IPSOS: Results from a Phase 3 study of first-line (1L) atezolizumab (atezo) vs single-agent chemotherapy (chemo) in patients (pts) with NSCLC not eligible for a platinum-containing regimen

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Background

- Pivotal clinical trials showed that 1L treatment for NSCLC with immunotherapy with or without chemotherapy improved overall survival vs platinum-doublet chemotherapy[1]
  - Guidelines recommend 1L single-agent immunotherapy options for patients with high PD-L1 expression (≥50%)[2,3]
  - However, these studies and most treatment recommendations are limited to patients with good performance status (ECOG PS 0/1)[3]

- In real-world settings, ≥40% of patients with NSCLC have poor performance status (ECOG PS ≥2) and/or are elderly with multiple co-morbidities and poor tolerance of treatment[4]
  - Many of these patients are deemed ineligible for 1L platinum-based regimens and are usually excluded from clinical trials of 1L treatments[5]

- Given the relatively poor prognosis and limited treatment options when compared with the significant progress achieved in patients with PS 0/1 and oncogenic driven NSCLC patients, this population represents an important, under-studied NSCLC group with an unmet medical need to examine the efficacy, safety and quality of life with novel therapeutic options[6,7]

- IPSOS (NCT03191786) is a Phase 3, global, multicentre, open-label, randomised, controlled study examining the efficacy, safety and patient-reported outcomes with atezolizumab vs single agent chemotherapy in patients who were considered unsuitable for 1L platinum-doublet chemotherapy

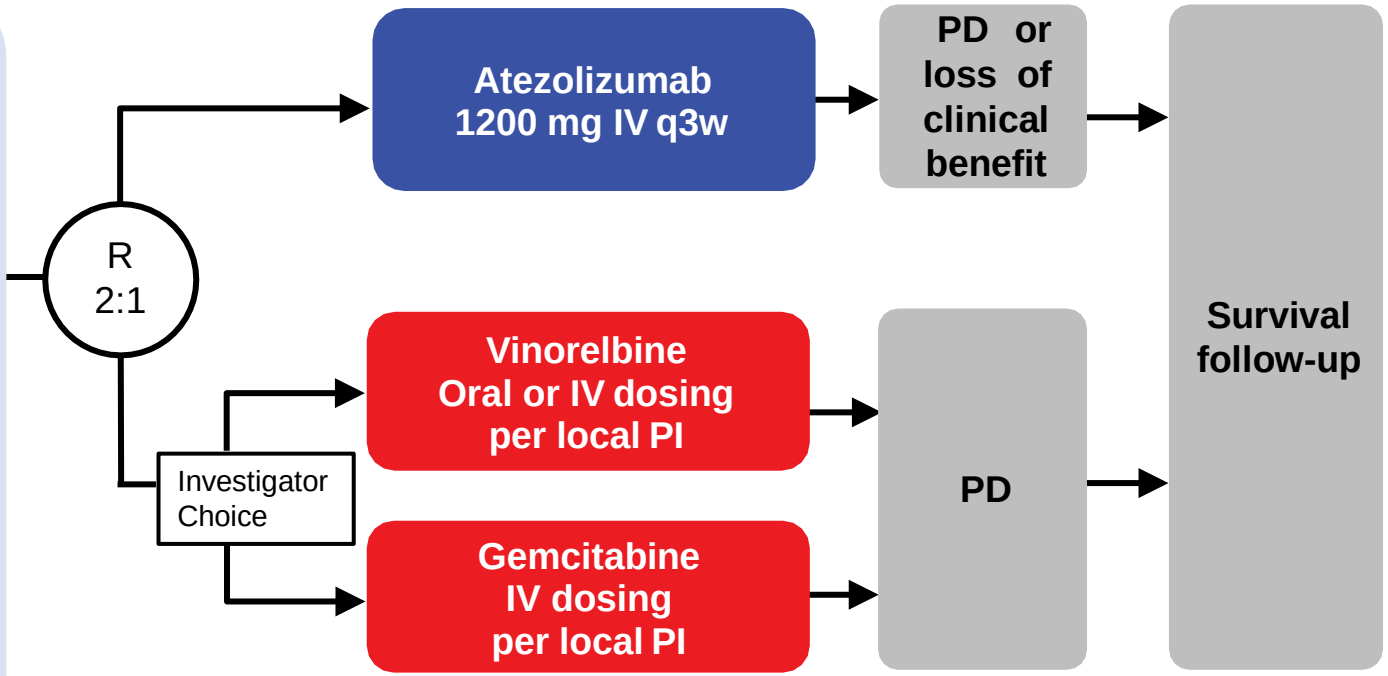
1L, first line; ECOG PS, Eastern Cooperative Oncology Group performance status. 1. Grant MJ, et al. Nat Rev Clin Oncol. 2021;18(10):625-644. 2. Planchard D, et al. Ann Oncol. 2018;29(Suppl 4):iv192-iv237. 3. Hanna NH, et al. J Clin Oncol. 2020;38(14):1608-1632. 4. Lilenbaum RC, et al. J Thorac Oncol. 2008;3(2):125-129. 5. De Marinis F, et al. Clin Lung Cancer 2015;16(6):399-405. 6. Middleton G, et al. Lancet Respir Med. 2020;8(9):895-904. 7. Mojsak et al. Adv Med Sci. 2021;66(2):381-387.

IPSOS Study Design

Treatment-naive stage IIIB[a]/IV (AJCC 7th edition) NSCLC

- Squamous or non-squamous histology
- Platinum ineligible because of:
  - ECOG PS 2 or 3
  - ECOG PS 0 or 1 permitted if ≥70 years of age with substantial comorbidities or other contraindictions to platinum chemotherapy
- *EGFR*+ (L858R or exon 19 deletion) or *ALK*+ excluded
- Patients with treated asymptomatic brain metastases permitted

n=453



Stratification factors:
- Histology (squamous or non-squamous)
- PD-L1 expression level by SP142 IHC assay (TC3 or IC3 vs TC0/1/2 or IC0/1/2[b] vs unknown)
- Brain metastases (yes/no)

Primary endpoint:
- OS

Secondary endpoints:
- OS rates at 6, 12, 18 and 24 months
- PFS
- Objective response rate
- Duration of response
- OS and PFS in PD-L1 positive subgroup[c]

Other endpoints:
- PROs
- Safety
- Exploratory biomarker analyses

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD, progressive disease; PI, prescribing information; PROs, patient-reported outcomes; q3w, every 3 weeks.
R, randomised. [a] Not amenable for multimodality treatment. [b] TC0/1/2 or IC0/1/2 =TC0/1/2/3 or IC0/1/2/3 excluding TC3 or IC3. [c] Per SP263 IHC assay.

Statistical Plan

Enrolment occurred from 2017 Sept to 2019 Sept

≈380 events were estimated to result in **90%** power and an overall type I error of 5% to detect a true difference in OS for atezolizumab vs chemotherapy at interim or final analysis

- OS was estimated using Kaplan-Meier method
- Treatment comparison used a stratified log-rank test
- HRs were estimated using a stratified Cox proportional hazards model

All efficacy analyses were done in the intention-to-treat population of all randomised patients

- Interim Analysis
  - Performed by iDMC when 304 events had been observed
  - iDMC recommended study proceed to final analysis
- Final Analysis

iDMC, independent Data Monitoring Committee.

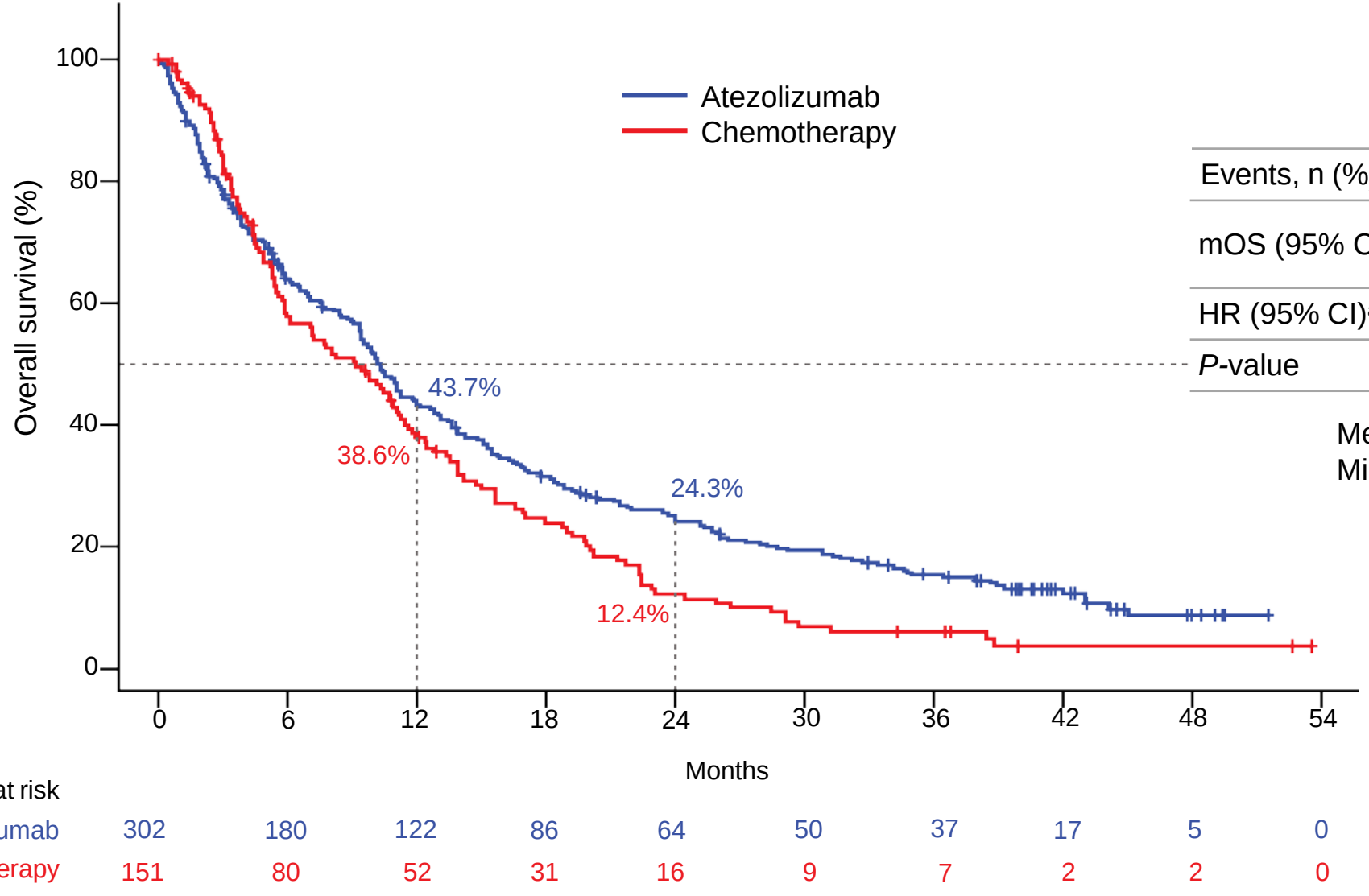
Baseline Characteristics

	Atezolizumab (n=302)	Chemotherapy (n=151)
Age		
Median (range), y	75.0 (33, 94)	75.0 (37, 89)
<70 y, n (%)	80 (26.5)	43 (28.5)
70-79 y, n (%)	125 (41.4)	65 (43.0)
≥80 y, n (%)	97 (32.1)	43 (28.5)
ECOG PS, n (%)		
0/1	56 (18.5)	19 (12.6)
2	228 (75.5)	116 (76.8)
3	18 (6.0)	16 (10.6)
Sex, male, n (%)	220 (72.8)	108 (71.5)
Race, n (%)[a]		
White	203 (67.2)	95 (62.9)
Asian	75 (24.8)	38 (25.2)
Histology, n (%)[b]		
Non-squamous	173 (57.3)	87 (57.6)
Squamous	129 (42.7)	64 (42.4)

	Atezolizumab (n=302)	Chemotherapy (n=151)
Brain metastases, n (%)[b]		
Yes	27 (8.9)	13 (8.6)
No	273 (90.4)	137 (90.7)
Missing	2 (0.7)	1 (0.7)
Smoking status, n (%)		
Previous	209 (69.2)	103 (68.2)
Current	58 (19.2)	28 (18.5)
Never	35 (11.6)	20 (13.2)
PD-L1 expression level, n (%)[c]		
TC <1%	151 (50.0)	61 (40.4)
TC ≥1%	127 (42.1)	78 (51.7)
TC 1-49	77 (25.5)	53 (35.1)
TC ≥50%	50 (16.6)	25 (16.6)
Unknown	24 (7.9)	12 (7.9)

Clinical cutoff: 30 Apr 2022. [a] In the atezolizumab arm, 12 patients were American Indian or Alaska Native, 2 Black or African American, 6 multiple races, and 4 unknown. In the chemotherapy arm, 9 patients were American Indian or Alaska Native, 1 Black or African American, 6 multiple races, and 2 unknown. [b] Per electronic case report form. [c] By SP263 IHC assay.

Primary Endpoint: OS



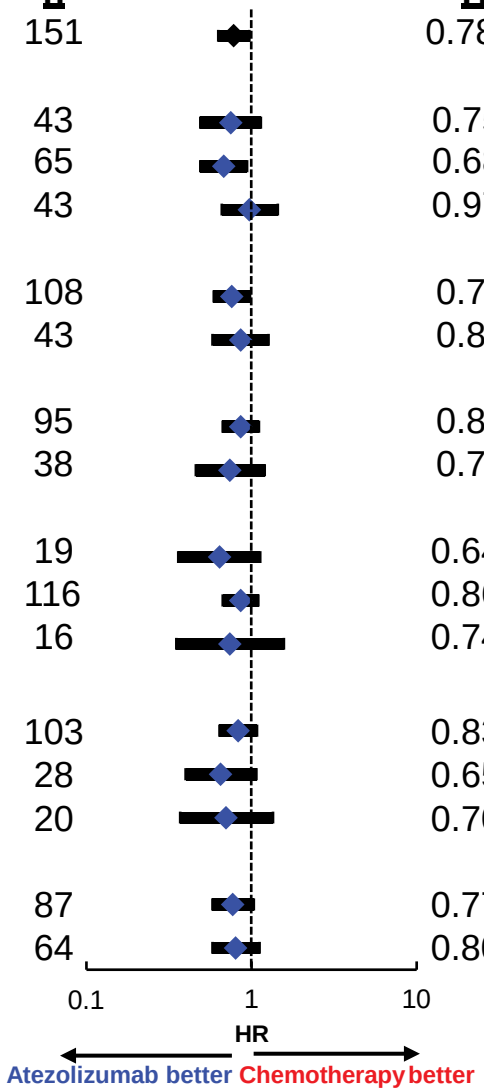
	Atezo (n=302)	Chemo (n=151)
Events, n (%)	249 (82.5)	130 (86.1)
mOS (95% CI), mo	10.3 (9.4, 11.9)	9.2 (5.9, 11.2)
HR (95% CI)[a]	**0.78 (0.63, 0.97)**	
P-value	0.028[b]	

Median follow-up: 41.0 months
Minimum follow-up: 32.0 months

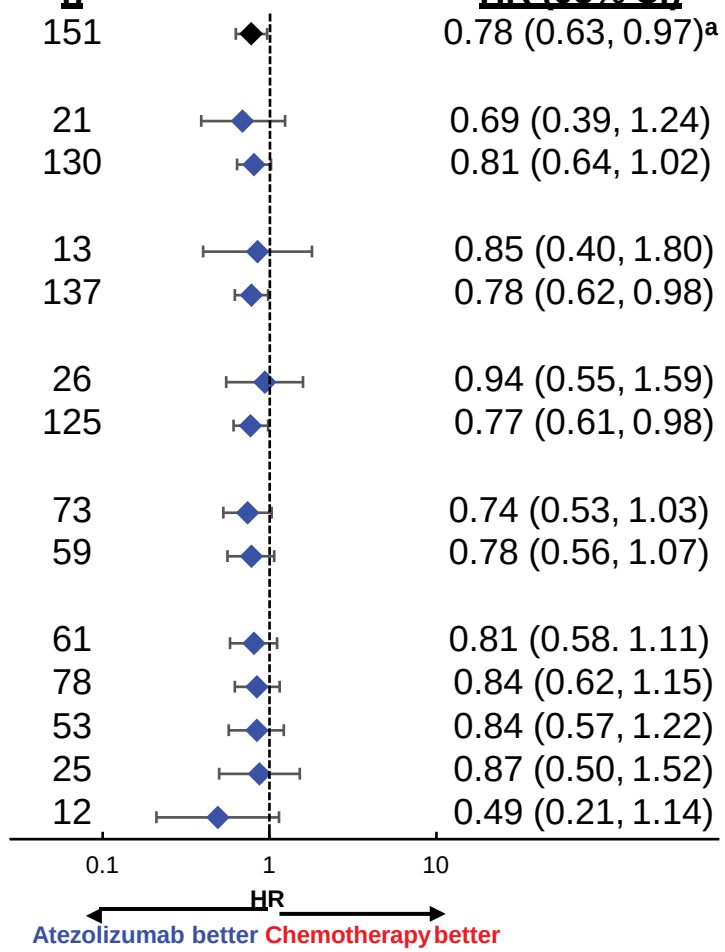
Clinical cutoff: 30 Apr 2022. [a] Stratified. [b] Statistical significance boundary crossed.

OS in Key Patient Subgroups

Subgroup	Atezo n	Chemo n	HR (95% CI)
All patients	302	151	0.78 (0.63, 0.97)[a]
Age			
<70 y	80	43	0.75 (0.49, 1.14)
70-79 y	125	65	0.68 (0.49, 0.94)
≥80 y	97	43	0.97 (0.66, 1.44)
Sex			
Male	220	108	0.76 (0.59, 0.98)
Female	82	43	0.86 (0.58, 1.27)
Race			
White	203	95	0.86 (0.67, 1.11)
Asian	75	38	0.74 (0.46, 1.20)
ECOG PS			
0/1	56	19	0.64 (0.36, 1.13)
2	228	116	0.86 (0.67, 1.10)
3	18	16	0.74 (0.35, 1.57)
Tobacco use history			
Previous	209	103	0.83 (0.64, 1.08)
Current	58	28	0.65 (0.40, 1.07)
Never	35	20	0.70 (0.37, 1.35)
Histology			
Non-squamous	173	87	0.77 (0.58, 1.03)
Squamous	129	64	0.80 (0.58, 1.12)



Subgroup	Atezo n	Chemo n	HR (95% CI)
All patients	302	151	0.78 (0.63, 0.97)[a]
Stage			
IIIB	41	21	0.69 (0.39, 1.24)
IV	261	130	0.81 (0.64, 1.02)
Brain metastases			
Yes	27	13	0.85 (0.40, 1.80)
No	273	137	0.78 (0.62, 0.98)
Liver metastases			
Yes	44	26	0.94 (0.55, 1.59)
No	258	125	0.77 (0.61, 0.98)
Number of metastatic sites			
<3	124	73	0.74 (0.53, 1.03)
≥3	141	59	0.78 (0.56, 1.07)
P D-L1 expression level[b]			
TC <1%	151	61	0.81 (0.58. 1.11)
TC ≥1%	127	78	0.84 (0.62, 1.15)
TC 1-49%	77	53	0.84 (0.57, 1.22)
TC ≥50%	50	25	0.87 (0.50, 1.52)
Unknown	24	12	0.49 (0.21, 1.14)



Clinical cutoff: 30 Apr 2022. [a] Stratified for all patients; unstratified for all other subgroups. [b] Per SP263 IHC assay.

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70-79 y	125	65	0.68 (0.49, 0.94)
≥80 y	97	43	0.97 (0.66, 1.44)
Sex			
Male	220	108	0.76 (0.59, 0.98)
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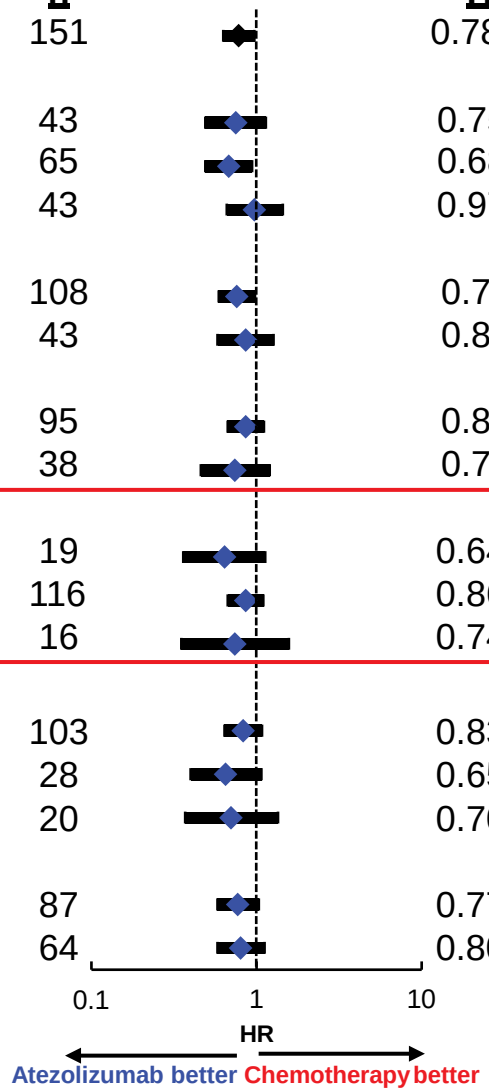

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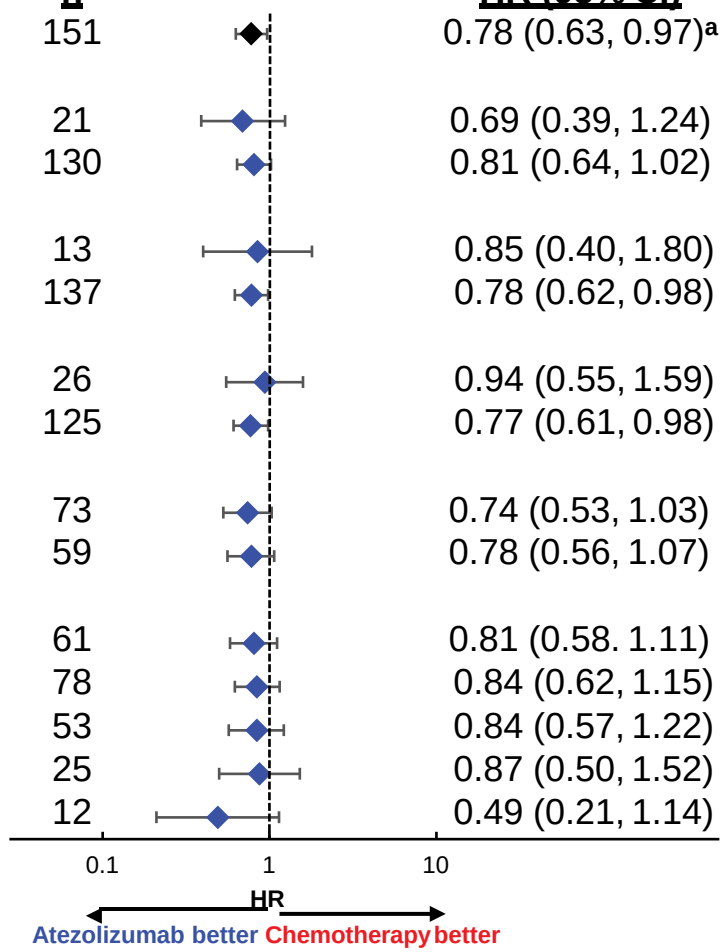

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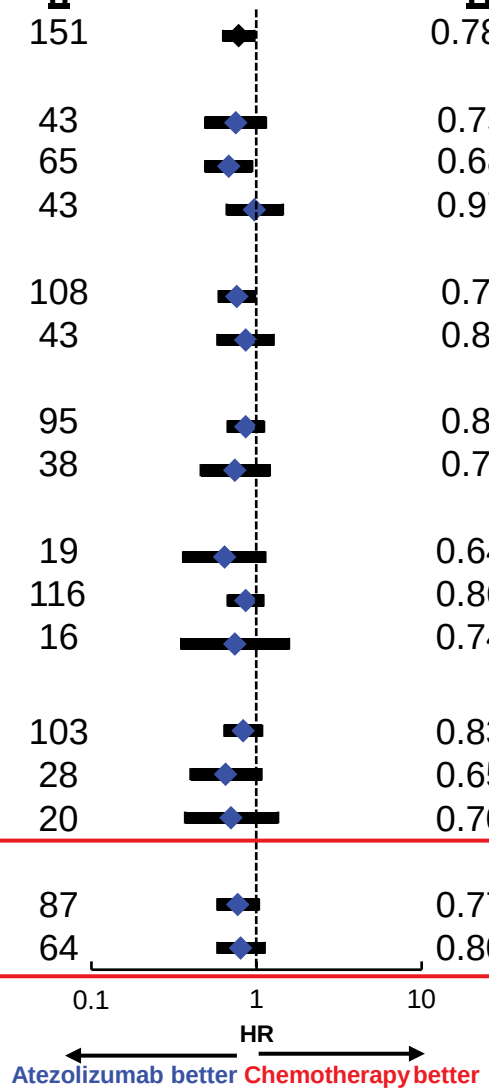

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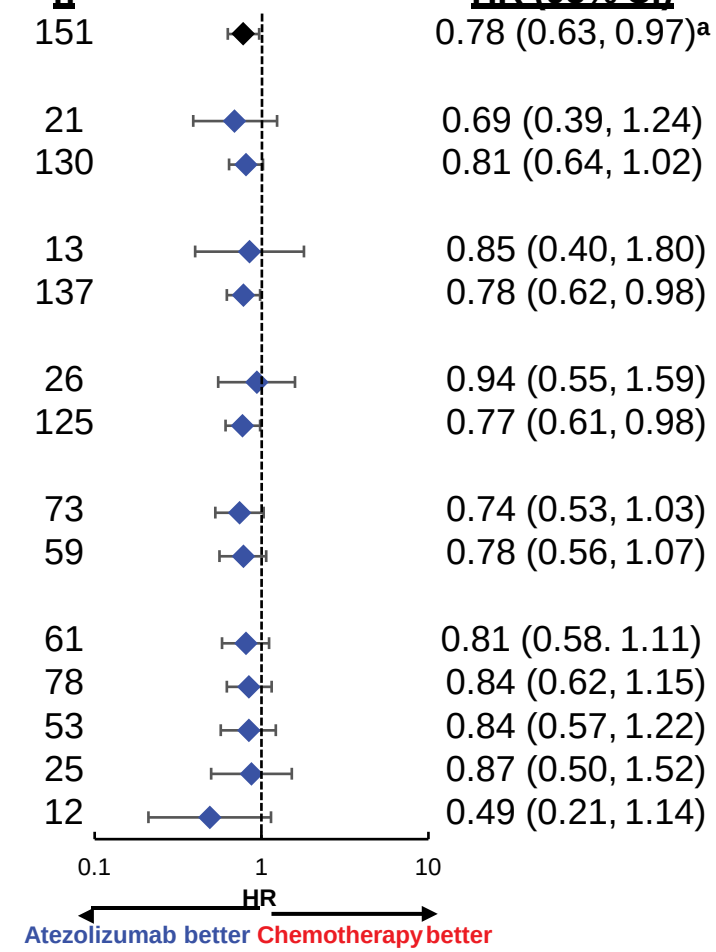

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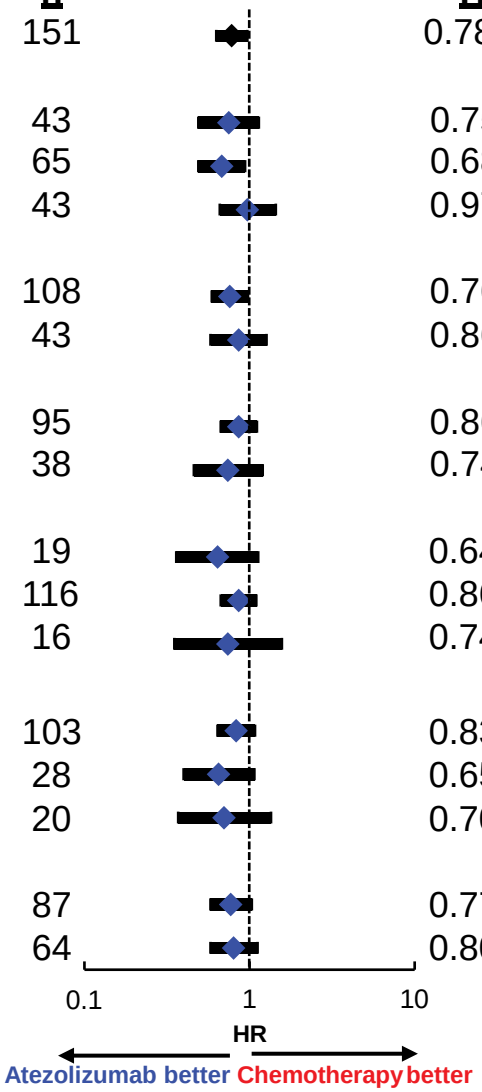

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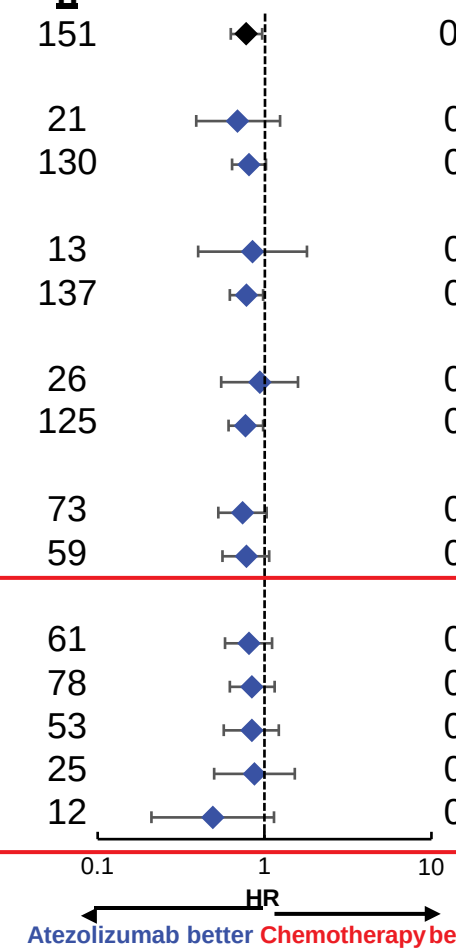

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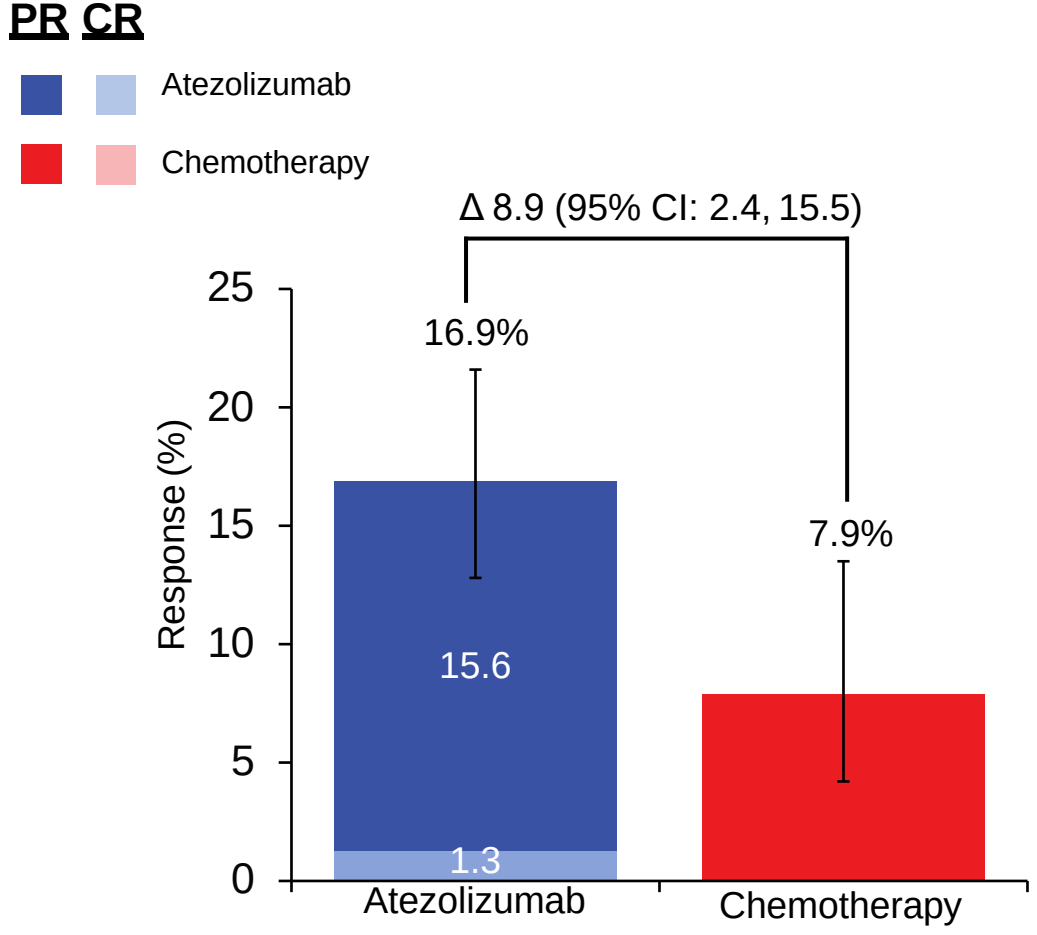
Secondary Endpoints: ORR and DOR

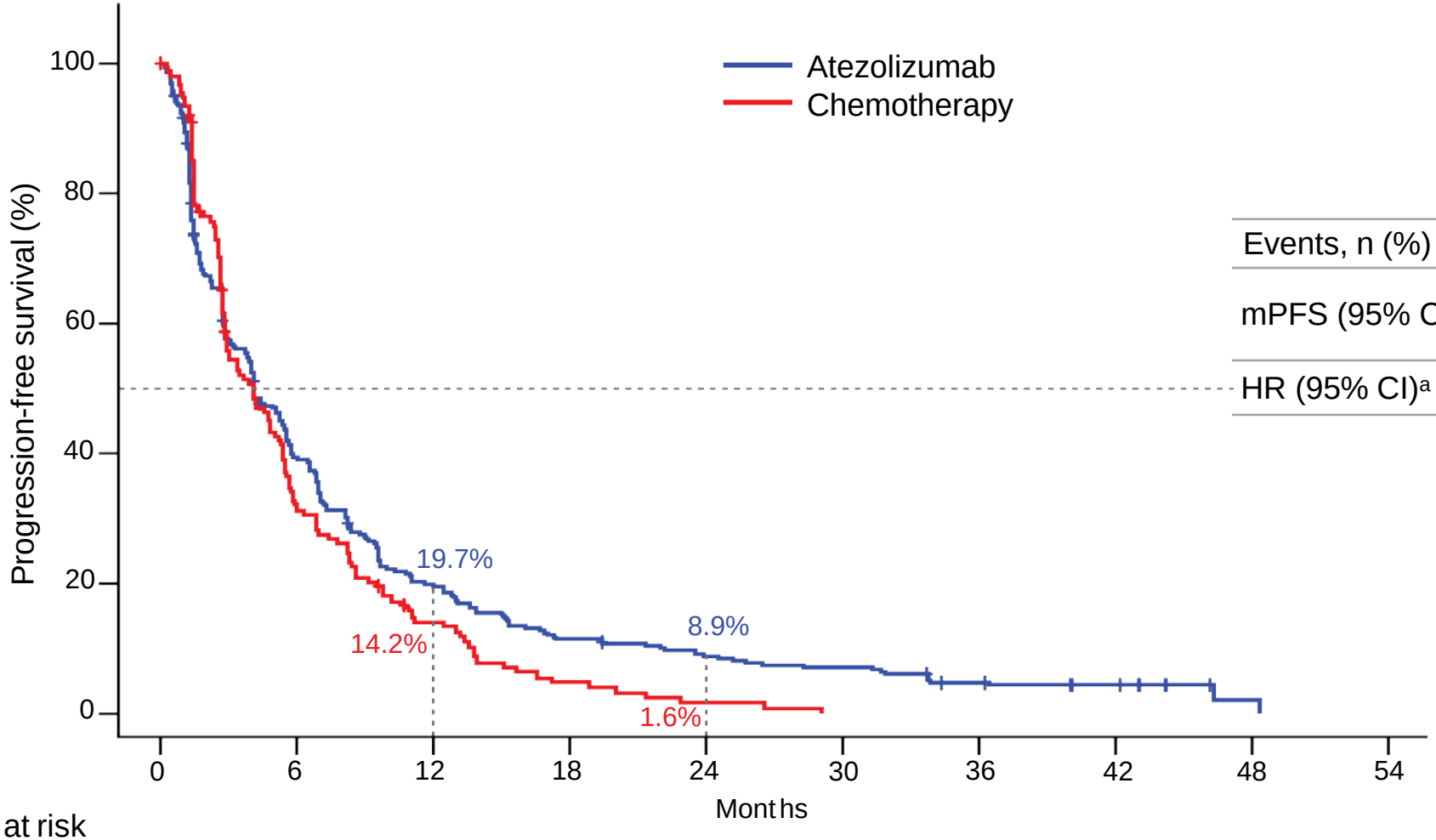


	Atezolizumab (n=302)	Chemotherapy (n=151)
ORR, n (%) 95% CI	51 (16.9) (12.8, 21.6)	12 (7.9) (4.2, 13.5)
CR, n (%)	4 (1.3)	0 (0)
PR, n (%)	47 (15.6)	12 (7.9)
Stable disease, n (%)	122 (40.4)	73 (48.3)
Disease control rate, n (%)	173 (57.3)	85 (56.3)
Progressive disease, n (%)	67 (22.2)	36 (23.8)
Non-evaluable, n (%)	14 (4.6)	12 (7.9)
Missing, n (%)	48 (15.9)	18 (11.9)

Median DOR, months (95% CI)	14.0 (8.1, 20.3)	7.8 (4.8, 9.7)

Clinical cutoff: 30 Apr 2022. CR, complete response; DOR, duration of response ORR, objective response rate; PR, partial response. Error bars represent 95% CI.

Secondary Endpoints: PFS



	Atezo (n=302)	Chemo (n=151)
Events, n (%)	276 (91.4)	138 (91.4)
mPFS (95% CI), mo	4.2 (3.7, 5.5)	4.0 (2.9, 5.4)
HR (95% CI)[a]	0.87 (0.70, 1.07)	

Clinical cutoff: 30 Apr 2022. [a] Stratified.

Subsequent Anti-cancer Therapies[a]

	Atezolizumab (n=302)	Chemotherapy (n=151)
Number of patients with any subsequent anti-cancer therapy, n (%)	**61 (20.2)**	**45 (29.8)**
Chemotherapy, n (%)	48 (15.9)	16 (10.6)
Cancer Immunotherapy, n (%)	4 (1.3)	28 (18.5)
TKI, n (%)	10 (3.3)	5 (3.3)
Other, n (%)	3 (1.0)	1 (0.7)

Clinical cutoff: 30 Apr 2022. [a] Subsequent anti-cancer therapies included those that were received in combination with or sequential to the study treatment.

Safety Summary

	Atezolizumab (n=300)	Gemcitabine (n=63)	Vinorelbine (n=84)
Median treatment duration, months (range)	3.5 (0-51)	2.3 (0-13)	1.8 (0-21)
Median number of cycles initiated (range)	6.0 (1-73)	4.0 (1-19)	3.0 (1-31)
	Atezolizumab (n=300)	**Chemotherapy (n=147)**	
All-grade AE, n (%)	275 (91.7)	143 (97.3)	
Treatment-related AE	171 (57.0)	118 (80.3)	
Grade 3-4 AE, n (%)	136 (45.3)	71 (48.3)	
Treatment-related Grade 3-4 AE	49 (16.3)	49 (33.3)	
Serious AE, n (%)	146 (48.7)	53 (36.1)	
Treatment-related SAE	35 (11.7)	23 (15.6)	
Grade 5 AE, n (%)	35 (11.7)	13 (8.8)	
Treatment-related Grade 5 AE	3 (1.0)	4 (2.7)	
AE leading to discontinuation of study drug, n (%)	39 (13.0)	20 (13.6)	
AE leading to modification/interruption of study drug, n (%)	96 (32.0)	71 (48.3)	

Clinical cutoff: 30 Apr 2022.

AESIs[a] >1% in either arm

	Atezolizumab (n=300)	Chemotherapy (n=147)
All-grade AESI, n (%)	102 (34.0)	27 (18.4)
Immune-mediated rash	45 (15.0)	11 (7.5)
Immune-mediated hepatitis (diagnosis and lab abnormalities)	32 (10.7)	9 (6.1)
Immune-mediated hepatitis (lab abnormalities)	27 (9.0)	8 (5.4)
Immune-mediated hepatitis (diagnosis)	7 (2.3)	1 (0.7)
Immune-mediated hypothyroidism	27 (9.0)	1 (0.7)
Immune-mediated pneumonitis	13 (4.3)	3 (2.0)
Immune-mediated hyperthyroidism	7 (2.3)	3 (2.0)
Immune-mediated diabetes mellitus	4 (1.3)	0
Grade 3-4 AESI, n (%)	20 (6.7)	3 (2.0)
All-grade AESI requiring use of corticosteroids, n (%)	34 (11.3)	7 (4.8)

Clinical cutoff: 30 Apr 2022. [a] Adverse event of special interest as defined in Roche basket file.

AESIs[a] >1% in either arm

	Atezolizumab monotherapy historical data[b] (n=3178)	Atezolizumab (n=300)	Chemotherapy (n=147)
All-grade AESI, n (%)	1101 (34.6)	102 (34.0)	27 (18.4)
Immune-mediated rash	613 (19.3)	45 (15.0)	11 (7.5)
Immune-mediated hepatitis (diagnosis and lab abnormalities)	343 (10.8)	32 (10.7)	9 (6.1)
Immune-mediated hepatitis (lab abnormalities)	315 (9.9)	27 (9.0)	8 (5.4)
Immune-mediated hepatitis (diagnosis)	62 (2.0)	7 (2.3)	1 (0.7)
Immune-mediated hypothyroidism	164 (5.2)	27 (9.0)	1 (0.7)
Immune-mediated pneumonitis	91 (2.9)	13 (4.3)	3 (2.0)
Immune-mediated hyperthyroidism	30 (0.9)	7 (2.3)	3 (2.0)
Immune-mediated diabetes mellitus	10 (0.3)	4 (1.3)	0
Grade 3-4 AESI, n (%)	-	20 (6.7)	3 (2.0)
All-grade AESI requiring use of corticosteroids, n (%)	-	34 (11.3)	7 (4.8)

Clinical cutoff: 30 Apr 2022. [a] Adverse event of special interest as defined in Roche basket file. [b] Historical atezolizumab monotherapy population includes pooled data from 3178 patients in mixed tumor types (studies: IMvigor210, IMvigor211, OAK, BIRCH, POPLAR, FIR, IMmotion150 and PCD4989g).

Health-Related QOL Patient-Reported Outcomes

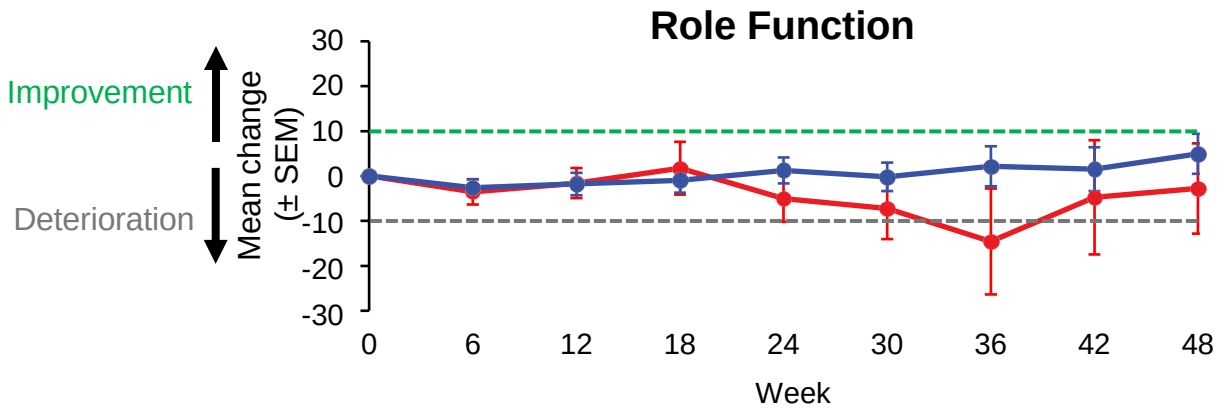
Prespecified patient-reported outcome measures[a] assessed by EORTC QLQ-C30[b] and QLQ-LC13[c]:

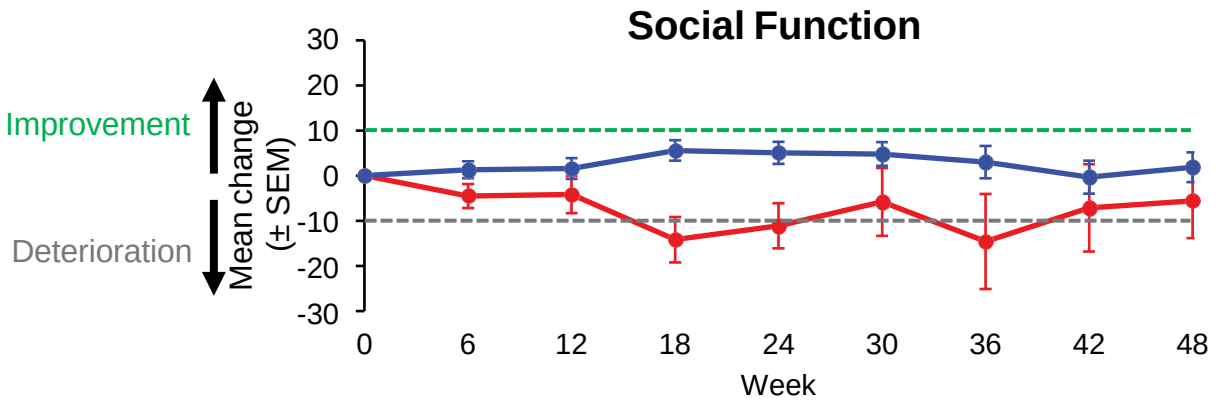
- **Change from baseline summaries**
  - ≥10-point change in a treatment arm was considered clinically meaningful
- **Time to confirmed deterioration in patient-reported lung cancer symptoms** of cough, dyspnoea, chest pain, arm/shoulder pain, or fatigue
  - Time to confirmed deterioration is defined as the time from randomisation to the first confirmed clinically meaningful deterioration in EORTC symptom scores
  - Confirmed deterioration is defined as ≥10-point increase above baseline in ≥2 consecutive assessments or followed by death

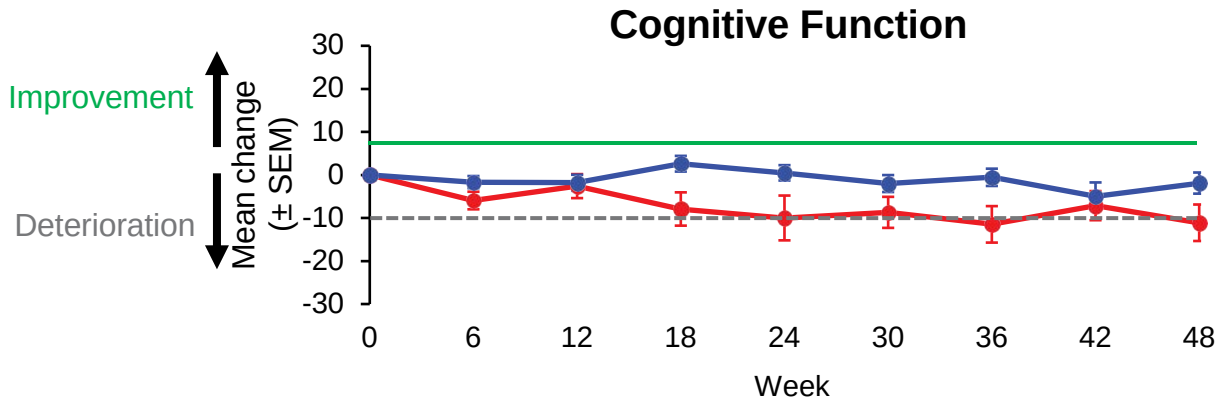
Clinical cutoff: 30 Apr 2022. EORTC, European Organisation for Research and Treatment of Cancer. [a] Patient-reported outcome questionnaires completed with each tumor assessment (q6w for 48 weeks and q9w thereafter) until disease progression per RECIST v1.1. [b] EORTC QLQ-C30 covers general aspects of health-related QOL. [c] EORTC QLQ-LC13 is a 13-item lung cancer-specific questionnaire.

Health-Related QOL Patient-Reported Outcomes: Functioning Scales

- Atezolizumab arm remained stable (≤10%) across all domains, while chemotherapy arm showed some deterioration





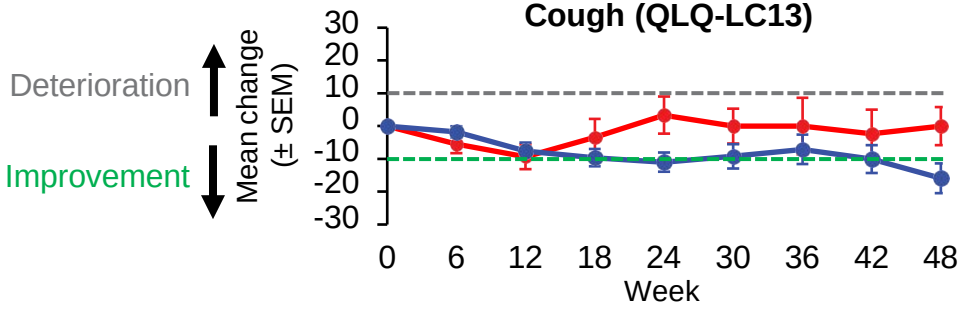


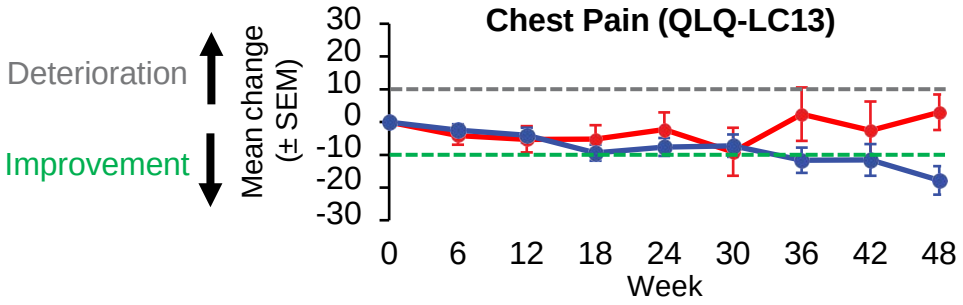
Atezolizumab (n=302)
Chemotherapy (n=151)

Clinical cutoff: 30 Apr 2022. QOL, quality of life. Only time points with data for ≥10 patients in either treatment group are shown. Completion rates out of expected patients were mostly comparable between treatment arms and were >70%, with the exception of Week 36 (67%). No meaningful changes were observed in either arm for physical functioning, emotional functioning, or Global Health Status. Error bars represent SEM.

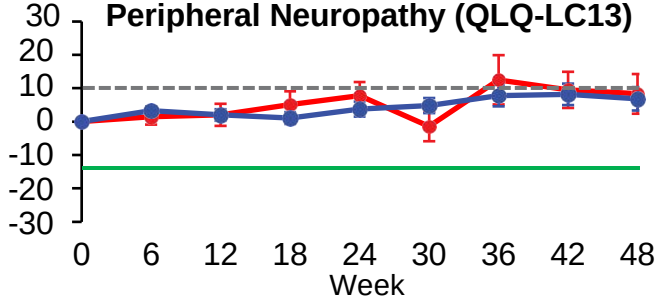
Health-Related QOL Patient-Reported Outcomes: EORTC QLQ-C30 and QLQ-LC13 Symptoms

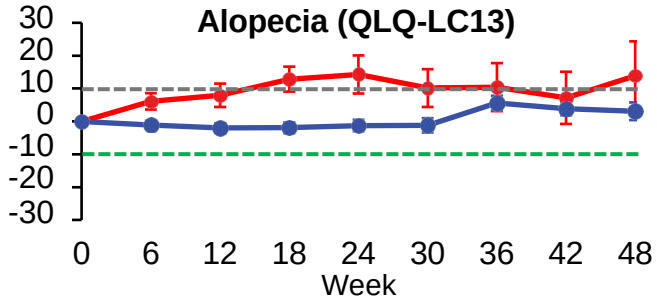
Improvement in atezolizumab arm



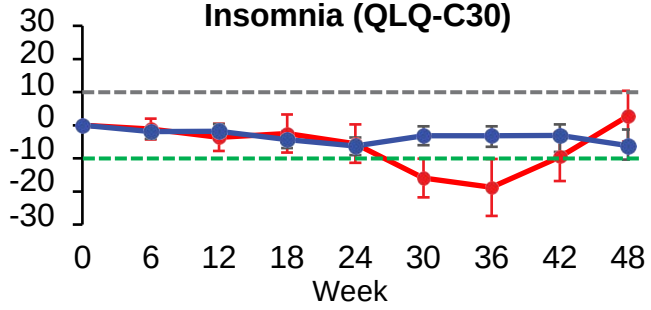


Deterioration in chemotherapy arm

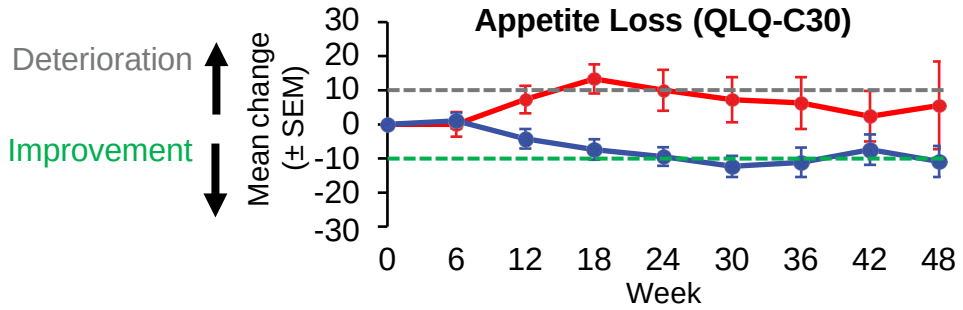




Improvement in chemotherapy arm



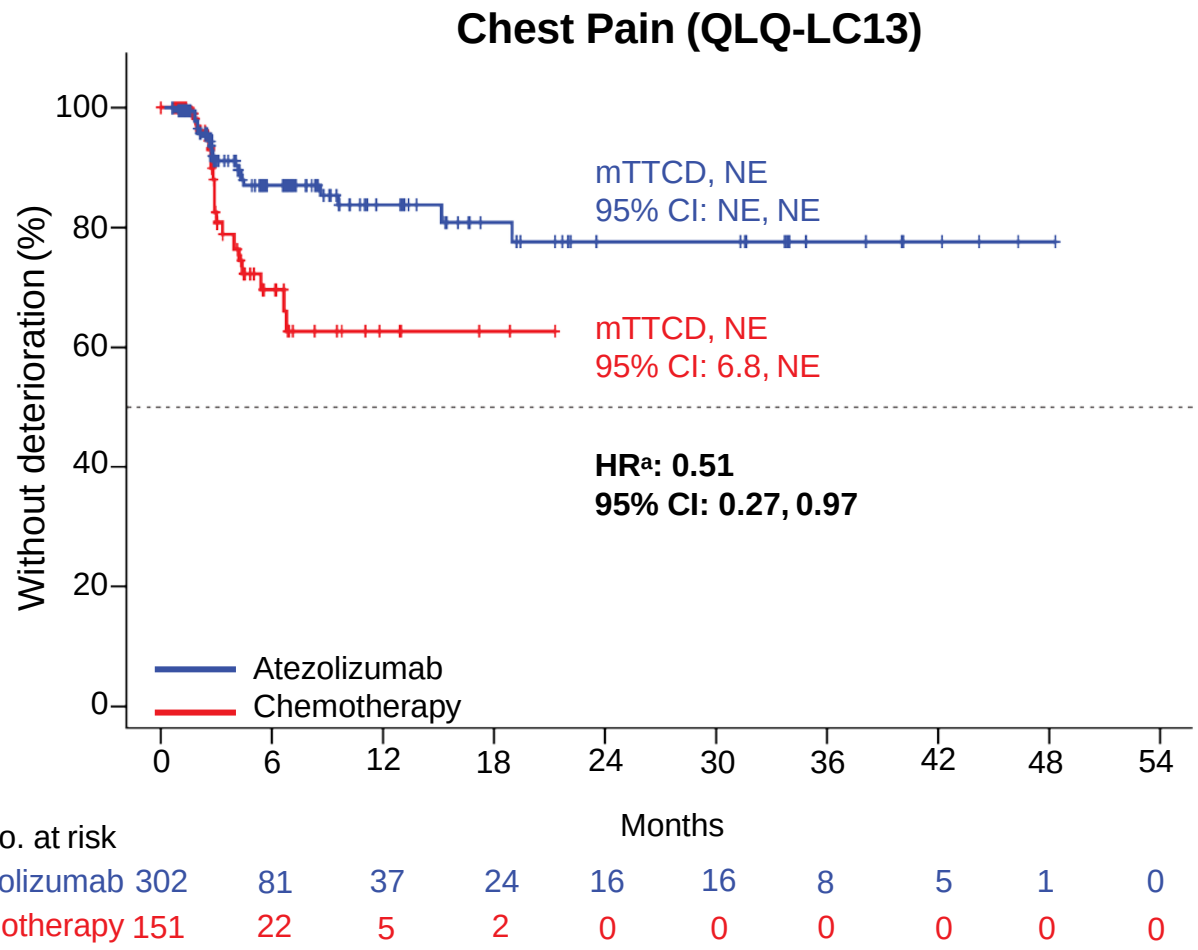
Improvement in atezolizumab arm and deterioration in chemotherapy arm



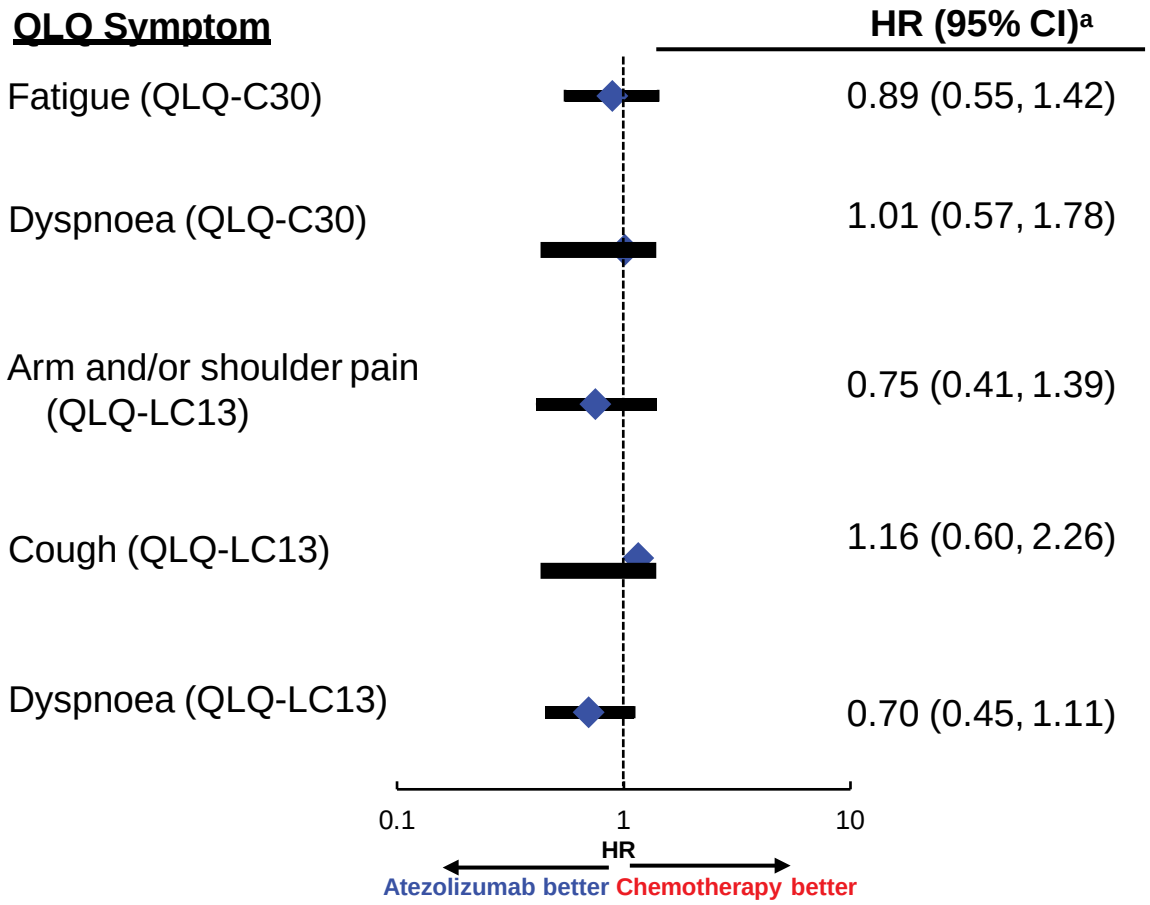
Atezolizumab (n=302)
Chemotherapy (n=151)

Clinical cutoff: 30 Apr 2022. Meaningful improvement or deterioration defined as ≥10% change from baseline. Only time points with data for ≥10 patients in either treatment arm are shown. Completion rates out of expected patients were mostly comparable between treatment arms and were >70%, with the exception of Week 36 (67%). No meaningful change observed for fatigue, nausea and vomiting, pain, dyspnoea, constipation, diarrhoea, financial difficulties, haemoptysis, sore mouth, dysphagia, pain in arm or shoulder, or pain in other parts. Error bars represent SEM.

Time to Confirmed Deterioration



No. at risk										
Atezolizumab	302	81	37	24	16	16	8	5	1	0
Chemotherapy	151	22	5	2	0	0	0	0	0	0



Clinical cutoff: 30 Apr 2022. mTTCD, median time to confirmed deterioration. NE, not evaluable. [a] Stratified.

Conclusions

- 1L atezolizumab significantly improved OS over third generation single-agent chemotherapy (HR, 0.78) in patients with NSCLC deemed ineligible to receive platinum-doublet chemotherapy regardless of histology, PD-L1 expression level and ECOG PS
  - 2-year OS rate nearly doubled with atezolizumab (24.3% vs 12.4%)
- ORR was higher with atezolizumab with durable responses (14 vs 7.8 months)
- Atezolizumab was associated with stabilization in health-related QoL functioning domains and significant improvement in time to deterioration of chest pain (HR, 0.51) vs chemotherapy
- No new or unexpected AESI's were identified with atezolizumab in this study population
  - Treatment-related Grade 3-4 AEs occurred in a smaller proportion of patients receiving atezolizumab vs chemotherapy (16.3% vs 33.3%)
- IPSOS is the first randomised study to show that 1L treatment with atezolizumab improves OS in this poor-prognosis NSCLC population with no *EGFR* and *ALK* alterations regardless of histology, PD-L1 status and ECOG PS with no new safety signals identified, while maintaining QoL

Comments

- Interestingly, not a PDL1 stratified study, benefit across all histologies, all PDL1 expressions and ECOG performance statuses ? Different biology.

- Amazing data set of under represented population in clinical trial. Data to make decisions in real world clinic.

- Gemcitabine or Navelbine – not a standard of care in this population. Pemetrexed not to be left out – well tolerated in this similar population.
- Financial toxicity of medications. We want patients to be on these therapy – encouraging results, prolonging lives, keeping good QoL. However 90% patient receiving chemotherapy crossed over to Immunotherapy arm.