An indirect treatment comparison of ifinatamab deruxtecan (I-DXd) versus real-world physicians' choice of therapy in patients previously treated with at least 2 lines of therapy for extensive-stage small cell lung cancer

RWD122

Jie Meng,[1] Jingjing Yin,[2] Françoise Diamand,[3] Maha Karnoub,[2] Sajid Ahmed,[2] Carsyn Norway,[2] Kamya Sankar[4]

[1]Daiichi Sankyo Europe GmbH, Munich, Germany; [2]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [3]Daiichi Sankyo France SAS, Rueil-Malmaison, France; [4]Cedars-Sinai Medical Center, Samuel Oschin Cancer Center, Los Angeles, CA, USA

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OBJECTIVES

- An ITC using MAIC methodology was conducted to contextualize the results from the Phase 2 IDeate-Lung01 study (NCT05280470)[1] by considering standard therapies using an EHR–derived dataset from Flatiron Health
- The objective of this study was to compare the efficacy of I-DXd 12 mg/kg with rwPCT among patients with previously treated ES-SCLC

CONCLUSIONS

- The results of this ITC suggest that I-DXd 12 mg/kg appears to provide improved clinical benefit in terms of OS, PFS, and TTD/D compared to rwPCT in patients with ES-SCLC receiving treatment in 3L or 4L
- These findings support the potential of I-DXd as a promising treatment option for patients with previously treated ES-SCLC

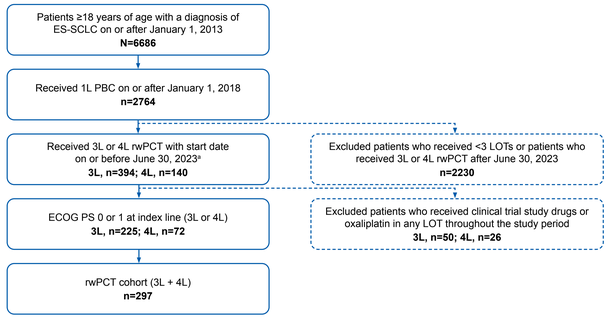
INTRODUCTION

- Patients with ES-SCLC experience rapid disease progression and, while their disease initially responds to systemic 1L SOC PBC ± IO, most patients relapse within 6 months.[2–5] Prognosis remains poor[2–5]
- Among patients with ES-SCLC who are treated in the 2L, <50% go on to receive 3L therapy,[6] for which there is no global SOC[5,7,8]
- In a recent real-world study of patients with previously treated ES-SCLC, 3L treatment patterns were heterogeneous and outcomes were poor, with a median rwOS of only 4.5 (95% CI, 3.7–5.4) months and a confirmed rwRR of 11.7% (95% CI, 5.5–21.0)[9]
- An urgent unmet need remains for effective treatments for patients with relapsed ES-SCLC
- The B7-H3–directed antibody–drug conjugate I-DXd demonstrated promising efficacy in patients with previously treated ES-SCLC in the Phase 2 IDeate-Lung01 study (NCT05280470), with a median OS of 10.3 (95% CI, 9.1–13.3) months and a confirmed objective response rate of 48.2% (95% CI, 39.6–56.9)[10]
- Understanding the characteristics and clinical outcomes among patients with ES-SCLC receiving I-DXd versus current standard therapies may help inform the future role of I-DXd in managing patients in this setting

METHODS

- This ITC used aggregated data reported in a previous natural history study that used real-world data from the Flatiron Health database[9] and data from the primary analysis of the IDeate-Lung01 study[10]
- The "rwPCT cohort" included patients ≥18 years of age with a diagnosis of ES-SCLC on or after January 1, 2013, who had initiated 1L therapy on or after January 1, 2018 and received 3L or 4L real-world PCT (chemotherapy [including lurbinectedin], anti–PD-[L]1, or chemotherapy + anti–PD-[L]1) on or before June 30, 2023 (**Figure 1**)
  - Patients must have had an ECOG PS of 0 or 1 at index line (3L or 4L)
  - Patients were excluded if they received clinical trial study drugs or oxaliplatin in any LOT during the study period
- The "unadjusted I-DXd cohort" comprised patients who received I-DXd 12 mg/kg as 3L or 4L treatment in IDeate-Lung01 (data cutoff: March 3, 2025)
  - Patients who received I-DXd 12 mg/kg as 2L treatment in IDeate-Lung01 were excluded to obtain a cohort of patients who received either 3L or 4L therapy, as in the rwPCT cohort
- Due to the availability of individual-patient data for IDeate-Lung01 but only aggregate data for the rwPCT cohort, a "weighted I-DXd cohort" was derived. Unanchored MAIC methodology was used to weight patients in the unadjusted I-DXd cohort to adjust for differences in key prognostic factors and treatment-effect modifiers between cohorts
  - The goal of MAIC is to match the weighted I-DXd cohort with the rwPCT cohort to have the same distributions in the pre-selected key prognostic factors and treatment-effect modifiers
  - Age at diagnosis, sex, smoking status, ECOG PS, presence of brain metastases, number of previous LOTs, and CTFI were identified as key prognostic factors and treatment-effect modifiers, and were included as matching variables
  - Presence of liver metastases, time from initial diagnosis to index treatment, and previous receipt of an anti–PD-(L)1 inhibitor were identified as key prognostic factors and treatment-effect modifiers, but were not included as matching variables because the data were not reported in the rwPCT cohort
- Median OS, PFS, and TTD/D for each cohort were estimated using Kaplan–Meier methodology, and CIs were computed using the Brookmeyer–Crowley method; no adjustment for multiplicity was performed
  - PFS by investigator and TTD/D data were available from IDeate-Lung01, while for the rwPCT cohort, TTD/D data were only available from digitization of the rwTTD/D Kaplan–Meier curve reported in the previous natural history study[9]
  - To allow comparisons with PFS data from IDeate-Lung01, rwTTD/D data were used as a proxy for rwPFS
- To supplement these median time-to-event outcomes, RMSTs were estimated by calculating the area under the time-to-event curve from time 0 to each selected time point
  - The proportional hazards assumption was assessed for all time-to-event outcomes and was not met; therefore, the Cox proportional hazards model was not used, and RMST was reported instead to summarize the time-to-event outcomes over time by treatment

Figure 1. Patient selection: rwPCT cohort



[a]Six months before end of study period.

RESULTS

- A total of 297 and 105 patients with ES-SCLC met the criteria for the rwPCT (**Figure 1**) and unadjusted I-DXd cohorts, respectively
- Following matching adjustment of the identified key prognostic factors and treatment-effect modifiers (except those not available for the rwPCT cohort), the weighted I-DXd cohort had an ESS of 68.5, retaining 65.2% of the unadjusted I-DXd cohort
  - An ESS of 65.2% indicates a good overlap between treatment populations, consistent with recommendations from key methodological publications and health technology assessment guidance,[11–13] supporting the robustness and reliability of the ITC
- Patient characteristics were identical between the weighted I-DXd cohort and the rwPCT cohort (**Table 1**)
  - Mean age was 65.1 years, 75.8% of patients had received 2 prior LOTs, and 24.2% had received 3 prior LOTs

Table 1. Baseline sociodemographic and clinical characteristics

	Unadjusted I-DXd cohort	Weighted I-DXd cohort	rwPCT cohort[a]
N	105	82.4[b]	297
ESS	–	68.5[c]	–
Age, mean, years	61.4	65.1	65.1
Female, %	36.2	52.5	52.5
ECOG PS 0, %	21.9	25.3	25.3
Current / former smoker, %	91.4	97.3	97.3
Brain metastases, %	41.0	30.3	30.3
Number of previous LOTs, % 2 / 3	71.4 / 28.6	75.8 / 24.2	75.8 / 24.2
CTFI,[d] % <90 days / ≥90 days and <180 days / ≥180 days	41.9 / 30.5 / 27.6[e]	37.4 / 34.7 / 27.9	37.4 / 34.7 / 27.9

[a]rwPCT cohort baseline characteristics data were calculated as the weighted average of summary statistics from the 3L and 4L rwPCT cohorts, weighted by the respective sample size of each cohort. [b]Weighted N derived from the sum of weights for the total number of patients in the unadjusted I-DXd cohort (n=105). [c]ESS is calculated by the square of the sum of the individual weights divided by the sum of the individual squared weights. [d]Defined as the time interval from the end of 1L PBC to the date of disease progression. For patients who received I-DXd that were missing the day (but with month and year) of the end date of 1L PBC and / or date of disease progression, CTFI was imputed as the mean of the narrower possible CTFI and the wider possible CTFI. Patients with a missing end date of 1L PBC and / or date of disease progression were assigned to the "CTFI ≥180 days" category. [e]Included 4 (3.8%) patients who had missing CTFI data.

- Lurbinectedin-containing regimens were the most common treatment in the rwPCT cohort, received by 65 (21.9%) patients (**Table 2**)
  - Additional 3L or 4L treatments received by >10% of patients were topoisomerase inhibitors (n=64 [21.5%]), chemotherapy "other" (n=52 [17.5%]), and PBC + topoisomerase inhibitor (n=34 [11.4%])
  - Any regimen containing PBC (PBC + topoisomerase inhibitor, PBC + anti–PD-[L]1 + topoisomerase inhibitor, or PBC "other") was received by 58 (19.5%) patients
- I-DXd (weighted cohort) demonstrated improved OS, PFS, and TTD/D compared with rwPCT (**Figure 2**). Median outcomes (95% CI) were:
  - OS: 10.4 (9.4–14.0) versus 6.1 (5.1–6.8) months
  - PFS: 4.3 (3.2–5.4) versus 2.8 (2.5–3.1) months
  - TTD/D: 4.9 (4.1–5.8) versus 2.8 (2.5–3.1) months
- RMSTs for all outcomes across all selected timepoints were longer with I-DXd (weighted cohort) than with rwPCT (**Figure 2**)

Table 2. Treatments received by the rwPCT cohort

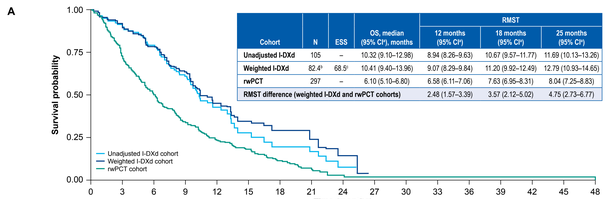
Treatment category, n (%)	Total (N=297)
Any lurbinectedin-containing regimen	65 (21.9)
Topoisomerase inhibitor(s) only	64 (21.5)
Chemotherapy "other"[a]	52 (17.5)
PBC + topoisomerase inhibitor	34 (11.4)
Anti–PD-(L)1 monotherapy	28 (9.4)
Anti–PD-(L)1 "other"[b]	21 (7.1)
PBC + anti–PD-(L)1 + topoisomerase inhibitor	14 (4.7)
PBC "other"[c]	10 (3.4)
Other	9 (3.0)

Data is not reported for tarlatamab as it was approved as a treatment for patients with ES-SCLC after the study period for the rwPCT cohort.[14]

[a]Included paclitaxel, gemcitabine, temozolomide, paclitaxel protein-bound (3L only), docetaxel (4L only), and any other chemotherapy regimens that would not meet criteria for inclusion in other treatment categories. [b]Ipilimumab and nivolumab in combination (3L only), excluding any regimens that would meet criteria for inclusion in other treatment categories. [c]Carboplatin and paclitaxel in combination (3L only), or other PBC regimens that would not meet criteria for inclusion in other treatment categories.

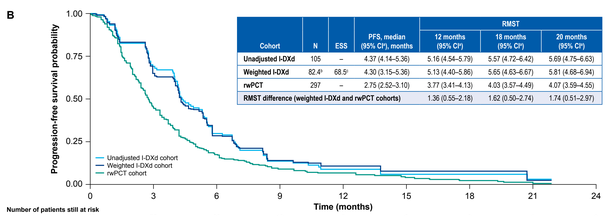
Figure 2. OS (A), PFS (B), and TTD/D (C) among patients receiving 3L or 4L therapy

A



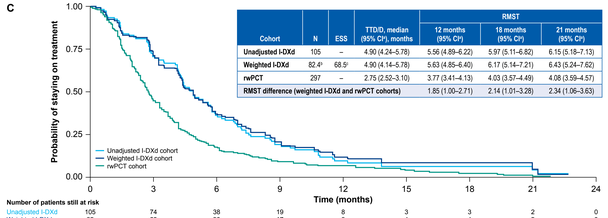
Cohort	N	ESS	OS, median (95% CI[a]), months	RMST 12 months (95% CI[a])	RMST 18 months (95% CI[a])	RMST 25 months (95% CI[a])
Unadjusted I-DXd	105	–	10.32 (9.10–12.98)	8.94 (8.26–9.63)	10.67 (9.57–11.77)	11.69 (10.13–13.26)
Weighted I-DXd	82.4[b]	68.5[c]	10.41 (9.40–13.96)	9.07 (8.29–9.84)	11.20 (9.92–12.49)	12.79 (10.93–14.65)
rwPCT	297	–	6.10 (5.10–6.80)	6.58 (6.11–7.06)	7.63 (6.95–8.31)	8.04 (7.25–8.83)
RMST difference (weighted I-DXd and rwPCT cohorts)				2.48 (1.57–3.39)	3.57 (2.12–5.02)	4.75 (2.73–6.77)

B



Cohort	N	ESS	PFS, median (95% CI[a]), months	RMST 12 months (95% CI[a])	RMST 18 months (95% CI[a])	RMST 20 months (95% CI[a])
Unadjusted I-DXd	105	–	4.37 (4.14–5.36)	5.16 (4.54–5.79)	5.57 (4.72–6.42)	5.69 (4.75–6.63)
Weighted I-DXd	82.4[b]	68.5[c]	4.30 (3.15–5.36)	5.13 (4.40–5.86)	5.65 (4.63–6.67)	5.81 (4.68–6.94)
rwPCT	297	–	2.75 (2.52–3.10)	3.77 (3.41–4.13)	4.03 (3.57–4.49)	4.07 (3.59–4.55)
RMST difference (weighted I-DXd and rwPCT cohorts)				1.36 (0.55–2.18)	1.62 (0.50–2.74)	1.74 (0.51–2.97)

C



Cohort	N	ESS	TTD/D, median (95% CI[a]), months	RMST 12 months (95% CI[a])	RMST 15 months (95% CI[a])	RMST 21 months (95% CI[a])
Unadjusted I-DXd	105	–	4.90 (4.24–5.78)	5.56 (4.89–6.22)	5.97 (5.11–6.82)	6.15 (5.18–7.13)
Weighted I-DXd	82.4[b]	68.5[c]	4.90 (4.14–5.78)	5.63 (4.85–6.40)	6.17 (5.14–7.21)	6.43 (5.24–7.62)
rwPCT	297	–	2.75 (2.52–3.10)	3.77 (3.41–4.13)	4.03 (3.57–4.49)	4.08 (3.59–4.57)
RMST difference (weighted I-DXd and rwPCT cohorts)				1.85 (1.00–2.71)	2.14 (1.01–3.28)	2.34 (1.06–3.63)

[a]95% CIs are provided for information only; no adjustment for multiplicity was performed. [b]Weighted N derived from the sum of weights for the total number of patients in the unadjusted I-DXd cohort (n=105). [c]ESS is calculated by the square of the sum of the individual weights divided by the sum of the individual squared weights.

DISCUSSION AND STUDY LIMITATIONS

- For the rwPCT cohort, only aggregated data were available from a previous natural history study from which the data were derived[9]; therefore, individual-patient data were reconstructed from digitization of reported Kaplan–Meier curves for each of the time-to-event endpoints
- Several of the identified key prognostic factors and treatment-effect modifiers (presence of liver metastases, time from initial diagnosis to index treatment, and previous receipt of an anti–PD-[L]1 inhibitor) were not extracted from the Flatiron database for this study, and thus, could not be adjusted for between the rwPCT cohort and the unadjusted I-DXd cohort
  - MAIC with rwPCT cohort data is subject to bias, with potential residual confounding not being accounted for
  - As the rwPCT cohort data consisted of aggregated EHRs and physician's notes, which may not consistently document key study variables, undocumented data may not have been missing at random and estimates may be biased
- The rwPCT cohort TTD/D was used as a proxy for PFS in the real-world cohort; however, this approach is subject to bias against rwPCT
  - rwTTNT was not used as a proxy for PFS in the rwPCT cohort, as these data were not extracted from the Flatiron database for this study
- Patients with missing CTFI data in the I-DXd cohorts were assumed to have had a CTFI ≥180 days; this approach is consistent with another recent real-world analysis in patients with previously treated SCLC[15]
- It was not possible to capture data for tarlatamab use in the rwPCT cohort since tarlatamab received accelerated approval in the US in May 2024,[14] which was after the end of the study period for this cohort

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ABBREVIATIONS

1L / 2L / 3L / 4L, first- / second- / third- / fourth-line; **B7-H3**, B7 homolog 3; **CI**, confidence interval; **CTFI**, chemotherapy-free interval; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EHR**, electronic health record; **ESS**, effective sample size; **(ES-)SCLC**, (extensive-stage) small cell lung cancer; **I-DXd**, ifinatamab deruxtecan; **IO**, immunotherapy; **ITC**, indirect treatment comparison; **LOT**, line of therapy; **MAIC**, matching-adjusted indirect comparison; **PBC**, platinum-based chemotherapy; **PD-(L)1**, programmed death (ligand) 1; **RMST**, restricted mean survival time; **(rw)OS**, (real-world) overall survival; **(rw)PCT**, (real-word) physicians' choice of therapy; **(rw)PFS**, (real-world) progression-free survival; **rwRR**, real-world response rate; **(rw)TTD/D**, (real-world) time to treatment discontinuation or death; **rwTTNT**, real-world time to next treatment; **SOC**, standard-of-care; **US**, United States.

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DISCLOSURES

Jie Meng is an employee of Daiichi Sankyo Europe GmbH.

Correspondence email address: jie.meng@daiichisankyo.com