NY-ESO-1 TCR T (GSK3377794) – case studies – sarcoma and MRCLS – correlates of predictable response characteristics

Abstract number: 3256175

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Background

- Genetically engineered NY-ESO-1–specific T cells (NY-ESO-1 T cells; GSK3377794) are autologous CD4+ and CD8+ T cells transduced with a self-inactivating lentiviral vector to express an affinity-enhanced NY-ESO-1–specific T-cell receptor.[1]
- Ongoing Phase I and II trials are evaluating GSK3377794 in NY-ESO-1+ and/or LAGE1a+ solid tumors and hematologic malignancies.
- The NY-ESO-1 cancer testis antigen is expressed in approximately 76% of synovial sarcomas (SS)[2] and is ubiquitously expressed in myxoid/round-cell liposarcoma (MRCLS) tumors.[3]

Objectives

- We reviewed the biomarker data of eight patients from two ongoing Phase I/II pilot studies investigating the use of GSK3377794 in the treatment of patients with SS (NCT01343043; n=7) and MRCLS (NCT02992743; n=1) with prolonged complete and/or partial response or stable disease.

Methods

- Patients with SS or MRCLS who were progression free ≥4 months following first infusion were selected.
- All patients received lymphodepletion (30 mg/m^2 x3D fludarabine, 600 mg/m^2 x3D cyclophosphamide) prior to infusion of GSK3377794. Six patients with SS were eligible for a second infusion; prior to this, they received a higher dose of lymphodepletion (30 mg/m^2 x4D fludarabine, 1800 mg/m^2 x2D cyclophosphamide).
- Pre-treatment biopsies were analyzed for CD3+ T-cell infiltration by RNAScope,[4] persistence of transduced cells was measured by quantitative polymerase chain reaction analysis of transgene vector copies in peripheral blood mononuclear cell (PBMC) DNA, cytokine expression was measured by Meso Scale Discovery[5] immunoassay and PBMC phenotypes were characterized by flow cytometry.
  - Cytokine expression data were normalized to the day of infusion (serum collected prior to infusion).
- Response Evaluation Criteria in Solid Tumours v1.1 (RECIST 1.1) criteria[6] were used to determine whether patients had stable disease, partial response or complete response.

Results

Patient characteristics

- Following the first infusion, five of seven patients with SS had stable disease and two had a partial response.
  - The duration of stable disease ranged from 25.3 to 47.3 weeks in the five patients with SS who had stable disease as their best response.
  - The duration of response for two patients with SS was 14.3 and 93.6 weeks, respectively.
    - Tumor images of the upper pelvis lesion over time are shown for the patient having the longest PR in **Figure 1**.
    - The single patient with MRCLS had a partial response, lasting 8.8 months (**Table 1; Figure 1**).
- Six of the seven patients with SS received a second infusion with a higher lymphodepletion regimen.
  - Following second infusion, one of these six patients had a complete response lasting 16.1 weeks, one patient had a partial response lasting 21.3 weeks, and four patients had stable disease (**Table 1**).
  - The duration of stable disease ranged from 11.9 to 36.3 weeks in those four patients.
- Prior to first treatment, immunohistochemistry revealed ≥50% of cells with 2+/3+ intensity of NY-ESO-1 expression; when available, biopsies prior to second infusion confirmed expression of NY-ESO-1.

CD3 infiltration

- Baseline tumor samples consistently (ie, five of five evaluated [eight total]) showed "cold" tumors with low (<2%) CD3+ T-cell infiltration (**Figure 2**).
  - Week 8 biopsies were available for three of eight patients (**Figure 2**).
  - The Week 8 biopsy for Patient 3 was mostly necrotic with evidence of some CD3+ T cells; the Week 8 biopsy for Patient 8 contained mostly stroma and few tumor cells, but infiltration of CD3+ T cells and NY-ESO-1–transduced T cells was evident (**Figure 2**).

Patients receiving 2 infusions

- In three of six patients with SS who received a second infusion, a >10-fold increase in transduced cell peak persistence was observed between the first and second infusion.
  - In these three patients with enhanced peak persistence of transduced cells, one patient had a complete response (Patient 2) and one patient had a partial response (Patient 7) following the second infusion (**Figure 3**).
- Increased expression of cytokines reflecting immune cell activation (eg, IFNγ, IL-6, and IL-2Rα) was observed in patient serum 4–7 days after infusion with GSK3377794 (**Figure 4**); representative examples from patients 4 and 8 are shown in **Figure 4**.
  - The substantial increases in IFNγ and IL-6 observed in Patient 4 were preceded by a higher-dose lymphodepletion regimen; other changes included a 2.7-fold increase in IL-2Rα after second infusion.
  - The patient with MRCLS (Patient 8) showed substantial increases in IL-6 and IL-8, as well as a 2.6-fold increase in IL-1Rα and a 6.3-fold increase in IL-2Rα.

T cells

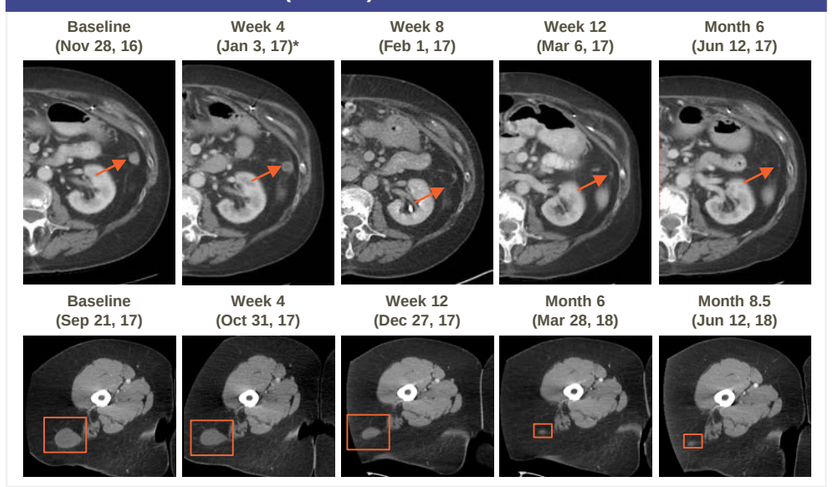
- Post-stimulation T cells within the manufactured product showed an increase in expression of activation markers, such as CD28, inducible T-cell costimulator (ICOS), and CD40L, compared with T cells from apheresis, whereas pentamer-positive transduced cells showed increased CD27 expression relative to non-transduced T cells (example in **Figure 5**).
- In two patients (Patients 2 and 6), transduced CD8+ cells primarily had T effector memory RA+ (T_{EMRA}; CD45RA+CCR7-) and T effector memory (T_{EM}; CD45RA-CCR7-) phenotype, respectively (**Figure 6**).
- Transduced CD8+ T cells in Patient 7 showed the highest proportion (34.3%) of T stem cell memory phenotype (T_{SCM}; CD45RA+CCR7+) with the remainder more evenly distributed over T_{EMRA} (25%), T_{EM}, and T_{CM} (both 20%; **Figure 6**).

Table 1. Patient characteristics

Patient	Best response (1st/ 2nd infusion)	Duration of response or duration of SD (1st/ 2nd infusion), days	NY-ESO-1 expression (screening)	Persistence (peak day), (1st/2nd infusion), copies/µg DNA
1 (SS)	PR	655	80% at 3+ 10% at 2+ 10% at 1+	68,281 (D9)
2 (SS)	PR/CR	100/113	100% at 3+	11,994 (d12) / 128,248 (d14)
3 (SS)	SD/SD	278/83	70% at 3+ 20% at 2+ 10% at 1+	111,259 (d4) / 62,463 (d5)
4 (SS)	SD/SD	331/85	50% at 3+ 30% at 2+ 20% at 1+	69,257 (d7) / 117,909 (d8)
5 (SS)	SD/SD	268/168	20% at 3+ 30% at 2+ 30% at 1+	3,013 (d7)/ 3,174 (d4)
6 (SS)	SD/PR	186/149	30% at 3+ 50% at 2+ 20% at 1+	10,147 (d7) / 185,802 (d7)
7 (SS)	SD/SD	177/254	80% at 3+ 10% at 2+	21,349 (d14) / 341,498 (d7)
8 (MRCLS)	PR	Week 12–Month 9	100% at 3+	78,092 (d7)

CR, complete response; NA, not applicable; PR, partial response; SD, stable disease

Figure 1. Upper pelvis lesion in Patient 1 with SS (top) and leg lesion in Patient 8 with MRCLS (bottom)



*Necrosis is evident as a dark signal within the enhancing lesion

Figure 2. Biopsies from baseline and Week 8 analyzed by RNAScope for CD3+ T-cell infiltration (blue) and NY-ESO-1–transduced cells (red), 20× magnification

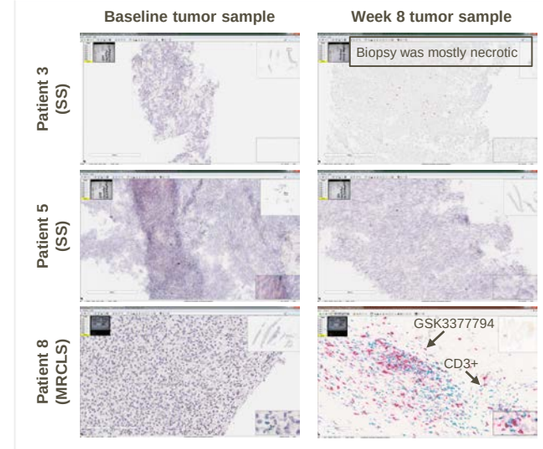


Figure 3. Peak persistence in Patients 2 (left), 6 (middle), and 7 (right)

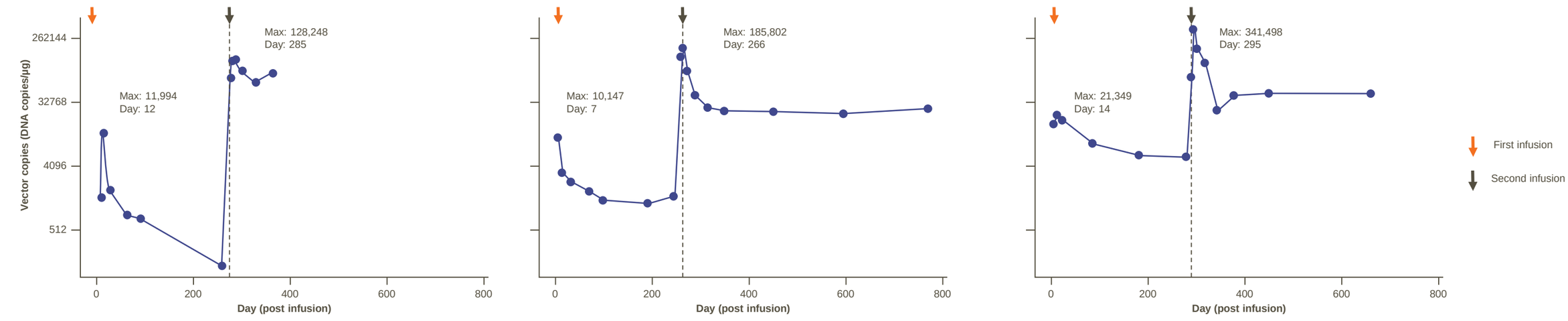


Figure 4. Cytokine fold changes in a patient with SS who received 2 infusions (left) and a patient with MRCLS who received a single infusion of GSK3377794 (right)

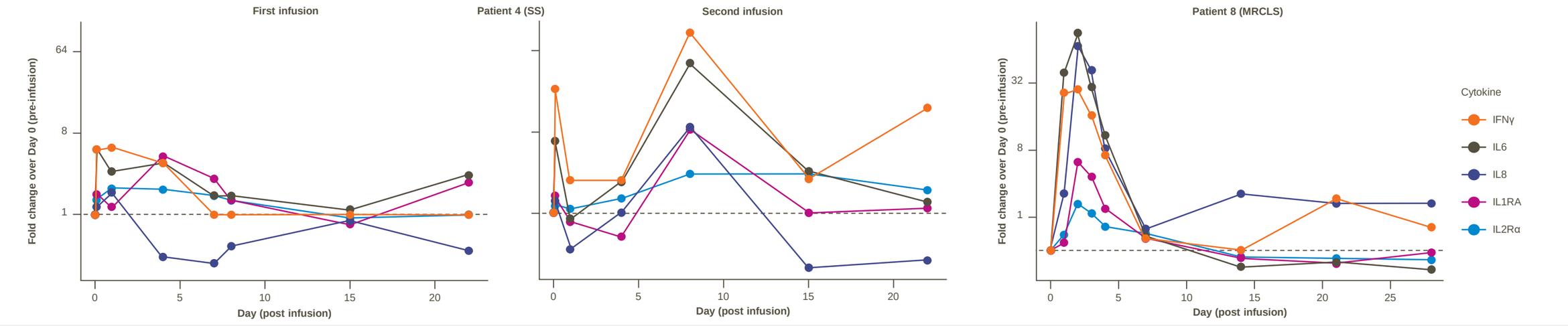


Figure 5. Expression of activation markers in T cells from apheresis (top) and manufactured product (middle and bottom), Patient 2

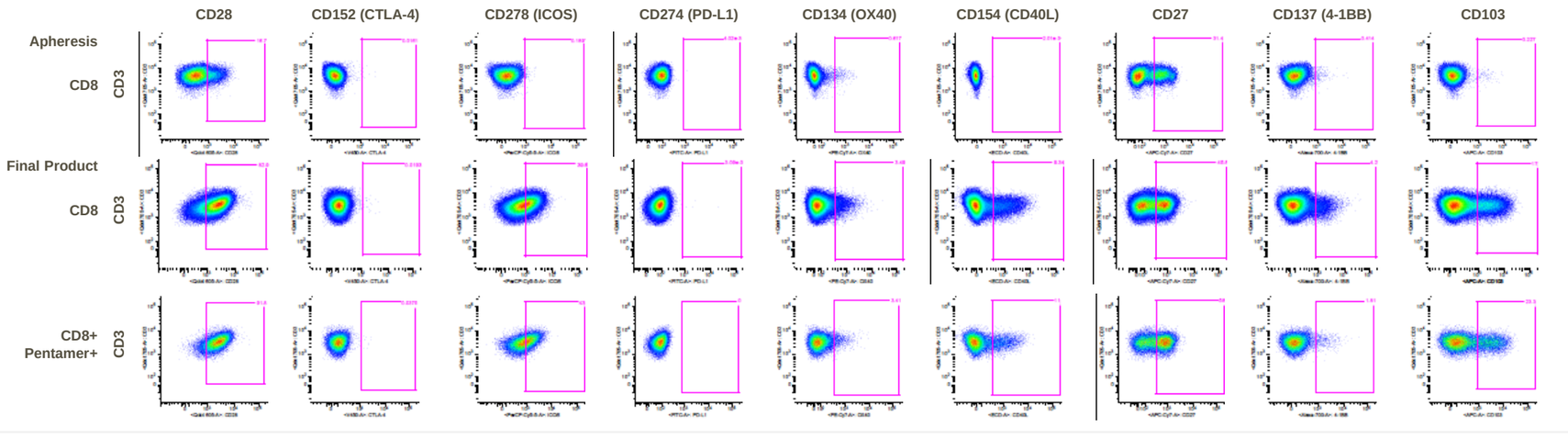
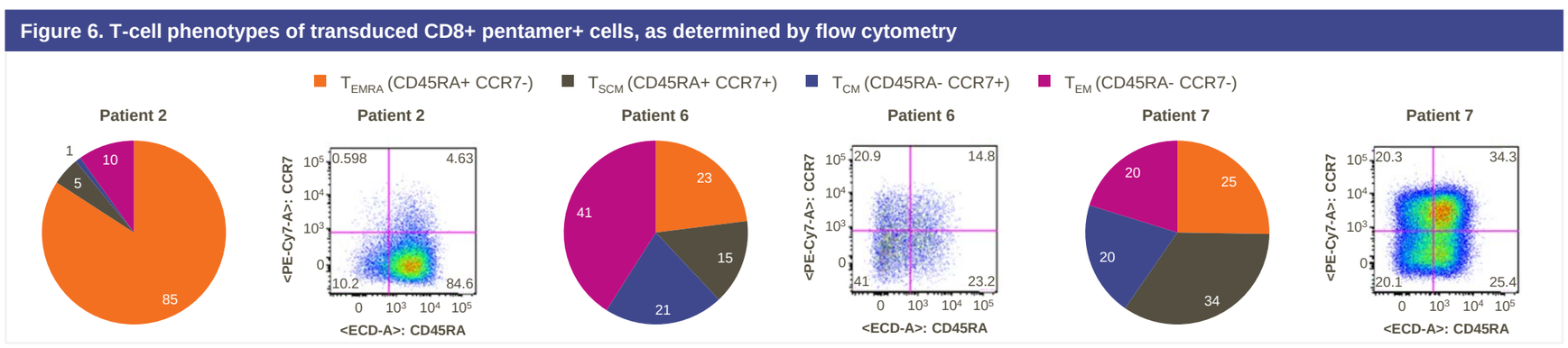


Figure 6. T-cell phenotypes of transduced CD8+ pentamer+ cells, as determined by flow cytometry



Conclusions

- SS and MRCLS tumors showed low immune cell infiltration in five of five evaluated tumor biopsies before NY-ESO-1 T cell infusion.
- Peak persistence of transduced T cells increased >10-fold in three of six evaluated patients with SS who received a second infusion.
- Increased expression of serum cytokines with GSK3377794 infusion was observed in five of five evaluated patients.
- Higher expression of activation markers was observed in transduced T cells within the manufactured product compared with those from apheresis.
- Further analysis may identify predictive biomarkers of clinical response characteristics or of safety.

References

1. NIH National Cancer Institute. NCI Drug Dictionary 2019. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/autologous-anti-ny-eso-1-tage-1-tcr-transduced-c259-t-lymphocytes [Accessed September 2019]; 2. Lai JP, et al. *Mod Pathol* 2012;6:854–8; 3. Pollack SM, et al. *Cancer* 2012;118(18):4564–70; 4. Advanced Cell Diagnostics. RNAscope® Technology: A Novel RNA in situ Hybridization Research Platform 2019. Available from: https://acdbio.com/ mascope%C2%AE-technology-novel-ma-situ-hybridization-research-platform [Accessed September 2019]; 5. Meso Scale Diagnostics. MSD 2019. Available from https://www.mesoscale.com/ [Accessed September 2019]; 6. Eisenhauer EA, et al. *Eur J Cancer* 2009;45(2):228–47.

Disclosures

BAVT: consulting role: Epizyme, Lilly, Janssen, Immune Design, Daiichi-Sankyo, Bayer; paid presentation: Lilly; research support: Pfizer, Merck, TRACON; editorial role: *Journal of Clinical Oncology* and *Rare Tumours*; **SPDA**: advisory or consulting role: Incyte, Merck, Nektar, Amgen, EMD Serono, GSK, Immune Design; travel expenses: Adaptimmune, EMD Serono, Nektar; **AG**: stock/stock options: Amgen; employee and stockholder in GSK; **LAJ**: intellectual property: University of Pennsylvania; employee and stockholder in GSK; **ANH**: royalties: Atara Biotherapeutics, stock/stock options: Merck; employee and stockholder in GSK; **JT**, **DT**, **MPD**, and **YW** are employees of and stockholders in GSK; **DA** has nothing to disclose.

Ethics approval statement

- This study was approved by the appropriate institutional review boards and independent ethics committees.
- The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol.

Acknowledgments

- These studies (NCT01343043 and NCT02992743) were funded by GlaxoSmithKline (GSK).
- We thank Jeff Wetherington for his contribution to biomarker data analysis.
- Editorial support was provided by Gillian Wallace, MSc, of Fishawack Indicia Ltd, UK, and was funded by GSK.

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Presented at the Connective Tissue Oncology Society (CTOS) Annual Meeting, Tokyo, Japan, November 13–16, 2019