

Phase I trial of NY-ESO-1-specific adoptive T-cell therapy with GSK3377794 in patients with advanced synovial sarcoma: report of Cohorts 2 and 4

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D'Angelo SP¹, Demetri G², Van Tine BA³, Druta M⁴, Glod J⁵, Chow W⁶, Tress J⁷, DeYoung MP⁷, Hasan AN⁷, Wu Y⁷, Turner DC⁷, Ji R⁷, Gyurdivia A⁷, Araujo D⁸

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Dana Farber Cancer Institute, Boston, MA, USA; ³Washington University in St. Louis, MO, USA; ⁴H. Lee Moffitt Cancer Center, Tampa, FL, USA; ⁵National Cancer Institute, Bethesda, MD, USA; ⁶City of Hope Comprehensive Cancer Center, Duarte, CA, USA; ⁷GSK, Collegeville, PA, USA; ⁸University of Texas/MD Anderson Cancer Center, Houston, TX, USA

Background

- Adoptive T-cell receptor (TCR) therapy is a promising treatment for recurrent or metastatic solid and hematologic malignancies with encouraging activity demonstrated in patients with synovial sarcoma, melanoma, and multiple myeloma.¹⁻³
- New York esophageal antigen-1 (NY-ESO-1) is a member of the cancer-testis family of tumor antigens that generates a SLLMWITQC peptide bound to HLA-A*02.
- NY-ESO-1 is expressed across multiple malignancies including in 76% of stage IV synovial sarcomas,⁴ but its expression is restricted to the germ cells of the adult testis in healthy adult tissue.^{5,6}
- 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 affinity-enhanced NY-ESO-1-specific TCRs, recognizing the SLLMWITQC/human leukocyte A (HLA)-A*02:01,*02:05 and/or 02*06 peptide complex (Figure 1).
- Ongoing Phase I and II trials are evaluating GSK3377794 in solid tumors and multiple myeloma.
- Study NCT01343043 (208466) is a Phase I clinical trial assessing GSK3377794 in patients with previously treated advanced metastatic synovial sarcoma (Figure 2), stratified into 4 cohorts by NY-ESO-1 expression and lymphodepletion regimen (Table 1).
 - Previously reported information on 12 patients receiving GSK3377794 infusion in Cohort 1 showed that responses were observed in 6 patients, including 1 complete and 5 partial responses (overall response rate [ORR] of 50%, with a 95% confidence interval [CI] of 0.21, 0.79).⁷ Updated data (as of March 4, 2019) showed that:
 - Median progression-free survival (PFS) was 15.4 weeks (95% CI: 7.7, 38.0).
 - Median duration of response (DoR) was 31.0 weeks (95% CI: 13.4, not available [NA]).
 - Median overall survival (OS; as of January 28, 2019) was 24.3 months (95% CI: 8.5, NA).
 - Cohort 3 was not enrolled further for utility.

Figure 1. GSK3377794 mechanism of action

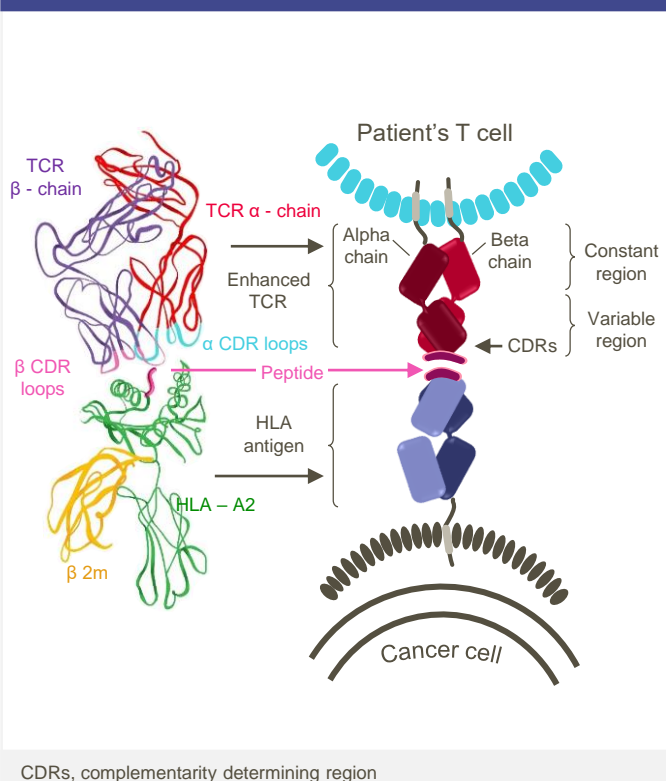


Table 1. Antigen expression and lymphodepleting regimen for each cohort in study 208466

	NY-ESO-1 expression	Lymphodepletion regimen
Cohort 1 n=12	HIGH IHC score 2+ or 3+ in ≥50% of tumor cells	HIGH doses of fludarabine and cyclophosphamide • Fludarabine 30 mg/m ² IV on Days -5 to -2 • Cyclophosphamide 1800 mg/m ² IV on Days -3 and -2
Cohort 2 n=13	LOW IHC score ≥1+ in ≥1% cells but not exceeding 2+ or 3+ in ≥50% cells	HIGH doses of fludarabine and cyclophosphamide • Fludarabine 30 mg/m ² IV on Days -5 to -2 • Cyclophosphamide 1800 mg/m ² IV on Days -3 and -2
Cohort 3 n=5	HIGH IHC score 2+ or 3+ in ≥50% of tumor cells	HIGH dose of cyclophosphamide only • Cyclophosphamide 1800 mg/m ² IV on Days -3 and -2
Cohort 4 n=15	HIGH IHC score 2+ or 3+ in ≥50% of tumor cells	LOW doses of fludarabine and cyclophosphamide • Fludarabine 30 mg/m ² IV • Cyclophosphamide 600 mg/m ² IV on Days -7 to -5

Objectives

- Report response data and peak persistence of GSK3377794 for Cohort 2 (patients with low NY-ESO-1 expression who received high dose lymphodepletion) and Cohort 4 (patients with high NY-ESO-1 expression who received low dose lymphodepletion) of the Phase I study and evaluate the relationship between these parameters.

Results

Patients

- As of April 2019, 50 patients were enrolled on the study; 14 and 16 patients enrolled in Cohorts 2 and 4, respectively (Table 2).
 - 13 patients in Cohort 2 and 15 patients in Cohort 4 received ≥1 GSK3377794 infusion and were included in the mITT population.
- The median time on study was 107 days (range, 3–534) for patients in Cohort 2 and 242 days (range, 33–739) for patients in Cohort 4.

Efficacy

- The ORR was 31% for Cohort 2 and 27% for Cohort 4 (Table 3).
 - Figure 3 shows depths of responses.
- The median DoR was 9.1 weeks in Cohort 2 and 16.4 weeks in Cohort 4.
 - Median duration of stable disease was longest in Cohort 4.
- Median PFS was 13.1 weeks for patients in Cohort 2 and 22.4 weeks for patients in Cohort 4 (Table 3).
- Median OS was 9.9 and 24.2 months for patients in Cohort 2 and 4, respectively (Table 3); 6 patients in Cohort 4 received a second infusion.

GSK3377794 persistence

- Persistence of GSK3377794 was measured to explore relationships with response, as well as a long-term safety measure.
- At the first week post infusion, median peak (range) persistence was ~64,712 DNA copies/μg (range, 13,364–197,546) in Cohort 2 and ~16,468 DNA copies/μg (range, 163–131,175) in Cohort 4 (Figure 4A).
- The median time to peak persistence was 8 days (range, 4–18) for Cohort 2 and 8 days (range, 5–16) for Cohort 4.
- No statistically significant correlation was observed between peak persistence and best overall response in Cohorts 2 and 4 (logistic regression P>0.05) (Figure 4B).

Safety

- Treatment-related adverse events (TRAEs) that occurred in ≥40% patients across all cohorts (n=45) were pyrexia (69%), leukopenia/white blood cell count decreased (60%), neutropenia/neutrophil count decreased (56%), anemia/red blood cell count decreased (53%), thrombocytopenia/platelet count decreased (49%), cytokine release syndrome (CRS; 44%), lymphopenia/lymphocyte count decreased (44%), dyspnea (42%), and nausea (40%).
 - When assessed by cohort, additional TRAEs that occurred in ≥40% patients were rash/maculopapular rash in 54% of the 13 patients in Cohort 2 and febrile neutropenia and hypotension in 40% of the 15 patients in Cohort 4.
- Across all cohorts (n=45), Grade 3/4 AEs that occurred in ≥40% of patients were leukopenia (89%), neutropenia (78%), anemia (67%), thrombocytopenia (67%), lymphopenia (64%), and hypophosphatemia (42%).
- No additional Grade 3/4 AEs occurred in ≥40% of the 13 patients in Cohort 2 or the 15 patients in Cohort 4.
- For AEs of special interest, CRS occurred in 54% of patients in Cohort 2 and 33% of patients in Cohort 4 (shown by Grade in Figure 5).
 - Additional AEs of special interest that occurred in Cohort 2 were Grade 5 recurrent pancytopenia and Grade 5 bone marrow failure in 1 (8%) patient, Grade 3 Guillain-Barré syndrome in 2 (15%) patients and Grade 1 peripheral sensory neuropathy in 1 (8%) patient; none of these events occurred in Cohort 4.

Table 2. Patient demographics and baseline characteristics (ITT population)

	Cohort 2 (n=14)	Cohort 4 (n=16)
Male, n (%)	7 (50)	8 (50)
Median age, years (range)	32.5 (11–73)	36.5 (20–69)
NY-ESO status		
High	0	16 (100)
Low	14 (100)	0
HLA status		
HLA-A*02:01	14 (100)	15 (94)
HLA-A*02:05	0	1 (6)
HLA-A*02:06	0	0
Histology		
Monophasic	10 (71)	11 (69)
Biphasic	3 (21)	3 (19)
Other	1 (7)	2 (13)
Disease stage at screening, n (%)		
I	1 (7)	1 (6)
II	0	1 (6)
III	11 (79)	10 (63)
IV	2 (14)	4 (25)
Other		

Table 3. Summary of response timing, duration, and survival outcomes in study Cohorts 2 and 4 (mITT population)

Primary endpoint	Cohort 2 (n=13)	Cohort 4 (n=15)
ORR, n (%), 95% CI	4 (30.8) 0.09, 0.61	4 (26.7) 0.08, 0.55
Best overall response, n (%)		
Complete response	0	0
Partial response	4 (30.8)	4 (26.7)
Stable disease	7 (53.8)	10 (66.7)
Progressive disease	1 (7.7)	1 (6.7)
Not evaluable	1 (7.7)	0
Additional efficacy outcomes, median (95% CI)		
Time to response, weeks	4.5 (4.1, 6.0)	6.6 (3.7, 12.1)
DoR, weeks	9.1 (8.0, 13.0)	16.4 (14.3, 93.6)
Duration of stable disease, weeks	13.1 (7.9, 17.6)	22.4 (11.3, 26.6)
PFS, weeks	13.1 (7.9, 13.9)	22.4 (11.3, 26.6)
OS, months	9.9 (3.9, 19.6)	24.2 (9.2, NA)

Methods

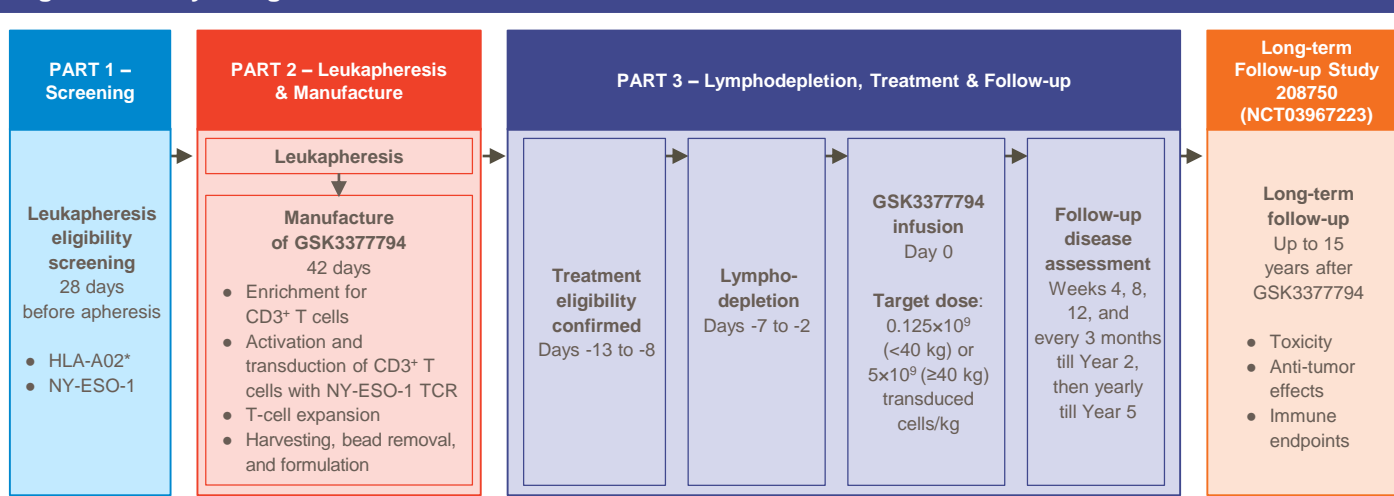
Key eligibility criteria

- Inclusion criteria:
 - Age ≥4 years
 - Histologically confirmed unresectable, metastatic, progressive, persistent, or recurrent disease
 - HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 positive
 - Tumor expression of NY-ESO-1 antigen (by immunohistochemistry [IHC])
 - Prior treatment with standard chemotherapy containing ifosfamide and/or doxorubicin
 - Measurable disease according to Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1)
 - Eastern Cooperative Oncology Group 0–1; for children aged ≤10 years, Lansky >60
- Exclusion criteria:
 - Active HIV, hepatitis C/B, or human T-lymphotropic virus 1/2 infection
 - Clinically significant systemic illness
 - Untreated central nervous system metastasis
 - Previous treatment with genetically engineered NY-ESO-1 specific T cells

Study design

- Patients were enrolled to one of four cohorts based on NY-ESO-1 expression by IHC (Table 1).
- Depending on cohort, patients underwent high dose or low dose lymphodepletion with cyclophosphamide with or without fludarabine (Figure 2), before receiving a single intravenous (IV) infusion of GSK3377794.

Figure 2. Study design



Outcome measures

- Primary outcome:
 - ORR, per investigator assessment using RECIST v1.1.
- Additional outcomes:
 - Duration of response
 - PFS, defined as the interval between first T-cell infusion and first documented disease progression or death
 - OS, defined as the interval between the date of first T-cell infusion and date of death due to any cause
 - GSK3377794 persistence in transduced peripheral blood mononuclear cells, with transgene vector copies measured by quantitative polymerase chain reaction
 - Safety was monitored throughout and evaluated using Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0)

Statistical analysis

- The intent-to-treat (ITT) population included all enrolled patients, and was used to describe patient demographic and clinical characteristics.
 - Safety and efficacy were evaluated in all enrolled patients who received ≥1 dose of study drug (modified ITT [mITT] population).
 - All efficacy outcomes are summarized based on first infusion.
- The study was not designed/powerd for cohort comparison.
- The data cutoff date for these analyses was March 4, 2019, except for OS data, which used a January 28, 2019 cutoff.

Figure 3. Maximal reduction in sum of diameters of target lesions from baseline through progression or prior to surgical resection for patients receiving their first GSK3377794 infusion (mITT population) in (A) Cohort 2 and (B) Cohort 4

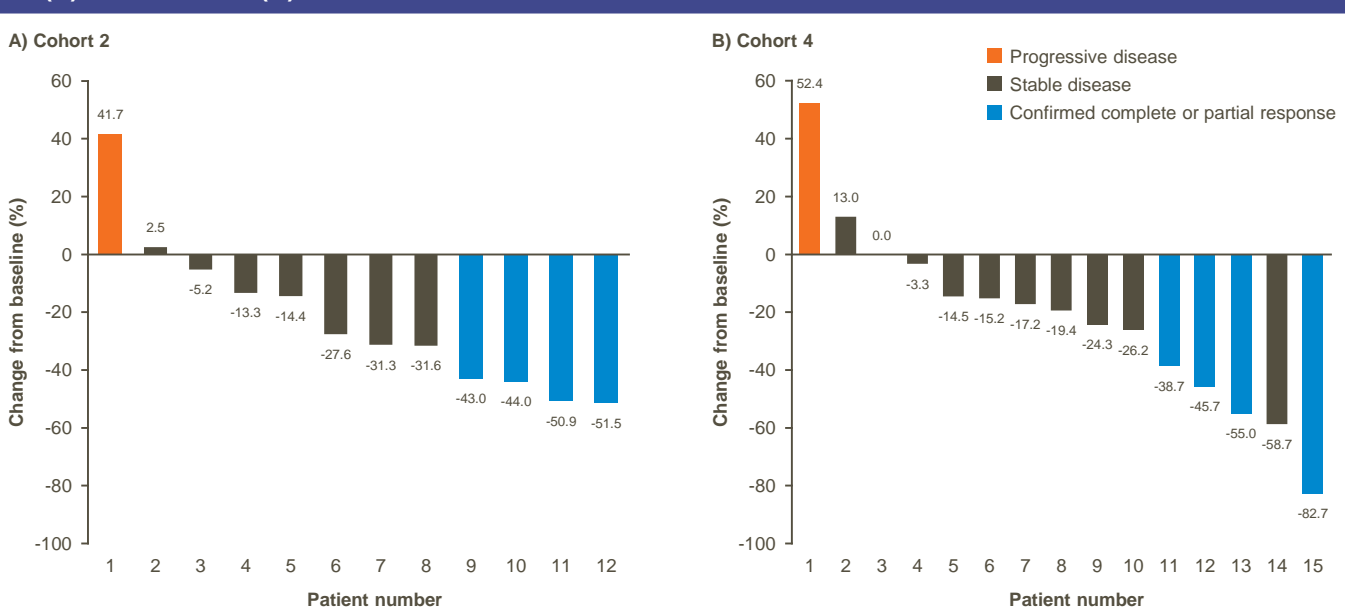
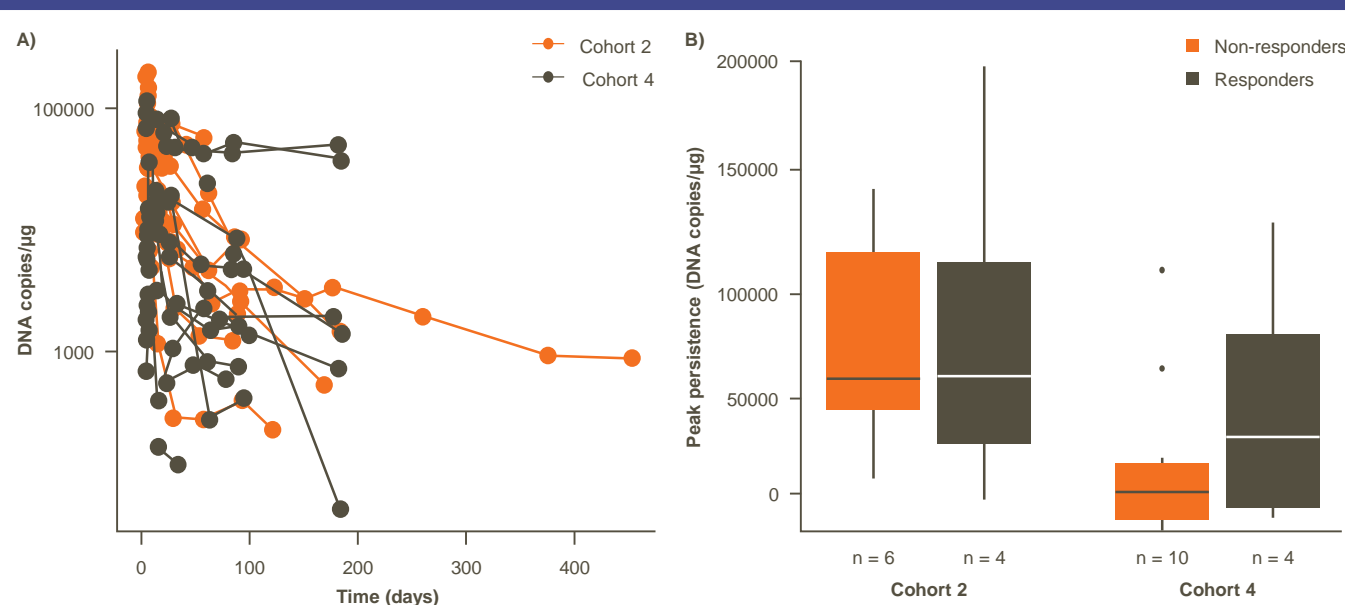
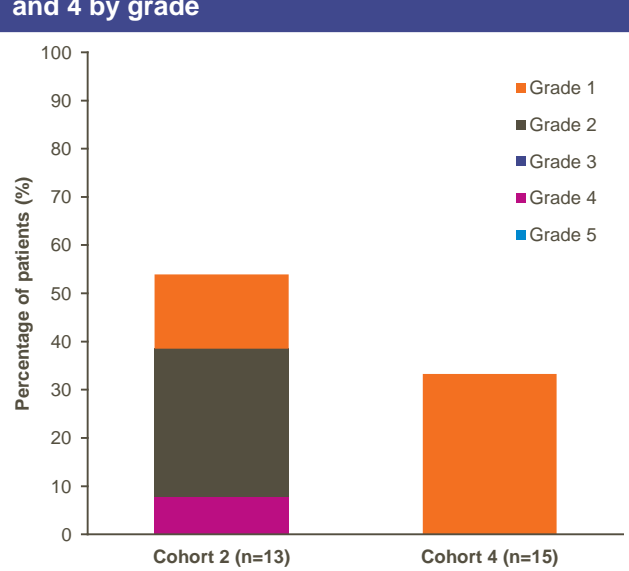


Figure 4. (A) GSK3377794 peak persistence and (B) relationship between GSK3377794 peak persistence and best overall response (including complete and partial response)*



*Data were missing for four patients (Cohort 2, n=3; Cohort 4, n=1)

Figure 5. Incidence of CRS in Cohorts 2 and 4 by grade



Conclusions

- Cohorts 2 and 4 showed similar ORRs; however, more durable responses were observed in Cohort 4, with prolonged DoR, duration of stable disease, and PFS.
- Peak persistence of GSK3377794 was higher in Cohort 2, though there was no detectable correlation with response, unlike data previously reported for Cohort 1.⁷
- The ORR observed in Cohort 1 was higher, with prolonged DoR and OS, in comparison with Cohorts 2 and 4. Further development of GSK3377794 in synovial sarcoma is based on data from Cohort 1.

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Disclosures
• SPDA: advisory or consulting role: Incyte, Merck, Nektar, Amgen, EMD Serono, GSK, Immune Design, travel expenses: Adaplimmune, EMD Serono, Nektar; GD: advisory or consulting role: Adaplimmune, Blueprint, Caris Life Sciences, Daiichi-Sankyo, Eisai, EMD-Serono, Janssen Oncology, Kolltan Pharmaceuticals, Novartis, PharmaMar, Blueprint, Merimack Pharmaceuticals, Caris Life Sciences, Daiichi-Sankyo; research funding: Bayer, Janssen Oncology, Novartis, Pfizer; stock holdings in Blueprint, Caris Life Sciences, G1 Therapeutics, Merimack Pharmaceuticals; BAVT: consulting role: Epizyme, Lilly, Janssen, Immune Design, Daiichi-Sankyo, Bayer; paid presentation: Lilly; research support: Pfizer, Merck, TRACON; editorial role: *J Clin Oncol* and *Rare Tumors*; MD: consulting role: Daiichi-Sankyo, Blueprint; paid presentation: Eisai; WC: advisory or consulting role: GSK, Novartis, AdvenChen; ANH: royalties: Atara Biotherapeutics, stock/stock options: Merck; employee and stockholder in GSK; AG: stock/stock options: Amgen; employee and stockholder in GSK; MPD, JT, YW, and DCT are employees of and stockholders in GSK; RJ is an employee of GSK; JG and DA have 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 entirely and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol.
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