutical compositions for use according to any one of Claims 13 to 17, wherein the soft tissue sarcoma is leiomyosarcoma.
19. A medicament comprising olaratumab, doxorubicin and dexrazoxane for use in the treatment of soft tissue sarcoma, wherein:
 - i) olaratumab is to be administered to a patient, wherein the patient has soft tissue sarcoma; and
 - ii) doxorubicin is to be administered to the patient, wherein following a fourth administration of doxorubicin to the patient dexrazoxane is to be administered to the patient, wherein dexrazoxane is to be administered following administration of olaratumab to the patient and prior to administration of doxorubicin to the patient, and wherein dexrazoxane is to be

administered at a dose of about 600 mg/m² to about 750 mg/m², or wherein the dosage ratio of dexrazoxane to doxorubicin is 10:1.

20. A medicament for use according to Claim 19, wherein the olaratumab is to be administered at a dose of about 15 mg/kg.
21. The medicament for use according to any one of Claims 19 to 20, wherein the doxorubicin is to be administered at a dose of about 60 mg/m² or about 75 mg/m².
22. The medicament for use according to Claim 21, wherein the doxorubicin is to be administered at a dose of about 75 mg/m².
23. The medicament for use according to any one of Claims 19 to 23, wherein the olaratumab is to be administered at a dose of about 15 mg/kg, wherein the doxorubicin is to be administered at a dose of about 75 mg/m², and wherein the cardioprotective agent is dexrazoxane and is to be administered at a dose of about 750 mg/m².
24. The medicament for use according to any one of Claims 19 to 24, wherein the soft tissue sarcoma is leiomyosarcoma.