Abstract

Background: Gemcitabine plus nab-paclitaxel (GnP) has been a standard treatment for unresectable pancreatic cancer (uPC); however, the current treatment status and usefulness in older adults with uPC remain unclear. Therefore, we aimed to investigate the patient background and compare the efficacy and safety of GnP versus other treatments in older adults with uPC.

Patients and Methods: In this prospective observational study, we enrolled 233 eligible patients aged ≥76 years with pathologically proven, clinically uPC, and no history of chemotherapy from 55 Japanese centers during September 2018-September 2019. The main endpoints were

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overall survival (OS), progression-free survival (PFS), and safety. Geriatric assessments were performed upon registration and after 3 months. To adjust for confounders, we conducted propensity score-matched analyses.

Results: GnP, gemcitabine alone (Gem), best supportive care, and other therapies were administered to 116, 72, 16, and 29 patients, respectively. In the propensity score-matched analysis, 42 patients each were selected from the GnP and Gem groups. The median OS was longer in the GnP group than in the Gem group (12.2 vs. 9.4 months; hazard ratio [HR], 0.65; 95% CI, 0.37-1.13). The median PFS was significantly longer in the GnP group than in the Gem group (9.2 vs. 3.7 months; HR, 0.38; 95% CI, 0.23-0.64). The incidence of severe adverse events was higher with GnP than with Gem; however, the difference was not significant.

Conclusion: GnP is more efficacious than Gem in patients aged ≥76 years with uPC despite demonstrating a higher incidence of severe adverse events.

Key words: albumin-bound paclitaxel; gemcitabine; pancreatic cancer; aged; vulnerable population; geriatric assessment.

Implications for Practice
Gemcitabine plus nab-paclitaxel (GnP) has demonstrated survival benefits superior to those of gemcitabine monotherapy (Gem) for patients with advanced pancreatic cancer (PC) in a phase III study; however, the indications of GnP for older adults have been debated because of limited evidence. We conducted a multicenter prospective observational study involving geriatric assessments to compare the benefits of GnP and Gem for PC patients aged ≥76 years. The results of propensity score-matched analyses showed that GnP was more efficacious than Gem despite its associated higher incidence of grades 3-4 adverse events. Geriatric assessment may be useful for predicting prognosis and determining treatment.

Introduction
Pancreatic cancer (PC) is the seventh leading cause of cancer-related deaths worldwide, accounting for approximately 466 000 cases in 2020. The incidence of PC increases with an aging society. In Japan, the world’s fastest aging country, patients aged ≥75 years accounted for approximately 60% of all deaths from PC in 2019.

Surgical resection is the only curative treatment for PC; however, it is rare that patients are candidates for surgical resection, and the disease often recurs after surgery. For patients with unresectable or recurrent disease, supportive care with or without systemic chemotherapy is the main treatment option. In recent years, some combination regimens have been developed for advanced PC, including fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), as well as the gemcitabine plus nab-paclitaxel regimen (GnP). Toxicities observed in the phase III study of FOLFIRINOX (PRODIGE4/ACCORD11), such as neutropenia, thrombocytopenia, fatigue, vomiting, diarrhea, and peripheral sensory neuropathy, were relatively severe compared with those in gemcitabine (Gem) alone in patients aged ≤76 years. Thus, FOLFIRINOX is recommended only for patients with good performance status (PS) or those aged <76 years. GnP demonstrated superior overall survival (OS) in the phase III trial (MPACT) compared with Gem. Patients older than 75 years and those with poor PS were eligible for MPACT; therefore, GnP may be applied to the aforementioned group of patients in daily clinical practice. However, only 10% of the patients aged >75 years were included in MPACT. Despite some studies evaluating the effectiveness of GnP in the older adults, they were retrospectively designed using a single arm. This warrants a prospective study comparing GnP with other treatments in older adults with unresectable PC.

The treatment guidelines for older adults with cancer by the American Society of Clinical Oncology, National Comprehensive Cancer Network, and International Society of Geriatric Oncology recommend the use of the geriatric assessment, which can detect impairment unidentified in routine history or physical examination. Moreover, it can predict the incidence of severe adverse events and prognosis in older adults receiving systemic chemotherapy for cancer.
Table 1. Background characteristics of patients in the full analysis set.

|                          | GnP | Gem | Other* | \(P\)-value |
|--------------------------|-----|-----|--------|-------------|
| No. of patients (%)      | 116 (49.8) | 72 (30.9) | 45 (19.3) | –           |
| Age, years               |     |     |        | <.0001      |
| Median (range)           | 77 (76-85) | 81 (76-88) | 81 (76-88) | .9787       |
| NLR                      | 2.79 (1.15-33.54) | 2.90 (0.82-11.80) | 2.92 (0.75-89.00) | .9787       |
| CA19-9 (U/mL)            | 541.0 (0.4-223731.0) | 2850.0 (2.0-500 000.0) | 968.0 (1.0-703036.0) | .0129       |
| Sex                      |     |     |        | .0420       |
| Male                     | 67 (57.8) | 28 (38.9) | 23 (51.1) | .0066       |
| Female                   | 49 (42.2) | 44 (61.1) | 22 (48.9) | .0066       |
| Stage                    |     |     |        | .0066       |
| I                        | 0 (0.0) | 2 (2.8) | 3 (6.7) | .0066       |
| II                       | 2 (1.7) | 4 (5.6) | 6 (13.3) | .0066       |
| III                      | 28 (24.1) | 19 (26.4) | 11 (24.4) | .0066       |
| IV                       | 86 (74.1) | 47 (65.3) | 25 (55.6) | .0066       |
| ECOG PS                  |     |     |        | .0066       |
| 0                        | 71 (61.2) | 25 (34.7) | 16 (35.6) | .0066       |
| 1                        | 41 (35.3) | 40 (55.6) | 20 (44.4) | .0066       |
| 2                        | 4 (3.4) | 7 (9.7) | 6 (13.3) | .0066       |
| 3                        | 0 (0.0) | 0 (0.0) | 3 (6.7) | .0066       |
| G8                       |     |     |        | .1030       |
| ≤14                      | 99 (85.3) | 69 (95.8) | 42 (93.3) | .1030       |
| >14                      | 15 (12.9) | 3 (4.2) | 2 (4.4) | .1030       |
| Null                     | 2 (1.7) | 0 (0.0) | 1 (2.2) | .1030       |
| IADL: male               |     |     |        | .1568       |
| ≤4                       | 24 (35.8) | 15 (53.6) | 10 (43.5) | .1568       |
| 5                        | 42 (62.7) | 13 (46.4) | 11 (47.8) | .1568       |
| Null                     | 1 (1.5) | 0 (0.0) | 2 (8.7) | .1568       |
| IADL: female             |     |     |        | .1043       |
| ≤7                       | 17 (34.7) | 23 (52.3) | 13 (59.1) | .1043       |
| 8                        | 30 (61.2) | 21 (47.7) | 8 (36.4) | .1043       |
| Null                     | 2 (4.1) | 0 (0.0) | 1 (4.5) | .1043       |
| CCI                      |     |     |        | .0785       |
| 0                        | 90 (77.6) | 57 (79.2) | 27 (60.0) | .0785       |
| ≥1                       | 25 (21.6) | 15 (20.8) | 17 (37.8) | .0785       |
| Null                     | 1 (0.9) | 0 (0.0) | 1 (2.2) | .0785       |
| Mini-COG                 |     |     |        | .3484       |
| ≤2                       | 12 (10.3) | 14 (19.4) | 8 (17.8) | .3484       |
| ≥3                       | 102 (87.9) | 57 (79.2) | 36 (80.0) | .3484       |
| Null                     | 2 (1.7) | 1 (1.4) | 1 (2.2) | .3484       |

*Other includes patients who received best supportive care, S-1 monotherapy, S-1 with concurrent radiotherapy, gemcitabine with concurrent radiotherapy and unknown in 16, 10, 5, 1, and 13, respectively.

\(P\)-value, \(P\)-value calculated using Wilcoxon rank-sum test for quantitative data/\(P\)-value calculated using Fisher’s exact test for qualitative data.

Abbreviations: GnP, gemcitabine + nab-paclitaxel; Gem, gemcitabine; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NLR, neutrophil-to-lymphocyte ratio; CA19-9, carbohydrate antigen 19-9; G8, geriatric 8; IADL, instrumental activity of daily living; CCI, Charlson comorbidity index; Mini-COG, Mini Cognitive Scale.
Therefore, it is preferable to include geriatric assessment data in a clinical study comprising older adults with cancer.

Based on the above information, we aimed to conduct a multicenter, prospective, observational study to investigate patient background, including geriatric assessment, and to compare the efficacy and safety of GnP versus other treatments in older adults with unresectable PC.

Materials and Methods

Patients

We conducted a prospective observational study across 55 Japanese institutions. We enrolled patients with PC aged ≥76 years upon registration. Other inclusion criteria were as follows: (1) clinically and radiologically diagnosed with PC; (2) histologically or cytologically proven ductal carcinoma; (3) no history of irradiation or systemic chemotherapy for the treatment of PC, except adjuvant chemotherapy at least 6 months before registration; (4) unresectable PC because of advanced disease, patient’s condition, and willingness; (5) capable of receiving geriatric assessment; and (6) provided written informed consent. The study was approved by the institutional review board of each participating institution. The study was conducted according to the tenets of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects (clinical trial registration number: UMIN000034265).

Treatment and Assessment

Upon registration, we evaluated patients’ conditions, including Eastern Cooperative Oncology Group (ECOG) PS, clinical stage, and laboratory data, such as neutrophil count, lymphocyte count, and carbohydrate antigen 19-9 (CA19-9). In addition, we performed geriatric assessment using the Geriatric-8 (G8), the instrumental activity of daily living (IADL), Charlson comorbidity index (CCI), and Mini Cognitive Scale (Mini-COG). The G8 and IADL were re-evaluated 3 months after registration. Treatment groups were defined according to first-line treatment. Dose modification and treatment rest were performed at the physician’s discretion during each treatment. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0. We collected the incidence of grade 4 hematological and grades 3-4 non-hematological adverse events and emergent admission to the hospital within 3 months of first-line treatment. The best radiological response was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.1. Progression-free survival (PFS) was defined as the duration from the date of initiating first-line treatment to the date of documented progression based on radiological or clinical findings, death from any cause, or final survival confirmation date. OS was calculated from the date of initiating first-line treatment to the date of death from any cause or the final survival confirmation date.

Statistical Analyses

For patient characteristics in each treatment group, continuous variables are expressed as medians with ranges, and categorical values are expressed as frequencies with percentages. We performed Fisher’s exact test and the Mann-Whitney U test to compare the continuous and categorical variables, respectively. We used the Kaplan-Meier method to calculate the cumulative survival rate and median event-free time of PFS and OS with a 95% CI. The log-rank test and Cox regression hazards model were used to compare the aforementioned
time-to-event parameters between GnP and Gem. A propensity score-matched analysis was conducted to compare the efficacy and safety of GnP and Gem for cases in which OS could be calculated and patient factors were not missing (N = 185). We used a propensity score model incorporating age, sex, clinical stage, ECOG PS, CA19-9 level, and neutrophil-to-lymphocyte ratio as factors to estimate the propensity score for each patient. The caliper, which is the limit of the range of the distance of the propensity score when selecting matching targets, was set at a generally recommended value of 0.2. Age, CA19-9 level (log-transformed), and neutrophil-to-lymphocyte ratio (log-transformed) were included in the model as continuous values, while gender, clinical stage (IV/not), and ECOG PS (0/not) were categorical variables. Furthermore, we used the results of this analysis to determine PFS. While analyzing geriatric assessment scores as a prognostic and predictive value, we used the following cutoff scores reported in the original literature: vulnerability should be fully evaluated in patients with a G8 score of ≤14, an IADL score of ≤4 in men and that of ≤7 in women, a CCI score of ≥1, and a Mini-COG score of ≤2. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics
A total of 235 patients were enrolled between September 2018 and September 2019. 2 patients were excluded from the full analysis set due to duplicate registration in one patient and unavailable data in the other patient who was transferred to another hospital immediately after registration. In the efficacy analysis, we additionally excluded 36 patients from the full analysis set because of missing data on treatment outcomes and patient background characteristics in 33 and 3 cases, respectively (Fig. 1). Therefore, the efficacy analysis set consisted of 115, 70, and 12 patients who received GnP, Gem, and other treatments, respectively.

In the full analysis set, the median age in patients who received GnP was 77 years (range: 76-85), and that in those who received Gem and other treatments was 81 years (range: 76-88) for both. Patients with a G8 score of >14 were rare in the study population (n = 20). There were significant differences between each treatment group in terms of age, sex, CA19-9 level, ECOG PS, and clinical stage (Table 1). Similar trends were observed in the patient characteristics in the efficacy analysis set (Supplementary Table S1). The physicians’ selected treatments other than GnP for 62 cases, while 28 patients selected treatments other than GnP of their own volition. Reasons behind the physicians’ selection of treatments were general condition, aging, and social support problems in 32, 31, and 1 patient, respectively. The initial dose reduction was used in 36 (31.0%) and 14 (19.4%) patients who received GnP and Gem, respectively, with P-value of .074. None of them received the primary prophylaxis with granulocyte colony stimulating factor. In the propensity score-matched analysis, 42 patients each were selected from the GnP and Gem groups. Unlike the entire population, the patient characteristics were well balanced (Table 2). The initial dose reduction was used in 16 (38%) and 9 (21%) patients who received GnP and Gem, respectively, with P-value of .152.

Clinical Outcomes

Efficacy and Safety of GnP in the Efficacy Analysis Set
The data cutoff was determined on 31 December 2020. The median observation period was 11.0 months (95% CI, 9.0-12.4). The median OS and PFS in the GnP group were 11.3 months (95% CI, 9.0-13.3) and 7.0 months (95% CI, 5.7-8.9), respectively (Supplementary Fig. S1a, S1b). The overall response and disease control rates were 30.8% and 75.0%, respectively. We observed a total of 28 grade 4 hematologic adverse events and 30 grade 3 non-hematologic adverse events. Supplementary Table S2 summarizes the number of each adverse event. The following reasons for treatment discontinuation were reported for 55 of 64 patients: disease...
progression, adverse events, and willingness not related to adverse events in 27 (49.1%), 22 (40.0%), and 6 (10.9%) patients, respectively. Thirty-four patients (30%) required emergent hospitalization, and 14 (12%) required emergent hospitalization for GnP-related adverse events. The G8 score at 3 months after registration was reported for 99 patients, and a decline in the score was observed in 38 (38.4%). The IADL score at 3 months was reported for 45 patients, and a decline was observed in 24 (53.3%).

Comparison of GnP and Gem in the Propensity Score-Matched Cohort

The median OS was 12.2 months (95% CI, 7.1–not evaluable) and 9.4 months (95% CI, 6.6–12.5) in the GnP and Gem groups, respectively (Fig. 2a). The hazard ratio (HR) of OS was 0.63 (95% CI, 0.37–1.13; P = .120). The median PFS was 9.2 months (95% CI, 5.9–16.1) and 3.7 months (95% CI, 2.8–5.7) in the GnP and Gem groups, respectively (Fig. 2b). The HR of PFS was 0.38 (95% CI, 0.23–0.64; P = .0002). We observed an objective response in 11 of 38 (28.9%) and 4 of 37 (10.8%) patients with target lesions at baseline in the GnP and Gem groups, respectively (P = .082). Disease control was observed in 33 (80.5%) and 25 (61.0%) patients who had been radiologically evaluated at least once (n = 41 each) in the GnP and Gem groups, respectively (P = .088). The subgroup analysis demonstrated that GnP was favorable to Gem in every geriatric assessment subgroup for OS, except for patients with a G8 score of >14. However, these results were statistically insignificant, possibly because of the small sample size (Fig. 3).

Table 3. Adverse events in the propensity score-matched analysis.

| Eligible patients (n = 84) | GnP | Gem | P-value |
|---------------------------|-----|-----|--------|
| No. of patients (%)       | 42 (50.0) | 42 (50.0) | - |
| Grade 4 hematologic adverse events, n (%)<sup>a</sup> | | | |
| Leukopenia                 | 1 (2.5) | 2 (5.1) | .6153 |
| Neutropenia                | 9 (23.1) | 3 (7.7) | .1141 |
| Anemia                     | 2 (5.1) | 3 (7.7) | 1.0000 |
| Platelet count decreased   | 0 (0.0) | 1 (2.6) | .4937 |
| Grades 3–4 non-hematological adverse events, n (%)<sup>a</sup> | | | |
| Nausea                     | 1 (2.6) | 2 (5.1) | 1.0000 |
| Vomiting                   | 1 (2.6) | 2 (5.1) | 1.0000 |
| Diarrhea                   | 0 (0.0) | 0 (0.0) | - |
| Fatigue                    | 6 (15.4) | 4 (10.3) | .7366 |
| Malaise                    | 5 (12.8) | 3 (7.7) | .7115 |
| Mucositis, oral            | 0 (0.0) | 0 (0.0) | - |
| Peripheral sensory neuropathy | 2 (5.1) | 0 (0.0) | .4935 |
| Fever Neutropenia          | 0 (0.0) | 0 (0.0) | - |

P-values were calculated using Fisher's exact test.
<sup>a</sup>The denominator is the number of cases for which answers were obtained. Abbreviations: Gem, gemcitabine; GnP, Gem + nab-paclitaxel.
although they were not significantly different. None of the patients died due to adverse events. Thirteen (33%) and 10 (26%) patients in the GnP and Gem groups, respectively, required emergent hospitalization ($P = .620$). In patients for whom the relationship between chemotherapy and hospitalization was reported, 6 patients in the GnP group (60.0%) compared with none in the Gem group required hospitalization due to chemotherapy ($P = .0345$). The reasons for treatment discontinuation are summarized in Supplementary Table S3.

The G8 score 3 months after registration was reported for 37 and 32 patients in the GnP and Gem groups, respectively. We observed a decline in the G8 score at 3 months in 13 (35.1%) and 9 (28.1%) patients in the GnP and Gem groups, respectively ($P = .610$). The IADL score at 3 months was reported for 18 and 19 patients in the GnP and Gem groups, respectively, and a decline was observed in 11 (61.1%) and 7 (36.8%) patients, respectively ($P = .194$).

### Exploratory Analysis of the Cutoff Value of the G8 Scores

We additionally explored the best cutoff value of G8 as a prognostic factor in the efficacy analysis set. When the cutoff value changed from 14 to 7 points, the HR for OS in patients with a score higher than the cutoff value was smaller than that in patients with a lower score (Fig. 4a). Using a cutoff value of 11 points resulted in 74 and 109 patients with higher and lower scores, respectively. The hazard ratio was 0.79 (95% CI, 0.54-1.16) in the higher score group, when compared with that in the lower score group. (b) Comparison of the overall survival between patients who received gemcitabine plus nab-paclitaxel and those who received gemcitabine monotherapy in the propensity score-matched analysis set. The hazard ratios for gemcitabine plus nab-paclitaxel compared with gemcitabine monotherapy were 0.51 (95% CI, 0.23-1.15) and 0.99 (95% CI, 0.45-2.19) in patients with a G8 score >11 points (right) and those with a G8 score ≤11 points (left), respectively.
cutoff of 11 points in the propensity score-matched analysis was a predictive factor for OS in the GnP group compared with the Gem group. While the HR in patients with a G8 score of >11 was 0.51 (95% CI, 0.23-1.15; P = .094), that for a G8 score of ≤11 was 0.99 (95% CI, 0.45-2.19; P = .978) (Fig. 4b).

Discussion

Our study revealed the differences in the background, including geriatric assessment data, between patients who received GnP and those who received other treatments. The propensity score-matched analysis suggested that GnP was more effective; however, it displayed a higher incidence of severe adverse events.

Comprehensive geriatric assessment (CGA) is used to elucidate problems that cannot be clarified by daily clinical evaluation, including activities of daily living, concomitant disease, drug, cognitive impairment, social support, nutritional status, and financial problems. Among them, the G8 is a useful screening tool for these problems, particularly in the evaluation of nutritional status. Our findings that the G8 score appeared to have prognostic significance are consistent with previous reports. Advanced PC tends to decrease nutritional status, termed cachexia, which could be a prognostic factor for patients with advanced PC. In addition, the G8 scores using a cutoff value of 11 points appeared to be a predictive factor of GnP. We recommend Gem rather than GnP for patients with a G8 score of >11. Taken together, G8 should be assessed to evaluate the efficacy and safety of systemic chemotherapy for older adults with advanced PC. The ongoing GrandPax study and GIANT study (NCT04233866) are expected to elucidate the importance of G8 assessment in GnP treatment in older adults.

Although the cutoff value of geriatric assessment scores is an issue that requires discussion, the usefulness of the prognostic value of G8 has been reported in several types of cancer. Our findings also demonstrate that the G8 score displayed prognostic significance in unresectable PC: the lower the G8 score, the worse the prognosis. These results are consistent with those of Gebbia et al who reported a significant correlation between the G8 score and OS in patients with advanced PC, but not between G8 vulnerability (G8 score ≤14) and OS. The reason that a G8 score of 14 points failed to discriminate prognoses might be attributed to the cutoff value. Patients with a G8 score of 13-14 points may have a prognosis comparable to those with a score of >14. In addition, only 6 patients (15%) were assigned to the good prognosis group, with a cutoff of 14 points. The proportion of patients with a G8 score of >14 was consistent with previous reports. The small number of patients with a score >14 might fail to stratify the prognoses of patients with unresectable PC. Therefore, the cutoff value of G8 for predicting prognosis is likely to be lower than that of a screening tool for CGA. Our findings suggest 9-11 points as the candidate value. Validation studies are expected to ensure the prognostic significance of a score of <14.

This study has some limitations. First, it was an observational study, and we did not control for treatment modification at initiation or during treatment. Therefore, the treatment intensity in each patient was unknown. In addition, there remained some potential bias despite the propensity score-matched analysis, such as background differences between the GnP and Gem groups and missing data on clinical outcomes, including geriatric assessment. Despite these limitations, this is the first report to compare GnP with Gem, including geriatric assessment data, in older adults with unresectable PC. This study suggested that GnP was more efficacious than Gem in patients aged ≥76 years, despite GnP displaying a higher incidence of grades 3-4 adverse events and decreasing geriatric assessment scores. An assessment of G8 may be useful to predict prognosis and determine treatment.

Conclusion

GnP is more efficacious than Gem in patients aged ≥76 years with uPC despite demonstrating a higher incidence of severe adverse events.

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Conflict of Interest

Satoshi Kobayashi: Bayer Yakuhin, Chugai Pharma, Eisai, Eli Lilly, GlaxoSmithKline, Taiho Pharmaceutical, Takeda, Yakult Honsha (personal fees outside the submitted work); Makoto Ueno: Taiho Pharmaceutical, AstraZeneca, Merck Biopharma, MSD, Astellas Pharma, Eisai, Ono Pharmaceutical, Incyte, Chugai Pharmaceutical (RF), Taiho Pharmaceutical, AstraZeneca, Merck Biopharma, MSD, Daiichi Sankyo, Nihon Servier, Ono Pharmaceutical, Chugai Pharmaceutical (personal fees); Naohiro Okano: Taiho Pharmaceutical, Eli Lilly Japan, Kyowa Hakko Kirin, Eisai, Bayer Yakuhin, Chugai Pharmaceutical, Takeda, GlaxoSmithKline, Ono Pharmaceutical (personal fees); Yasushi Kojima: Incyte, Ono Pharmaceutical Co., Eisai, MSD, Takeda, Chugai (RF), Chugai, Daiichi-Sankyo, Yakult Pharmaceutical Industry, Ono Pharmaceutical Co. (personal fees), AstraZeneca (support for attending meetings), AstraZeneca (SAB); Hajime Higuchi: Taiho Pharmaceutical Co., Ltd. (scholarship grant); Tatsuya Yamashita: Eli Lilly Japan (personal fees); Atsushi Naganuma: Taiho Pharmaceutical, Yakult Honsha (personal fees); Hironori Yamaguchi: Taiho Pharmaceutical, Co., Ltd. (personal fees for lectures and clinical research grants); Kumiko Umemoto: Taiho Pharmaceutical, Yakult Honsha, Chugai Pharmaceutical (personal fees); Junji Furuse: Eli Lilly Japan, Taiho Pharmaceutical (personal fees), Taiho Pharmaceutical (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: S.K., J.F., H.I. Provision of study material or patients: S.K., M.U., Y.M., N.O., A.T., M.O., K.T., K.S., K.D., Y.K., H.T., K.T., H.H., K.K., H.I., T.Y., H.M., H.N.,
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