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SCLC

1529MO The genomic landscape of small cell lung cancer in never smoking patients

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Background: Small cell lung cancer (SCLC) predominantly develops in patients with significant smoking history, but 6-8% of patients in recent SCLC datasets have no tobacco exposure. Prior reports have suggested that SCLC in never smoking patients may have unique genomic traits.

Methods: We retrospectively analyzed records from SCLC patients reporting "never smoking" (NS, n = 54) or "current/former smoking" (C/FS, n = 609) status. Tumors were sequenced with the Tempus xT assay, including a targeted DNA panel (595-648 genes) and whole exome capture RNA-seq. Tumor immune cell infiltration was estimated from RNA expression data. PD-L1 positivity was defined by tumor expression > 1% using 22C3 pharmDx IHC. Statistical significance was assessed with Pearson's chi-squared test or Fisher's exact test, using a threshold of $p < 0.05$ or false discovery rate-adjusted $q < 0.05$.

Results: Compared with CF/S patients, NS patients were more likely to be female (70% vs 55%, p = 0.031). Tumors of NS patients had a lower prevalence of *TP53* mutations (59% vs 85%, q < 0.001) but no significant difference in *RB1* mutations (57% vs 63%, q = 0.600). Meanwhile, NS patients had a higher prevalence of *EGFR* (26% vs 2.6%, q < 0.001) and *PIK3CA* (15% vs 3.6%, q = 0.022) mutations. We also observed a trend towards higher rates of mutations in *FGF4* (7.4% vs 1.6%, q = 0.100) and *NF1* (7.4% vs 1.3%, q = 0.092). Gene fusions were infrequently found, with no notable difference across cohorts. With regard to the immune environment, NS patients had lower tumor mutation burden (2.59/Mb vs 4.99/Mb, p < 0.001) and a trend towards higher PD-L1 positivity (20% vs 9%, p = 0.086). NS tumors also had decreased immune cell infiltration (median 2% vs 10%, p = 0.008), and specifically a lower proportion of CD4+ and CD8+ T cells and higher proportion of macrophages.

Conclusions: The mutational landscape of SCLC in NS patients significantly differs from that of C/FS patients. Tumors of NS patients were more likely to harbor mutations in oncogenic drivers — such as *EGFR* and *PIK3CA* — and exhibited lower TMB and immune cell infiltration. These findings suggest that the occurrence of SCLC in NS patients may represent a distinct genomic entity and treatment implications should be further explored.

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1530P Durvalumab (D) + platinum-etoposide (EP) in first-line extensive-stage SCLC (ES SCLC): Effect of age and platinum agent on outcomes in CASPIAN

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Background: In the Phase 3 CASPIAN trial in pts with ES-SCLC, first-line D+EP significantly improved overall survival (OS) vs EP alone, and OS benefit was sustained after >3 yrs median follow-up (HR 0.71; 95% CI 0.60−0.86; nominal p=0.0003). Many pts present with ES-SCLC at ≥70 yrs of age, and pts in CASPIAN could receive investigator's choice of cisplatin (cis) or carboplatin (carbo); here we assess outcomes in CASPIAN subgroups (subgps) defined by age and planned platinum.

Methods: Pts with treatment-naïve ES-SCLC received 4 cycles of D+EP q3w followed by maintenance D q4w until progression, or up to 6 cycles of EP q3w. In exploratory analyses, OS and safety (median follow-up 39.4 and 25.1 months, respectively) were assessed in age subgps (<70 or ≥70 yrs; post-hoc subgps) and planned platinum subgps (cis or carbo; prespecified subgps and stratification factor).

Results: Of 537 pts randomised to D+EP and EP, 433 (81%) were <70 yrs and 104 (19%) were ≥70 yrs; 135 (25%) were assigned to receive cis and 402 (75%) to receive carbo. Baseline characteristics were generally balanced between arms within each subgp. More pts received cis in the <70 yrs subgp vs ≥70 yrs subgp (28% vs 11%). In the cis subgp, more pts received ≥4 cycles of EP in the D+EP arm vs the EP arm (Table). In age subgps, median OS in the D+EP arm vs the EP arm was consistent in pts aged <70 and ≥70 yrs, and OS benefit was maintained over time in both subgps. In the D+EP arm, median OS was numerically higher in the cis subgp (wide CI) vs carbo subgp; OS benefit was maintained over time in both subgps. There were more AEs leading to treatment discontinuation in the cis subgp vs carbo subgp.

Conclusions: In CASPIAN, similar OS benefit was evident across age and platinum subgps, sustained over time, and consistent with the intent-to-treat population. D+EP was generally well tolerated across subgps. These data further support the use of D+EP as first-line standard of care in ES-SCLC regardless of age or platinum agent.

Clinical trial identification: NCT03043872, release date February 6, 2017.

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Table: 1530P

	Age				Planned platinum			
	<70 yrs		≥70 yrs		Cis		Carbo	
	D+EP	EP	D+EP	EP	D+EP	EP	D+EP	EP
Efficacy								
n	217	216	51	53	67	68	201	201
Median OS, months	12.9	10.5	12.0	10.2	14.6	11.1	12.5	10.2
95% CI	11.4–14.9	9.3–11.2	8.1–14.8	7.2–13.9	11.0–17.2	8.9–14.1	10.9–14.7	9.1–11.0
HR	0.71		0.74		0.65		0.74	
95% CI	0.58–0.88		0.49–1.11		0.45–0.94		0.60–0.91	
36-month OS, %	18	7	16	2	20	3	17	7
95% CI	13–24	4–11	7–27	0.2–9	11–30	0.6–10	12–22	4–11
Safety								
n	214	214	51	52	65	68	200	198
Received ≥4 cycles EP, %*	87	85	84	85	91	78	86	87
Any AE, %	98	97	98	96	100	96	98	97
Grade 3/4	61	60	67	73	58	66	64	62
Serious	29	33	47	52	38	47	30	33
Leading to treatment discontinuation	10	8	12	13	17	16	8	7
Leading to death	5	4	6	12	6	4	5	6
Immune-mediated	19	2	25	4	20	1	20	3

*Based on etoposide

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1531P Primary results from IMfirst, a phase IIIb open label safety study of atezolizumab (ATZ) + carboplatin (CB)/cisplatin (CP) + etoposide (ET) in an interventional real-world (RW) clinical setting of extensive-stage small cell lung cancer (ES-SCLC) in Spain

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Background: IMpower133 Phase III study showed that the addition of ATZ to CB+ET in 1L ES-SCLC statistically and clinically improved overall survival (OS) and progression-free survival (PFS) compared to CB+ET alone. IMfirst evaluates the safety of ATZ+CB/CP+ET in an interventional RW clinical setting of ES-SCLC. An induction safety analysis was previously reported and here we present primary safety and efficacy results.

Methods: In contrast to IMpower133, eligible patients (pts) also included those with ECOG Performance status (PS) 2, asymptomatic untreated central nervous system (CNS) metastases, stable autoimmune diseases and HIV+. Consolidation radiotherapy (CRt) and up to 6 chemotherapy (C) cycles were allowed.

Results: 155 pts were enrolled; 47% were ≥65 years old, 72% were male, 89% had ECOG PS 0-1 and 99% had smoking history. 17% of pts had baseline CNS metastases, 10% received prophylactic cranial irradiation, and 8% received CRt. 41% of pts received 5-6 cycles of C and 88% of pts received CB as induction C. 61% of pts met IMpower133 trial-like eligibility criteria. The median (m) number of cycles of ATZ received was 9 (range 1-35) and 86% of pts reached the maintenance phase. Grade (gr) 3-4 treatment-related (TR), serious (S) and immune-mediated (IM) adverse events (AEs) were 43 (27.8%), 15 (9.7%) and 3 (1.9%) respectively. One Gr 5 TRSAE (subileus) was reported. TRAEs led to discontinuation of ATZ, CB/CP or ET in 5.8%, 2.6% and 2.6% of pts, respectively. Median follow-up was 18.8 months (data cut-off: 19 January 2022). mOS was 10 mo (95% CI: 8.60, 11.93); OS at 12 and 18 mo was 42% and 25%.