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ORIGINAL ARTICLE

IMscin001 Part 2: a randomised phase III, open-label, multicentre study examining the pharmacokinetics, efficacy, immunogenicity, and safety of atezolizumab subcutaneous versus intravenous administration in previously treated locally advanced or metastatic non-small-cell lung cancer and pharmacokinetics comparison with other approved indications

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Background: Atezolizumab intravenous (IV) is approved for the treatment of various solid tumours. To improve treatment convenience and health care efficiencies, a coformulation of atezolizumab and recombinant human hyaluronidase PH20 was developed for subcutaneous (SC) use. Part 2 of IMscin001 (NCT03735121) was a randomised phase III, open-label, multicentre, noninferiority study comparing the drug exposure of atezolizumab SC with atezolizumab IV.

Patients and methods: Eligible patients with locally advanced/metastatic non-small-cell lung cancer were randomised 2 : 1 to receive atezolizumab SC (1875 mg; $n = 247$) or IV (1200 mg; $n = 124$) every 3 weeks. The co-primary endpoints were cycle 1 observed trough serum concentration (C_{trough}) and model-predicted area under the curve from days 0 to 21 ($AUC_{0\text{-}21\ d}$). The secondary endpoints were steady-state exposure, efficacy, safety, and immunogenicity. Exposure following atezolizumab SC was then compared with historical atezolizumab IV values across approved indications.

Results: The study met both of its co-primary endpoints: cycle 1 observed C_{trough} {SC: 89 μg/ml [coefficient of variation (CV): 43%] versus IV: 85 μg/ml (CV: 33%); geometric mean ratio (GMR), 1.05 [90% confidence interval (CI) 0.88-1.24]} and model-predicted $AUC_{0\text{-}21\ d}$ [SC: 2907 μg d/ml (CV: 32%) versus IV: 3328 μg d/ml (CV: 20%); GMR, 0.87 (90% CI 0.83-0.92)]. Progression-free survival [hazard ratio 1.08 (95% CI 0.82-1.41)], objective response rate (SC: 12% versus IV: 10%), and incidence of anti-atezolizumab antibodies (SC: 19.5% versus IV: 13.9%) were similar between arms. No new safety concerns were identified. C_{trough} and $AUC_{0\text{-}21\ d}$ for atezolizumab SC were consistent with the other approved atezolizumab IV indications.

Conclusions: Compared with IV, atezolizumab SC demonstrated noninferior drug exposure at cycle 1. Efficacy, safety, and immunogenicity were similar between arms and consistent with the known profile for atezolizumab IV. Similar drug exposure and clinical outcomes following SC and IV administration support the use of atezolizumab SC as an alternative to atezolizumab IV.

Key words: atezolizumab, cancer immunotherapy, non-small-cell lung cancer, pharmacokinetics, recombinant human hyaluronidase, subcutaneous

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INTRODUCTION

Numerous clinical trials have demonstrated the benefit of atezolizumab for the treatment of various solid tumour types, leading to its approval in intravenous (IV) form for the treatment of non-small-cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, urothelial

carcinoma, hepatocellular carcinoma, alveolar soft part sarcoma, and melanoma.[1-13]

Subcutaneous (SC) administration has emerged as an alternative route to IV infusion for the delivery of large therapeutic proteins.[14] Studies show that patients prefer the SC compared with the IV route of administration due to reduced pain and discomfort, shorter administration time, and reduced time in the clinic.[15-17] The SC formulations have also been shown to yield meaningful time and cost savings at health care centres.[18,19] To bring those benefits to atezolizumab IV users and health care centres, a coformulation of atezolizumab and recombinant human hyaluronidase PH20 (rHuPH20) was developed for SC use.[20,21] rHuPH20 (Hylenex) was first approved by the United States Food and Drug Administration (FDA) in 2005 for use in SC fluid administration to achieve hydration and to increase the dispersion and absorption of other injected drugs.[22] The product and concentration (2000 U/ml) of rHuPH20 used in the atezolizumab SC formulation is the same as those used in the approved SC formulations for trastuzumab, rituximab, the fixed-dose coformulation of pertuzumab and trastuzumab, and daratumumab, all of which have shown to yield similar pharmacokinetics (PK), efficacy, and safety profiles to their IV counterparts.[23-26]

IMscin001 is a two-part phase Ib/III study investigating atezolizumab SC in patients with locally advanced or metastatic NSCLC following progression under platinum-containing therapy.[27] Part 1 demonstrated that atezolizumab SC at a dosing regimen of 1875 mg every 3 weeks (Q3W) provided similar exposure to the approved IV dosing regimen of 1200 mg Q3W and was well tolerated.[27] Here we report the primary results of the randomised phase III (part 2) portion of the open-label, multicentre IMscin001 study (NCT03735121) and investigate whether these results support the use of atezolizumab SC in other indications for which atezolizumab IV is approved.

METHODS

This clinical study was sponsored by F. Hoffmann-La Roche Ltd (Basel, Switzerland). It was carried out in full concordance with the International Council for Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients

Enrolled patients were adults with histologically or cytologically documented locally advanced or metastatic NSCLC (i.e. stage IIIB not eligible for definitive chemoradiotherapy to stage IV per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 8th edition) who were cancer immunotherapy naïve and for whom first-line platinum-based therapy had failed. Patients must have had measurable disease as defined by RECIST version 1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1.

Patients were randomised 2 : 1 to receive single-agent atezolizumab administered as 1875 mg Q3W SC or 1200 mg Q3W IV, starting on day 1 of each 21-day cycle, until disease progression per RECIST version 1.1, loss of clinical benefit, or unacceptable toxicity. Crossover was not allowed.

Patients with symptomatic, untreated, or actively progressing central nervous system metastases were excluded. Patients with a sensitizing *EGFR* mutation or an *ALK* alteration must have experienced disease progression during or after treatment with, or intolerance to, a targeted therapy. *EGFR* and *ALK* tests could be carried out locally, or samples could be submitted for central laboratory testing. For patients with nonsquamous histology and without any other known driver mutations, known *EGFR* test results were required at the time of randomisation. Patients were required to provide tissue samples for programmed death-ligand 1 (PD-L1) analysis, and PD-L1 was assessed at a central laboratory by the SP142 immunohistochemistry assay (Ventana Medical Systems Inc., Tucson, AZ).[28] Although patients with any PD-L1 expression level were accepted, cases where testing had been already carried out, with an intent to treat the patient if positive, were not eligible.

Drug administration

Atezolizumab SC (15 ml) was administered as a ready-to-use formulation of 1875 mg atezolizumab (125 mg/ml) and 30 000 U rHuPH20 (2000 U/ml) into the anterior thigh of the patient by a health care professional, with a suggested delivery time $<$10 min. Atezolizumab IV was administered according to product guidelines, with the infusion recommended to be administered over 1 h initially, followed by 30 min for subsequent infusions, if well tolerated.[11-13]

Study endpoints

The co-primary PK endpoints were cycle 1 (predose cycle 2) observed trough serum concentration (C_{trough}) and model-predicted area under the curve from days 0 to 21 ($AUC_{0\text{-}21\ d}$).

The secondary PK endpoints were model-predicted C_{trough} at cycle 1 ($C_{trough\ cycle\ 1}$), model-predicted C_{trough} at steady state ($C_{trough,ss}$), and AUC at steady state (AUC_{ss}).

The secondary efficacy endpoints were objective response rate, duration of response, overall survival, and investigator-assessed progression-free survival.

Safety was also a secondary endpoint and was monitored throughout the study by a Joint Monitoring Committee. Verbatim adverse event (AE) terms were mapped to Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 thesaurus terms, and laboratory toxicities were defined based on the United States National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 and local laboratory normal ranges.

The secondary immunogenicity endpoints included the prevalence and incidence of antidrug antibodies (ADAs) to atezolizumab (both arms) and rHuPH20 (SC arm only). Baseline prevalence was defined as the number and percentage of patients who tested positive at baseline, and

postbaseline incidence was defined as the number and percentage of patients with treatment-emergent antibodies. The number of patients positive for treatment-emergent ADAs was equal to the number of postbaseline evaluable patients with either treatment-induced ADAs or treatment-enhanced ADAs during the study period. A patient was considered positive for treatment-induced ADAs if they had a negative or missing baseline ADA result and $\geq$1 positive postbaseline ADA result. A patient was considered positive for treatment-enhanced ADAs if they had a positive ADA result at baseline and $\geq$1 postbaseline result that was $\geq$0.60 titre units greater than the baseline titre.

Study populations

All PK endpoints were analysed with randomised patients grouped according to the treatment they received. The cycle 1 observed C_{trough} analysis was carried out in the per-protocol PK-evaluable analysis set, defined as the population of patients in the atezolizumab SC and atezolizumab IV arms who did not have protocol deviations that could affect cycle 1 observed C_{trough} results. Patients were excluded from the per protocol PK-evaluable analysis set if the cycle 1 C_{trough} PK sample was missing, a C_{trough} sample was collected outside the prespecified window (day 21 $\pm$ 2 days), administration of a dose amount deviated from the planned dose by $>$20% at cycle 1, an injection site other than the thigh was used at cycle 1, or duplicates were collected for the cycle 1 C_{trough} sample. Model-predicted PK endpoint (i.e. $AUC_{0\text{-}21\ d}$, $C_{trough\ cycle\ 1}$, $C_{trough,ss}$, and AUC_{ss}) analyses were carried out in the PK-evaluable analysis set, defined as all randomised patients with $\geq$1 postbaseline PK sample. Model-based PK endpoints were derived based on a population PK model, and developed using the nonlinear mixed effect approach, observed atezolizumab PK concentrations, actual dosing information, and baseline covariates. Additional details on the model development, analysis, and results can be found in the protocol in the Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2023.05.009.

Progression-free survival analyses were carried out in the full analysis set (FAS), defined as all patients who were randomised, with patients grouped according to their assigned treatment. Objective response rate was analysed among all patients in the FAS with measurable disease at baseline as defined by RECIST version 1.1. The safety-evaluable analysis set comprised all randomised patients who received $\geq$1 dose of protocol treatment. Immunogenicity analyses were carried out on the post-treatment ADA-evaluable analysis set, defined as patients who received $\geq$1 dose of protocol treatment and had $\geq$1 post-treatment ADA result.

Procedural assessments

PK assessments of atezolizumab were carried out in the SC arm on days 1 (predose and 8 h postdose), 2, 4, and 8 of cycle 1; day 1 (predose only) of cycles 2, 3, 4, 8, 12, and 16; and at the treatment discontinuation visit. The corresponding PK assessments were carried out in the IV arm on days 1 (predose and 30 min postdose), 4, and 8 of cycle 1; day 1 (predose and 30 min postdose) of cycle 2; day 1 (predose) of cycles 3, 4, 8, 12, and 16; and at the treatment discontinuation visit.

Tumour assessments occurred every 6 weeks ($\pm$3 business days) for the first 36 weeks following treatment initiation, and every 9 weeks ($\pm$7 days) thereafter, regardless of treatment delays. Tumour assessments continued according to schedule in patients who discontinued treatment for reasons other than disease progression or loss of clinical benefit, even if they started new anticancer therapy. Follow-up data capture, including survival status and subsequent anticancer therapies, continued for each patient until death, loss of follow-up, withdrawal of consent, or study termination by the sponsor, whichever occurred first.

Safety assessments consisted of incidence, nature, and severity of AEs and laboratory abnormalities graded per the United States National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. Laboratory safety assessments included the regular monitoring of haematology and blood chemistry, which were collected $\leq$4 days before day 1 of each cycle.

Immunogenicity assessments were carried out on day 1 (predose) of corresponding cycles where PK samples were collected and at the treatment discontinuation visit.

Statistical analyses

The noninferiority analysis was carried out by one-sided hypothesis testing using the Hochberg procedure[29] based on the co-primary endpoints, cycle 1 observed C_{trough}, and model-predicted $AUC_{0\text{-}21\ d}$. The lower bound of the 90% confidence interval (CI) for the geometric mean ratio (GMR) between the SC and IV arms for both primary endpoints ($C_{trough,SC}/C_{trough,IV}$ and $AUC_{0\text{-}21\ d,SC}/AUC_{0\text{-}21\ d,IV}$) were compared with the predefined noninferiority margin of 0.8, which is the lower bound of the bioequivalence range recommended by the FDA[30] and European Medicines Agency (EMA)[31] guidelines. The null hypothesis of inferiority was prespecified to be rejected, and concluded that SC administration is noninferior to IV administration based on the co-primary endpoints, if the observed lower bounds of the 90% CIs for the GMRs of the co-primary endpoints were equal to or greater than the predefined noninferiority margin. A total of 355 patients were planned for this study. With an observed drop-off rate of $\sim$24% for the PK-evaluable patients, this led to a sample size of $\geq$261 PK-evaluable patients to provide $\geq$80% power to conclude noninferiority of SC compared with IV for cycle 1 C_{trough} and $AUC_{0\text{-}21\ d}$.

The objective response rate and its 95% CI according to Pearson—Clopper were calculated and presented by treatment arm. The difference in response rates between treatment arms and the 95% two-sided CIs were calculated.[32] Progression-free survival was analysed using the Kaplan—Meier methodology, including survival plots,

median duration, and corresponding 95% CIs according to the Brookmeyer–Crowley method.

Cross-study PK comparison

To evaluate the systemic drug exposure following atezolizumab SC in the second-line setting for patients with NSCLC from IMScin001 compared with the other approved atezolizumab IV indications, the co-primary endpoints of observed C_{trough} and model-predicted $AUC_{0\text{-}21\ d}$ at cycle 1 were compared with observed and model-predicted PK data from 11 label-enabling studies (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.05.009). The individual model-predicted PK data in the 11 comparative studies were derived based on a previously published population PK model.[33,34]

RESULTS

Study population and demographics

Patients were enrolled from 2 December 2020 to 30 March 2022. At data cut-off (26 April 2022), the median follow-up was 4.7 months (range, 0.1-16.7 months). Of the 569 patients screened, 371 were randomised 2 : 1 to receive atezolizumab SC ($n = 247$) or atezolizumab IV ($n = 124$) and included in the FAS (Figure 1). The median age of the patient population was 64.0 years (range, 27-85 years). Baseline characteristics were similar (≤10%) between treatment groups, except for patients whose tumours were PD-L1 TC0 and IC0 by the SP142 assay (SC: 49% versus IV: 63%; Table 1).

Co-primary PK endpoints

Following a single dose of atezolizumab, the geometric mean for cycle 1 observed C_{trough} (predose cycle 2) was 89 μg/ml [coefficient of variation (CV): 43%] for atezolizumab SC and 85 μg/ml (CV: 33%) for atezolizumab IV (GMR, 1.05 [90% CI 0.88-1.24]; Figure 2A). The model-predicted geometric mean for $AUC_{0\text{-}21\ d}$ was μg·day/mL (CV: 32%) for atezolizumab SC compared with 3328 μg·day/mL (CV: 20%) for atezolizumab IV [GMR, 0.87 (90% CI 0.83-0.92); Figure 2B].

Secondary PK endpoints

Following multiple doses of atezolizumab, the model-predicted $C_{trough\ cycle\ 1}$ was 97 μg/ml (CV: 36%) for atezolizumab SC and 89 μg/ml (CV: 26%) for atezolizumab IV. The model-predicted $C_{trough,ss}$ was 205 μg/ml (CV: 46%) for atezolizumab SC and 179 μg/ml (CV: 36%) for atezolizumab IV, and model-predicted AUC_{ss} was 6163 μg d/ml (CV: 40%) for atezolizumab SC and 6107 μg d/ml (CV: 26%) for atezolizumab IV (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.05.009).

Efficacy

At the time of analysis, 68% of patients in each arm (SC: $n = 168$, IV: $n = 84$) had a progression-free survival event. The median progression-free survival was 2.8 months (95% CI 2.1-3.1 months) in the atezolizumab SC group compared with 2.9 months (95% CI 1.7-4.2 months) in the atezolizumab IV group (hazard ratio 1.08, 95% CI 0.82-1.41); Figure 3A].

Objective response rates were 12% ($n = 29$; 95% CI 8.07-16.56) for patients receiving atezolizumab SC and 10% ($n = 12$; 95% CI 5.10-16.29) for patients receiving atezolizumab IV, all of which were partial responses in both groups [Δ2.16 (95% CI −4.86 to 9.18); Figure 3B]. At data cut-off, median duration of response data was immature.

At the time of analysis, 35% of patients in the atezolizumab SC arm and 30% of patients in the atezolizumab IV

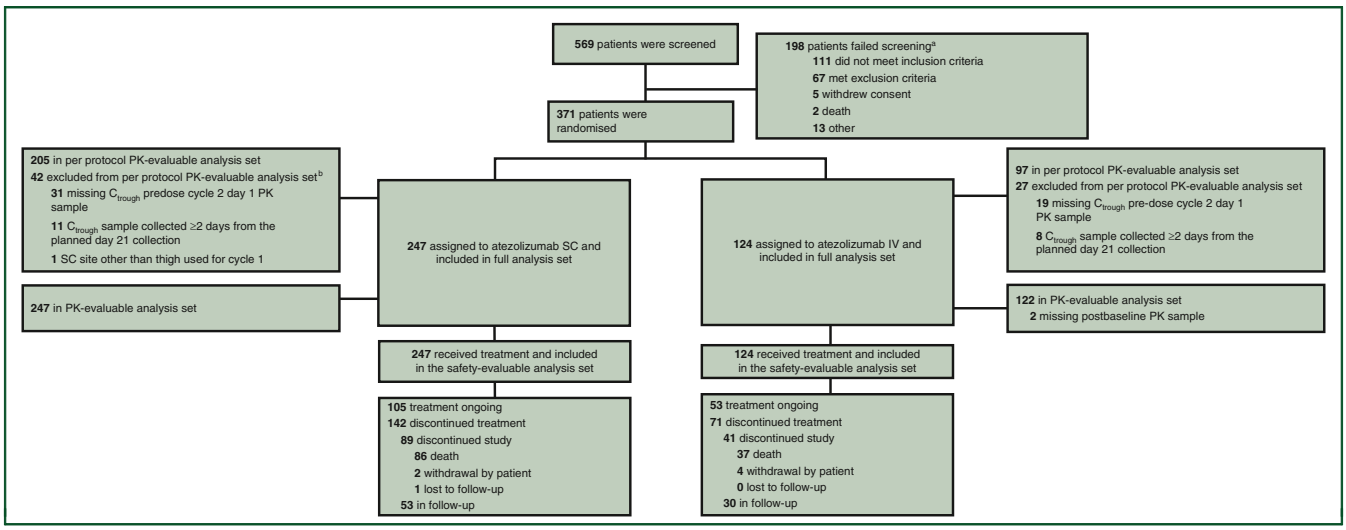

Figure 1. Patient disposition.
PK, pharmacokinetics; SC, subcutaneous; IV, intravenous.
[a]The most common reasons for screen failure were central nervous system metastases exclusion criteria ($n = 38$), *EGFR* mutation inclusion criteria ($n = 21$), and disease progression inclusion criteria ($n = 19$).
[b]Exclusion categories were not mutually exclusive.

Table 1. Baseline demographics and characteristics

	Atezolizumab SC (n = 247)	Atezolizumab IV (n = 124)
Age, years (range)	63.0 (27-85)	66.0 (42-85)
Age group, *n* (%)		
<65 years	137 (55)	58 (47)
≥65 years	110 (45)	66 (53)
Sex, *n* (%)		
Male	175 (71)	82 (66)
Female	72 (29)	42 (34)
Race, *n* (%)		
White	174 (70)	74 (60)
Asian	47 (19)	33 (27)
American Indian or Alaska Native	15 (6)	9 (7)
Black or African American	2 (<1)	1 (<1)
Native Hawaiian or other Pacific Islander	1 (<1)	2 (2)
Multiple	6 (2)	5 (4)
Unknown	2 (<1)	0 (0)
ECOG performance status, *n* (%)		
0	67 (27)	28 (23)
1	180 (73)	96 (77)
Tobacco use history, *n* (%)		
Previous	136 (55)	64 (52)
Current	40 (16)	20 (16)
Never	71 (29)	40 (32)
Histology, *n* (%)		
Nonsquamous	165 (67)	76 (61)
Squamous	82 (33)	48 (39)
Stage at initial diagnosis, *n* (%)		
IA	4 (2)	2 (2)
IB	3 (1)	3 (2)
IIA	3 (1)	2 (2)
IIB	9 (4)	6 (5)
IIIA	32 (13)	10 (8)
IIIB	25 (10)	14 (11)
IIIC	9 (4)	5 (4)
IVA	92 (37)	52 (42)
IVB	70 (28)	30 (24)
Current disease status, *n* (%)		
Locally recurrent	4 (2)	0 (0)
Locally advanced unresectable	8 (3)	10 (8)
Metastatic	235 (95)	114 (92)
Brain metastases, *n* (%)		
Yes	42 (17)	19 (15)
No	205 (83)	105 (85)
Liver metastases, *n* (%)		
Yes	77 (31)	26 (21)
No	170 (69)	98 (79)
Number of metastatic sites, median (range)	3.0 (1-8)	3.0 (1-7)
Number of prior therapies, *n* (%)		
1	200 (81)	97 (78)
2	41 (17)	21 (17)
3	6 (2)	5 (4)
4	0 (0)	1 (<1)
EGFR mutation status, *n* (%)		
Positive	11 (4)	8 (6)
Negative	198 (80)	95 (77)
Not evaluable	2 (<1)	2 (2)
Not done	33 (13)	16 (13)
Unknown	3 (1)	3 (2)
EML4-ALK status, *n* (%)		
Positive	4 (2)	2 (2)
Negative	196 (79)	100 (81)
Not evaluable	3 (1)	3 (2)
Not done	44 (18)	19 (15)
PD-L1 expression level by SP142 IHC assay, *n* (%)		
Assessed	218 (88)	115 (93)
TC0 and IC0	121 (49)	78 (63)
TC1/2/3 or IC1/2/3	97 (39)	37 (30)
TC2/3 or IC2/3	38 (15)	14 (11)
TC3 or IC3	13 (5)	3 (2)

ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; IV, intravenous; PD-L1, programmed death-ligand 1; SC, subcutaneous; TC, tumour cell.

arm experienced an overall survival event, and therefore overall survival data were immature at this data cut-off.

Safety

The safety-evaluable analysis set included all 371 patients from the FAS. The proportion of patients with ≥1 AE was 85.8% (n = 212) for atezolizumab SC and 83.9% (n = 104) for atezolizumab IV (Table 2). There were no all-grade AEs with a ≥5% higher incidence in the atezolizumab SC group compared with the atezolizumab IV group, whereas hyperglycaemia [SC: 2.8% (n = 7) versus IV: 8.1% (n = 10)] and hypercreatininaemia [SC: 1.2% (n = 3) versus IV: 6.5% (n = 8)] occurred in a greater proportion of patients in the atezolizumab IV group compared with the atezolizumab SC group. Treatment-related AEs occurred in 37.7% (n = 93) of patients receiving atezolizumab SC and 37.9% (n = 47) of patients receiving atezolizumab IV (Table 2).

The rate of patients with ≥1 grade 3/4 AE was 17.8% (n = 44) in the atezolizumab SC arm and 25.8% (n = 32) in the atezolizumab IV arm (Table 2). Grade 3/4 AEs were considered treatment related by the investigator in 3.6% (n = 9) of patients in the atezolizumab SC arm and 3.2% (n = 4) of patients in the atezolizumab IV arm (Table 2). Grade 5 AEs occurred in 5.7% (n = 14) of patients receiving atezolizumab SC and 3.2% (n = 4) of patients receiving atezolizumab IV. Grade 5 AEs were considered treatment related by the investigator in 0.8% (n = 2) of patients receiving atezolizumab SC and were pneumonia aspiration (n = 1) and toxic epidermal necrolysis (n = 1). No patients receiving atezolizumab IV experienced a grade 5 treatment-related AE (Table 2).

Serious AEs occurred in 15.4% (n = 38) of patients receiving atezolizumab SC and 17.7% (n = 22) of patients receiving atezolizumab SC (Table 2).

The proportion of patients who experienced ≥1 atezolizumab-specific AEs of special interest was 26.3% (n = 65) in the atezolizumab SC arm and 21.8% (n = 27) in the atezolizumab IV arm. Injection site reactions occurred in 4.5% (n = 11) of patients in the SC arm, all of which were grade 1 (n = 8) or grade 2 (n = 3), and in none of the patients in the IV arm. Infusion-related reactions occurred

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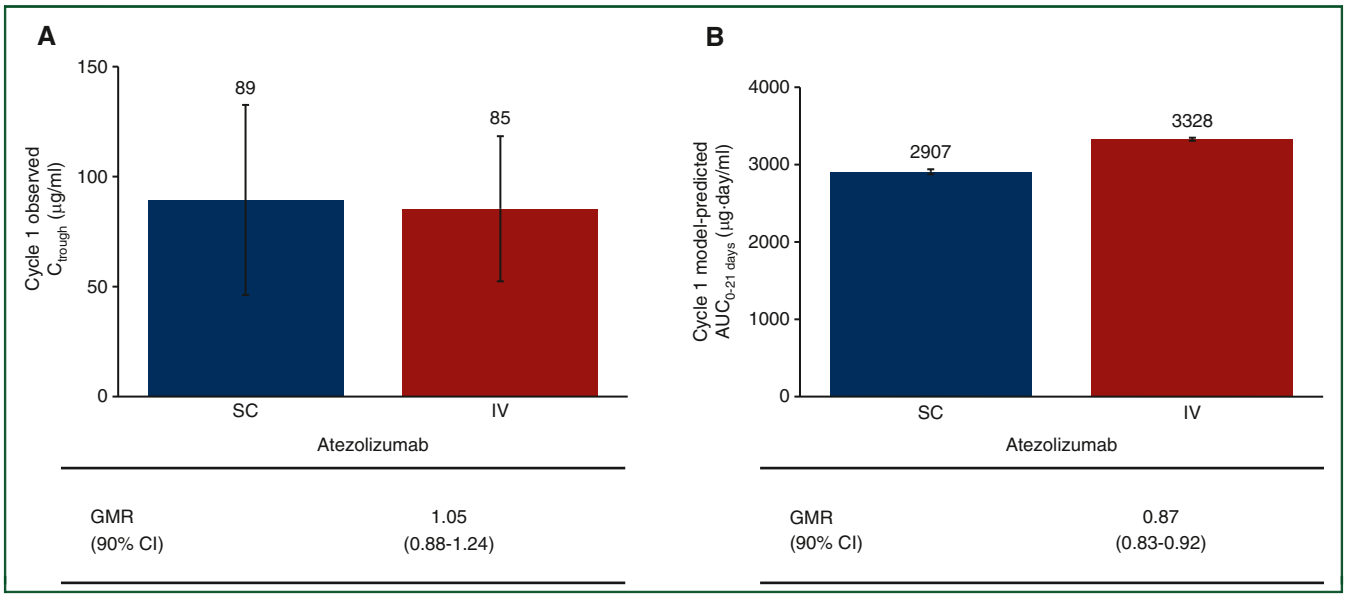

Figure 2. Geometric mean for co-primary pharmacokinetics endpoints: (A) cycle 1 observed C_{trough} and (B) cycle 1 model-predicted $AUC_{0\text{-}21\ d}$. Error bars represent % coefficient of variation.
AUC, area under the curve; CI, confidence interval; GMR, geometric mean ratio; IV, intravenous; SC, subcutaneous.

in 3.2% ($n = 4$) of patients in the IV arm and in none of the patients in the SC arm (Table 2).

AEs leading to atezolizumab discontinuation occurred in 1.6% ($n = 4$) of patients receiving atezolizumab SC and 3.2% ($n = 4$) receiving atezolizumab IV, and AEs leading to dose interruption occurred in 24.7% ($n = 61$) of patients receiving atezolizumab SC compared with 26.6% ($n = 33$) receiving atezolizumab IV (Table 2).

Immunogenicity

At baseline, 2.9% (7/241) of patients receiving atezolizumab SC and 2.6% (3/115) of patients receiving atezolizumab IV had a positive anti-atezolizumab sample (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.05.009). In the atezolizumab SC group, 19.5% (43/221) of patients were positive for treatment-emergent anti-atezolizumab antibodies. Of those, 2.3% ($n = 1$) had treatment-enhanced and 97.7% ($n = 42$) had treatment-induced ADAs. In the atezolizumab IV group, 13.9% (15/108) of patients were positive for treatment-emergent ADAs, all of which were treatment induced (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.05.009).

In the atezolizumab SC arm, the baseline prevalence and postbaseline incidence of antibodies to rHuPH20 were 11.4% ($n = 27/237$ patients) and 5.4% ($n = 12/224$ patients), respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.05.009).

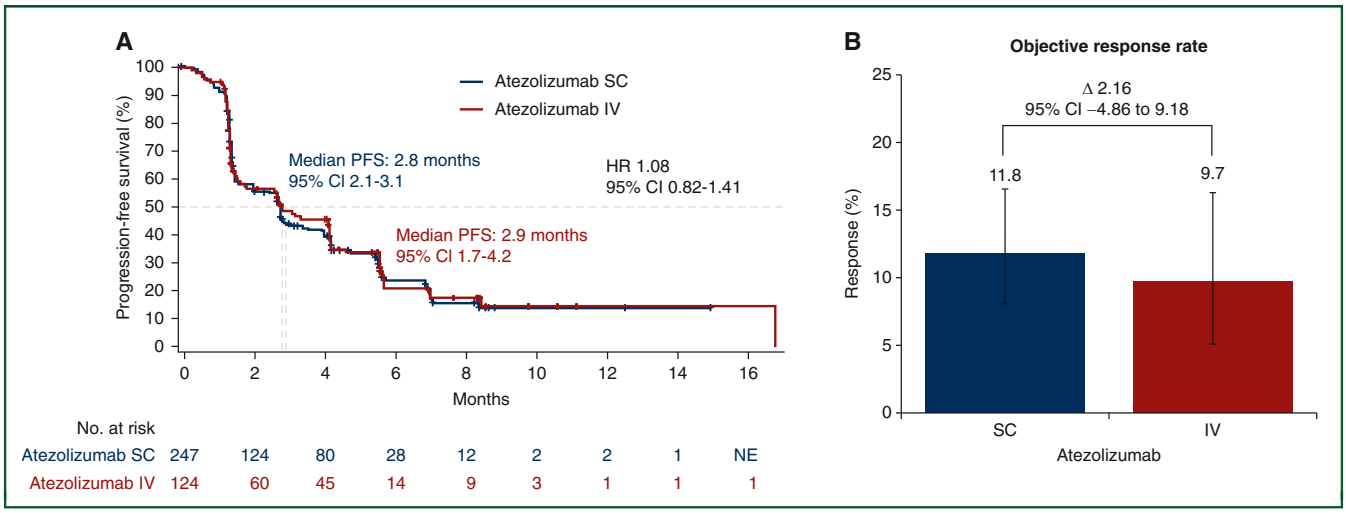

Figure 3. Efficacy for atezolizumab SC compared with atezolizumab IV for (A) progression-free survival and (B) objective response rate.
CI, confidence interval; HR, hazard ratio; IV, intravenous; NE, not estimable; PFS, progression-free survival; SC, subcutaneous.

Table 2. Safety summary

Patients with ≥1, *n* (%)	Atezolizumab	
	SC ($n = 247$)	IV ($n = 124$)
Any AE	212 (85.8)	104 (83.9)
Related AEs	93 (37.7)	47 (37.9)
AEs with fatal outcome	14 (5.7)	4 (3.2)
Related AE with fatal outcome	2 (0.8)	0 (0)
Serious AEs	38 (15.4)	22 (17.7)
Related serious AEs	4 (1.6)	3 (2.4)
Grade 3/4 AEs	44 (17.8)	32 (25.8)
Related grade 3/4 AEs	9 (3.6)	4 (3.2)
AEs leading to atezolizumab discontinuation	4 (1.6)	4 (3.2)
AEs leading to dose interruption	61 (24.7)	33 (26.6)
AEs of special interest	65 (26.3)	27 (21.8)
Grade 3/4 AEs of special interest	9 (3.6)	3 (2.4)
Grade 5 AEs of special interest	1 (0.4)	0 (0)
Infusion-related reaction	0 (0)	4 (3.2)
Injection site reaction	11 (4.5)	0 (0)

AE, adverse event; IV, intravenous; SC, subcutaneous.

Cross-study PK comparison. The co-primary endpoints, cycle 1 observed C_{trough} and model-predicted cycle 1 weekly AUC, were compared across atezolizumab SC and the other approved atezolizumab IV clinical studies. The systemic drug exposure following atezolizumab SC was consistent with the other approved IV clinical studies (Figure 4A and B).

DISCUSSION

IMscin001 met both of its co-primary endpoints, confirming that the SC dosing regimen of 1875 mg Q3W was noninferior, on the basis of systemic drug exposure at cycle 1, to the approved IV dosing regimen of 1200 mg Q3W. In addition, systemic drug exposures following multiple doses (i.e. at steady state) of atezolizumab were similar between SC and IV administration. As the active ingredient of atezolizumab in the SC and IV formulations is identical, it is expected that noninferior systemic exposure would yield a comparable degree of target-site saturation, and thus similar efficacy for both routes of administration. This is supported by the early efficacy and safety findings in this study, showing similar clinical outcomes between treatment arms.

Across all approved indications, the previously tested IV dosing regimens of atezolizumab, 1200 mg Q3W or 840 mg Q2W, were consistently shown to be in the flat portion of the exposure—response curve, suggesting that systemic drug exposure at these dose levels was not associated with patient response.[33,35] In addition, previous findings demonstrated that there was no meaningful impact of combination therapy or tumour type on atezolizumab PK.[33,35] The current analysis further showed that the systemic drug exposure following atezolizumab SC administration was consistent with the exposure following atezolizumab IV observed from 11 label-enabling studies across indications, including unresectable hepatocellular carcinoma, unresectable melanoma, advanced/metastatic urothelial bladder cancer, triple-negative breast cancer, extensive-stage small-cell lung cancer, and NSCLC.

Several phase III studies have examined the PK of cancer immunotherapies coformulated with rHuPH20 for SC administration compared with their IV counterparts. For example, the FeDeriCa study, in which patients with human epidermal growth factor receptor 2 (HER2)-positive early

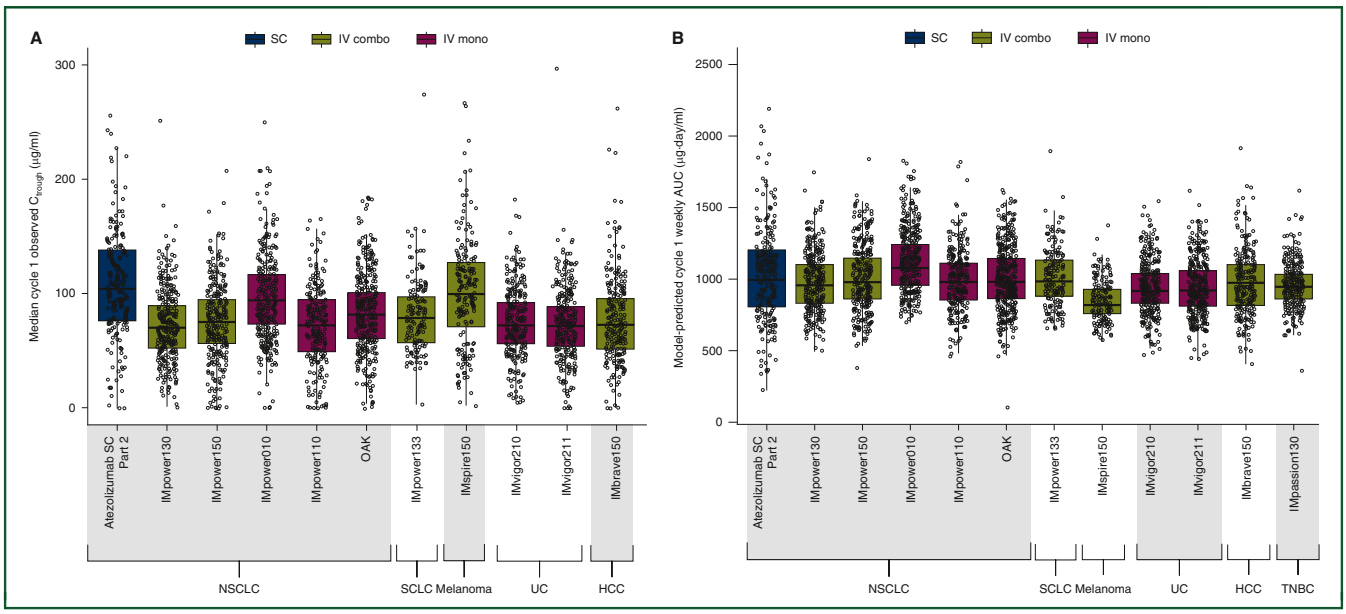

Figure 4. Exposure of atezolizumab SC and atezolizumab IV across approved indications for (A) cycle 1 observed C_{trough} and (B) model-predicted cycle 1 weekly AUC. The median for each group is shown by the horizontal line, and boxes represent the interquartile range.
[a]y-axis is capped at 300 µg/ml; actual data extend to ∼600 µg/ml (0.3% above 300 µg/ml).
[b]Cycle 1 represents single-dose PK; dosing for IMpassion130 occurred on days 1 and 15 of each cycle, and therefore, single-dose PK was not collected in IMpassion130.
[c]Observed day 14 or 21 C_{trough} (µg/ml).
AUC, area under the curve; HCC, hepatocellular carcinoma; IV, intravenous; NSCLC, non-small-cell lung cancer; PK, pharmacokinetics; SC, subcutaneous; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.

breast cancer were randomised 1 : 1 to receive SC or IV combinations of pertuzumab + trastuzumab, examined noninferiority of the cycle 7 serum C_{trough} as the primary endpoint.[25] Patients with multiple myeloma were randomised 1 : 1 to receive SC or IV daratumumab in the COLUMBA study, and co-primary endpoints were noninferiority of cycle 3 maximum C_{trough} and overall response.[23] Finally, in the HannaH study, patients were randomised 1 : 1 to receive chemotherapy concurrently with IV or SC trastuzumab, with co-primary endpoints of cycle 8 serum C_{trough} and pathological complete response.[26] These studies all showed that a similar benefit—risk profile could be established for the alternative SC formulation compared with the conventional IV product and demonstrated that when drug exposure was maintained, efficacy and safety were similar. Cycle 1 exposure metrics were selected for the co-primary endpoints of IMscin001 to mitigate response-dependent decreases of clearance over time.[36,37] The addition of AUC as a co-primary endpoint was a strength as it captured drug exposure in the cycle 1 dosing interval and is a more conservative PK endpoint than C_{trough} for the noninferiority determination.[37]

IMscin001 did not examine the noninferiority of efficacy endpoints. Progression-free survival and objective response rates were similar between arms and consistent with the OAK study (2.8 months and 14%, respectively),[10] which points towards similar efficacy between atezolizumab SC and IV in patients with NSCLC being treated in the second-line setting.

Based on the data from relatively short median safety follow-up in IMscin001 (4.4 months), the safety profile of atezolizumab SC was similar to atezolizumab IV and consistent with previous studies with atezolizumab IV across various cancer types,[1-8,10,38,39] with no new safety concerns identified for atezolizumab in this study. AEs, serious AEs, AEs of special interest, and AEs leading to atezolizumab discontinuation or dose interruption were similar between arms and within the known atezolizumab IV ranges.[10-13,40] Grade 5 AEs were reported across multiple system organ classes, and most were a single occurrence per MedDRA-preferred term. Following a review of the grade 5 events, no new safety concerns were identified.

The total injection volume of atezolizumab was 15 ml and identical to the loading dose of pertuzumab + trastuzumab coformulated with rHuPH20 used in HER2-positive early breast cancer.[25] rHuPH20 (ENHANZE drug delivery technology; Halozyme, Inc, San Diego, CA) is an endoglycosidase that transiently degrades hyaluronan at the SC injection site, resulting in enhanced tissue permeability and improved dispersion and absorption of large-volume, coadministered drugs, thereby acting as a bridge between IV and SC modalities.[20] In IMscin001, incidence of injection site reactions was low (4.5%), with the most common being injection site pain (2.4%) and injection site reaction (1.6%). Most were grade 1 and a few were grade 2, and most resolved without treatment. No interruption, discontinuation, or delay occurred for any patients in the atezolizumab SC arm who experienced an injection site reaction, suggesting that SC injections were well tolerated.

The incidence of treatment-emergent ADAs was similar between arms, and these were within the historical range for atezolizumab IV (13%-54%).[41] The baseline prevalence for anti-rHuPH20 antibodies was consistent with the prevalence of pre-existing antibodies to rHuPH20 as previously reported.[42] Postbaseline incidence was relatively low and within the range of other SC therapeutic antibody products (1%-21%).[43-45]

One limitation of IMscin001 is the relative immaturity of the efficacy and safety data. By contrast, the limited follow-up is unlikely to have impacted the assessment of immunogenicity because the median time to ADA onset was 3 weeks for both arms, and the majority of patients were positive at only one time point (not shown), consistent with past IV studies that demonstrate the early, transient nature of atezolizumab immunogenicity across indications.[41]

Higher PK variability was observed for the SC arm compared with the IV arm. Given the similar safety and efficacy rates in IMscin001, the wide therapeutic window for atezolizumab IV, and the confirmed flat exposure—response relationship following SC administration (not shown), the higher variability in systemic drug exposure is not expected to impact clinical outcomes.

In summary, IMscin001 demonstrated that atezolizumab SC (1875 mg Q3W) was noninferior, on the basis of C_{trough} and $AUC_{0\text{-}21\ d}$ at cycle 1, compared with atezolizumab IV (1200 mg Q3W). The totality of data, including similar systemic drug exposure, efficacy, safety, and immunogenicity data, between atezolizumab SC and atezolizumab IV, which is consistent with the known atezolizumab IV profile, validates the use of atezolizumab SC as an alternative to atezolizumab IV. The current clinical data, along with the wide therapeutic window for atezolizumab, support the use of atezolizumab SC in all patient populations for which atezolizumab IV is approved.

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DISCLOSURE

MB reports honoraria and/or consulting fees from, and has served on advisory boards for, F. Hoffmann-La Roche Ltd, Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, and Novartis. ZZ has served on advisory boards for AstraZeneca. AM reports stocks/shares in the MEDSI Hospital Group. LHB and NT are employees of, and have stocks/shares in, F. Hoffmann-La Roche Ltd. SNL, ESK, XL, and JAZ

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DATA SHARING

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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