# #1188P Concurrent chemoradiotherapy with cisplatin + S-1for locally advanced non-small-cell lung cancer: IPD meta-analysis

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## Introduction

・Concurrent chemo-radiotherapy with cisplatin-based regimen has been the standard therapy for locally advanced stage III non-small-cell lung cancer (NSCLC) which accounts for approximately 30% of all lung cancer patients.

・In the present clinical setting, cisplatin+vinorelbine, cisplatin+docetaxel, cisplatin+S-1, weekly carboplatin+ paclitaxel, and daily carboplatin for NSCLC and cisplatin+pemetrexed for non-Sq NSCLC are the options available.

・Recently, the PACIFIC study reported the promising treatment with the anti-PD1 inhibitor durvalumab as consolidation therapy following concurrent chemoradiotherapy.[1]

・Determining the most appropriate chemotherapy regimen to accompany thoracic RT is of the utmost importance for the fast-changing environment of stage III NSCLC treatment.

・We conducted individual-participant-data (IPD) meta-analyses to compare S-1/cisplatin (SP) versus other third-generation anti-cancer medications plus cisplatin regimens.

## Materials and Methods

**Identification of eligible trials**

・A literature search was performed in December 2019 to identify all published and unpublished randomized trials comparing S-1 to other third-generation anti-cancer agents combined with cisplatin for stage III NSCLC.

**IPD**

・IPD were requested from each data center for all patients enrolled in all identified trials, and were checked for missing values and consistency.

**Statistical analysis**

・The primary endpoint is the overall survival (OS).

・The secondary endpoint is the progression-free survival (PFS), response rate, and toxicity rate.

・A fixed-effect model was used to obtain a summary of each trial's treatment effect on the OS/ PFS and assess the heterogeneity among them.

・The relative effect of each treatment arm in different subgroups was investigated using the same stratified analyses.

## Results

**Characteristics of the trials (Table 1)**

・Three phase-2 randomized clinical trials, all conducted in Japan: the WJOG5008L[2], SPECTRA[3], and TORG1018[4] studies were identified.

・The eligibility criteria for three trials were similar, and included age 20-74, PS 0-1, and unresectable stage III NSCLC. Only the SPECTRA study restricted the inclusion criteria to non-Sq NSCLC, whereas the other two included all NSCLCs.

| | | WJOG5008L | SPECTRA | TORG1018 |
|---|---|---|---|---|
| CDDP; 60mg/m² | VS | CDDP; 80mg/m² | CDDP; 75mg/m² | CDDP; 80mg/m² |
| S-1; (day1-14) BSA < 1.25; 80mg 1.25- 1.5; 100mg ≥1.5 ; 120mg | VS | VNR; 20mg/m² (day1, 8) | PEM; 500mg/m² (day1) | DTX; 50mg/m² (day1) |

**Patients characteristics (Table 2)**

・316 patients were included in the identified trials, with 159 patients undergoing S-1-based regimens and 157 assigned to other regimens. The baseline characteristics of the patients showed no significant difference between each arm.

**Table 1 Characteristics of the trials**

| | WJOG5008L | SPECTRA | TORG1018 |
|---|---|---|---|
| Regimen | TRT+S-1+CDDP VS TRT+VNR+CDDP | TRT+S-1+CDDP VS TRT+PEM+CDDP | TRT+S-1+CDDP VS TRT+DTX+CDDP |
| N | 108 (54 each) | 102 (52 vs 50) | 106 (53 each) |
| Primary endpoint | 2-year OS rate | 2-year PFS rate | 2-year OS rate |
| Randomization period | Sep/ 2009 to Sep/ 2012 | Jan/ 2013 to Oct/ 2016 | May/ 2011 to Aug/ 2014 |
| Follow-up period (months) | 44.6 | 37.3 | 41.7 |
| HR for OS (95% CI) | 0.85(0.48-1.49) | 0.95(0.53-1.74) | 0.87(0.49-1.55) |
| Median OS (95% CI) | 40.9(61.7-85.0) VS 39.0 (54.3-79.1) | 48.3 (32.3-NR) VS 59.1 (24.1-65.6) | 55.2 (32.7-NR) VS 50.8 (30.1-NR) |
| Median PFS (95% CI) | 14.8(10.7-18.4) VS 12.3 (10.2-14.3) | 12.7 (9.46-17.5) VS 13.8 (7.85-16.4) | 11.8 (9.5-17.1) VS 19.9 (12.3-29.9) |

**Table 2 Patient characteristics**

| | | SP (n=159) | Others (n=157) | p value |
|---|---|---|---|---|
| gender, n (%) | | | | |
| | male | 119 (74.8%) | 118 (75.1%) | 1.000 |
| | female | 40 (25.2%) | 39 (24.9%) | |
| age, median (range) | | 63 (39-74) | 64 (32-74) | 0.690 |
| | ≥70 | 27 | 35 | |
| | <70 | 132 | 122 | 0.259 |
| Stage, n (%) | IIIA | 84 (52.8%) | 78 (49.7%) | 0.653 |
| | IIIB | 75 (47.2%) | 79 (50.3%) | |
| Histological type | adenocarcinoma | 109 (68.6%) | 105 (66.9%) | 0.810 (adeno versus non-adeno) |
| | squamous cell carcinoma | 31 (19.5%) | 28 (17.8%) | |
| | adenosquamous cell | 1 (0.6%) | 0 (0%) | |
| | NOS | 15 (9.4%) | 21 (13.4%) | |
| | others | 3 (1.9%) | 3 (1.9%) | |
| smoking history | never | 29 (18.2%) | 26 (16.6%) | 0.767 |
| | current/former | 130 (81.8%) | 131 (83.4%) | |
| PS | 0 | 103 (64.8%) | 94 (59.9%) | 0.417 |
| | 1 | 56 (35.2%) | 63 (40.1%) | |

**The OS and PFS**

・There were 143 deaths (68 in the SP arm, 75 in the other regimens arm), and the median OS was 48.2 and 42.4 months in the SP and other regimen arms, respectively.(Fig 1 a))

・Although the SP arm exceeded other regimens on the OS curve, there was no statistically significant difference. The combined HR of the OS was 0.895 (95% CI, 0.638-1.256), with no heterogeneity noted among the trials ($\chi^2$ test for heterogeneity p=0.87; $I^2$=0, 95% CI 0-0.23). (Fig. 2 a))

・A total of 218 cases of progression (108 in the SP arm, 110 in the other regimens arm) were observed. The median PFS in the SP arm were 12.8 months, while that for the other regimens arm was 14.1 months. (Fig 1 b))

・No significant difference in the PFS was noted between the groups. The corresponding HR for the PFS was 1.022 (95% CI, 0.776-1.347), and there was evidence of moderate heterogeneity among the trials ($\chi^2$ test for heterogeneity p=0.16; $I^2$=0.46, 95% CI 0-0.84). (Fig 2 b))

**Response (Table 3)**

・The objective response rates (ORRs) in the SP and other regimen arms were 69.7% (95% CI, 62.1%-76.7%) and 70.9% (95% CI, 63.7%-78.1%), and the disease control rates (DCRs) were 92.3% (95% CI, 88.1%-96.5) and 94.1% (95% CI, 90.4%-97.9%), respectively.

・There was no significant difference between the groups in the ORR or DCR.

**Fig 1 a) OS curve by treatment arm**

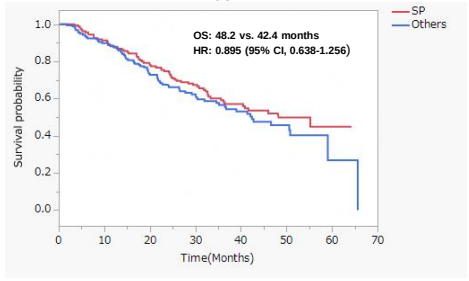


**Fig 1 b) PFS curve by treatment arm**

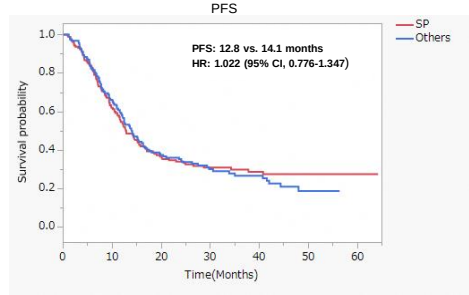


**Fig 2 a) Forest plot of OS by trial**

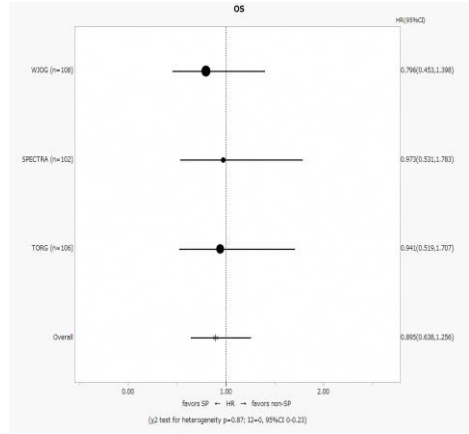


**Fig 2 b) Forest plot of PFS by trial**

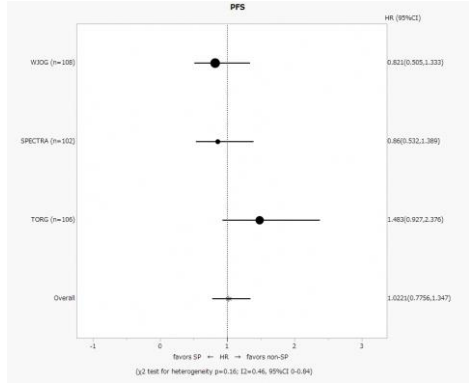


**Table 3 Response**

| | | SP (n=157) | others (n=155) | p-value |
|---|---|---|---|---|
| best response | CR | 2 | 4 | |
| | PR | 107 | 106 | |
| | SD | 36 | 36 | |
| | PD | 8 | 7 | |
| | NE | 4 | 2 | |
| ORR | CR+PR | 109 (69.4%) | 110 (70.9%) | 0.431 |
| | (95% CI) | (62.1-76.7) | (63.7-78.1) | |
| DCR | CR+PR+SD | 145 (92.3%) | 146 (94.1%) | 0.337 |
| | (95% CI) | (88.1-96.5) | (90.4-97.9) | |

**Fig. 3 Subgroup analysis**

・Subgroup analyses showed no factors from patients' baseline characteristics that affected the difference in the OS between the SP and other regimens arms.

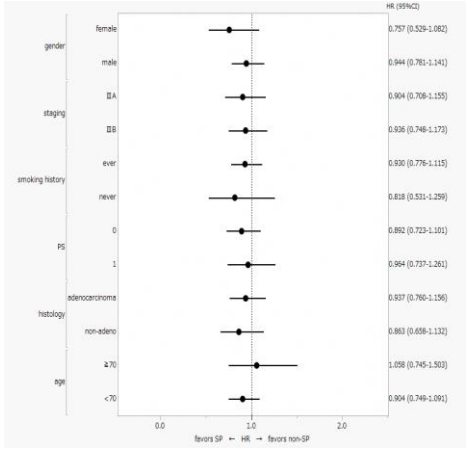


**Table 4 Treatment delivery**

・Of the patients who received more than 2 courses of chemotherapy, a dose reduction was needed in 26 (17.9%) and 42 (27.4%) (p=0.0493) in the SP and other regimen arms, and a delay in the treatment course was seen in 114 (78.6%) and 97 (63.4%) (p=0.0049), respectively.

| | | SP (n=159) | Others (n=157) | $\chi^2$ test P-value |
|---|---|---|---|---|
| chemotherapy | 1 | 14 | 4 | |
| | 2 | 18 | 17 | |
| | 3 | 6 | 12 | |
| | 4 | 121 (76.1%) | 124 (78.9%) | |
| RT | <40 Gy | 4 | 0 | |
| | 40-59 Gy | 3 | 4 | |
| | 60 Gy | 152 (95.5%) | 153 (97.4%) | |
| | median(range) | 60 (16-60) | 60 (40-60) | |
| | completed RT within 56 days | 149 (93.7%) | 150 (95.5%) | |
| more than 2 courses of chemotherapy | | 145 | 153 | |
| dose reduction | | 26 (17.9%) | 42 (27.4%) | 0.049 |
| delayed course | | 114(78.6%) | 97(63.4%) | 0.005 |
| relapse | | 108 | 110 | |
| subsequent therapy following relapse | | 100 (92.5%) | 89 (80.9%) | 0.010 |

**Table 5 Toxicity**

・Although most of the toxicity profiles were similar in both arms, grade 3-4 leukopenia and neutropenia were significantly more frequent in the other regimens arm than in the SP arm.

| | SP (N=159) | | Others (N=157) | | p-value |
|---|---|---|---|---|---|
| | all grade | Grade 3-4 | all grade | grade 3-4 | Grade 3-4 |
| Leukopenia | 148 | 59 | 153 | 103 | <0.001 |
| Neutropenia | 139 | 53 | 146 | 97 | <0.001 |
| Thrombocytopenia | 108 | 7 | 86 | 8 | 0.797 |
| Anemia | 143 | 23 | 150 | 28 | 0.447 |
| Febrile neutropenia | 11 | 11 | 16 | 16 | 0.321 |
| AST increased | 49 | 0 | 46 | 2 | 0.246 |
| ALT increased | 68 | 2 | 70 | 7 | 0.102 |
| Creatinine increased | 42 | 1 | 55 | 0 | 1.000 |
| Hyponatremia | 91 | 18 | 81 | 11 | 0.242 |
| Nausea | 102 | 3 | 118 | 9 | 0.084 |
| Vomiting | 23 | 2 | 34 | 1 | 1.000 |
| Anorexia | 119 | 16 | 128 | 26 | 0.099 |
| Diarrhea | 47 | 9 | 30 | 2 | 0.060 |
| Esophagitis | 107 | 7 | 107 | 6 | 1.000 |
| Pneumonitis | 35 | 7 | 36 | 9 | 0.618 |
| Alopecia | 9 | 0 | 51 | 0 | - |

## Conclusions

There was no significant difference found in the OS, PFS, or ORR between S-1/cisplatin and VNR, PEM, or DTX/cisplatin as a CCRT regimen for locally advanced NSCLC. SP is a well-tolerated regimen due to its acceptable toxicity and treatment compliance.

## References

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## Acknowledgements

We thank Dr. Koji Takeda for providing us with the WJOG5008L individual patient data. We would also like to thank all of the patients and their families involved in this study.

**Presenter DISCLOSURES; I do not have any financial relationships to disclose.**