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Short communication

Final overall survival and safety update for durvalumab in third- or later-line advanced NSCLC: The phase II ATLANTIC study

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ABSTRACT

Introduction: In the phase II ATLANTIC study, durvalumab provided durable responses with acceptable tolerability in heavily pretreated patients with advanced NSCLC, across three independent patient cohorts defined by *EGFR/ALK* status and tumour PD-L1 expression. Preliminary overall survival (OS) data were encouraging. We now report final OS and updated safety data.

Methods: Patients with advanced NSCLC with disease progression following ≥ 2 previous systemic regimens received durvalumab 10 mg/kg every 2 weeks. The primary endpoint was objective response rate among patients with increased PD-L1 expression (defined as $\geq 25\%$ or $\geq 90\%$ of tumour cells [TCs], cohort-dependent). Secondary endpoints included OS and safety.

Results: 444 patients received durvalumab: 111 in Cohort 1 (*EGFR*+/*ALK*+), 265 in Cohort 2 (*EGFR*-/*ALK*-), and 68 in Cohort 3 (*EGFR*-/*ALK*-; TC $\geq 90\%$). Median (95% CI) OS was 13.3 months (6.3–24.5) in patients with *EGFR*+/*ALK*+ NSCLC with TC $\geq 25\%$, 10.9 months (8.6–13.6) in patients with *EGFR*-/*ALK*- NSCLC with TC $\geq 25\%$, and 13.2 months (5.9–not reached) in patients with *EGFR*-/*ALK*- NSCLC with TC $\geq 90\%$. Median (95% CI) OS was slightly shorter in patients with TC < 25% (9.9 months [4.2–13.3] in patients with *EGFR*+/*ALK*+ NSCLC and 9.3 months [5.9–10.8] in those with *EGFR*-/*ALK*- NSCLC). Treatment-related adverse events of special interest occurred with similar incidences as reported previously.

Conclusions: After additional follow-up, final OS data remain encouraging across all cohorts, further supporting the clinical activity of durvalumab in patients with heavily pretreated advanced NSCLC, including those with *EGFR*+/*ALK*+ tumours. There were no new safety signals.

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1. Introduction

Treatment for advanced non-small cell lung cancer (NSCLC) has improved considerably since the introduction of immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway [1]. However, the clinical benefit of anti-PD-1/PD-L1 agents in patients with *EGFR* mutations or *ALK* receptor tyrosine kinase (*ALK*) rearrangements (*EGFR*+/*ALK*+) is not clear; moreover, there are few effective options for patients with advanced NSCLC who progress after two systemic treatment regimens, including those with *EGFR*−/*ALK*− tumours.

Durvalumab is a selective, high-affinity, PD-L1 blocking antibody that is approved for patients with unresectable, stage III NSCLC whose disease has not progressed following platinum-based chemoradiotherapy.

The phase II ATLANTIC study (NCT02087423) evaluated third- and later-line durvalumab monotherapy across three independent NSCLC patient cohorts defined by *EGFR*/*ALK* status and tumour cell (TC) PD-L1 expression. The final analysis of the primary endpoint, objective response rate (ORR), has been previously reported (data cut-off [DCO] 3 June 2016) [2]. Consistent with other durvalumab studies [3] and meta-analyses [4,5] in advanced NSCLC, the ORR was increased in patients with higher levels of tumour PD-L1 expression. Preliminary overall survival (OS) data were encouraging although the maturity was low, particularly in Cohort 1 (*EGFR*+/*ALK*+) and Cohort 3 (*EGFR*−/*ALK*−; TC ≥ 90 %), and the median OS had not been reached in Cohort 3 [2].

Here, with a later DCO of 7 November 2017, we report final OS and updated safety results from the ATLANTIC study.

2. Methods

2.1. Study design and patients

ATLANTIC was a phase II, open-label, single-arm, multicentre study of durvalumab in patients with stage IIIB/IV NSCLC that recurred or progressed following ≥2 systemic treatments, including one platinum-based regimen and, if indicated, tyrosine kinase inhibitor therapy. Full inclusion and exclusion criteria are described elsewhere [2].

Originally, ATLANTIC enrolled all patients, irrespective of PD-L1 expression; however, following the availability of a validated PD-L1 diagnostic, the protocol was amended to include only patients with TC ≥ 25 % membrane staining for PD-L1 per central assessment of recent or archival samples using the VENTANA PD-L1 (SP263) Assay. A further protocol amendment added a cohort of patients with TC ≥ 90 % membrane staining for PD-L1. Thus, patients were allocated to three independent cohorts; patients in Cohort 1 had *EGFR*+/*ALK*+ NSCLC and Cohorts 2 and 3 had *EGFR*−/*ALK*− NSCLC. Cohort 3 comprised patients with TC ≥ 90 %. Enrolment into Cohorts 2 and 3 was sequential, whereas enrolment into Cohort 1 continued throughout the study.

2.2. Treatment and study endpoints

Patients were treated with durvalumab 10 mg/kg intravenously every 2 weeks until disease progression, unacceptable toxicity, or for up to 12 months. Patients who achieved and maintained disease control (ie, complete response, partial response, or stable disease) through to the end of the initial 12-month treatment period entered follow-up and were offered retreatment on evidence of disease progression. The primary endpoint was ORR in patients with measurable disease at baseline, per independent central review (ICR), and with TC ≥ 25 % (Cohorts 1 and 2) or ≥ 90 % (Cohort 3). Secondary endpoints have been outlined previously [2] and included OS (time from first dose until death due to any cause) and safety and tolerability. ATLANTIC was

undertaken in accordance with the ethical principles of the Declaration of Helsinki and the International Council on Harmonisation guidelines on Good Clinical Practice. The study protocol, including this final OS analysis, was approved by the institutional review boards of all participating centres. All patients provided written informed consent.

2.3. Statistical analysis

OS was assessed by the Kaplan-Meier product-limit method in the full analysis set (all treated patients who had a baseline tumour assessment and measurable disease at baseline according to investigator assessment). Safety data, including adverse events (AEs) considered by the investigator to be possibly related to study treatment (hereafter referred to as treatment-related AEs [TRAEs]), and treatment-related AEs of special interest (AESIs) on the basis of their potential immune cause (in addition to infusion/hypersensitivity reactions), were summarised in the safety analysis set (all patients who received at least one dose of durvalumab and had post-dose data) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

3. Results

3.1. Patients and treatment

Between 25 February 2014 and 28 December 2015, 444 patients were enrolled and received durvalumab: 111, 265, and 68 in Cohorts 1, 2, and 3, respectively (Supplementary Fig. 1). In Cohorts 1 and 2, 38 and 167 patients were enrolled under the original protocol (irrespective of PD-L1 expression) [2]. The full analysis set included 111, 264, and 67 patients in Cohorts 1, 2, and 3, respectively: in Cohort 1, 77 and 30 patients had TC ≥ 25 % and TC < 25 % (4 patients had unknown or missing PD-L1 expression); in Cohort 2, 149 and 94 patients had TC ≥ 25 % and TC < 25 % (21 patients had unknown PD-L1 expression); 67 patients in Cohort 3 had TC ≥ 90 % (one patient had TC 70 % and a protocol deviation was reported). The primary endpoint of ORR was reported previously and the analysis included all treated patients with measurable disease at baseline per ICR (Supplementary Fig. 1) [2]. Baseline characteristics were previously reported [2]. Patients had received a median (range) of 3.0 (2–11), 3.0 (2–9), and 2.0 (2–5) previous anticancer regimens in Cohorts 1, 2, and 3, respectively. At the 7 November 2017 DCO, the median (range) actual treatment duration excluding dose delays was 12.0 (2–53), 16.1 (1–62), and 25.9 (2–52) weeks in Cohorts 1, 2, and 3, respectively.

3.2. Final overall survival

At DCO, 328 (73.9 %) of 444 patients across the study had died (safety analysis set). Most deaths (306; 93.3 %) were solely due to disease progression.

Patients with higher PD-L1 expression (TC ≥ 25 % and ≥ 90 %) had numerically longer median OS than those with TC < 25 %, regardless of *EGFR*/*ALK* status (Fig. 1). Median (95 % confidence interval [CI]) OS in Cohort 1 (*EGFR*+/*ALK*+) was 13.3 (6.3–24.5) months in TC ≥ 25 % patients and 9.9 (4.2–13.3) months in TC < 25 %. In Cohort 2 (*EGFR*−/*ALK*−), median OS was 10.9 (8.6–13.6) months in TC ≥ 25 % patients and 9.3 (5.9–10.8) months in TC < 25 % patients, and in Cohort 3 (*EGFR*−/*ALK*−; TC ≥ 90 %) it was 13.2 (5.9–not reached) months. Similarly, 12- and 24-month OS rates were increased in patients with higher PD-L1 expression, regardless of *EGFR*/*ALK* status (Fig. 1).

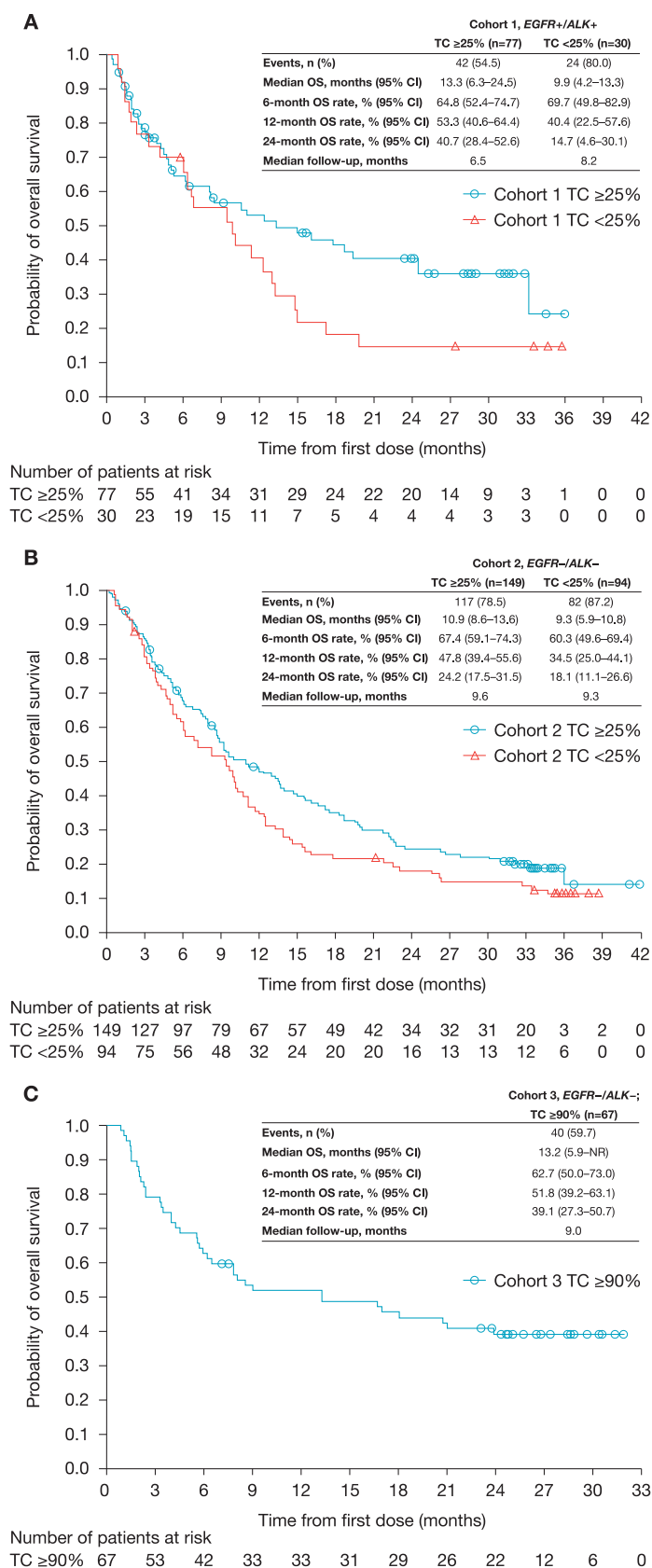


Fig. 1. Final overall survival by cohort.

Abbreviations: ALK, ALK receptor tyrosine kinase; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1; TC, tumour cell.

Table 1
Summary of treatment-related adverse events and frequency of treatment-related adverse events of special interest (safety analysis set).

	Cohort 1, <i>EGFR</i> + / <i>ALK</i> + (n = 111)		Cohort 2, <i>EGFR</i> – / <i>ALK</i> – ^a (n = 265)		Cohort 3, <i>EGFR</i> – / <i>ALK</i> – ^a ; TC ≥ 90% (n = 68)	
Any TRAE, n (%)	53 (48)		157 (59)		46 (68)	
Grade 3 or 4 TRAEs	6 (5)		23 (9)		13 (19)	
TRAEs leading to death	0		0 ^c		0	
Treatment-related serious AEs	5 (5)		14 (5)		9 (13)	
TRAEs leading to discontinuation	1 (1)		8 (3)		1 (1)	
	Grade 1/2	Grade 3 ^b	Grade 1/2	Grade 3 ^b	Grade 1/2	Grade 3 ^b
Any treatment-related AESI, n (%)	27 (24)	2 (2)	67 (25)	9 (3)	25 (37)	9 (13)
Dermatitis	6 (5)	0	20 (8)	1 (< 1)	10 (15)	0
Hypothyroidism	10 (9)	0	17 (6)	0	9 (13)	0
Rash	6 (5)	0	16 (6)	0	9 (13)	1 (1)
Diarrhoea	4 (4)	0	17 (6)	1 (< 1)	3 (4)	2 (3)
Hyperthyroidism	7 (6)	0	11 (4)	0	6 (9)	0
Pneumonitis	1 (1)	1 (1)	4 (2)	3 (1)	3 (4)	0
Hepatic laboratory parameters reported as AEs	1 (1)	0	3 (1)	2 (1)	2 (3)	3 (4)
Infusion reaction/hypersensitivity	0	1 (1)	3 (1)	1 (< 1)	1 (1)	1 (1)
Adrenal insufficiency	0	0	1 (< 1)	1 (< 1)	1 (1)	1 (1)
Thyroid laboratory parameters reported as AEs (decreased thyroid activity)	1 (1)	0	3 (1)	0	0	0
Renal laboratory investigations reported as AEs	1 (1)	0	2 (1)	0	1 (1)	0
Pancreatic laboratory investigations reported as AEs	1 (1)	0	0	0	2 (3)	0
Thyroid laboratory parameters reported as AEs (increased thyroid activity)	1 (1)	0	1 (< 1)	0	0	0
Colitis	0	0	0	0	1 (1)	0
Hepatitis	0	0	1 (< 1)	0	0	0
Hypophysitis	0	0	0	0	0	1 (1)
Nephritis	0	0	1 (< 1)	0	0	0
Thyroiditis	1 (1)	0	2 (1)	0	0	0

AESIs are grouped Medical Dictionary for Regulatory Activities v20.0 preferred terms. Includes all AEs considered by the investigator to be possibly related to study treatment with an onset date on or after the date of first dose or pretreatment AEs that increase in severity on or after the date of first durvalumab dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first). Each patient has been represented once with the maximum reported Common Terminology Criteria for Adverse Events v4.03 grade for each AESI. If a patient has multiple events within an AESI, then the maximum grade across those events is counted for that preferred term.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; *ALK*, *ALK* receptor tyrosine kinase; TC, tumour cell; TRAE, treatment-related adverse event.

^a Includes patients with unknown *EGFR/ALK* status.

^b There were no grade 4 or 5 treatment-related AESIs at the time of analysis.

^c There was one treatment-related pneumonitis event with an outcome of death that is not included in this table because the AE began after the start of subsequent therapy (the patient developed pneumonitis 65 days after discontinuing durvalumab because of disease progression and 2 days after starting subsequent therapy with erlotinib) [2].

An exploratory post-hoc analysis of TC ≥ 25 % patients in Cohort 1 separated into subgroups with *EGFR* + or *ALK* + NSCLC showed numerically longer median OS in the *EGFR* + subgroup (16.1 months [95 % CI 6.2–33.2]) compared with the *ALK* + subgroup (6.3 months [0.9–not reached]). Similarly, the 12-month OS rate was higher in patients with *EGFR* + NSCLC versus those with *ALK* + NSCLC (Supplementary Fig. 2).

3.3. Safety and tolerability

Grade 3/4 TRAEs occurred in 42 (9.5 %) of 444 patients and treatment-related serious AEs occurred in 28 (6.3 %) of patients (Table 1). TRAEs leading to treatment discontinuation occurred in 10 (2.3 %) patients. There were no deaths due to TRAEs before the start of subsequent therapy although, as previously reported [2], there was a treatment-related death due to pneumonitis after the start of subsequent *EGFR* tyrosine kinase inhibitor therapy.

Overall, 139 (31.3 %) of 444 patients had treatment-related AESIs; 29 (26.1 %) in Cohort 1, 76 (28.7 %) in Cohort 2, and 34 (50.0 %) in Cohort 3 (Table 1). The most common treatment-related AESIs were dermatitis (37 patients [8.3 %]), hypothyroidism (36 [8.1 %]), rash (32 [7.2 %]), diarrhoea (27 [6.1 %]), and hyperthyroidism (24 [5.4 %]). The most common grade 3 treatment-related AESIs were hepatic laboratory parameters reported as AEs (5 patients [1.1 %]), pneumonitis (4 [0.9 %]), diarrhoea (3 [0.7 %]), and infusion reactions (3 [0.7 %]). There were no grade 4/5 treatment-related AESIs before the start of subsequent therapy at the time of analysis.

4. Discussion

The mature final OS data from the ATLANTIC study are encouraging, with durvalumab showing clinical activity across subsets of clinical interest in a heavily pretreated patient population. Patients with higher tumour PD-L1 expression had numerically longer median OS, irrespective of *EGFR/ALK* status, although the OS in patients with TC < 25 % was also promising. The final OS results in Cohorts 1 and 2, including the median OS and 12-month OS rates, were consistent with the results reported at the earlier DCO [2]. The OS results observed in ATLANTIC were also similar to those seen with other single-agent anti-PD-1/PD-L1 therapies in patients with advanced NSCLC treated in the third-line and later setting in single-arm trials [6,7].

No new safety signals were evident at the later DCO. As previously reported [2], Cohort 3 had a higher incidence of treatment-related AESIs than Cohorts 1 and 2. AESIs were manageable with standard guidelines and most were grade 1/2 in severity. These results remain consistent with other anti-PD-1/PD-L1 therapies in pretreated advanced NSCLC [7–10].

Retrospective analyses have suggested that *EGFR* – /*ALK* – tumours respond better than *EGFR* + /*ALK* + tumours to anti-PD-1/PD-L1 therapy [11–13]. Although uncontrolled, ATLANTIC represents the largest prospective analysis of treatment with anti-PD-1/PD-L1 therapy in patients with *EGFR* + /*ALK* + NSCLC (n = 111) to date. Among pretreated (including prior tyrosine kinase inhibitor therapy) patients with advanced *EGFR* + /*ALK* + NSCLC (TC ≥ 25 %), the median OS was 13.3 months with a 24-month OS rate of 40.7 %, which was greater

than that observed in patients with TC \geq 25 % *EGFR* –/*ALK* – tumours (median OS of 10.9 months and 24-month OS of 24.2 %). Furthermore, when focusing on the subgroup of patients with *EGFR* + NSCLC (TC \geq 25 %), excluding those with *ALK* + NSCLC, the median OS was extended to 16.1 months. The phase III IMpower150 study also showed promising OS results with PD-L1 blockade in patients with *EGFR* + chemotherapy-naïve metastatic NSCLC, albeit in a combination therapy setting rather than with anti-PD-L1 monotherapy. In a subgroup of patients with sensitising *EGFR* mutations, atezolizumab in combination with bevacizumab plus chemotherapy provided OS benefit compared with bevacizumab plus chemotherapy alone [14]. In the present analysis of ATLANTIC, as observed at the earlier DCO [2], median OS was short in patients with TC \geq 25 % *ALK* + NSCLC (6.3 months), although this was a very small subgroup of only 12 patients meaning that no conclusions for this subgroup can be made from this study. Further clinical investigation in *EGFR* +/*ALK* + NSCLC using prospectively designed controlled studies is warranted to understand the role of durvalumab in this population.

In conclusion, final OS data from the ATLANTIC study continue to support the clinical activity of durvalumab in patients with heavily pretreated advanced NSCLC, including those with *EGFR* +/*ALK* + tumours.

5. Author contributions

J.E.G., C.W., P.A.D., and N.A.R. contributed to the study concepts and design. M.C.G., B-C.C., J-H.K., J.M., J.V., H.L., J.C.J., J.E.G., J.P., C.C., P.B., P.W-P., K.P., R.A.S., P.A.D., and N.A.R. collected the data. M.C.G., B-C.C., J-H.K., J.M., J.V., H.L., J.C.J., J.E.G., C.C., K.P., R.A.S., L.P., C.W., P.A.D., and N.A.R. analysed and interpreted the data. L.P. performed the statistical analysis. All authors contributed to the preparation, editing, and review of the manuscript and approved the final draft.

Role of the funding source

The study was funded by AstraZeneca who participated in study design, data collection, data management, data analysis, data interpretation, and writing of the report. All authors had full access to the data used to write the report, and the corresponding author had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

M.C.G. has received personal fees from and has other relationships with Eli Lilly, Boehringer Ingelheim, AstraZeneca, Novartis, Bristol-Myers Squibb, Roche, Pfizer, Celgene, Incyte, Takeda, Merck Sharp and Dohme, and Ignyta, has received personal fees from Inivata and Seattle Genetics, and has other relationships with Tiziana Science, Spectrum Pharmaceuticals, Foundation Medicine, AIRC, AIFA, Italian MoH, and TRANSCAN. B-C.C. has received research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, and Merck Sharp and Dohme, has provided consultancy for Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and Merck Sharp and Dohme, owns stock in TheraCanVac Inc, and has received royalties from Champions Oncology. J.V. has received institutional research funding from Merck Sharp and Dohme, advisory fees from Apotex, AstraZeneca, Boehringer Ingelheim, Merck Sharp and Dohme, Novartis, and Roche, and honoraria from AstraZeneca, Bristol-Myers Squibb, Merck Sharp and Dohme, and Roche. H.L. has received personal fees and non-financial

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Appendix A. Supplementary data

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