ESMO VIRTUAL JOURNAL CLUB

SESSION 3 - OCTOBER 2024

Chaired by Toni K. Choueiri, MD

Dana-Farber Cancer Institute, Boston, MA, USA

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

OUR SPEAKERS

Sanjay Popat, MBBS, PhD

The Royal Marsden, London, UK

Laurence Albiges, MD, PhD

Gustave Roussy, Villejuif, France

IMPOWER010 TRIAL

Sanjay Popat, MBBS, PhD

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October 2023

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial

E. Felip[1]*, N. Altorki[2], C. Zhou[3], E. Vallières[4], A. Martínez-Martí[1], A. Rittmeyer[5], A. Chella[6], M. Reck[7], O. Goloborodko[8], M. Huang[9], R. Belleli[10], V. McNally[11], M. K. Srivastava[9], E. Bennett[9], B. J. Gitlitz[9] & H. A. Wakelee[12]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, USA; [3]Department of Oncology, Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; [4]Swedish Cancer Institute, Seattle, USA; [5]LKI Lungenfachklinik Immenhausen, Immenhausen, Germany; [6]Cardiac and Thoracic Department, Pneumo-Oncology Day Hospital, Pisa, Italy; [7]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [8]Zaporizhzhia Regional Clinical Oncological Dispensary, Zaporizhzhia SMU Ch of Oncology, Zaporizhzhya, Ukraine; [9]Genentech Inc, South San Francisco, USA; [10]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [11]Roche Products Ltd, Welwyn Garden City, UK; [12]Stanford University School of Medicine/Stanford Cancer Institute, Stanford, USA

Ann Oncol. 2023;34(10):907-919. doi:10.1016/j.annonc.2023.07.001

IMPOWER010 TRIAL

- Patients were randomly assigned to atezolizumab (atezo) vs. best supportive care (BSC) in resected stage II-IIIA NSCLC following adjuvant platinum-based chemotherapy
- Atezo significantly improved DFS vs. BSC in PD-L1+
- Although OS was immature, atezo appears to extend OS vs. BSC in PD-L1 tumor cell ≥50%

EV-302 TRIAL

Laurence Albiges, MD, PhD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 7, 2024 VOL. 390 NO. 10

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

T. Powles, B.P. Valderrama, S. Gupta, J. Bedke, E. Kikuchi, J. Hoffman-Censits, G. Iyer, C. Vulsteke, S.H. Park, S.J. Shin, D. Castellano, G. Fornarini, J.-R. Li, M. Gümüş, N. Mar, Y. Loriot, A. Fléchon, I. Duran, A. Drakaki, S. Narayanan, X. Yu, S. Gorla, B. Homet Moreno, and M.S. van der Heijden, for the EV-302 Trial Investigators*

N Engl J Med. 2024;390(10):875-888. doi:10.1056/NEJMoa2312117

EV-302 TRIAL

- Patients with unresectable locally advanced or metastatic urothelial carcinoma
- The combination of EV + Pembrolizumab dethroned the SOC for 25 years of platinum-based chemotherapy (gemcitabine + either cisplatin or carboplatin)
- Significant improvement in both overall and progression-free survival

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Thank you!

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IMPOWER 010: OVERALL SURVIVAL ANALYSES RESULTS

Felip et al. Ann Oncol (2023) Oct;34(10):907-919

doi: 10.1016/j.annonc.2023.07.001

Professor Sanjay Popat FRCP PhD

Consultant Medical Oncologist, Professor of Thoracic Oncology

Royal Marsden Hospital, Institute of Cancer Research

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DISCLOSURES

Personal financial interests:

Consultancy/Honoraria: Anheart, Amgen, Arcus Biosciences, AstraZeneca, Bayer, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, Eisai, Elevation Oncology, Ellipses, EQRx, Gilead, GlaxoSmithKline, Guardant Health, IO Biotech, Janssen, Lilly, Merck KGaA, Mirati, MSD, Novocure, Novartis, Pfizer, PharmaMar, Pierre Fabre, Regeneron, Roche, Sanofi, Takeda, Turning Point Therapeutics

Leadership: Nil

Stock: Nil

Licencing: Nil

Direct funding: Elsevier, Medscape, VJ Oncology

Institutional financial interests:

Institutional research funding: Abbvie, Amgen, Arrivent, Artelo Biosciences, AstraZeneca, Blueprint, BMS, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Guardant Health, Ikena Oncology, Janssen, Lilly, Mirati Therapeutics, MSD, Nuvalent, Pierre Fabre, Revolution Medicines, Roche, RS Oncology, Takeda, Seattle Genetics, Summit Therapeutics, Trizell, Turning Point Therapeutics, Verastem Oncology

Non-financial interests:

Advisor: ALK Positive UK, Lung Cancer Europe, Ruth Strauss Foundation

Leadership: ESMO Guidelines Committee, BTOG Steering Committee, ETOP Foundation Council

SO…WHAT ARE WE REVIEWING?

Felip et al. Ann Oncol (2023) Oct;34(10):907-919; doi: 10.1016/j.annonc.2023.07.001

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ANNALS OF ONCOLOGY

ORIGINAL ARTICLE

Overall survival with adjuvant atezolizumab after chemotherapy in resected stage II-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase III trial

E. Felip[1], N. Altorki[2], C. Zhou[3], E. Vallières[4], A. Martinez-Marti[5], A. Rittmeyer[6], A. Chella[7], M. Reck[8], O. Goloborodko[9], M. Huang[10], R. Bellel[11], V. McNally[12], M. K. Srivastava[13], E. Bennett[14], B. J. Gitlitz[15] & H. A. Wakelee[16]

[1]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]NewYork-Presbyterian Hospital, Weill Cornell Medicine, New York, USA; [3]Department of Oncology, Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China; [4]Swedish Cancer Institute, Seattle, USA; [5]LKI Lungenfachklinik Immenhausen, Immenhausen, Germany; [6]Cardiac and Thoracic Department, Pneumo-Oncology Day Hospital, Pisa, Italy; [7]Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [8]Zaporizhzhia Regional Clinical Oncological Dispensary, Zaporizhzhia SMU Ch of Oncology, Zaporizhzhya, Ukraine; [9]Genentech Inc, South San Francisco, USA; [10]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [11]Roche Products Ltd, Welwyn Garden City, UK; [12]Stanford University School of Medicine/Stanford Cancer Institute, Stanford, USA

Available online 17 July 2023

Background: IMpower010 (NCT02486718) demonstrated significantly improved disease-free survival (DFS) with adjuvant atezolizumab versus best supportive care (BSC) following platinum-based chemotherapy in the programmed death-ligand 1 (PD-L1)-positive and all stage II-IIIA non-small-cell lung cancer (NSCLC) populations, at the DFS interim analysis. Results of the first interim analysis of overall survival (OS) are reported here.

Patient and methods: The design, participants, and primary-endpoint DFS outcomes have been reported for this phase III, open-label, 1 : 1 randomised study of atezolizumab (1200 mg q3w; 16 cycles) versus BSC after adjuvant platinum-based chemotherapy (1-4 cycles) in adults with completely resected stage IB (≥4 cm)-IIIA NSCLC (per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system, 7th edition). Key secondary endpoints included OS in the stage IB-IIIA intent-to-treat (ITT) population and safety in randomised treated patients. The first pre-specified interim analysis of OS was conducted after 251 deaths in the ITT population. Exploratory analyses included OS by baseline PD-L1 expression level (SP263 assay).

Results: At a median of 45.3 months' follow-up on 18 April 2022, 127 of 507 patients (25%) in the atezolizumab arm and 124 of 498 (24.9%) in the BSC arm had died. The median OS in the ITT population was not estimable; the stratified hazard ratio (HR) was 0.995 [95% confidence interval (CI) 0.78-1.28]. The stratified OS HRs (95% CI) were 0.95 (0.74-1.24) in the stage II-IIIA ($n = 882$), 0.71 (0.49-1.03) in the stage II-IIIA PD-L1 tumour cell (TC) ≥1% ($n = 476$), and 0.43 (95% CI 0.24-0.78) in the stage II-IIIA PD-L1 TC ≥50% ($n = 229$) populations. Atezolizumab-related adverse event incidences remained unchanged since the previous analysis [grade 3/4 in 53 (10.7%) and grade 5 in 4 (0.8%) of 495 patients, respectively].

Conclusions: Although OS remains immature for the ITT population, these data indicate a positive trend favouring atezolizumab in PD-L1 subgroup analyses, primarily driven by the PD-L1 TC ≥50% stage II-IIIA subgroup. No new safety signals were observed after 13 months' additional follow-up. Together, these findings support the positive benefit–risk profile of adjuvant atezolizumab in this setting.

Key words: IMpower010, atezolizumab, NSCLC

INTRODUCTION

The recommended treatment for patients with early-stage resectable non-small-cell lung cancer (NSCLC) is surgery, which has been associated with 5-year survival rates ranging from 41% in those with stage IIA NSCLC to 92% in those with stage IA1 disease.[1] To improve these outcomes, adjuvant therapy is given to treat micrometastatic disease and prevent recurrence.[2] Adjuvant cisplatin-based doublet chemotherapy became the standard of care for resected early-stage NSCLC in 2004.[3] The 5-year survival rates with adjuvant chemotherapy are 4%-5% higher than with observation,[4,5] leaving an unmet need for improvement.

In patients with *EGFR* mutations, osimertinib is now the standard-of-care adjuvant therapy, as monotherapy or after

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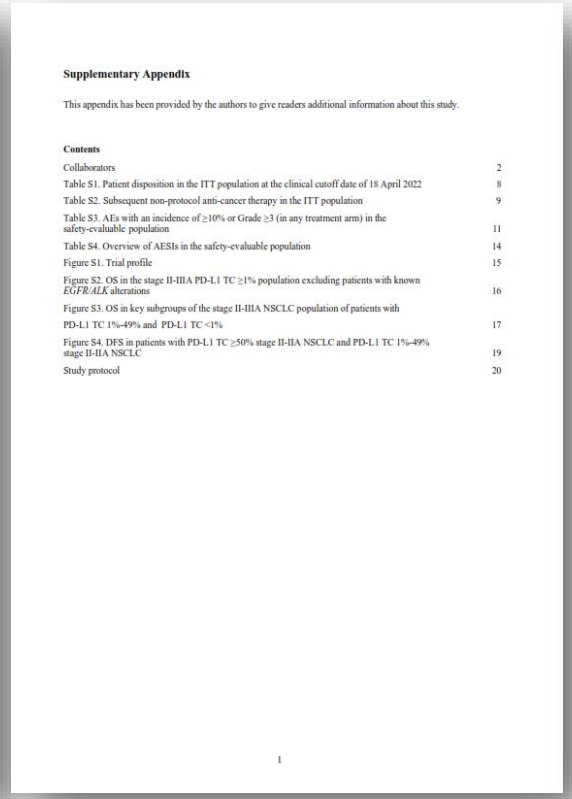
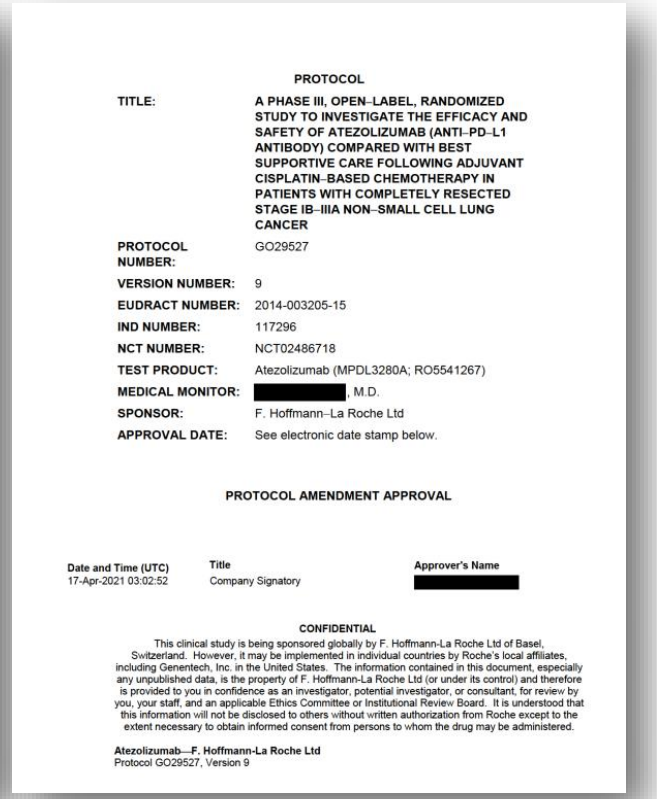


Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about this study.

Contents



PROTOCOL

TITLE:	**A PHASE III, OPEN–LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD–L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN–BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29527
VERSION NUMBER:	9
EUDRACT NUMBER:	2014-003205-15
IND NUMBER:	117296
NCT NUMBER:	NCT02486718
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann–La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
17-Apr-2021 03:02:52	Company Signatory	[redacted]

CONFIDENTIAL

Felip et al. Ann Oncol (2023)

SO…WHAT ARE WE REVIEWING?

Felip et al. Ann Oncol (2023) Oct;34(10):907-919; doi: 10.1016/j.annonc.2023.07.001

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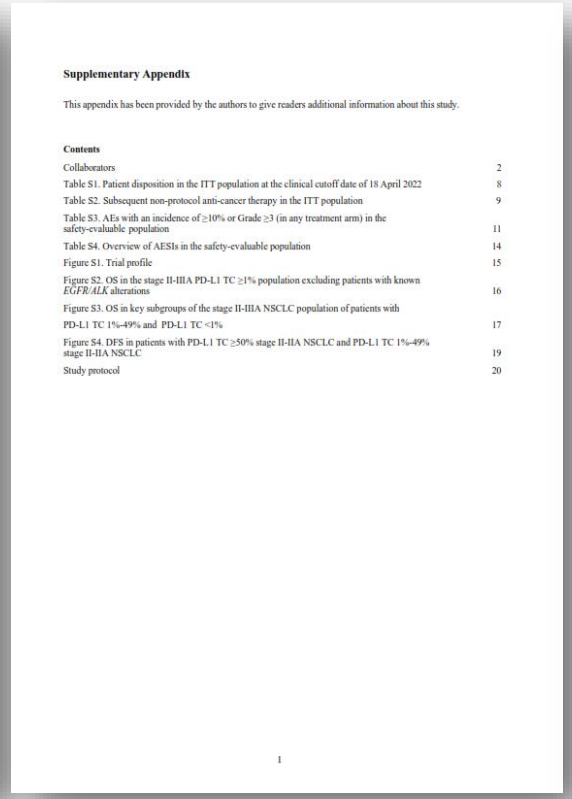

Supplementary Appendix

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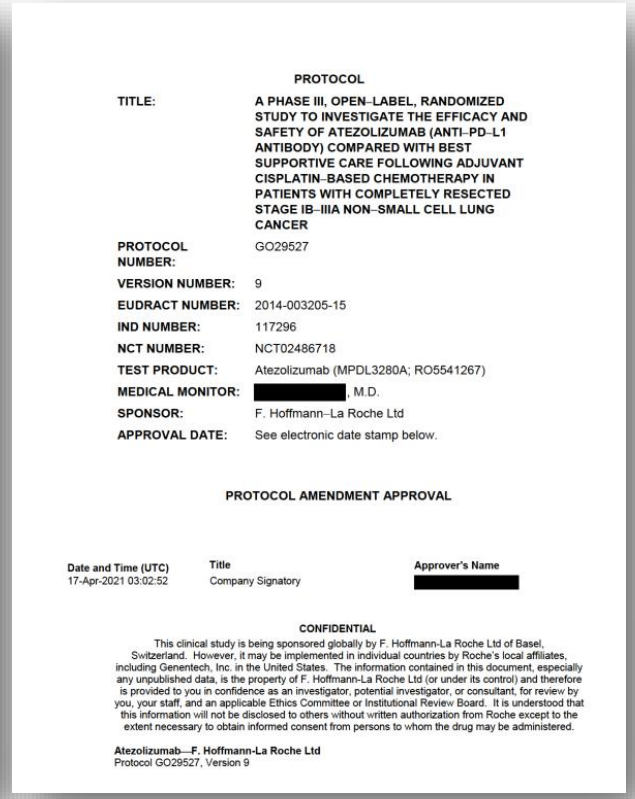

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PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
17-Apr-2021 03:02:52	Company Signatory	[redacted]

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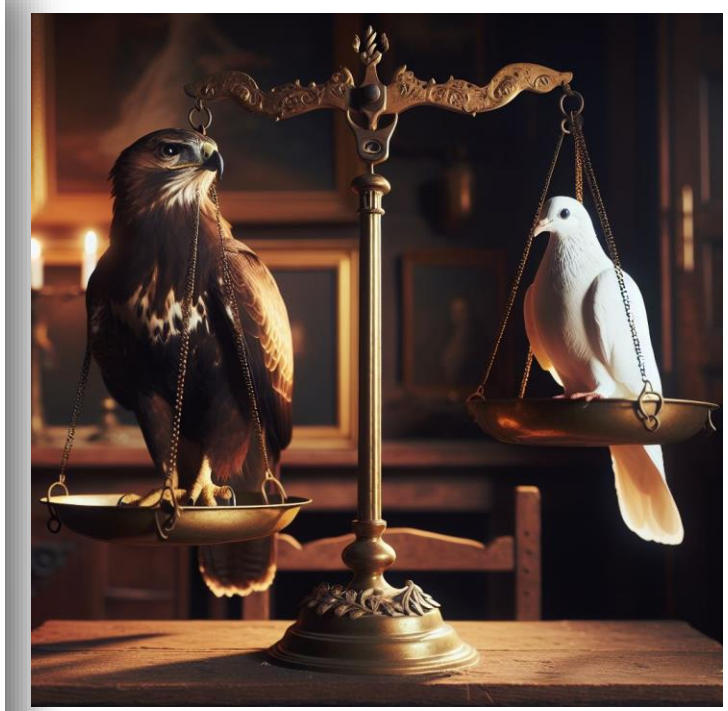
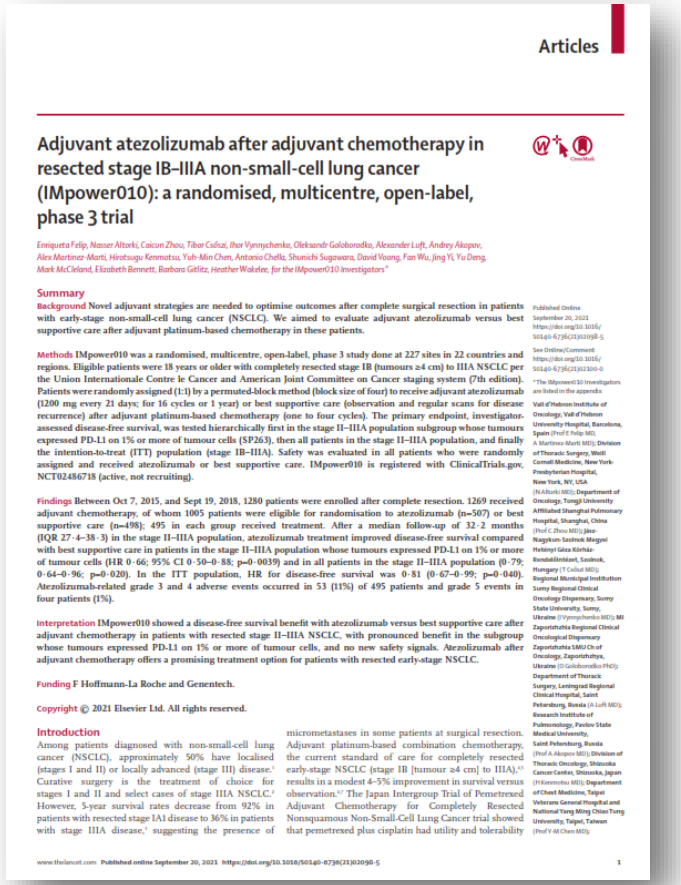


Felip et al. Ann Oncol (2023); Image created with AI

WHAT DID WE KNOW PRIOR TO MANUSCRIPT PUBLICATION?

Current publication: Felip et al. Ann Oncol (2023) Oct;34(10):907-919



Articles

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloboroda, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators*

Summary

Background Novel adjuvant strategies are needed to optimise outcomes after complete surgical resection in patients with early-stage non-small-cell lung cancer (NSCLC). We aimed to evaluate adjuvant atezolizumab versus best supportive care after adjuvant platinum-based chemotherapy in these patients.

Methods IMpower010 was a randomised, multicentre, open-label, phase 3 study done at 227 sites in 22 countries and regions. Eligible patients were 18 years or older with completely resected stage IB (tumours ≥4 cm) to IIIA NSCLC per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system (7th edition). Patients were randomly assigned (1:1) by a permuted-block method (block size of four) to receive adjuvant atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year) or best supportive care (observation and regular scans for disease recurrence) after adjuvant platinum-based chemotherapy (one to four cycles). The primary endpoint, investigator-assessed disease-free survival, was tested hierarchically first in the stage II–IIIA population subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells (SP263), then all patients in the stage II–IIIA population, and finally the intention-to-treat (ITT) population (stage IB–IIIA). Safety was evaluated in all patients who were randomly assigned and received atezolizumab or best supportive care. IMpower010 is registered with ClinicalTrials.gov, NCT02486718 (active, not recruiting).

Findings Between Oct 7, 2015, and Sept 19, 2018, 1280 patients were enrolled after complete resection. 1269 received adjuvant chemotherapy, of whom 1005 patients were eligible for randomisation to atezolizumab (n=507) or best supportive care (n=498); 495 in each group received treatment. After a median follow-up of 32·2 months (IQR 27·4–38·3) in the stage II–IIIA population, atezolizumab treatment improved disease-free survival compared with best supportive care in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells (HR 0·66; 95% CI 0·50–0·88; p=0·0039) and in all patients in the stage II–IIIA population (0·79; 0·64–0·96; p=0·020). In the ITT population, HR for disease-free survival was 0·81 (0·67–0·99; p=0·040). Atezolizumab-related grade 3 and 4 adverse events occurred in 53 (11%) of 495 patients and grade 5 events in four patients (1%).

Interpretation IMpower010 showed a disease-free survival benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC, with pronounced benefit in the subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells, and no new safety signals. Atezolizumab after adjuvant chemotherapy offers a promising treatment option for patients with resected early-stage NSCLC.

Funding F Hoffmann-La Roche and Genentech.

Introduction

Among patients diagnosed with non-small-cell lung cancer (NSCLC), approximately 50% have localised (stages I and II) or locally advanced (stage III) disease.[1] Curative surgery is the treatment of choice for stages I and II and select cases of stage IIIA NSCLC.[2] However, 5-year survival rates decrease from 92% in patients with resected stage IA1 disease to 36% in patients with stage IIIA disease,[3] suggesting the presence of micrometastases in some patients at surgical resection. Adjuvant platinum-based combination chemotherapy, the current standard of care for completely resected early-stage NSCLC (stage IB [tumour ≥4 cm] to IIIA),[4] results in a modest 4–5% improvement in survival versus observation.[5] The Japan Intergroup Trial of Pemetrexed Adjuvant Chemotherapy for Completely Resected Nonsquamous Non-Small-Cell Lung Cancer trial showed that pemetrexed plus cisplatin had utility and tolerability

Published Online September 20, 2021 https://doi.org/10.1016/S1470-2045(22)00518-6
See Online/Comment https://doi.org/10.1016/S1470-2045(22)00510-0

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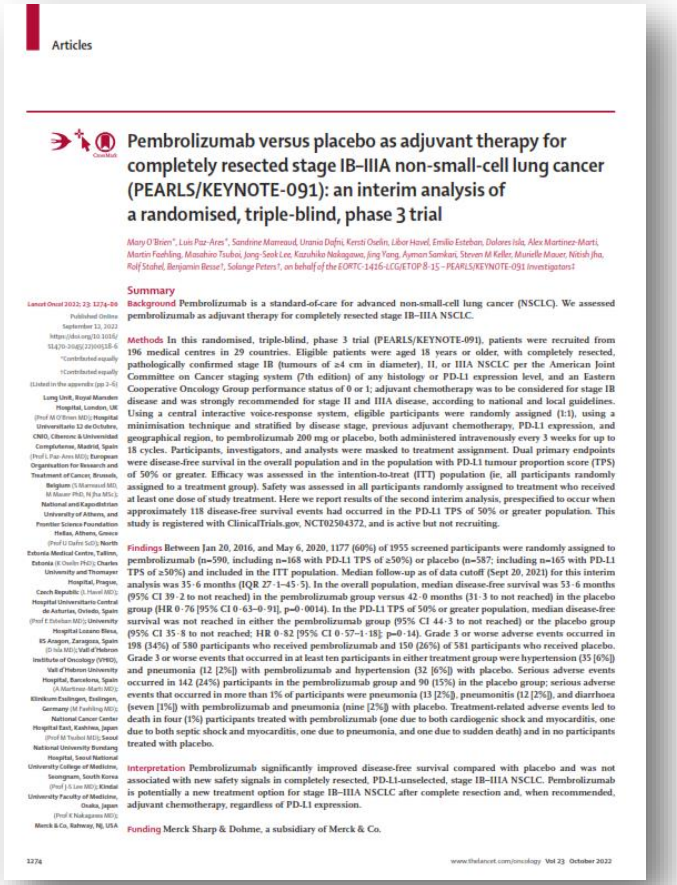


Articles

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

Mary O'Brien*, Luis Paz-Ares*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡

Lancet Oncol 2022; 23: 1274–86
Published Online September 12, 2022 https://doi.org/10.1016/S1470-2045(22)00518-6

Summary

Background Pembrolizumab is a standard-of-care for advanced non-small-cell lung cancer (NSCLC). We assessed pembrolizumab as adjuvant therapy for completely resected stage IB–IIIA NSCLC.

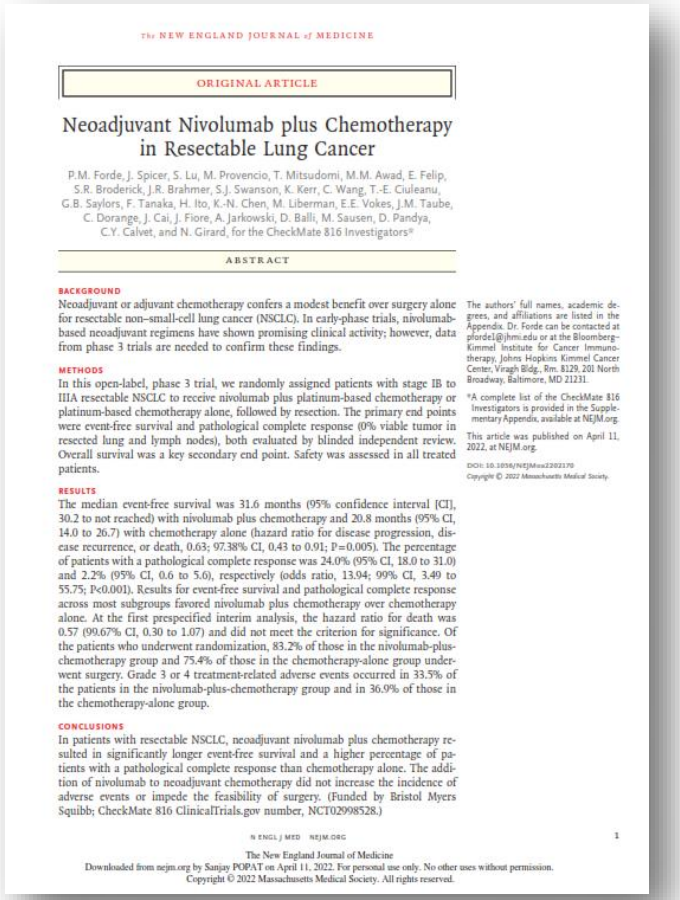
Methods In this randomised, triple-blind, phase 3 trial (PEARLS/KEYNOTE-091), patients were recruited from 196 medical centres in 29 countries. Eligible patients were aged 18 years or older, with completely resected, pathologically confirmed stage IB (tumours of ≥4 cm in diameter), II, or IIIA NSCLC per the American Joint Committee on Cancer staging system (7th edition) of any histology or PD-L1 expression level, and an Eastern Cooperative Oncology Group performance status of 0 or 1; adjuvant chemotherapy was to be considered for stage IB disease and was strongly recommended for stage II and IIIA disease, according to national and local guidelines. Using a central interactive voice-response system, eligible participants were randomly assigned (1:1), using a minimisation technique and stratified by disease stage, previous adjuvant chemotherapy, PD-L1 expression, and geographical region, to pembrolizumab 200 mg or placebo, both administered intravenously every 3 weeks for up to 18 cycles. Participants, investigators, and analysts were masked to treatment assignment. Dual primary endpoints were disease-free survival in the overall population and in the population with PD-L1 tumour proportion score (TPS) of 50% or greater. Efficacy was assessed in the intention-to-treat (ITT) population (ie, all participants randomly assigned to a treatment group). Safety was assessed in all participants randomly assigned to treatment who received at least one dose of study treatment. Here we report results of the second interim analysis, prespecified to occur when approximately 118 disease-free survival events had occurred in the PD-L1 TPS of 50% or greater population. This study is registered with ClinicalTrials.gov, NCT02504372, and is active but not recruiting.

Findings Between Jan 20, 2016, and May 6, 2020, 1177 (60%) of 1955 screened participants were randomly assigned to pembrolizumab (n=590, including n=168 with PD-L1 TPS of ≥50%) or placebo (n=587; including n=165 with PD-L1 TPS of ≥50%) and included in the ITT population. Median follow-up as of data cutoff (Sept 20, 2021) for this interim analysis was 35·6 months (IQR 27·1–45·5). In the overall population, median disease-free survival was 53·6 months (95% CI 39·2 to not reached) in the pembrolizumab group versus 42·0 months (31·3 to not reached) in the placebo group (HR 0·76 [95% CI 0·63–0·91], p=0·0014). In the PD-L1 TPS of 50% or greater population, median disease-free survival was not reached in either the pembrolizumab group (95% CI 44·3 to not reached) or the placebo group (95% CI 35·8 to not reached; HR 0·82 [95% CI 0·57–1·18]; p=0·14). Grade 3 or worse adverse events occurred in 198 (34%) of 580 participants who received pembrolizumab and 150 (26%) of 581 participants who received placebo. Grade 3 or worse events that occurred in at least ten participants in either treatment group were hypertension (35 [6%]) and pneumonia (12 [2%]) with pembrolizumab and hypertension (32 [6%]) with placebo. Serious adverse events occurred in 142 (24%) participants in the pembrolizumab group and 90 (15%) in the placebo group; serious adverse events that occurred in more than 1% of participants were pneumonia (13 [2%]), pneumonitis (12 [2%]), and diarrhoea (seven [1%]) with pembrolizumab and pneumonia (nine [2%]) with placebo. Treatment-related adverse events led to death in four (1%) participants treated with pembrolizumab (one due to both cardiogenic shock and myocarditis, one due to both septic shock and myocarditis, one due to pneumonia, and one due to sudden death) and in no participants treated with placebo.

Interpretation Pembrolizumab significantly improved disease-free survival compared with placebo and was not associated with new safety signals in completely resected, PD-L1-unselected, stage IB–IIIA NSCLC. Pembrolizumab is potentially a new treatment option for stage IB–IIIA NSCLC after complete resection and, when recommended, adjuvant chemotherapy, regardless of PD-L1 expression.

Funding Merck Sharp & Dohme, a subsidiary of Merck & Co.

Lung Unit, Royal Marsden Hospital, London, UK (Prof M O'Brien MD); Hospital Universitario 12 de Octubre, CNIO, Cibercnc & Universidad Complutense, Madrid, Spain (Prof E Felip MD, A Martinez-Marti MD); European Organisation for Research and Treatment of Cancer, Brussels, Belgium (S Marreaud MD, M Mauer PhD, N Jha MSc); National and Kapodistrian University of Athens, and Frontier Science Foundation Hellas, Athens, Greece (Prof U Dafni ScD); North Estonia Medical Centre, Tallinn, Estonia (K Oselin PhD); Charles University and Thomayer Hospital, Prague, Czech Republic (L Havel MD); Hospital Universitario Central de Asturias, Oviedo, Spain (Prof E Esteban MD); University Hospital Lozano Blesa, IIS Aragon, Zaragoza, Spain (D Isla MD); Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain (A Martinez-Marti MD); Klinikum Esslingen, Esslingen, Germany (M Faehling MD); National Cancer Center Hospital East, Kashiwa, Japan (Prof M Tsuboi MD); Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea (Prof J-S Lee MD); Kindai University Faculty of Medicine, Osaka, Japan (Prof K Nakagawa MD); Merck & Co, Rahway, NJ, USA (Prof Y-M Chen MD);



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

ABSTRACT

BACKGROUND

Neoadjuvant or adjuvant chemotherapy confers a modest benefit over surgery alone for resectable non–small-cell lung cancer (NSCLC). In early-phase trials, nivolumab-based neoadjuvant regimens have shown promising clinical activity; however, data from phase 3 trials are needed to confirm these findings.

METHODS

In this open-label, phase 3 trial, we randomly assigned patients with stage IB to IIIA resectable NSCLC to receive nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. The primary end points were event-free survival and pathological complete response (0% viable tumor in resected lung and lymph nodes), both evaluated by blinded independent review. Overall survival was a key secondary end point. Safety was assessed in all treated patients.

RESULTS

The median event-free survival was 31.6 months (95% confidence interval [CI], 30.2 to not reached) with nivolumab plus chemotherapy and 20.8 months (95% CI, 14.0 to 26.7) with chemotherapy alone (hazard ratio for disease progression, disease recurrence, or death, 0.63; 97.38% CI, 0.43 to 0.91; P=0.005). The percentage of patients with a pathological complete response was 24.0% (95% CI, 18.0 to 31.0) and 2.2% (95% CI, 0.6 to 5.6), respectively (odds ratio, 13.94; 99% CI, 3.49 to 55.75; P<0.001). Results for event-free survival and pathological complete response across most subgroups favored nivolumab plus chemotherapy over chemotherapy alone. At the first prespecified interim analysis, the hazard ratio for death was 0.57 (99.67% CI, 0.30 to 1.07) and did not meet the criterion for significance. Of the patients who underwent randomization, 83.2% of those in the nivolumab-plus-chemotherapy group and 75.4% of those in the chemotherapy-alone group underwent surgery. Grade 3 or 4 treatment-related adverse events occurred in 33.5% of the patients in the nivolumab-plus-chemotherapy group and in 36.9% of those in the chemotherapy-alone group.

CONCLUSIONS

In patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone. The addition of nivolumab to neoadjuvant chemotherapy did not increase the incidence of adverse events or impede the feasibility of surgery. (Funded by Bristol Myers Squibb; CheckMate 816 ClinicalTrials.gov number, NCT02998528.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Forde can be contacted at pforde1@jhmi.edu or at the Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Viragh Bldg., Rm. 8129, 201 North Broadway, Baltimore, MD 21231.

*A complete list of the CheckMate 816 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 11, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2202170

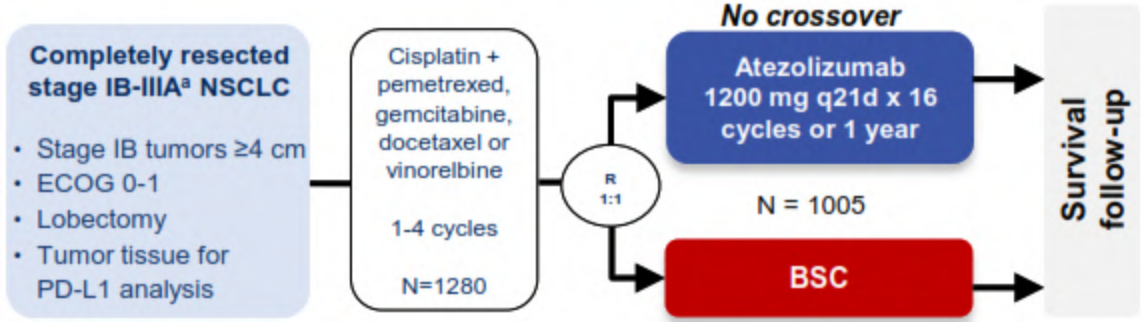
Felip et al. Lancet (2021); Sept 20

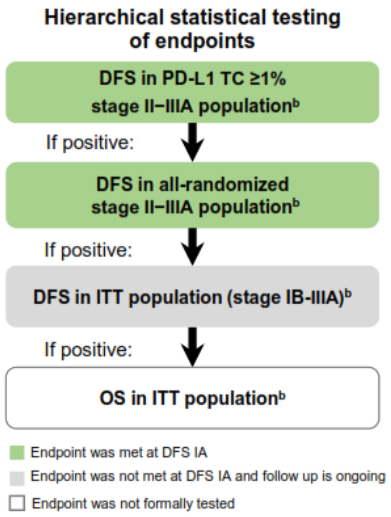
O'Brien et al. Lancet (2021); Sept 20

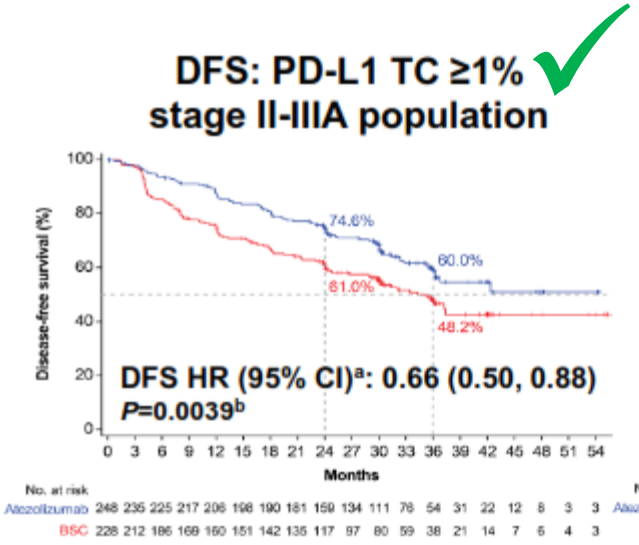
Forde et al. NEJM (2022); April 11

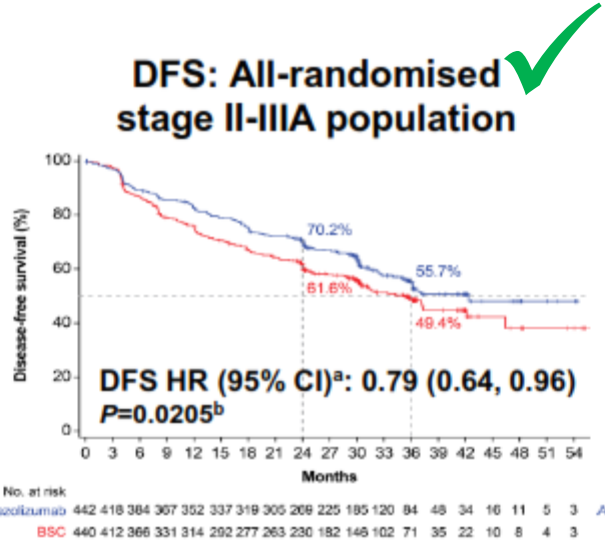
WHAT DID WE KNOW ABOUT IMP-010 ALREADY?

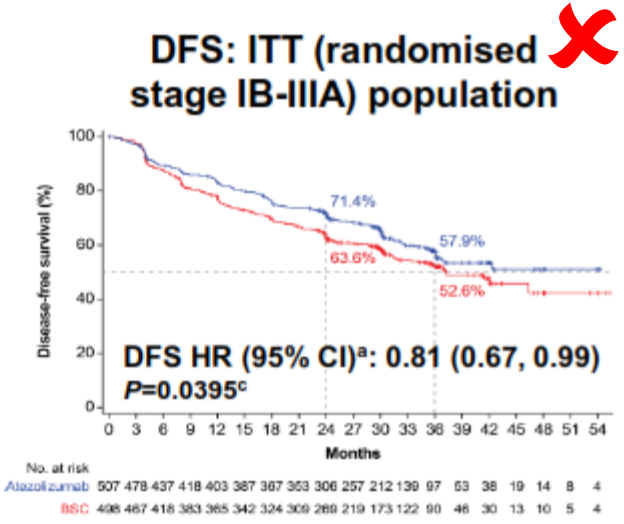
Prior presentation and publications on IMP-010: DFS results







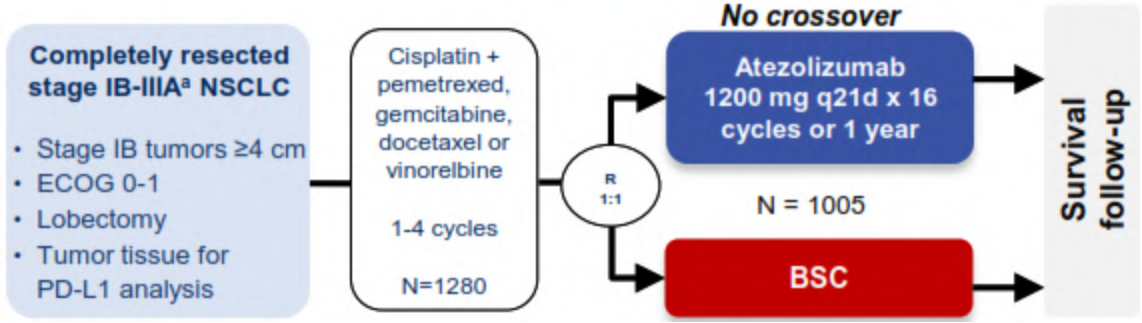


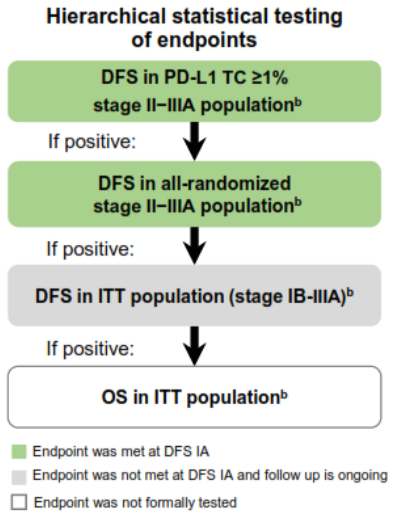


Felip et al WCLC (2022)

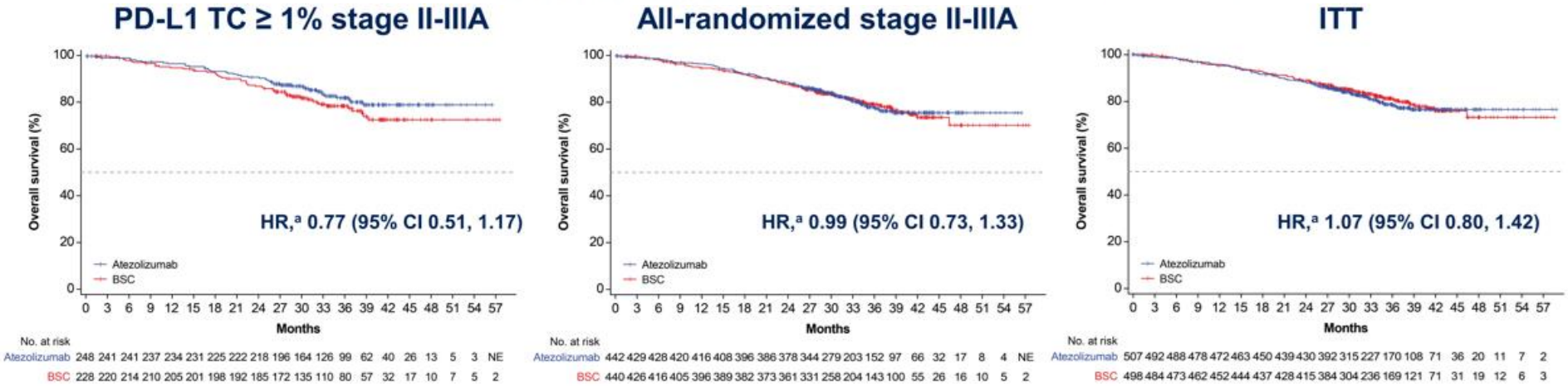
WHAT DID WE KNOW ABOUT IMP-010 ALREADY?

Prior presentation and publications on IMP-010: OS results





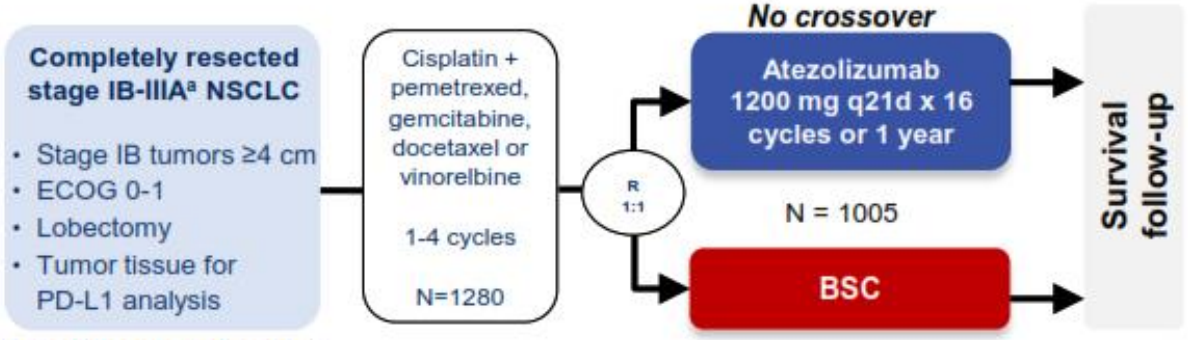
IMpower010: early OS data at interim DFS analysis EXPLORATORY OS analysis



Felip et al WCLC (2022); Wakelee et al. ASCO (2021)

DESIGN

Population and endpoints



Stratification factors
- Sex | Stage | Histology | PD-L1 status

Primary endpoint
- Investigator-assessed DFS tested hierarchically

Key secondary endpoints
- OS in ITT | DFS in PD-L1 TC ≥50% | 3-yr and 5-year DFS

Key exploratory endpoints
- OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

Felip et al WCLC (2022)

RP3 trial evaluation 1yr adjuvant atezolizumab
After 1-4# cisplatin-based chemotherapy

Is the population appropriate?

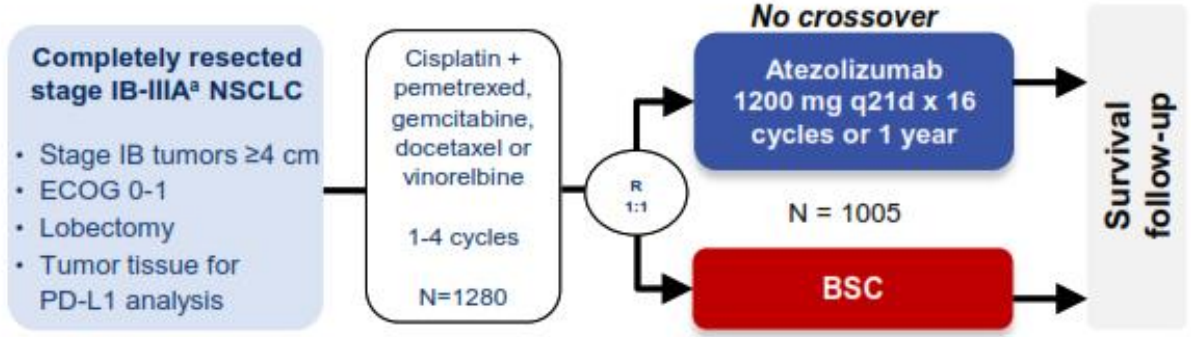
When are patients enrolled?

When are patients randomized?

What are the endpoints and when are they triggered?

DESIGN

Population and endpoints



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Felip et al WCLC (2022)

RP3 trial evaluation 1yr adjuvant atezolizumab

After 1-4# cisplatin-based chemotherapy

Is the population appropriate?

Yes, the group you would give adj chemo to; includes EGFR/ALK+ pts, reasonable at time of study

When are patients enrolled?

After anatomical surgery: typical for this type of trial

When are patients randomized?

AFTER completion of #1-4 chemo, meeting eligibility, without recurrence; note attrition of pts

What are the endpoints and when are they triggered?

Let's check the stats section

METHODS

Procedures

Enrolment: chemotherapy within 28-84 days after surgery: note on patient selection, biasing for fitter patients

- cis 75 + (vin 30 IV d1 d8) or (doce 75 d1) or (gemcitabine 1250 d1 d8) or (pemetrexed 500 d1) q21: note on cisplatin eligibility, biasing for fitter patients

Randomization: 1:1, **without blinding** to BSC or atezolizumab: note on interpreting AEs and DFS endpoints (more subjectivity bias potential, underestimates AEs and over-estimates HRs)

Imaging: CT-TA, 4 monthly (1st year), 6 monthly (2nd year); alternating CXR or CT-Thorax every 6 months (years 3-5); CXRs thereafter: appropriate schedule: no CNS imaging protocolized

Tissue: central PDL1 (SP263): appropriate

Data lock: 18 April 2022

METHODS

Endpoints and Statistics

Primary endpoints: INV-reported DFS, already reported: POSITIVE (INV reported, potential biases)

Key secondary endpoints: incl OS in ITT population of stage IB-IIIA (all randomized patients, ITT population)

SAP specified 4 interim and 1 final OS analyses: specified powered analyses, accounting for multiple testing

Exploratory OS performed at time of 1st interim DFS & reported: unpowered, not planned, and exploratory, a quick look-and-see, meaningless p value

This is now the first prespecified interim analysis (of four) of OS, at DB lock 18th April 22 (last lock 18th Jan 2021)

DFS are not updated as protocol mandated one interim analysis: hey, but they could (and would) have done an exploratory DFS analysis if they had wanted to! Always think about what is presented and why and what is not presented and why!

With these assumptions, the DFS final analysis will be conducted when approximately 237 DFS events in the PD-L1 subpopulation (defined by SP263 TC≥1%) within the Stage II–IIIA population have been observed. This is expected to occur approximately 68 months after the first patient is randomized. This number of events corresponds to a minimum detectable difference in HR of approximately 0.758 in the PD-L1 subpopulation within the Stage II–IIIA population.

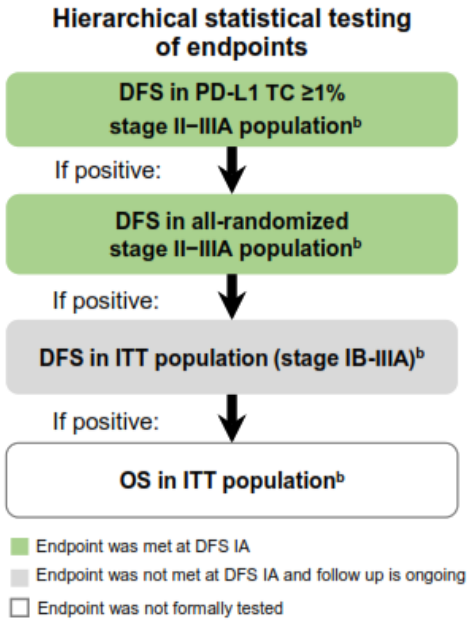
Felip et al. Ann Oncol (2023) & Protocol

METHODS

Endpoints and Statistics

DFS was analysed by PDL1+ subpopulations

Initially in the protocol this was by TC/IC+ status (SP142); protocol later amended to SP263 testing allowing PDL1 TPS scoring



OS was not formally tested previously (just exploratory look-see)

This is the first prespecified interim OS interim analysis: planned at around 254 deaths in ITT population

The first pre-specified interim analysis of OS was planned when around 254 deaths had occurred in the ITT population, based on the α spending function with a one-sided α of 0.001

Felip et al. Ann Oncol (2023) & Protocol

METHODS

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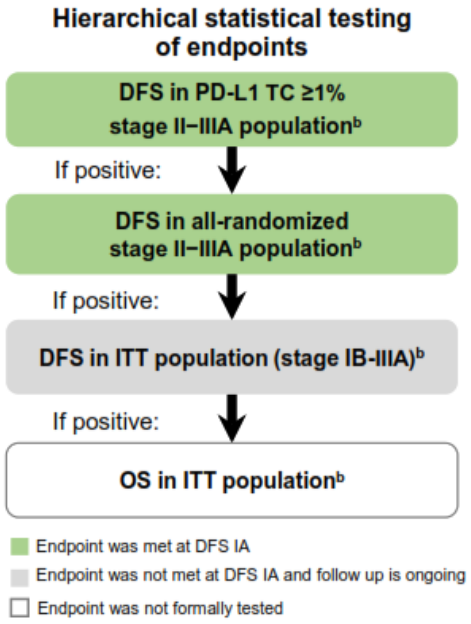

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OS was not formally tested previously (just exploratory look-see)

This is the first prespecified interim OS interim analysis: planned at around 254 deaths in ITT population

The first pre-specified interim analysis of OS was planned when around 254 deaths had occurred in the ITT population, based on the α spending function with a one-sided α of 0.001 (25% deaths)

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the ITT population (i.e., Stage IB-IIIA)
- 77% power to detect an HR of 0.78, corresponding to an improvement in median OS from 66 months to 84.6 months in the ITT population
- Four interim OS analyses to be performed, one at the time of the DFS interim analysis, the second one at the time of DFS final analysis, and the other two when approximately 73% and 88% of the total OS events required for the final analysis have occurred, respectively. The stopping boundaries for OS interim and final analyses will be determined based on the alpha spending function with the cumulative one-sided alpha of 0.001, 0.012, 0.022, 0.024, and 0.025 in the order of analyses (DeMets and Lan 1994; refer to Section 6.8.2 for details of the planned OS interim analyses).
- Dropout rate of 5% per 36 months

METHODS

Endpoints and Statistics: OS, what analyses are planned, what are exploratory

Pre-specified exploratory analyses of OS:

- II-IIIA population (all)
- II-IIIA population (PDL1 ≥1%)
- 3yr landmark (from randomization)

Post hoc exploratory analyses of OS:

- II-IIIA population (PDL1 ≥50%)
- II-IIIA population (PDL1 1-49%)
- II-IIIA population (PDL1 <1%)

“P values are shown for descriptive purposes only.”

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RESULTS

Patients and flows

Table S1. Patient disposition in the ITT population at the clinical cutoff date of 18 April 2022

	Atezolizumab (n = 507)	Best supportive care (n = 498)
Received treatment[a]	495 (97.6)	495 (99.4)
On study status		
Ongoing	346 (68.2)	329 (66.1)
Discontinued	161 (31.8)	169 (33.9)
Reason for study discontinuation		
Death	122 (24.1)	122 (24.5)
Disease relapse	1 (0.2)	0
Lost to follow-up	3 (0.6)	5 (1.0)
Physician decision	0	3 (0.6)
Protocol deviation	2 (0.4)	0
Withdrawal by patient	32 (6.3)	39 (7.8)
Other	1 (0.2)	0

Data are n (%).

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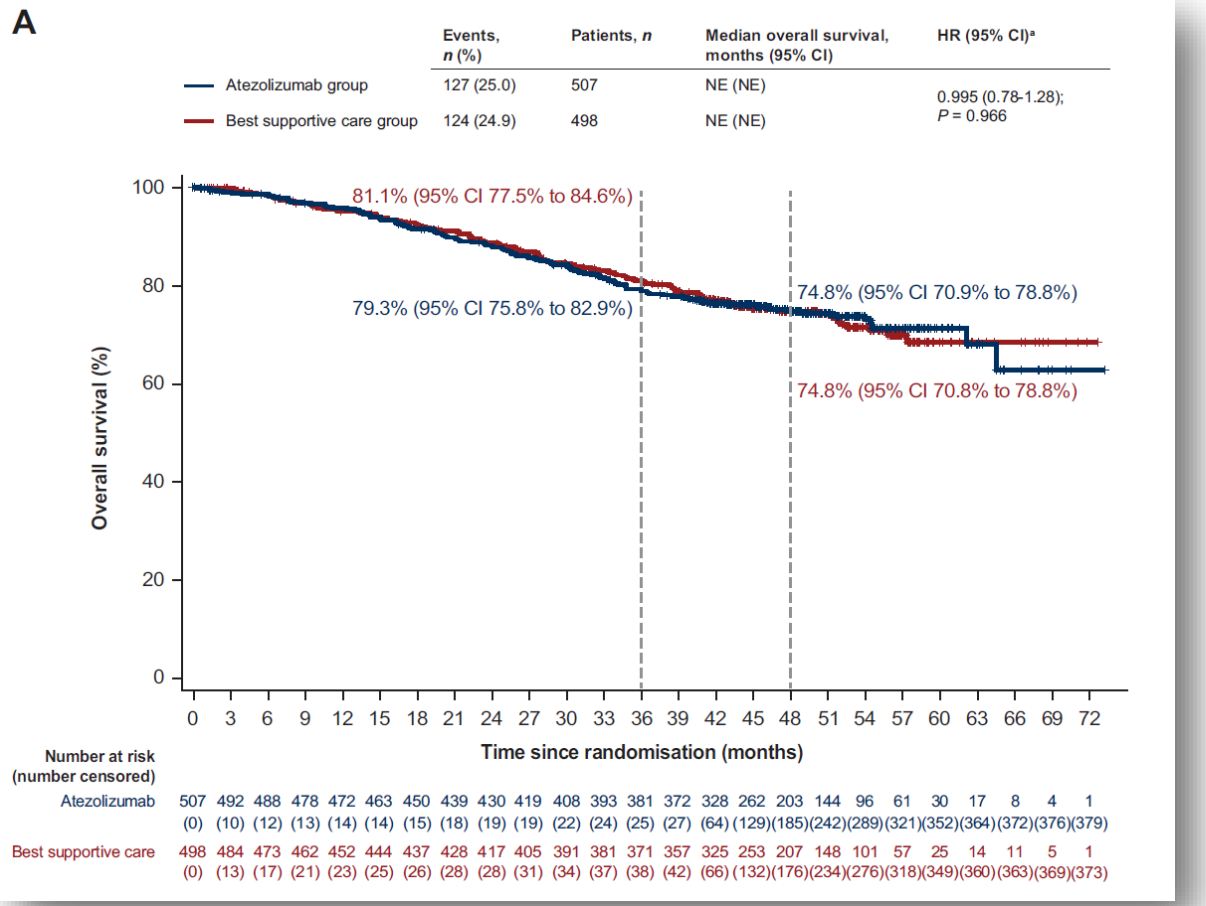
Table 1. Baseline characteristics in the stage II-IIIA PD-L1 TC ≥50% population

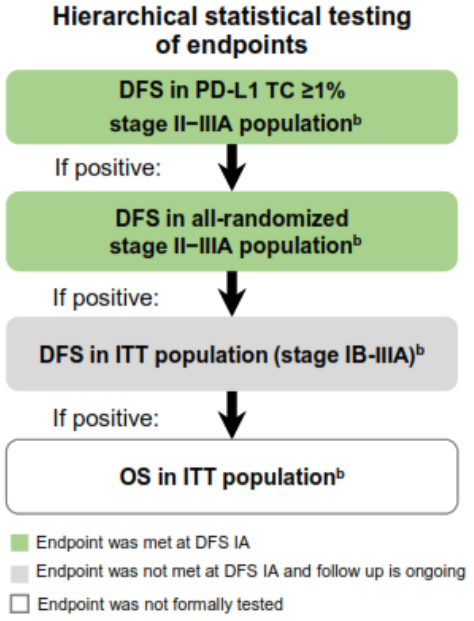
	Atezolizumab (n = 115)	Best supportive care (n = 114)
Age, median (IQR), years	62 (55-67)	62 (56-67)
Age group		
<65 years	70 (60.9)	68 (59.6)
≥65 years	45 (39.1)	46 (40.4)
Sex		
Male	89 (77.4)	78 (68.4)
Female	26 (22.6)	36 (31.6)
Race		
White	75 (65.2)	86 (75.4)
Asian	36 (31.3)	26 (22.8)
Other	2 (1.7)	0
Unknown	2 (1.7)	2 (1.8)
ECOG performance status		
0	71 (61.7)	60 (52.6)
1	44 (38.3)	53 (46.5)
2	0	1 (0.9)
Tobacco use history		
Never	16 (13.9)	14 (12.3)
Current or previous	99 (86.1)	100 (87.7)
Histology		
Squamous	47 (40.9)	45 (39.5)
Non-squamous	68 (59.1)[a]	69 (60.5)[b]
Stage		
II	62 (53.9)	57 (50.0)
IIIA	53 (46.1)	57 (50.0)
Regional lymph node stage (pN)		
N0	30 (26.1)	21 (18.4)
N1	43 (37.4)	52 (45.6)
N2	42 (36.5)	41 (36.0)
***EGFR* mutation status**[c]		
Detected	6 (5.2)	8 (7.0)
Not detected	60 (52.2)	64 (56.1)
Not tested	49 (42.6)	42 (36.8)
***ALK* rearrangement status**[c]		
Detected	3 (2.6)	3 (2.6)
Not detected	62 (53.9)	62 (54.4)
Not tested	50 (43.5)	49 (43.0)
***EGFR* mutation or ALK rearrangement**[c]		
Detected	9 (7.8)	11 (9.6)
Not detected	52 (45.2)	54 (47.4)
Not tested	54 (47.0)	49 (43.0)
Chemotherapy regimen		
Cisplatin plus docetaxel	13 (11.3)	20 (17.5)
Cisplatin plus gemcitabine	22 (19.1)	17 (14.9)
Cisplatin plus pemetrexed	35 (30.4)	37 (32.5)
Cisplatin plus vinorelbine	45 (39.1)	40 (35.1)
Completed three or four cisplatin cycles[d]	108 (93.9)	100 (87.7)
Type of surgery		
Lobectomy[e]	87 (75.7)	86 (75.4)
Bilobectomy	7 (6.1)	7 (6.1)
Pneumonectomy	20 (17.4)	20 (17.5)
Other	1 (0.9)	1 (0.9)

RESULTS

OS in the ITT population



"OS was not formally tested at this interim analysis because formal testing cannot be conducted until a statistically significant difference between arms is observed for DFS in the ITT population."



DFS: HR= 0.81 (0.67-0.99)

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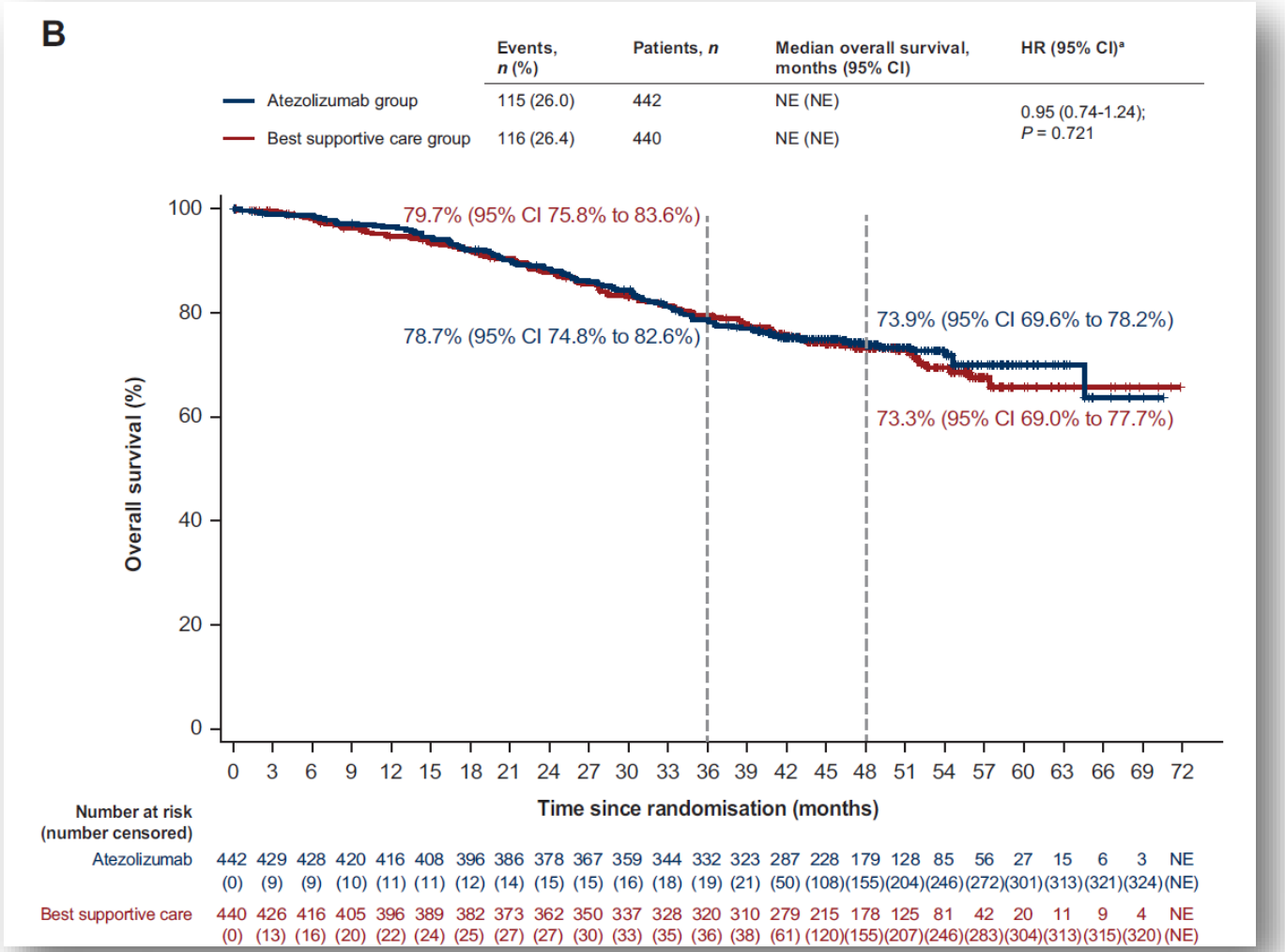
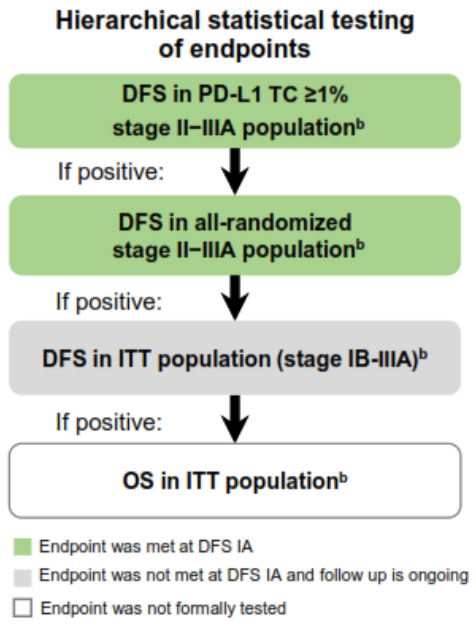
RESULTS

OS in the II-IIIA population





DFS: HR= 0.79 (0.64-0.96)

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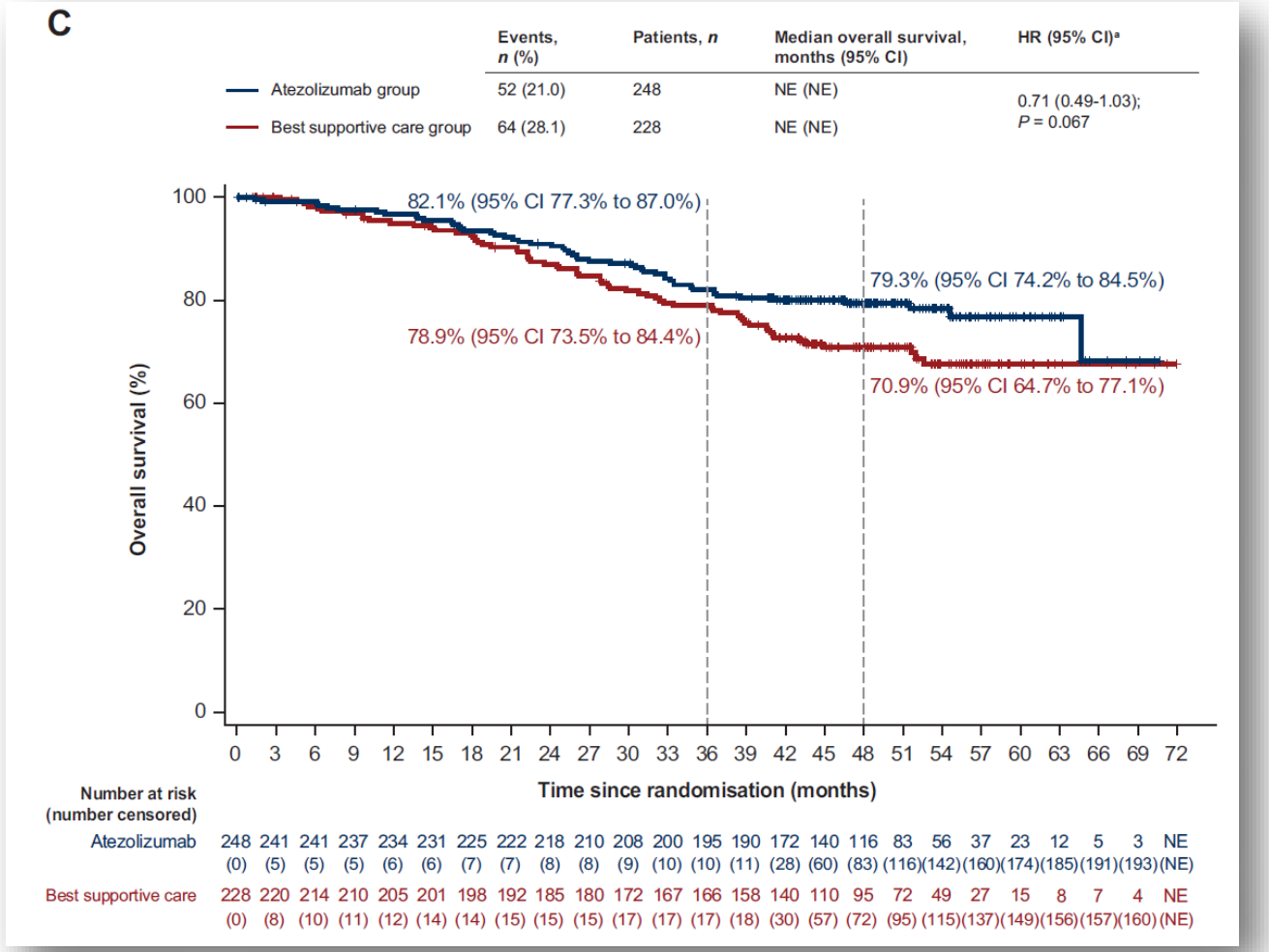
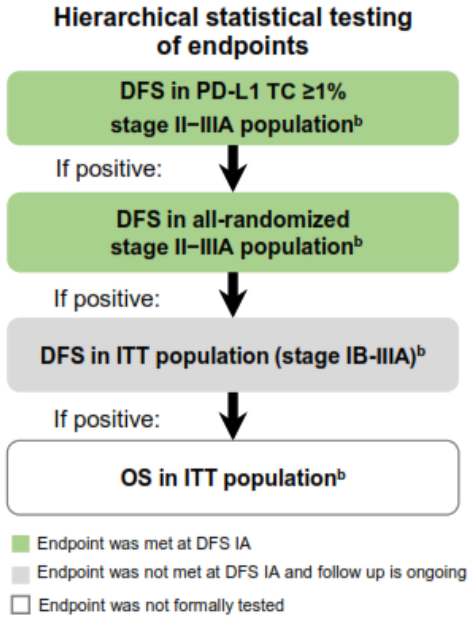
RESULTS

OS in the II-IIIA PDL1 ≥1%





DFS: HR= 0.66 (0.50-0.88)

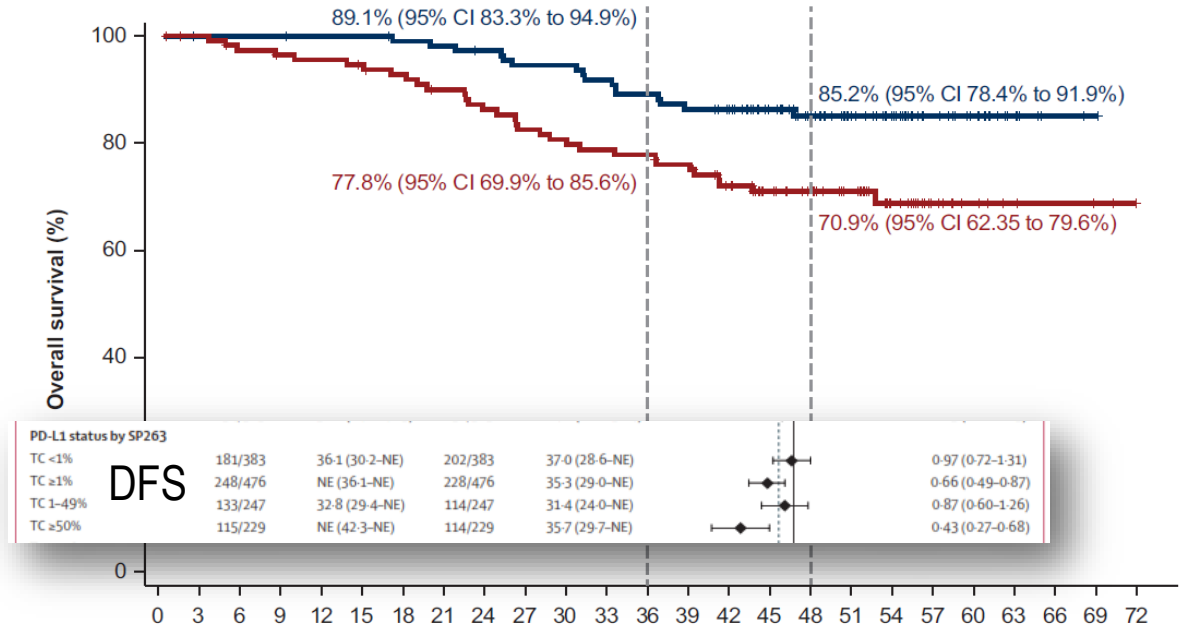
Felip et al. Ann Oncol (2023)

RESULTS

OS in the II-IIIA PDL1 ≥50% (with and without EGFR/ALK+ patients)

D

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	16 (13.9)	115	NE (NE)	0.43 (0.24-0.78); *P* = 0.0045
Best supportive care group	32 (28.1)	114	NE (NE)	



DFS

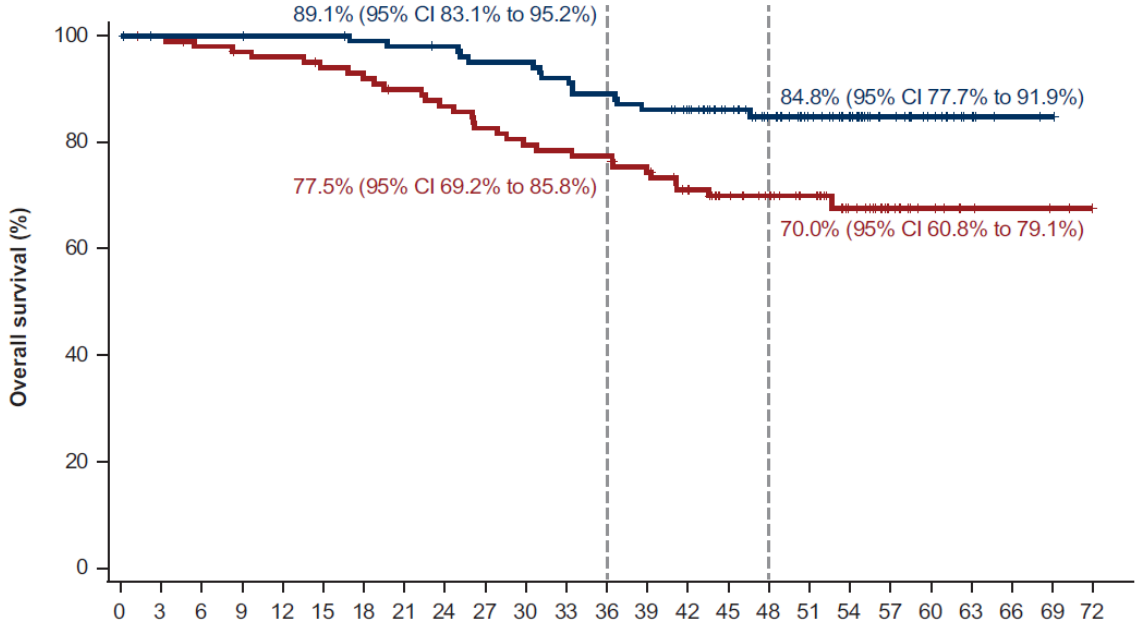
PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)

Number at risk (number censored)

Atezolizumab	115 (0)	113 (2)	113 (2)	113 (2)	112 (3)	112 (3)	110 (4)	109 (4)	107 (5)	104 (5)	104 (5)	101 (5)	98 (5)	95 (5)	91 (9)	77 (23)	64 (35)	45 (54)	36 (63)	23 (76)	16 (83)	7 (92)	2 (97)	1 (98)	NE (NE)
Best supportive care	114 (0)	112 (2)	108 (3)	106 (4)	105 (4)	101 (6)	99 (6)	96 (7)	92 (7)	88 (7)	85 (7)	84 (7)	83 (7)	79 (8)	71 (13)	57 (26)	49 (34)	39 (44)	26 (56)	14 (68)	8 (74)	4 (78)	3 (79)	2 (80)	NE (NE)

E

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	15 (14.2)	106	NE (NE)	0.42 (0.23-0.78); *P* = 0.005
Best supportive care group	30 (29.1)	103	NE (NE)	



Number at risk (number censored)

Atezolizumab	106 (0)	104 (2)	104 (2)	104 (2)	103 (3)	103 (3)	101 (4)	100 (4)	99 (5)	96 (5)	96 (5)	93 (5)	90 (5)	87 (5)	83 (9)	69 (23)	58 (33)	41 (50)	32 (59)	20 (71)	13 (78)	6 (85)	2 (89)	1 (90)	NE (NE)
Best supportive care	103 (0)	101 (2)	98 (3)	96 (4)	95 (4)	92 (5)	90 (5)	87 (6)	84 (6)	80 (6)	77 (6)	76 (6)	75 (6)	71 (7)	64 (11)	52 (22)	45 (29)	35 (39)	24 (49)	14 (59)	8 (65)	4 (69)	3 (70)	2 (71)	NE (NE)

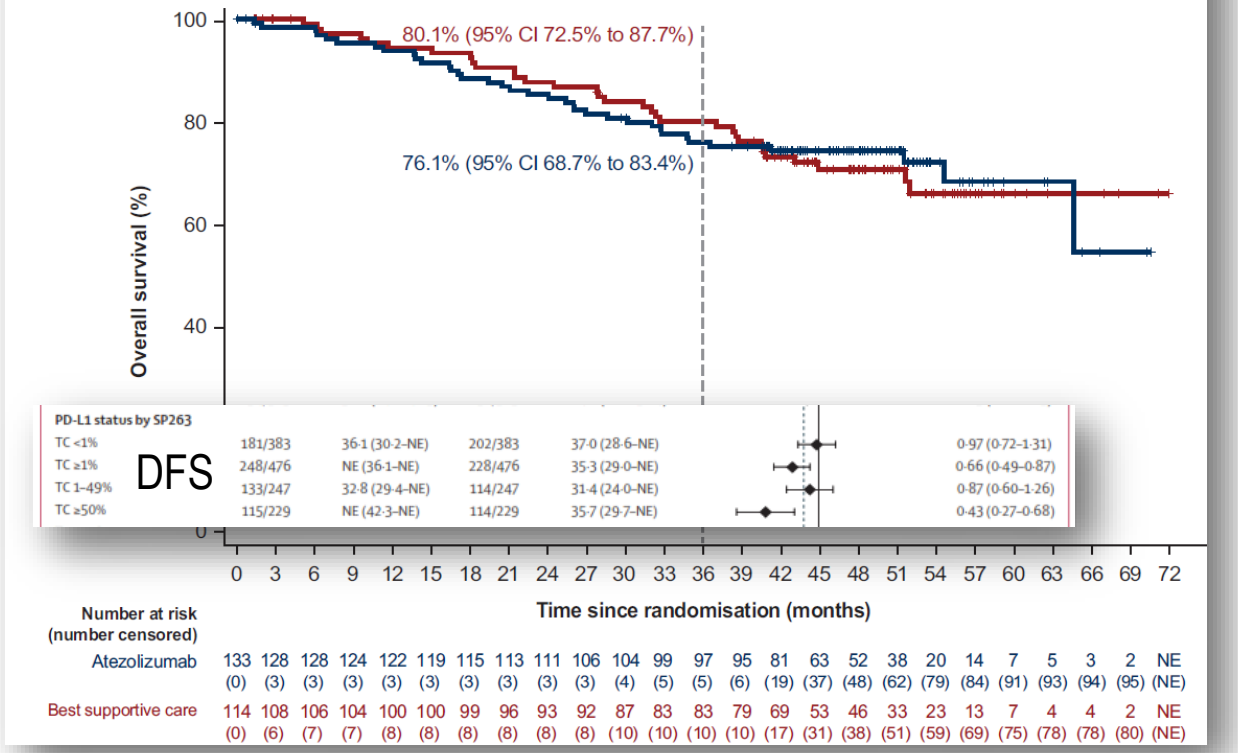
Felip et al. Ann Oncol (2023); Felip et al Lancet Oncol (2021)

RESULTS

OS in the II-IIIA PDL1 ≥1-49% and <1% populations

F

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	36 (27.1)	133	NE (64.6, NE)	0.95 (0.59-1.54); *P* = 0.845
Best supportive care group	32 (28.1)	114	NE (NE)	



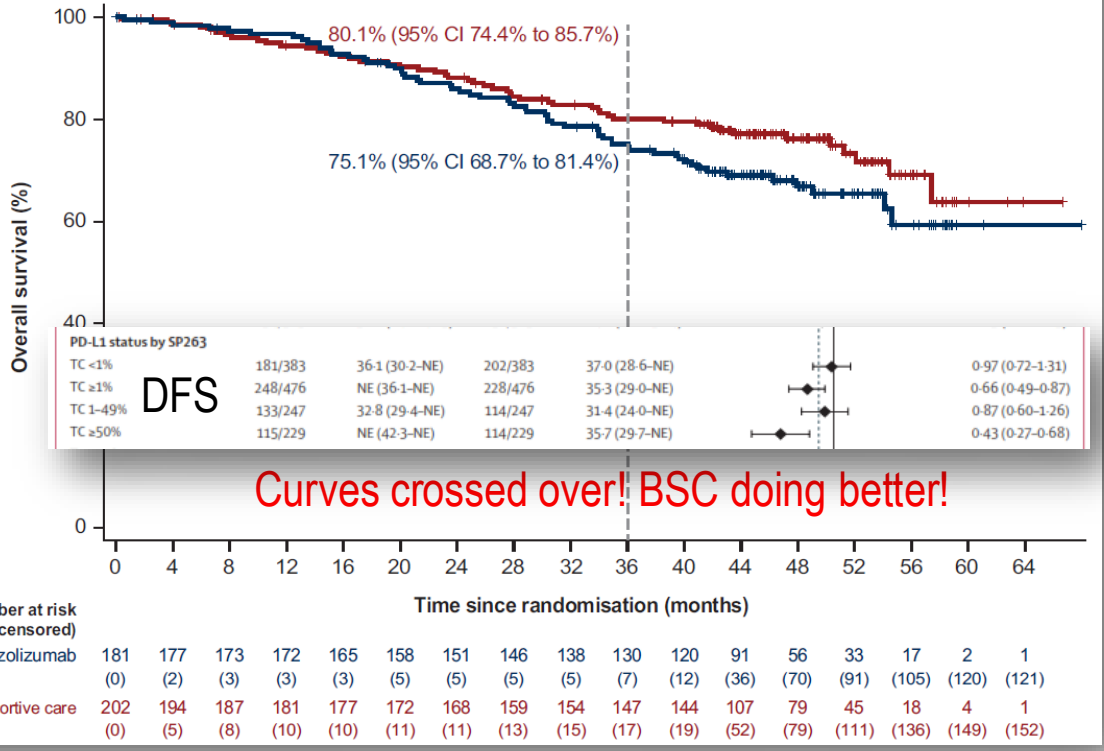
DFS

PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)

Number at risk (number censored)																									
Atezolizumab	133 (0)	128 (3)	128 (3)	124 (3)	122 (3)	119 (3)	115 (3)	113 (3)	111 (3)	106 (3)	104 (4)	99 (5)	97 (5)	95 (6)	81 (19)	63 (37)	52 (48)	38 (62)	20 (79)	14 (84)	7 (91)	5 (93)	3 (94)	2 (95)	NE (NE)
Best supportive care	114 (0)	108 (6)	106 (7)	104 (7)	100 (8)	100 (8)	99 (8)	96 (8)	93 (8)	92 (8)	87 (10)	83 (10)	83 (10)	79 (10)	69 (17)	53 (31)	46 (38)	33 (51)	23 (59)	13 (69)	7 (75)	4 (78)	4 (78)	2 (80)	NE (NE)

G

	Events, *n* (%)	Patients, *n*	Median overall survival, months (95% CI)	HR (95% CI)[b]
Atezolizumab group	59 (32.6)	181	NE (54.6, NE)	1.36 (0.93-1.99); *P* = 0.109
Best supportive care group	49 (24.3)	202	NE (NE)	



DFS

PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)

Curves crossed over! BSC doing better!

Number at risk (number censored)																	
Atezolizumab	181 (0)	177 (2)	173 (3)	172 (3)	165 (3)	158 (5)	151 (5)	146 (5)	138 (5)	130 (7)	120 (12)	91 (36)	56 (70)	33 (91)	17 (105)	2 (120)	1 (121)
Best supportive care	202 (0)	194 (5)	187 (8)	181 (10)	177 (10)	172 (11)	168 (11)	159 (13)	154 (15)	147 (17)	144 (19)	107 (52)	79 (79)	45 (111)	18 (136)	4 (149)	1 (152)

Care: Post Hoc unstratified analyses!

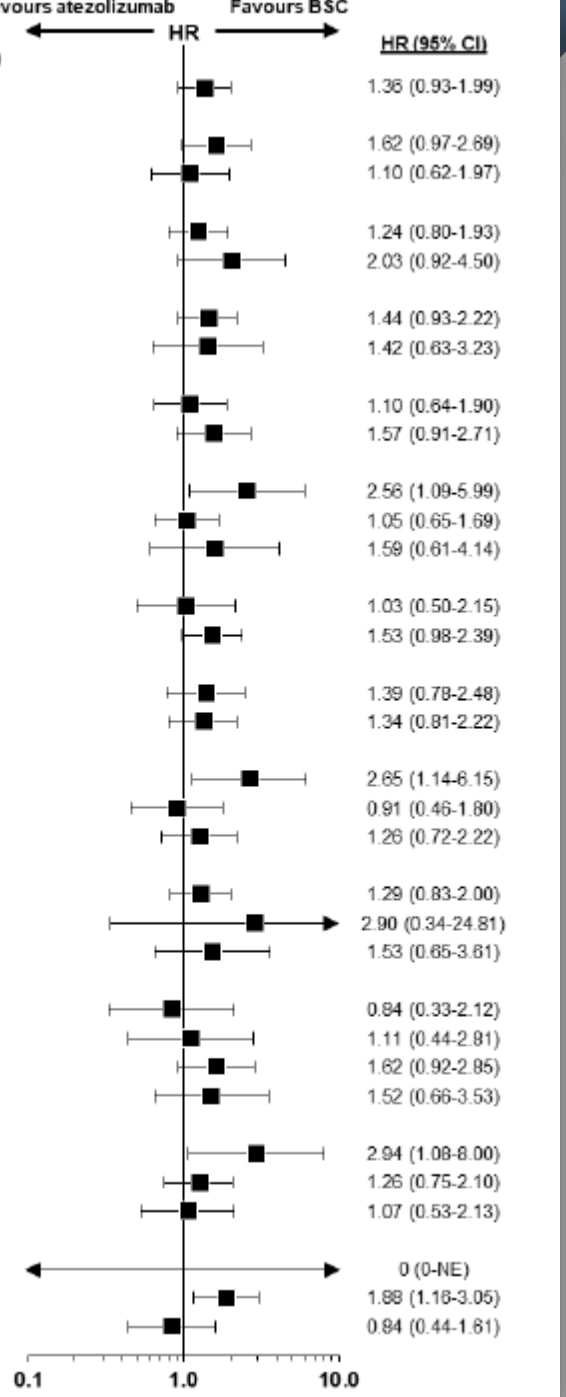
Felip et al. Ann Oncol (2023); ; Felip et al Lancet Oncol (2021)

RESULTS

Multivariable analyses: figure S3

OS in the II-IIIA PDL1 <1% population

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
All patients	383	181	NE (54.6-NE)	202	NE (NE)	1.36 (0.93-1.99)
Age						
<65 years	240	116	NE (NE)	124	NE (NE)	1.62 (0.97-2.69)
≥65 years	143	65	54.6 (54.1-NE)	78	57.4 (54.4-NE)	1.10 (0.62-1.97)
Sex						
Male	258	115	NE (54.1-NE)	143	NE (57.4-NE)	1.24 (0.80-1.93)
Female	125	66	NE (49.1-NE)	59	NE (NE)	2.03 (0.92-4.50)
Race						
White	286	135	NE (54.1-NE)	151	NE (NE)	1.44 (0.93-2.22)
Asian	91	43	NE (NE)	48	NE (57.4-NE)	1.42 (0.63-3.23)
ECOG PS						
0	216	94	NE (NE)	122	NE (57.4-NE)	1.10 (0.64-1.90)
1	166	86	NE (43.0-NE)	80	NE (NE)	1.57 (0.91-2.71)
Tobacco use history						
Never	98	47	NE (47.9-NE)	51	NE (NE)	2.56 (1.09-5.99)
Previous	224	106	NE (54.6-NE)	118	NE (57.4-NE)	1.05 (0.65-1.69)
Current	61	28	NE (46.3-NE)	33	NE (NE)	1.59 (0.61-4.14)
Histology						
Squamous	108	51	NE (54.6-NE)	57	NE (54.4-NE)	1.03 (0.50-2.15)
Non-squamous	275	130	NE (54.1-NE)	145	NE 57.4-NE)	1.53 (0.98-2.39)
Stage						
II	209	97	NE (54.6-NE)	112	NE (NE)	1.39 (0.78-2.48)
IIIA	174	84	NE (43.0-NE)	90	NE (54.4-NE)	1.34 (0.81-2.22)
Regional lymph node stage (pN)						
N0	114	52	NE (49.1-NE)	62	NE (NE)	2.65 (1.14-6.15)
N1	145	66	NE 54.6-NE)	79	NE (57.4-NE)	0.91 (0.46-1.80)
N2	124	63	NE (39.6-NE)	61	NE (51.3-NE)	1.26 (0.72-2.22)
Type of surgery						
Lobectomy	298	139	NE (54.6-NE)	159	NE (57.4-NE)	1.29 (0.83-2.00)
Bilobectomy	23	15	NE (31.5-NE)	8	NE (NE)	2.90 (0.34-24.81)
Pneumonectomy	60	26	NE (34.3-NE)	34	NE (NE)	1.53 (0.65-3.61)
Chemotherapy regimen						
Cisplatin + docetaxel	52	24	NE (46.3-NE)	28	NE (42.5-NE)	0.84 (0.33-2.12)
Cisplatin + gemcitabine	58	29	NE (54.6-NE)	29	NE (54.4-NE)	1.11 (0.44-2.81)
Cisplatin + pemetrexed	170	82	NE (NE)	88	57.4 (52.1-NE)	1.62 (0.92-2.85)
Cisplatin + vinorelbine	103	46	NE (54.1-NE)	57	NE (NE)	1.52 (0.66-3.53)
***EGFR* mutation status**						
Yes	64	26	NE (39.5-NE)	38	NE (NE)	2.94 (1.08-8.00)
No	201	98	NE (54.1-NE)	103	NE (57.4-NE)	1.26 (0.75-2.10)
Not tested	118	57	NE (54.6-NE)	61	NE (54.4-NE)	1.07 (0.53-2.13)
***ALK* rearrangement status**						
Yes	8	2	NE (NE)	6	47.2 (43.5-NE)	0 (0-NE)
No	244	114	NE (49.1-NE)	130	NE (57.4-NE)	1.88 (1.16-3.05)
Not tested	131	65	NE(54.6-NE)	66	NE (54.4-NE)	0.84 (0.44-1.61)



Felip et al. Ann Oncol (2023)

RESULTS

Multivariable analyses:

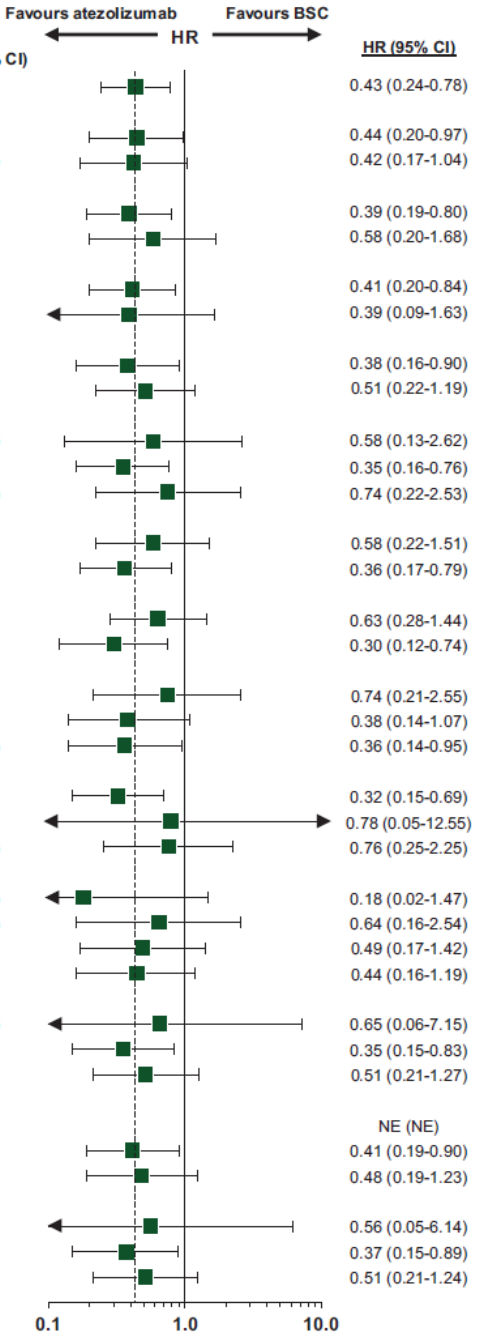
OS in the II-IIIA PDL1 ≥50% population

Felip et al. Ann Oncol (2023)

B

Stage II-IIIA PD-L1 TC ≥50%

Subgroup	N	Atezolizumab n	Atezolizumab Median OS (95% CI)	BSC n	BSC Median OS (95% CI)	HR (95% CI)
All patients	229	115	NE (NE)	114	NE (NE)	0.43 (0.24-0.78)
Age						
<65 years	138	70	NE (NE)	68	NE (NE)	0.44 (0.20-0.97)
≥65 years	91	45	NE (NE)	46	NE (52.6-NE)	0.42 (0.17-1.04)
Sex						
Male	167	89	NE (NE)	78	NE (NE)	0.39 (0.19-0.80)
Female	62	26	NE (NE)	36	NE (NE)	0.58 (0.20-1.68)
Race						
White	161	75	NE (NE)	86	NE (NE)	0.41 (0.20-0.84)
Asian	62	36	NE (NE)	26	NE (NE)	0.39 (0.09-1.63)
ECOG PS						
0	131	71	NE (NE)	60	NE (NE)	0.38 (0.16-0.90)
1	97	44	NE (NE)	53	NE (NE)	0.51 (0.22-1.19)
Tobacco use history						
Never	30	16	NE (NE)	14	NE (41.1-NE)	0.58 (0.13-2.62)
Previous	161	83	NE (NE)	78	NE (NE)	0.35 (0.16-0.76)
Current	38	16	NE (NE)	22	NE (38.9-NE)	0.74 (0.22-2.53)
Histology						
Squamous	92	47	NE (NE)	45	NE (NE)	0.58 (0.22-1.51)
Non-squamous	137	68	NE (NE)	69	NE (NE)	0.36 (0.17-0.79)
Stage						
II	119	62	NE (NE)	57	NE (NE)	0.63 (0.28-1.44)
IIIA	110	53	NE (NE)	57	NE (NE)	0.30 (0.12-0.74)
Regional lymph node stage (pN)						
N0	51	30	NE (NE)	21	NE (NE)	0.74 (0.21-2.55)
N1	95	43	NE (NE)	52	NE (NE)	0.38 (0.14-1.07)
N2	83	42	NE (NE)	41	NE (41.1-NE)	0.36 (0.14-0.95)
Type of surgery						
Lobectomy	169	84	NE (NE)	85	NE (NE)	0.32 (0.15-0.69)
Bilobectomy	14	7	NE (NE)	7	NE (NE)	0.78 (0.05-12.55)
Pneumonectomy	40	20	NE (38.5-NE)	20	NE (28.6-NE)	0.76 (0.25-2.25)
Chemotherapy regimen						
Cisplatin + docetaxel	33	13	NE (NE)	20	NE (26.2-NE)	0.18 (0.02-1.47)
Cisplatin + gemcitabine	39	22	NE (NE)	17	NE (43.5-NE)	0.64 (0.16-2.54)
Cisplatin + pemetrexed	72	35	NE (NE)	37	NE (NE)	0.49 (0.17-1.42)
Cisplatin + vinorelbine	85	45	NE (NE)	40	NE (NE)	0.44 (0.16-1.19)
***EGFR* mutation status**						
Yes	14	6	NE (NE)	8	NE (22.3-NE)	0.65 (0.06-7.15)
No	124	60	NE (NE)	64	NE (NE)	0.35 (0.15-0.83)
Not tested	91	49	NE (NE)	42	NE (NE)	0.51 (0.21-1.27)
***ALK* rearrangement status**						
Yes	6	3	NE (NE)	3	NE (NE)	NE (NE)
No	124	62	NE (NE)	62	NE (NE)	0.41 (0.19-0.90)
Not tested	99	50	NE (NE)	49	NE (NE)	0.48 (0.19-1.23)
***EGFR* mutation or *ALK* rearrangement status**						
Yes	20	9	NE (NE)	11	NE (NE)	0.56 (0.05-6.14)
No	106	52	NE (NE)	54	NE (NE)	0.37 (0.15-0.89)
Not tested	103	54	NE (NE)	49	NE (NE)	0.51 (0.21-1.24)



RESULTS

Safety

Table 2. Safety summary in the safety-assessable population

	Atezolizumab (n = 495)	Best supportive care (n = 495)
Any-grade adverse event	458 (92.5)[a]	351 (70.9)
Treatment-related adverse event	336 (67.9)	0
Grade 3/4 adverse event	109 (22.0)	57 (11.5)
Treatment-related grade 3/4 adverse event	53 (10.7)	0
Serious adverse event	88 (17.8)	42 (8.5)
Treatment-related serious adverse event	37 (7.5)	0
Grade 5 adverse event	9 (1.8)[a]	3 (0.6)
Treatment-related grade 5 adverse event	4 (0.8)	0
Adverse event leading to atezolizumab dose interruption	142 (28.7)	0
Adverse event leading to atezolizumab withdrawal	90 (18.2)	0
Any-grade AESI	258 (52.1)	47 (9.5)
Grade 3/4 AESI	39 (7.9)	3 (0.6)
Treatment-related grade 3/4 AESI	31 (6.3)	0
Grade 5 AESI	2 (0.4)	0
Treatment-related grade 5 AESI	2 (0.4)	0
Any-grade AESI leading to dose interruption of atezolizumab	58 (11.7)	0
Any-grade AESI leading to atezolizumab discontinuation	52 (10.5)	0

Felip et al. Ann Oncol (2023)

RESULTS: RECAP

OS ITT: HR=0.995 (0.78-1.28), p=0.996

Pre-specified exploratory analyses of OS:

- II-IIIA population (all) HR=0.995 (0.78-1.28), p=0.996
- II-IIIA population (PDL1 ≥1%) HR=0.95 (0.74-1.24), p=0.721

Post hoc exploratory analyses of OS:

- II-IIIA population (PDL1 ≥50%) + EGFR/ALK, HR=0.43 (0.24-0.78), p=0.0045
- II-IIIA population (PDL1 ≥50%) - EGFR/ALK, HR=0.42 (0.23-0.78), p=0.005
- II-IIIA population (PDL1 1-49%) HR=0.95 (0.59-1.54), p=0.845
- II-IIIA population (PDL1 <1%) HR=1.36 (0.93-1.99), p=0.109

“P values are shown for descriptive purposes only.”

Felip et al. Ann Oncol (2023)

DISCUSSION

- OS not formally tested
- Benefit strongest in PDL1 50%+
- Removal of EGFR/ALK+ NSCLC made no impact to the HR
- No OS benefit in the PDL1 negatives (? evidence of harm) “However, due to the exploratory nature of the subgroup analyses and lack of formal testing, these data should be interpreted with caution.”
- No OS benefit in PDL1 1-49%: “a numerically improved DFS with atezolizumab versus BSC was observed in this subgroup [HR for disease recurrence or death was 0.87 (95% CI 0.60-1.26)]. In a potentially curative setting, preventing early lung cancer recurrence or progression to metastatic disease could significantly reduce cost and resource utilisation and thereby benefit patients and payers” (Hmmm…..really? Depends on the effect size)
- No new safety issues

HOW DO THESE RESULTS COMPARE WITH PEARLS/KN-091

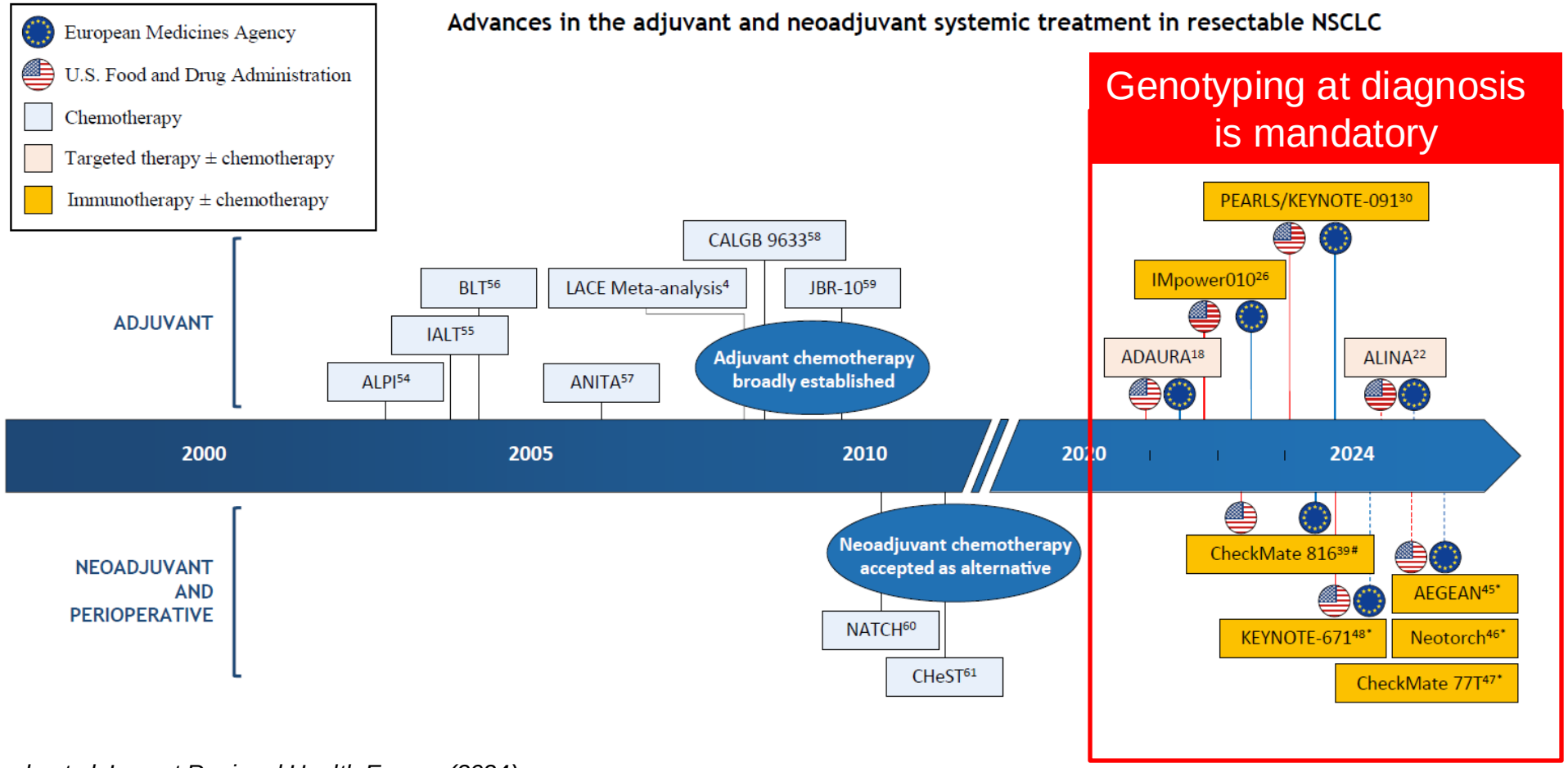
When making adjuvant immunotherapy decisions

	IMP-010[1,2]	PEARLS/KN0-91[3]
DFS II-IIIA 1%+	0.66 (0.50-0.88)	
DFS II-IIIA all	0.79 (0.64-0.96)	
DFS IB-IIIA all	0.81 (0.67-0.99)	0.76 (0.63-0.91)
DFS IB-IIIA ≥50%	Not presented	0.82 (0.57-1.18)
OS events	25%	18%
OS IB-IIIA all	0.995 (0.78-1.28)	0.87 (0.67-1.15)
OS II-IIIA	0.95 (0.74-1.24)	
OS II-IIIA PDL1 <1%	1.36 (0.93-1.99)	
OS II-IIIA PDL1 1-49%	0.95 (0.59-1.54)	
OS II-IIIA PDL1 ≥50% (-EGFR/ALK)	0.42 (0.23-0.78)	

1, Felip et al Lancet Oncol (2021); 2, Felip et al. Ann Oncol (2023); ; Felip et al Lancet Oncol (2021); 3, O'Brien et al Lancet Oncol (2022)

OPERABLE NSCLC: CHANGES IN DRUG THERAPY

Approval changes over time



Houda et al. Lancet Regional Health Europe (2024)

TREATMENT STRATEGIES IN RESECTABLE NSCLC

How do we decide?

Surgery

Adjuvant chemotherapy

Adjuvant immunotherapy

Trial	DFS	Approval
IMP-010[1]; TPS 1%+	0.66 (0.49-0.87)	
IMP-010[1]; TPS 50%+	0.43 (0.27-0.68)	
PEARLS/KM-091[2]; TPS 0%+	0.76 (0.63-0.91)	
BR.31[3]; TPS 25%+	0.935 (0.71-1.25)	

Neoadjuvant Chemo-immunotherapy

Trial	EFS	Approval
CM-816[4]; TPS 0%+	0.63 (0.43-0.91)	
CM-816[4]; TPS 1%+	0.41 (0.24-0.70)	

Neoadjuvant Chemo-immunotherapy

Adjuvant immunotherapy

Trial	EFS	Approval
KN-671[5]; TPS 0%+	0.58 (0.46-0.72)	
AGEAN[6]; TPS 0%+	0.68 (0.53-0.88)	
CM-77T[7]; TPS 0%+	0.58 (0.42-0.81)	

1, Felip et al. Lancet Oncol (2021);2, O'Brien et al. Lancet Oncol (2022); 3, Goss et al. ESMO (2024); 4, Forde et al. NEJM (2022); 5, Wakelee et al. NEJM 2023; 6, Heymach et al. NEJM 2023; 7, Cascone et al. NEJM (2024)

CONCLUSION

Felip et al. Ann Oncol (2023) Oct;34(10):907-919

At the first prespecified EXPLORATORY OS analysis, 25% of events;

- OS improvements (formally untested) in II-IIIA TPS ≥50%; approved by FDA and EMA
- No obvious IS improvement in II-IIIA TPS 1-49%; approved by FDA not EMA
- Concern for OS deterioration with atezo in II-IIIA TPS <1%

Additional follow up will be required to gain maturity and review role in other PDL1 subests

Data for PEARLS/KN-091; significant DFS benefit across 1b-IIIA ITT population, hence FDA and EMA approval

- OS at 18% events, no significant improvement in ITT population, similar to IMP-010
- DFS TPS ≥50%, no significant improvement: no good explanation, makes other subsets more difficult to interpret

Pre operative #3 chemo-nivo or peri-operative chemo-pembro/nivo/durva all have supporting data: optimal choice of strategy is currently uncertain, but HRs favour starting with chemo-immunotherapy

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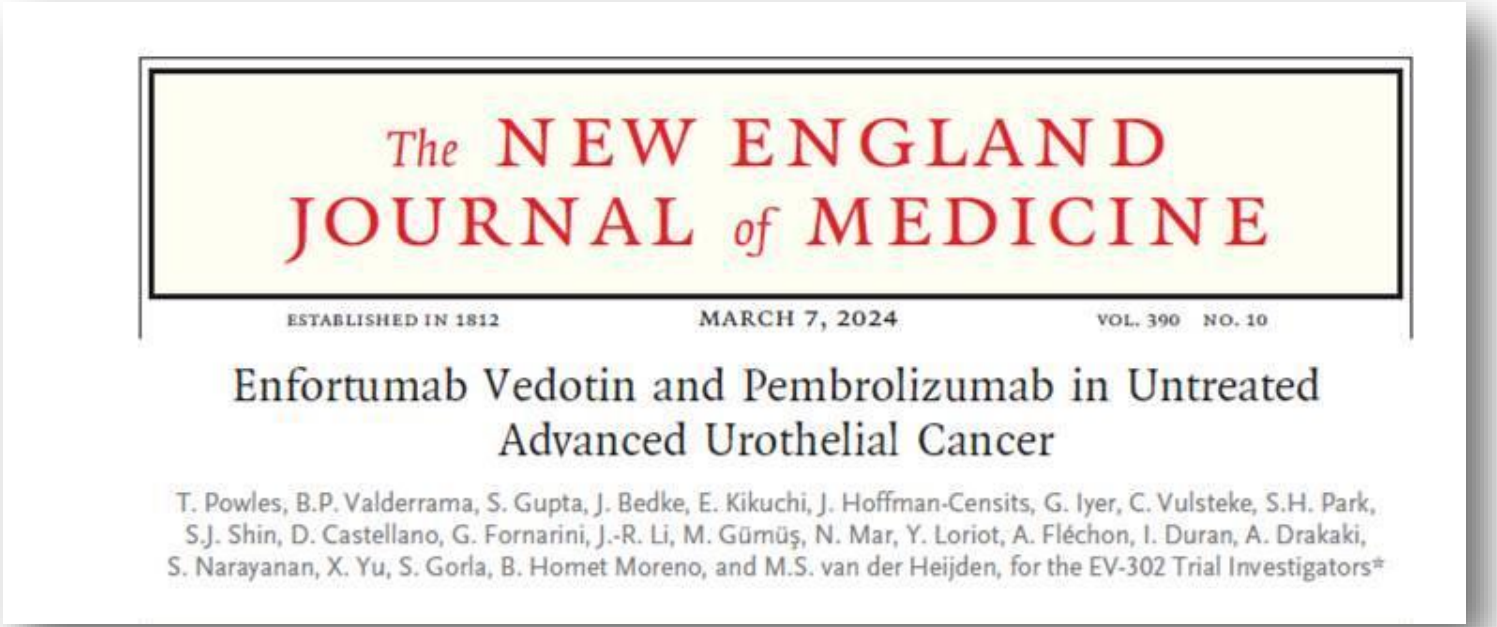
AMGEN, Astellas, BMS, EISAI, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Roche, Telix.

- **Received travel, accommodations**, from Bristol-Myers Squibb, Ipsen, MSD, Pfizer.

REVIEWING … A GAME CHANGING TRIAL

Powles T et al. N Engl J Med. 2024 Mar 7;390(10):875-888.



The NEW ENGLAND JOURNAL of MEDICINE

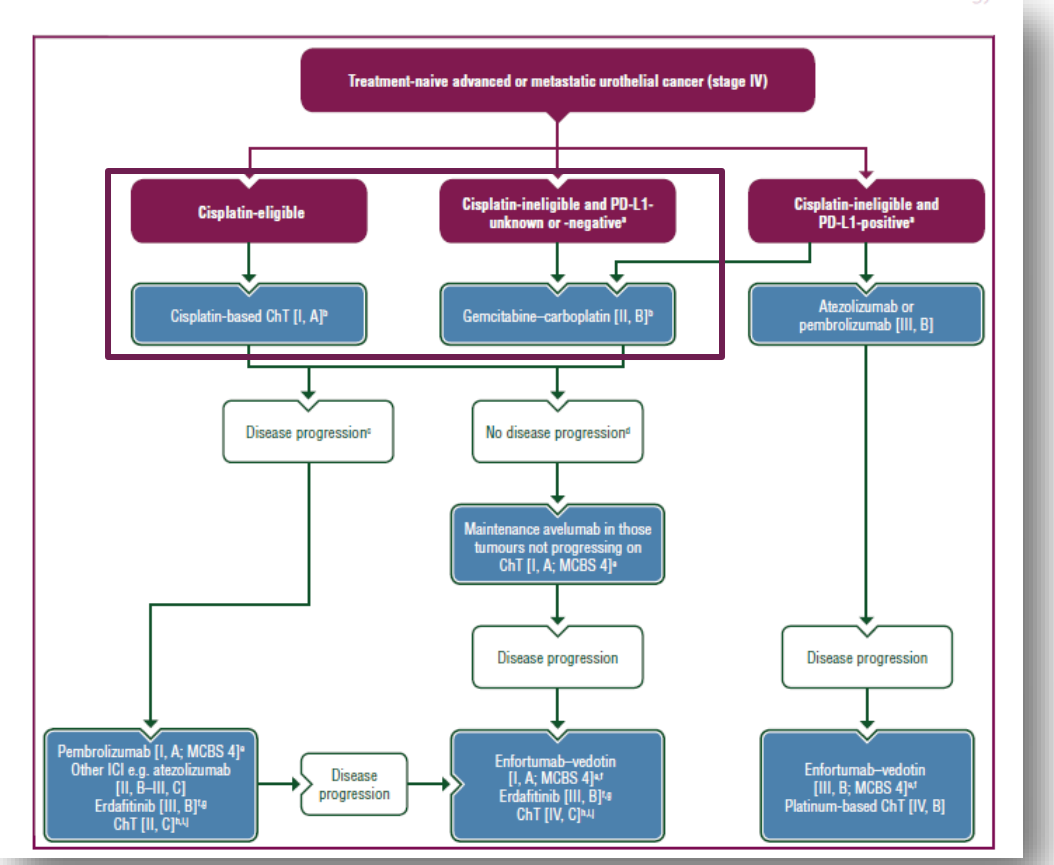
ESTABLISHED IN 1812 MARCH 7, 2024 VOL. 390 NO. 10

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

T. Powles, B.P. Valderrama, S. Gupta, J. Bedke, E. Kikuchi, J. Hoffman-Censits, G. Iyer, C. Vulsteke, S.H. Park, S.J. Shin, D. Castellano, G. Fornarini, J.-R. Li, M. Gümüş, N. Mar, Y. Loriot, A. Fléchon, I. Duran, A. Drakaki, S. Narayanan, X. Yu, S. Gorla, B. Homet Moreno, and M.S. van der Heijden, for the EV-302 Trial Investigators*

WHERE DID WE STAND BEFORE?

ESMO GUIDELINES ***BEFORE ESMO 2023 ANNUAL MEETING***



2 decades of combination therapy had failed to dethrone chemotherapy in patients with platinum eligible metastatic urothelial carcinoma

- **Cisplatin-ineligible**[1]

Carboplatin + gemcitabine[4]

- **Cisplatin-eligible**

Cisplatin + gemcitabine[2]

Dose-dense methotrexate

+ vinblastine + doxorubicin

+ cisplatin (ddMVAC)[3]

1. Galsky, et al. JCO 2011 Jun 10;29(17):2432-8 *2. Von der Maase, et al. JCO 2000 Sep 18;(17):3068-77* *3.Sternerg, et al. JCO 2001 May 15;19(10):268-46* *4. De Santis, et al. JCO 2012 Jan 10;30(2):191-9*

WHERE DID WE STAND BEFORE

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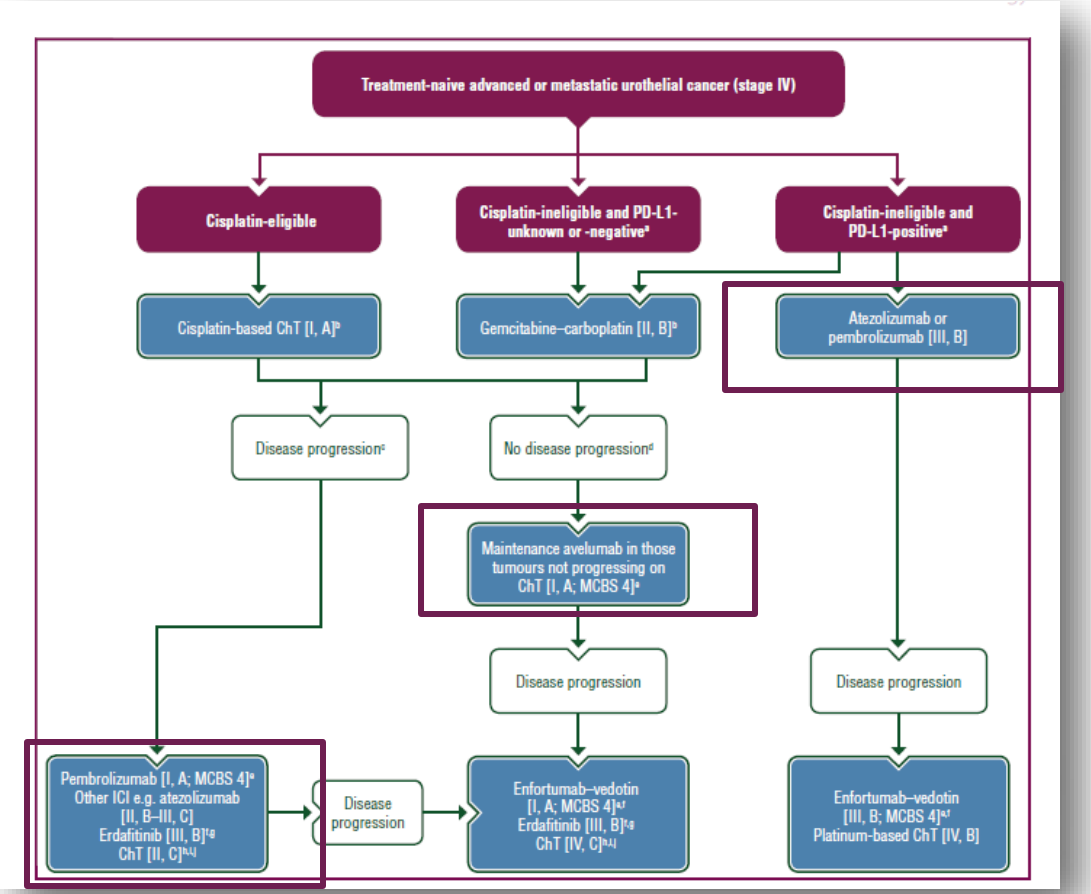


PD1/PDL1 single agent was SOC in

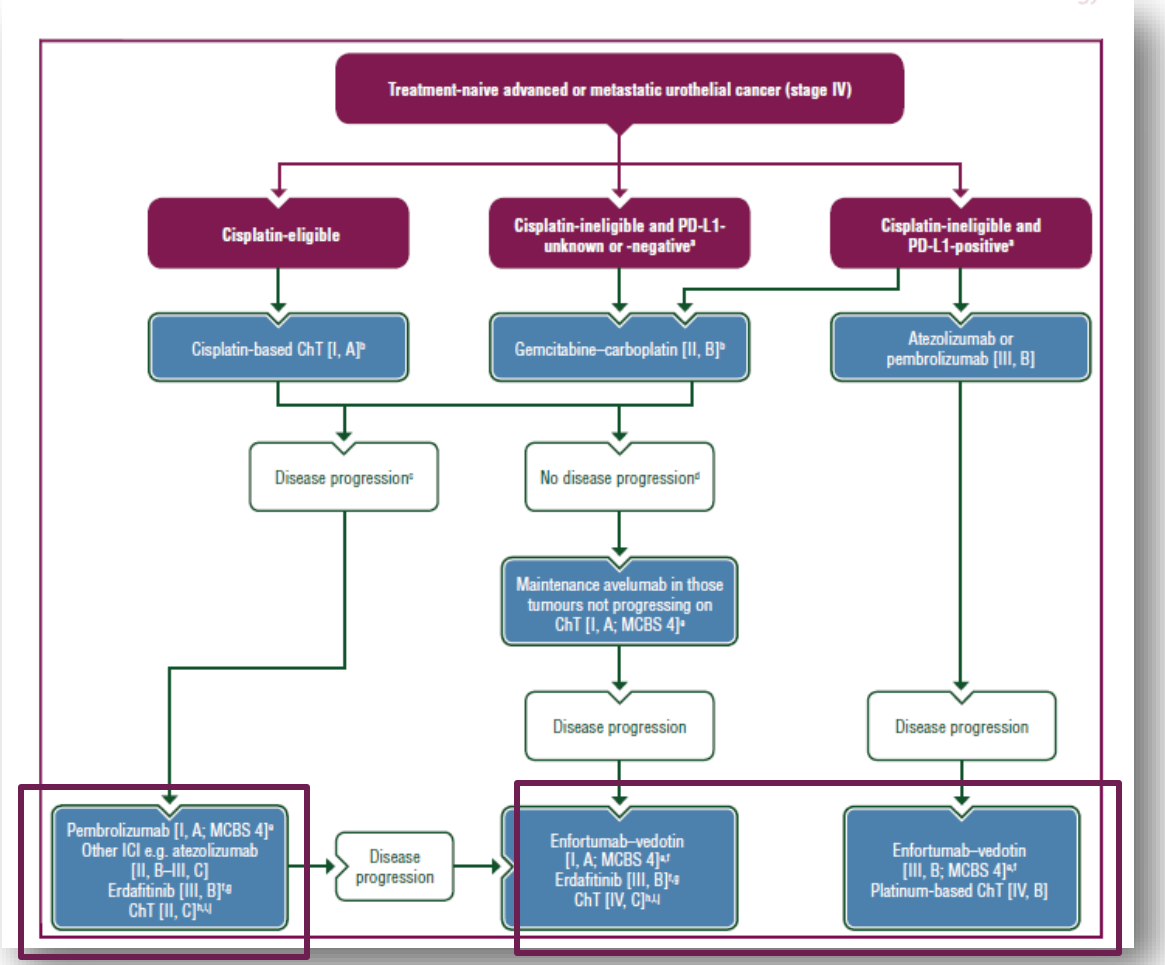
- **Platin-ineligible**
- **Maintenance strategy after L1[1]**
- **2nd line Therapy[2]**

1. Powles, et al., N Engl J Med 2020 Sep 24;383(13):1218-1230

2. Bellmunt et al., N Engl J Med 2017; 376:1015-1026

WHERE DID WE STAND BEFORE

ESMO GUIDELINES ***BEFORE ESMO 2023 ANNUAL MEETING***



New MoA/ New agents were integarted in later line setting

- Enfortumab Vedotin[1]
- Erdafitinib (if tumor +FGFR 2/3 genetic alterations)[2]
- Sacituzumab govitecan[3]

1.Powles T et al., N Engl J Med 2021;384:1125-35

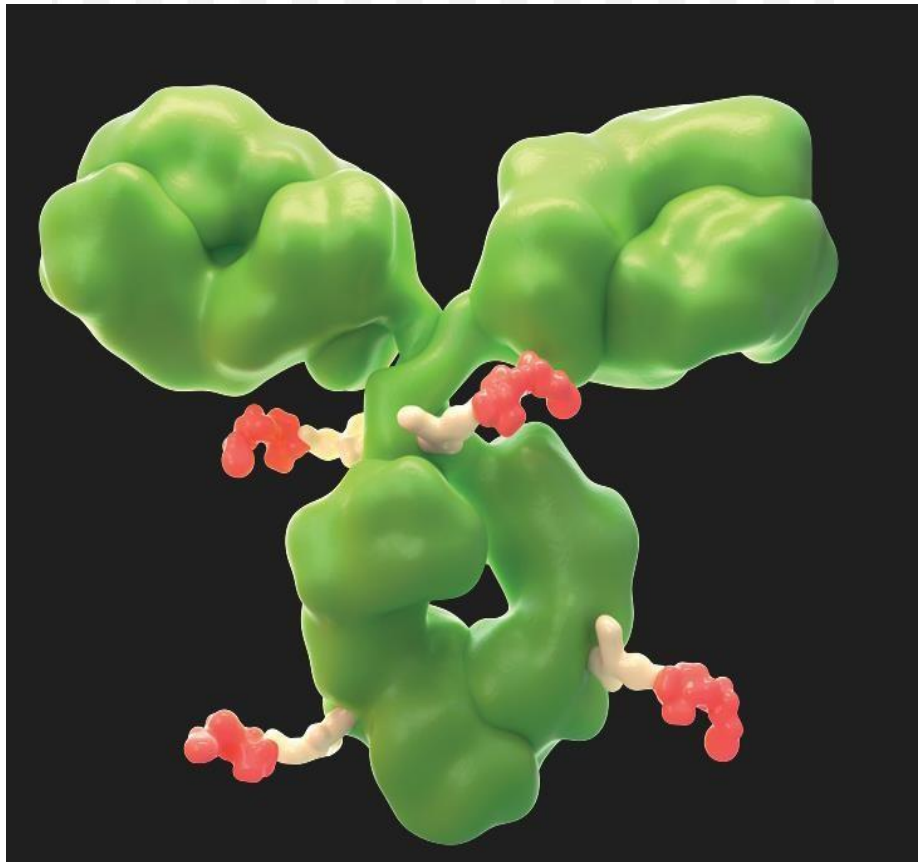
2.Loriot Y, et al. N Engl J Med. 2019;381:338-348

3. Tagawa CT et al., JCO 2021 Aug 1;39(22):2474-2485

ENFORTUMAB VEDOTIN (EV), AN ANTIBODY-DRUG CONJUGATE TARGETING NECTIN-4

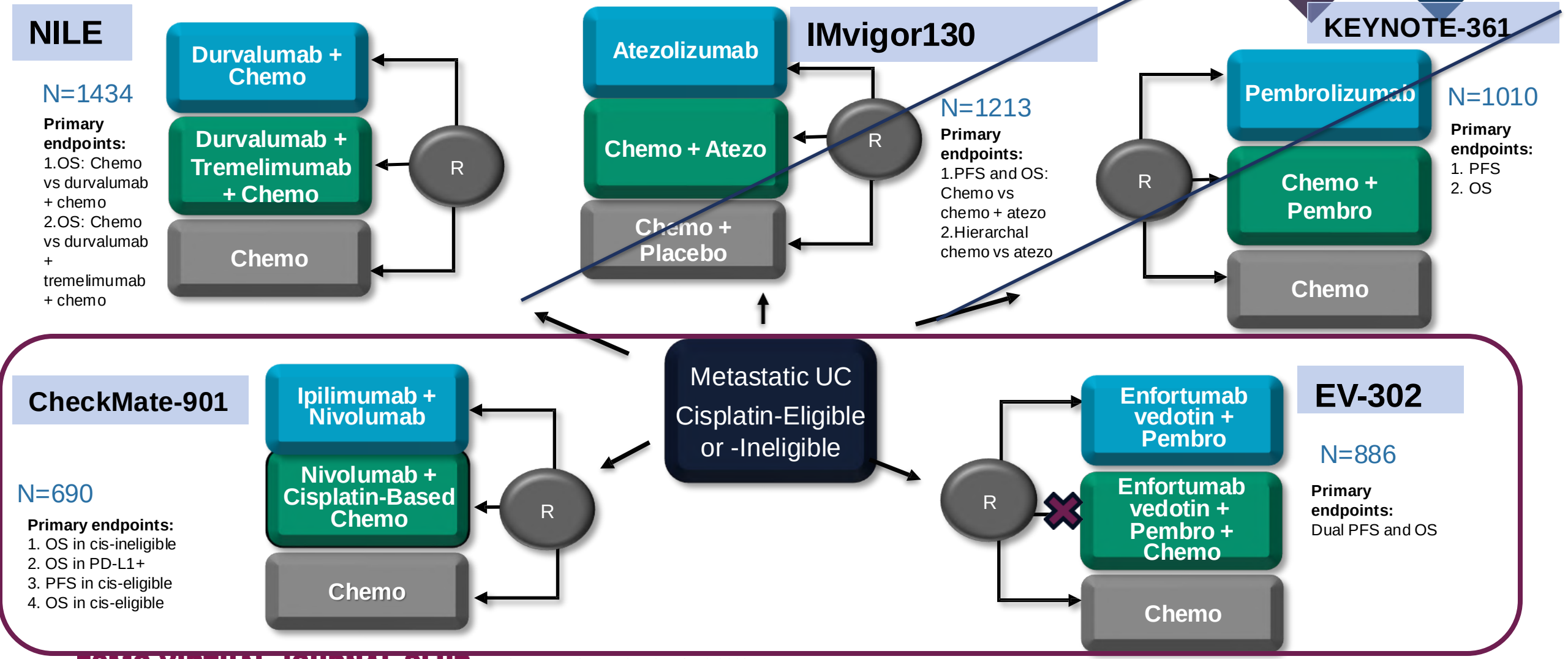
- Antibody-drug conjugates are made up of 3 parts:
  - **The antibody: Anti-nectin-4**
  - **The payload: MMAE**
  - **The linker (stable in circulation, but releases the cytotoxic agent in the target cell)**

- Nectin-4 is highly expressed in metastatic urothelial cancer patients not necessitating tumor screening
- The payload MMAE (plus linker) is vedotin, a microtubule-disrupting agent (200x more potent than vinblastine)
- December 2019, FDA granted accelerated approval of EV for 2 indications 1]Platinum and PD-1/PD-L1 refractory metastatic urothelial carcinoma; 2] cisplatin-ineligible and have previously received PD-1/PD-L1 therapy



Rosenberg, J et al., J Clin Oncol. 2019 10;37(29):2592-2600

First-line Phase 3 Trials with Checkpoint-Inhibitor Combinations vs Platinum-based Chemo for Metastatic Urothelial Carcinoma



Courtesy of A. APOLLO, ESMO 2023

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Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

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ABSTRACT

BACKGROUND

No treatment has surpassed platinum-based chemotherapy in improving overall survival in patients with previously untreated locally advanced or metastatic urothelial carcinoma.

METHODS

We conducted a phase 3, global, open-label, randomized trial to compare the efficacy and safety of enfortumab vedotin and pembrolizumab with the efficacy and safety of platinum-based chemotherapy in patients with previously untreated locally advanced or metastatic urothelial carcinoma. Patients were randomly assigned in a 1:1 ratio to receive 3-week cycles of enfortumab vedotin (at a dose of 1.25 mg per kilogram of body weight intravenously on days 1 and 8) and pembrolizumab (at a dose of 200 mg intravenously on day 1) (enfortumab vedotin–pembrolizumab group) or gemcitabine and either cisplatin or carboplatin (determined on the basis of eligibility to receive cisplatin) (chemotherapy group). The primary end points were progression-free survival as assessed by blinded independent central review and overall survival.

RESULTS

A total of 886 patients underwent randomization: 442 to the enfortumab vedotin–pembrolizumab group and 444 to the chemotherapy group. As of August 8, 2023, the median duration of follow-up for survival was 17.2 months. Progression-free survival was longer in the enfortumab vedotin–pembrolizumab group than in the chemotherapy group (median, 12.5 months vs. 6.3 months; hazard ratio for disease progression or death, 0.45; 95% confidence interval [CI], 0.38 to 0.54; P<0.001), as was overall survival (median, 31.5 months vs. 16.1 months; hazard ratio for death, 0.47; 95% CI, 0.38 to 0.58; P<0.001). The median number of cycles was 12 (range, 1 to 46) in the enfortumab vedotin–pembrolizumab group and 6 (range, 1 to 6) in the chemotherapy group. Treatment-related adverse events of grade 3 or higher occurred in 55.9% of the patients in the enfortumab vedotin–pembrolizumab group and in 69.5% of those in the chemotherapy group.

CONCLUSIONS

Treatment with enfortumab vedotin and pembrolizumab resulted in significantly better outcomes than chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma, with a safety profile consistent with that in previous reports. (Funded by Astellas Pharma US and others; EV-302 ClinicalTrials.gov number, NCT04223856.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Powles can be contacted at thomas.powles1@nhs.net.

*A complete list of the investigators in the EV-302 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on March 7, 2024, at NEJM.org.

N Engl J Med 2024;390:875-88.
DOI: 10.1056/NEJMoa2312117

ORIGINAL ARTICLE

Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma

M.S. van der Heijden, G. Sonpavde, T. Powles, A. Necchi, M. Burotto, M. Schenker, J.P. Sade, A. Bamias, P. Beuzeboc, J. Bedke, J. Oldenburg, G. Chatta, Y. Ürün, D. Ye, Z. He, B.P. Valderrama, J.H. Ku, Y. Tomita, J. Filian, L. Wang, D. Purcea, M.Y. Patel, F. Nasroulah, and M.D. Galsky, for the CheckMate 901 Trial Investigators*

ABSTRACT

BACKGROUND

No new agent has improved overall survival in patients with unresectable or metastatic urothelial carcinoma when added to first-line cisplatin-based chemotherapy.

METHODS

In this phase 3, multinational, open-label trial, we randomly assigned patients with previously untreated unresectable or metastatic urothelial carcinoma either to receive intravenous nivolumab (at a dose of 360 mg) plus gemcitabine–cisplatin (nivolumab combination) every 3 weeks for up to six cycles, followed by nivolumab (at a dose of 480 mg) every 4 weeks for a maximum of 2 years, or to receive gemcitabine–cisplatin alone every 3 weeks for up to six cycles. The primary outcomes were overall and progression-free survival. The objective response and safety were exploratory outcomes.

RESULTS

A total of 608 patients underwent randomization (304 to each group). At a median follow-up of 33.6 months, overall survival was longer with nivolumab-combination therapy than with gemcitabine–cisplatin alone (hazard ratio for death, 0.78; 95% confidence interval [CI], 0.63 to 0.96; P=0.02); the median survival was 21.7 months (95% CI, 18.6 to 26.4) as compared with 18.9 months (95% CI, 14.7 to 22.4), respectively. Progression-free survival was also longer with nivolumab-combination therapy than with gemcitabine–cisplatin alone (hazard ratio for progression or death, 0.72; 95% CI, 0.59 to 0.88; P=0.001). The median progression-free survival was 7.9 months and 7.6 months, respectively. At 12 months, progression-free survival was 34.2% and 21.8%, respectively. The overall objective response was 57.6% (complete response, 21.7%) with nivolumab-combination therapy and 43.1% (complete response, 11.8%) with gemcitabine–cisplatin alone. The median duration of complete response was 37.1 months with nivolumab-combination therapy and 13.2 months with gemcitabine–cisplatin alone. Grade 3 or higher adverse events occurred in 61.8% and 51.7% of the patients, respectively.

CONCLUSIONS

Combination therapy with nivolumab plus gemcitabine–cisplatin resulted in significantly better outcomes in patients with previously untreated advanced urothelial carcinoma than gemcitabine–cisplatin alone. (Funded by Bristol Myers Squibb and Ono Pharmaceutical; CheckMate 901 ClinicalTrials.gov number, NCT03036098.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. van der Heijden can be contacted at ms.vd.heijden@nki.nl or at the Department of Medical Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands.

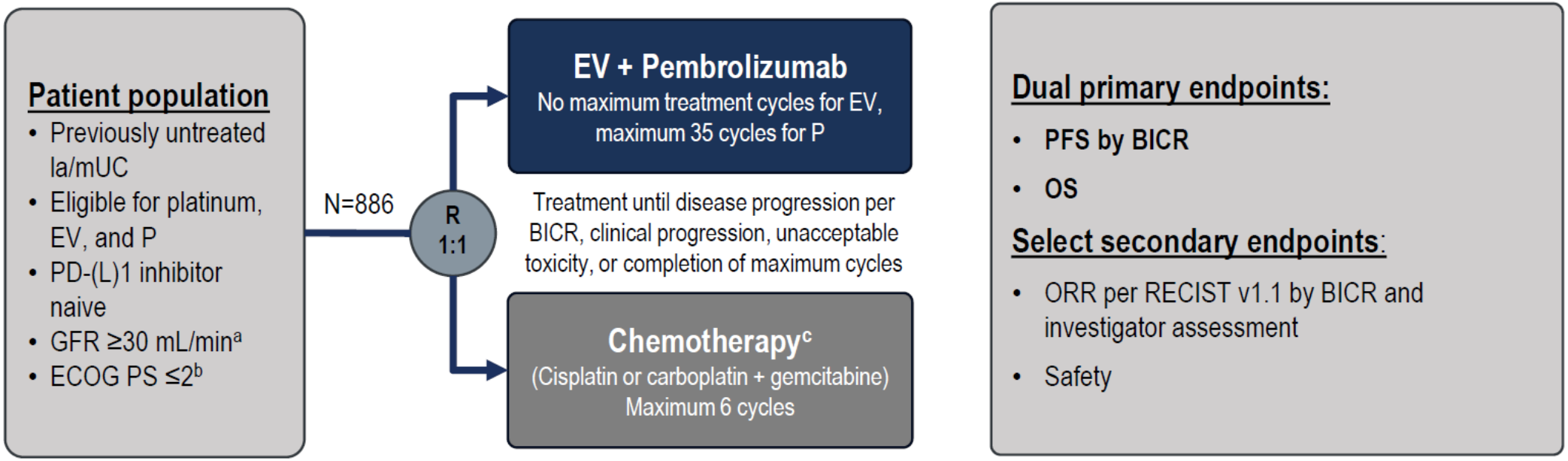
*A complete list of the investigators in the CheckMate 901 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. van der Heijden and Sonpavde contributed equally to this article.

This article was published on October 22, 2023, at NEJM.org.

N Engl J Med 2023;389:1778-89.
DOI: 10.1056/NEJMoa2309863

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine
[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure
[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

Key Demographic and Baseline Disease Characteristics

Balanced between treatment arms and representative of 1L la/mUC population

	EV+P (N=442)	Chemotherapy (N=444)
Male sex, n (%)	344 (77.8)	336 (75.7)
Age (yrs), median (range)	69.0 (37,87)	69.0 (22,91)
Race, n (%)		
White	308 (69.7)	290 (65.3)
Asian	99 (22.4)	92 (20.7)
Geographic location, n (%)		
North America	103 (23.3)	85 (19.1)
Europe	172 (38.9)	197 (44.4)
Rest of World	167 (37.8)	162 (36.5)
ECOG PS, n (%)		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
2	15 (3.4)	11 (2.5)
Primary tumor location, n (%)		
Upper tract	135 (30.5)	104 (23.4)
Lower tract	305 (69.0)	339 (76.4)

	EV+P (N=442)	Chemotherapy (N=444)
Cisplatin eligible[a], n (%)	240 (54.3)	242 (54.5)
Metastatic category, n (%)		
Visceral metastases	318 (71.9)	318 (71.6)
Bone	81 (18.3)	102 (23.0)
Liver	100 (22.6)	99 (22.3)
Lung	170 (38.5)	157 (35.4)
Lymph node only disease	103 (23.3)	104 (23.4)
PD-L1 expression[b], n/N (%)		
High (CPS ≥ 10)	254/438 (58.0)	254/439 (57.9)
Low (CPS < 10)	184/438 (42.0)	185/439 (42.1)

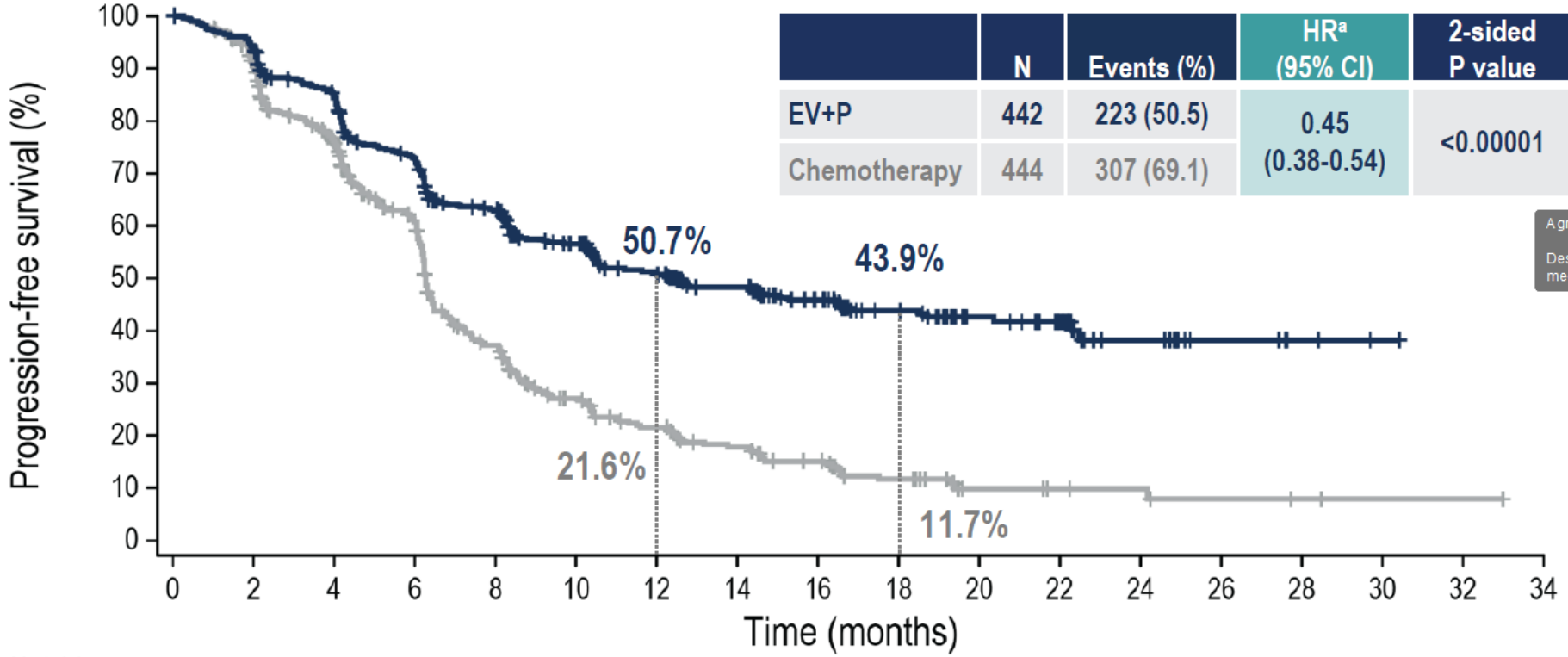
Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

CPS, combined positive score
[a]Represents eligibility at time of randomization
[b]CPS status was determined using the validated PD-L1 IHC 22C3 pharmDx assay at Neogenomics and Labcorp; 4 patients in the EV+P arm and 5 patients in the chemotherapy arm had samples that were of inadequate tissue quality for analysis

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



A graph of a graph

Description automatically generated with medium confidence

N at risk

EV+P	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1
Chemotherapy	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

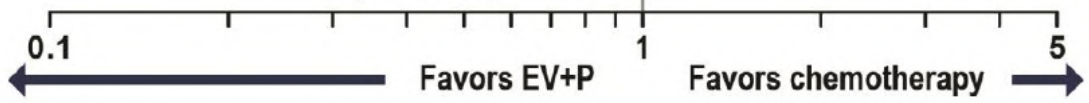
Data cutoff: 08 Aug 2023

PFS at 12 and 18 months as estimated using Kaplan-Meier method
HR, hazard ratio; mPFS, median progression-free survival
[a]Calculated using stratified Cox proportional hazards model; a hazard ratio <1 favors the EV+P arm

Subgroup Analysis of PFS per BICR

PFS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)



Data cutoff: 08 Aug 2023

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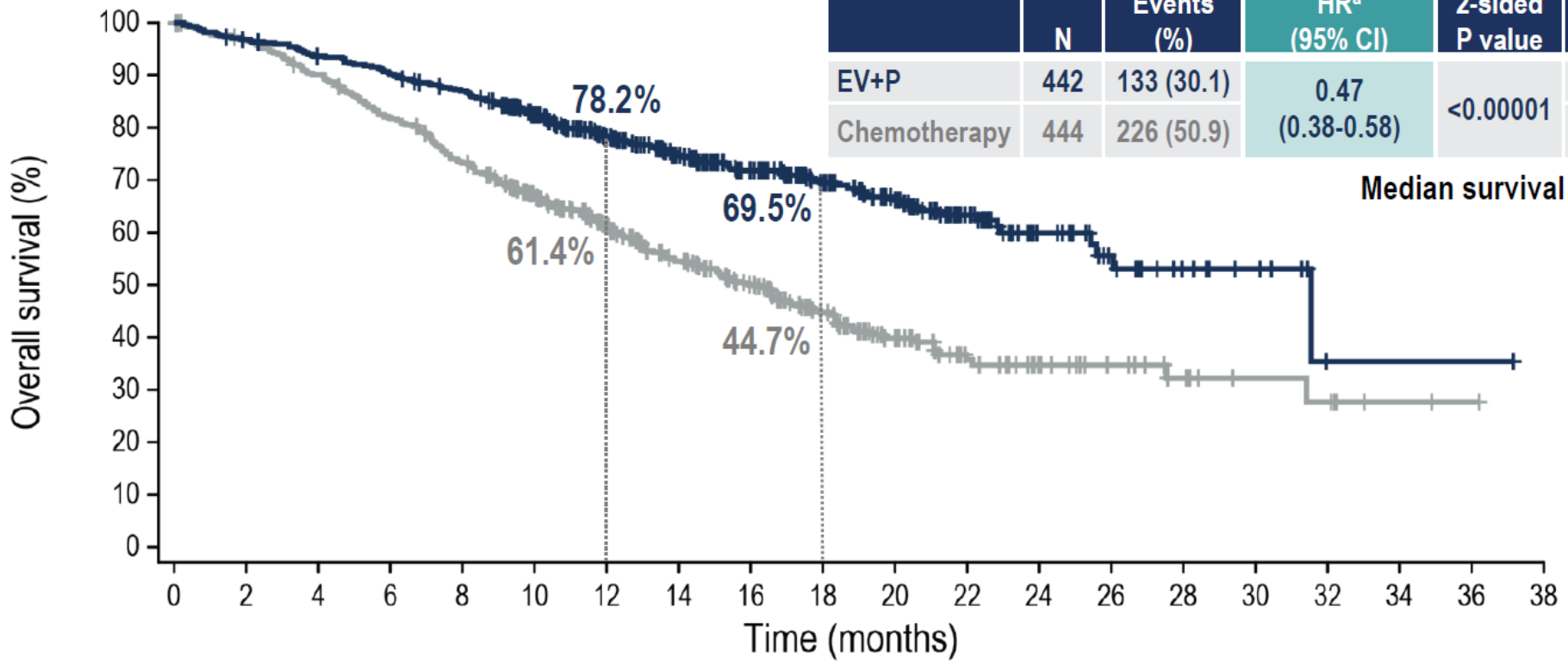
Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



N at risk

EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Data cutoff: 08 Aug 2023

OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

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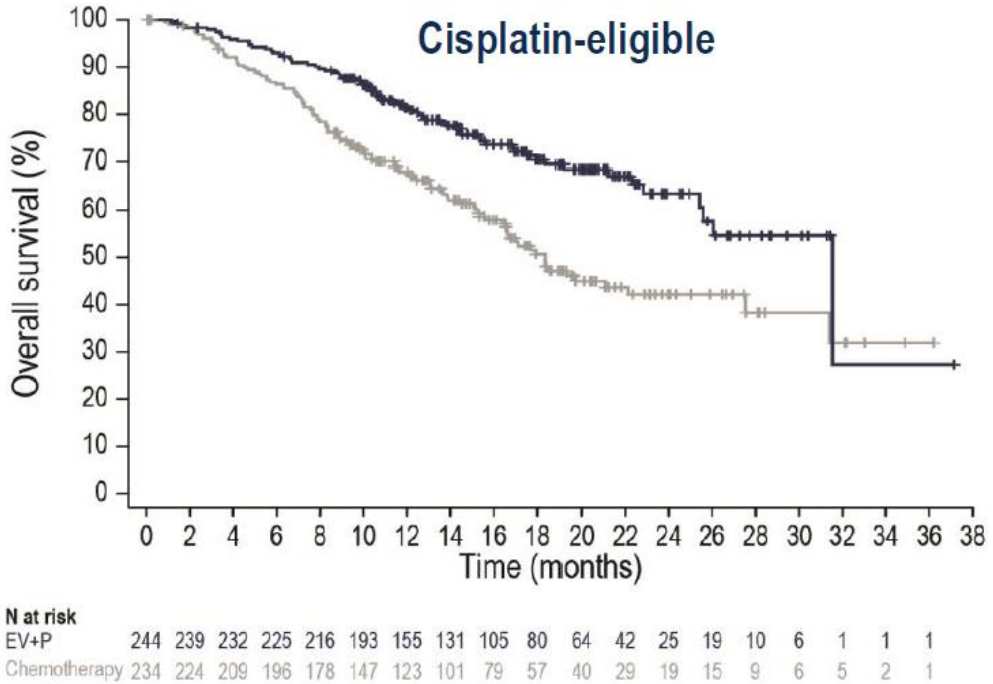
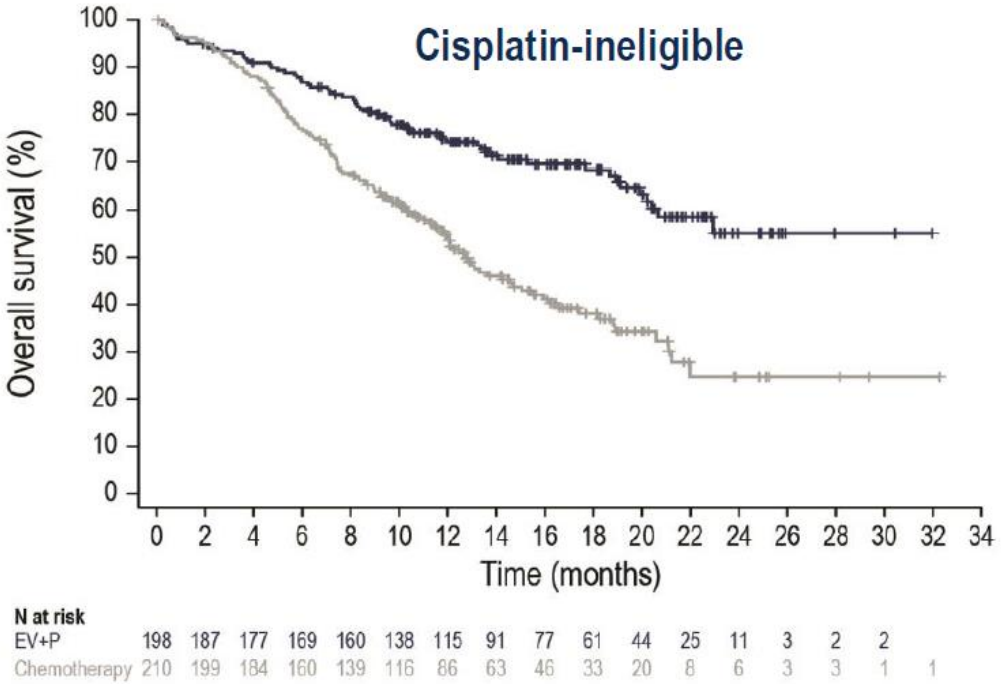
OS Subgroup Analysis: Cisplatin Eligibility

OS benefit was consistent with overall population regardless of cisplatin eligibility



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	69	0.53 (0.39-0.72)	31.5 (25.4-NR)
Chemotherapy	106		18.4 (16.4-27.5)

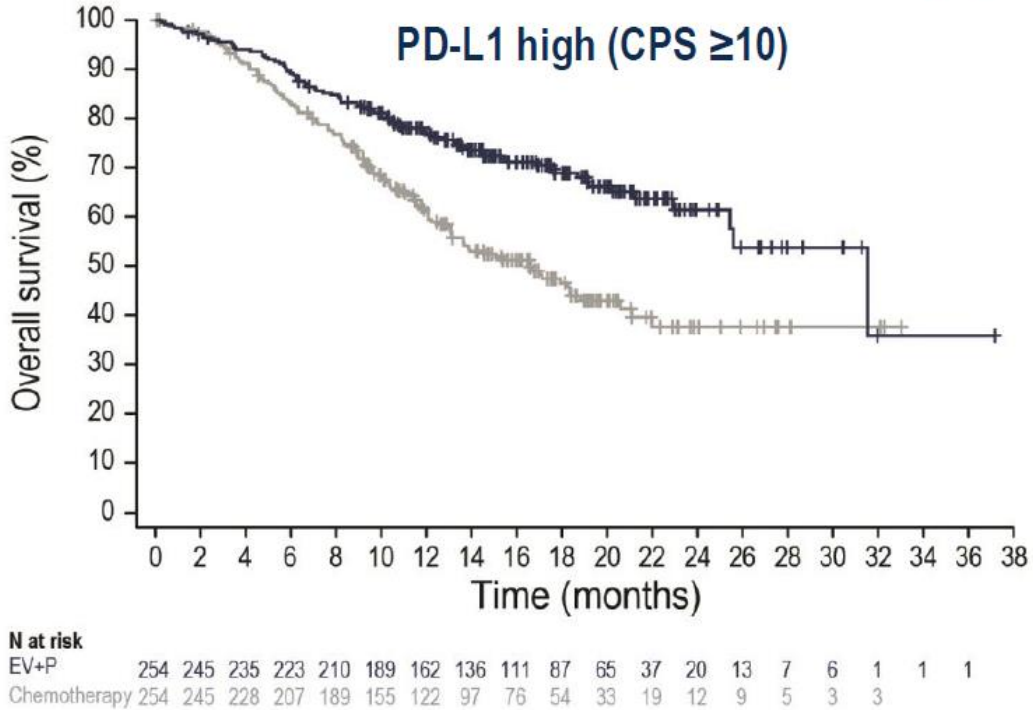


	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	64	0.43 (0.31-0.59)	NR (20.7-NR)
Chemotherapy	120		12.7 (11.4-15.5)

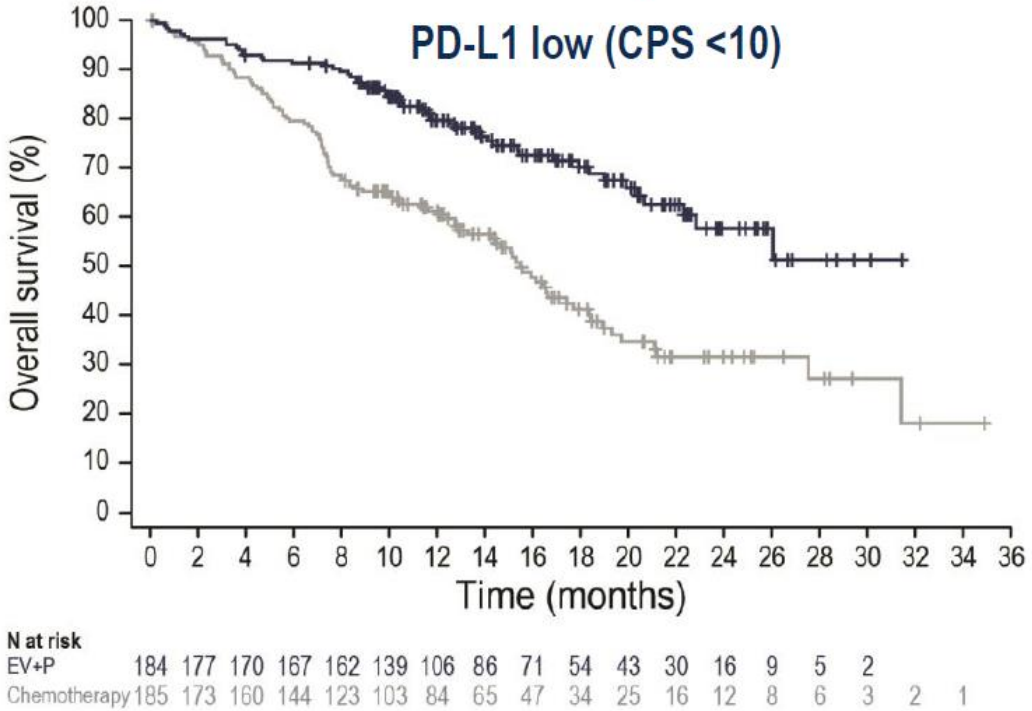
Data cutoff: 08 Aug 2023

OS Subgroup Analysis: PD-L1 Expression

OS benefit was consistent with overall population regardless of PD-L1 expression status



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	79	0.49 (0.37-0.66)	31.5 (25.4-NR)
Chemotherapy	125		16.6 (13.1-20.6)



	Events, n	HR (95% CI)	mOS (95% CI), months
EV+P	53	0.44 (0.31-0.61)	NR (22.3-NR)
Chemotherapy	99		15.5 (12.9-17.7)

Data cutoff: 08 Aug 2023

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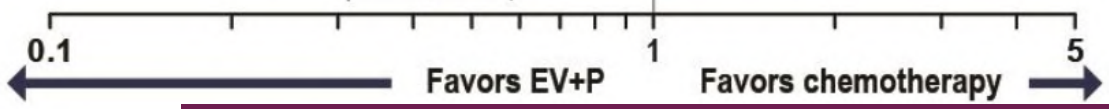
Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



Data cutoff: 08 Aug 2023

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EV+Pembro is highly active regardless of

- **PD-L1 status**
- **Liver metastases**
- **Cisplatin eligibility**

Summary of Subsequent Systemic Therapy

59% of patients in chemotherapy arm received subsequent PD-1/L1 inhibitors

	EV+P (N=442) n (%)	Chemotherapy (N=444) n (%)
First subsequent systemic therapy[a]	128 (28.9)	294 (66.2)
Platinum-based therapy	110 (24.9)	17 (3.8)
PD-1/L1 inhibitor-containing therapy	7 (1.6)	260 (58.6)
Maintenance therapy	0	143 (32.2)
Avelumab maintenance	0	135 (30.4)
PD-1/L1 inhibitor-containing therapy following progression	7 (1.6)	117 (26.4)
Other	11 (2.5)	17 (3.8)

[a]144 (32.6%) patients in the EV+P arm remain on treatment at time of analysis

Data cutoff: 08 Aug 2023

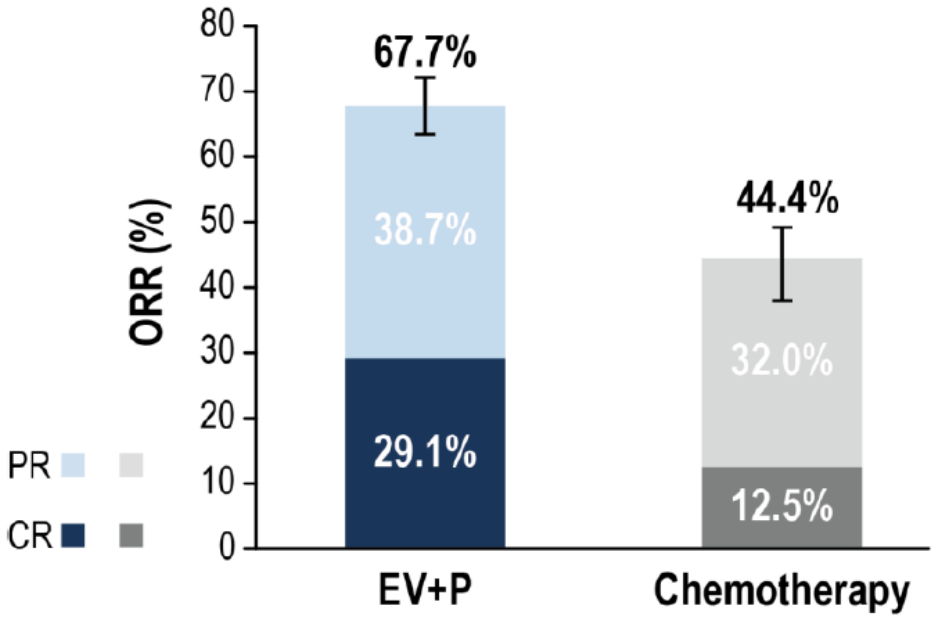
#1: Were patients in control ARM under exposed to PD-1/PDL1?

MADRID 2023 ESMO congress

Powles et al.

Confirmed Overall Response per BICR

Significant improvement in objective response rate was observed with EV+P



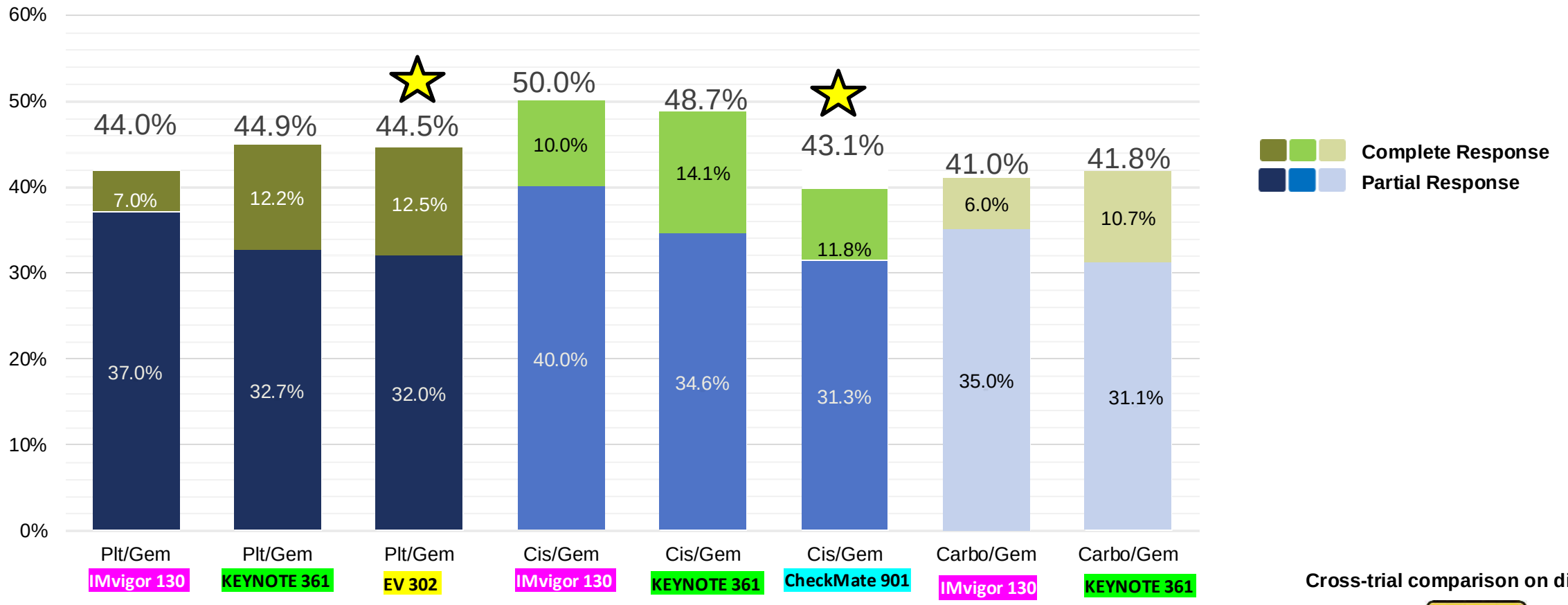
	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	**296 (67.7) (63.1-72.1)**	**196 (44.4) (39.7-49.2)**
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)

Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

CR, complete response; DOR, duration of response; PR, partial response
[a]Best overall response according to RECIST v1.1 per BICR. CR or PR was confirmed with repeat scans ≥28 days after initial response
[b]Patients had either post-baseline assessment and the best overall response was determined to be not evaluable per RECIST v1.1 or no response assessment post-baseline

Data cutoff: 08 Aug 2023

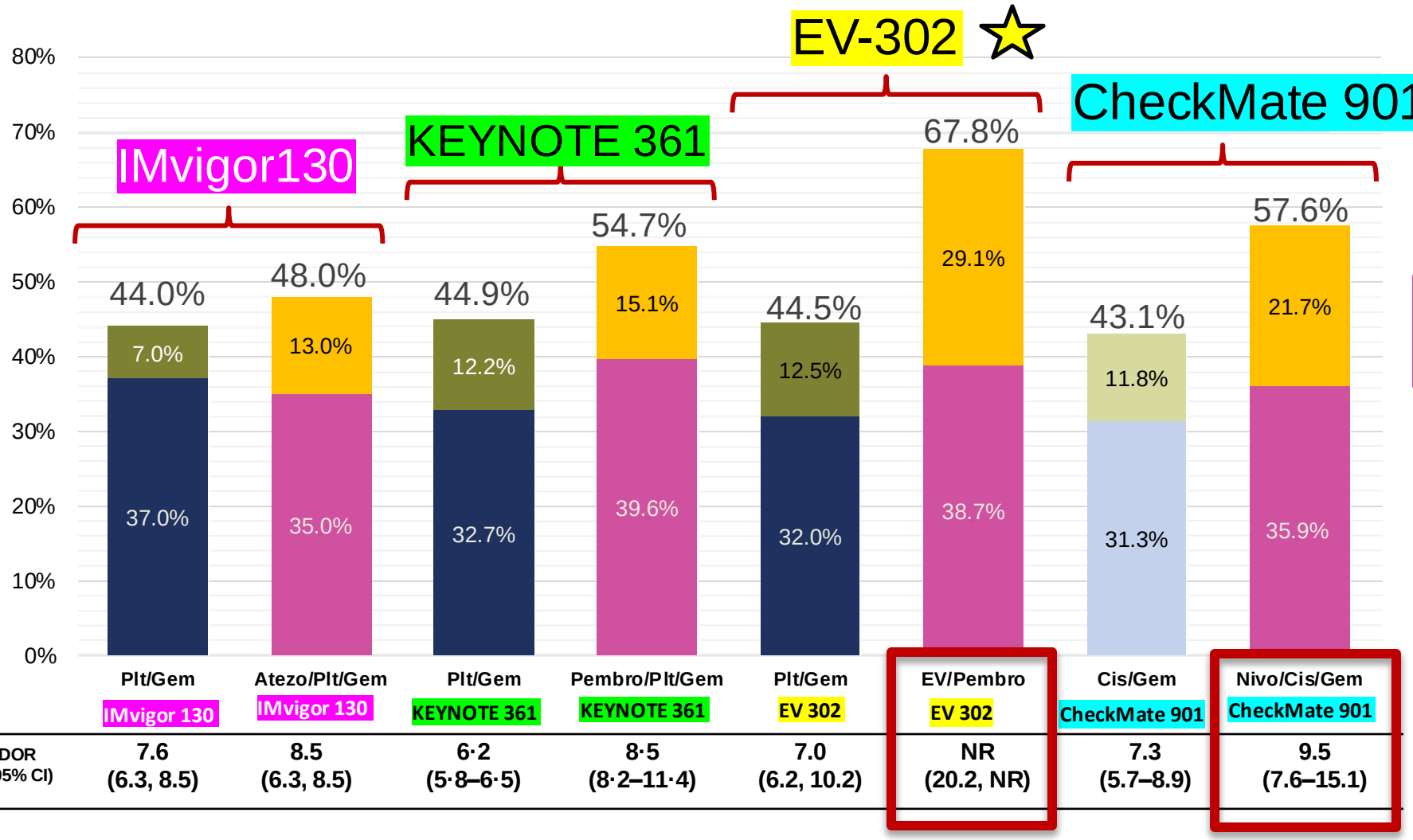
EVP RESPONSE RATE COMPARED TO OTHER RCTS



Cross-trial comparison on display

Courtesy of A. APOLO, ESMO 2023

EVP DOR COMPARED TO OTHER RCTS



	Plt/Gem IMvigor 130	Atezo/Plt/Gem IMvigor 130	Plt/Gem KEYNOTE 361	Pembro/Plt/Gem KEYNOTE 361	Plt/Gem EV 302	EV/Pembro EV 302	Cis/Gem CheckMate 901	Nivo/Cis/Gem CheckMate 901
Median DOR Months, (95% CI)	7.6 (6.3, 8.5)	8.5 (6.3, 8.5)	6·2 (5·8–6·5)	8·5 (8·2–11·4)	7.0 (6.2, 10.2)	NR (20.2, NR)	7.3 (5.7–8.9)	9.5 (7.6–15.1)

EV302 and CM901:
Time to response was ~2 months or first restaging scan

Cross-trial comparison on display

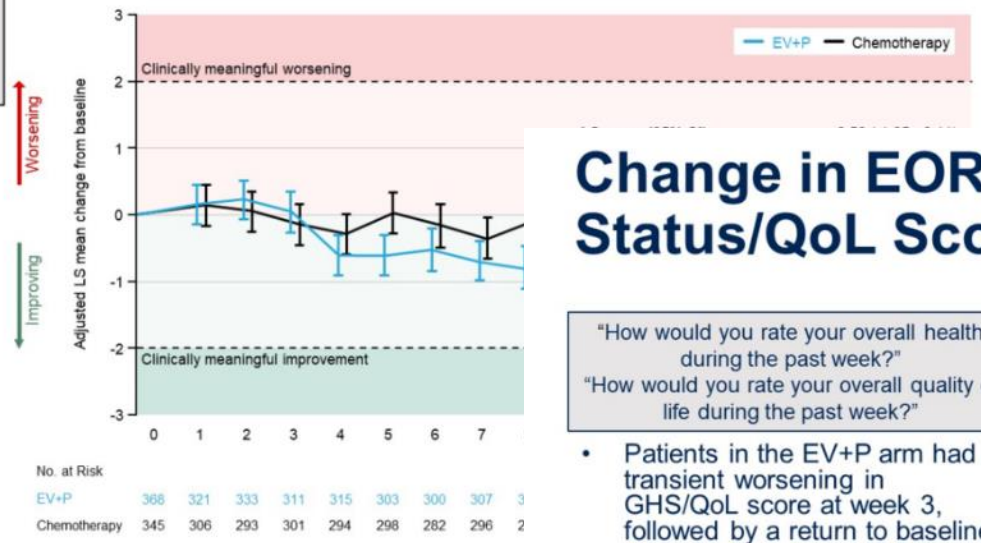
Courtesy of A. APOLO, ESMO 2023

#2: DOES THE RESPONSE CONVERT IN PAIN & QOL?

Change in Worst Pain (BPI-SF)

"Please rate your pain from 0 (no pain) to 10 (pain as bad as you can imagine) that best describes your pain at its worst in the last 24 hours."

- Although pre-defined clinically meaningful thresholds were not met in either treatment arm:
  - Patients in the EV+P arm reported improved pain compared to baseline.
  - Larger improvements in pain were demonstrated in the EV+P arm than in the CT arm.

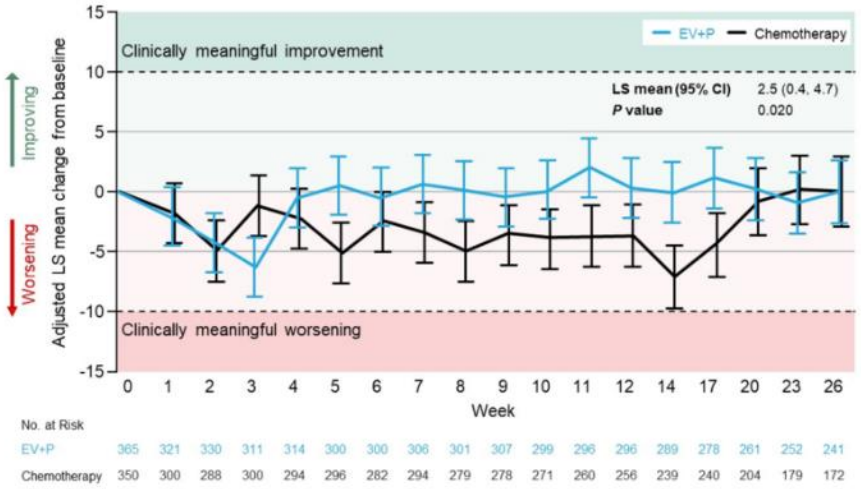


*Nominal *P* value.
BPI-SF, Brief Pain Inventory-Short Form; CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; LS, least squares.

Change in EORTC QLQ-C30 Global Health Status/QoL Score

"How would you rate your overall health during the past week?"
"How would you rate your overall quality of life during the past week?"

- Patients in the EV+P arm had a transient worsening in GHS/QoL score at week 3, followed by a return to baseline at week 4.
- Patients in the CT arm had a worsening from week 1 through week 17; scores returned to baseline from week 20.
- Median time to confirmed deterioration (mTTCD) was 5.9 months with EV+P and 3.2 months with CT, (HR 0.98 [95% CI: 0.79, 1.2]).



TTCD was defined as a clinically meaningful decrease (a 10-point decrease in EORTC QLQ-C30 from baseline for two consecutive visits).
CT, chemotherapy; EV+P, enfortumab vedotin plus pembrolizumab; GHS, global health status; HR, hazard ratio; LS, least squares; QoL, quality of life.

Courtesy S GUPTA, ASCO 2024

EV Treatment-Related Adverse Events of Special Interest*

Majority of treatment-related AESIs were low grade

	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

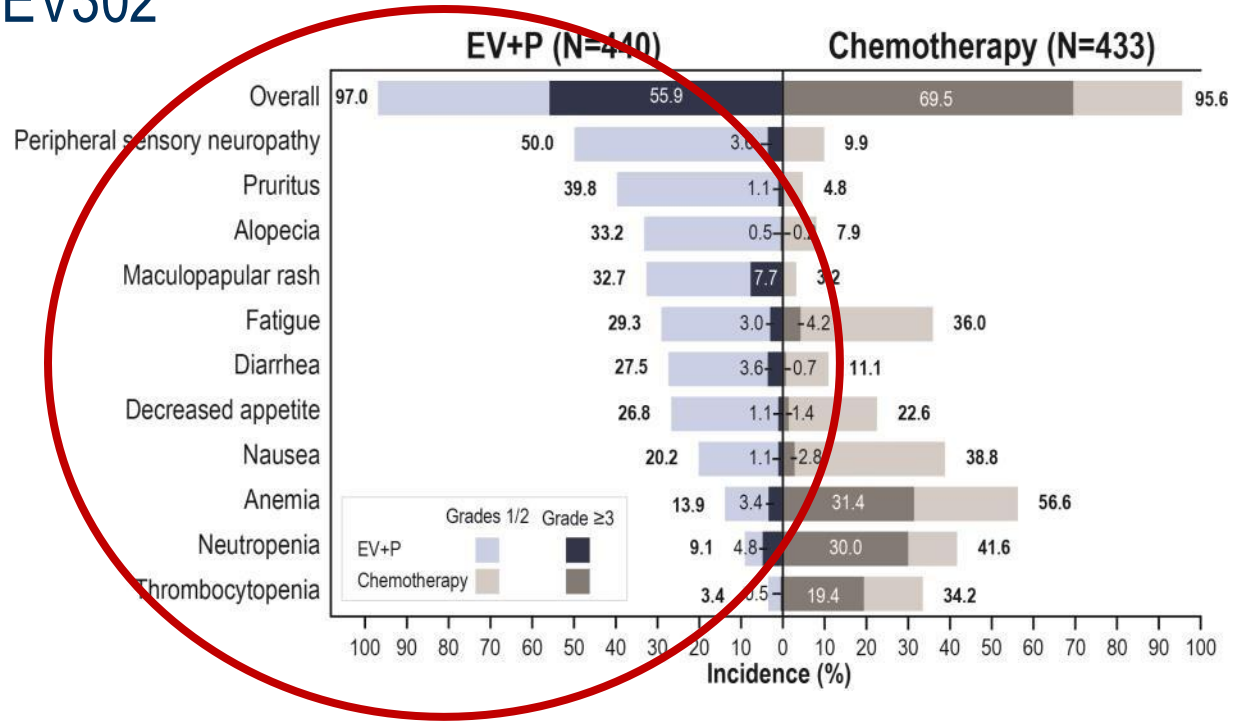
#3: TOXICITY - Will skin toxicity be an issue in RW practice?

SIs and P TEAEs of special interest because monotherapies, respectively

Data cutoff: 08 Aug 2023

#3: HOW CAN WE REDUCE THE TOXICITY OF EV+PEMBRO?

EV302



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

- Grade ≥3 events were 56% in EV+P and 70% in chemotherapy
- EV has a unique toxicity profile including peripheral neuropathy (can be treatment-limiting), skin reactions, ocular disorders, and hyperglycemia
- Can we give EV for 6 months then continue pembro for maintenance? Can we dose-reduce EV in responders?
- It will be crucial to assess the efficacy of dose-de-escalation strategies

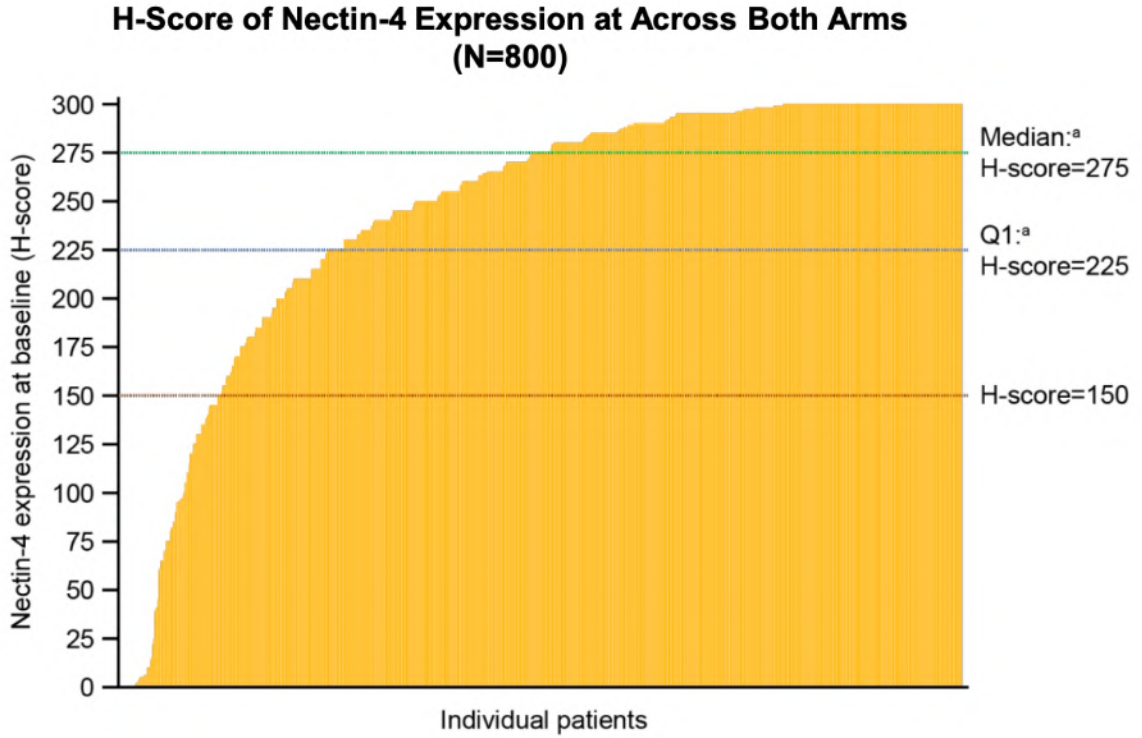
Courtesy of A. APOLO, ESMO 2023

#4: A NEED OF A BIOMARKER?

Exploratory Nectin-4 Biomarker Analysis

- Retrospective assessment of Nectin-4 expression[a] by a CAP/CLIA validated Nectin-4 IHC assay in primary or metastatic tumor tissue[b]
  - Nectin-4 expression and Nectin-4/PD-L1 expression were available for 800 of 886 randomized patients (EV+P: n=394; chemotherapy: n=406)
  - PD-L1 expression status was determined as high (CPS ≥10) or low (CPS <10) using a validated PD-L1 IHC assay[c]
- Clinical efficacy (PFS, OS, and ORR) was assessed in Nectin-4 expression subgroups

CAN NECTIN 4 BE USED FOR PATIENT SELECTION?



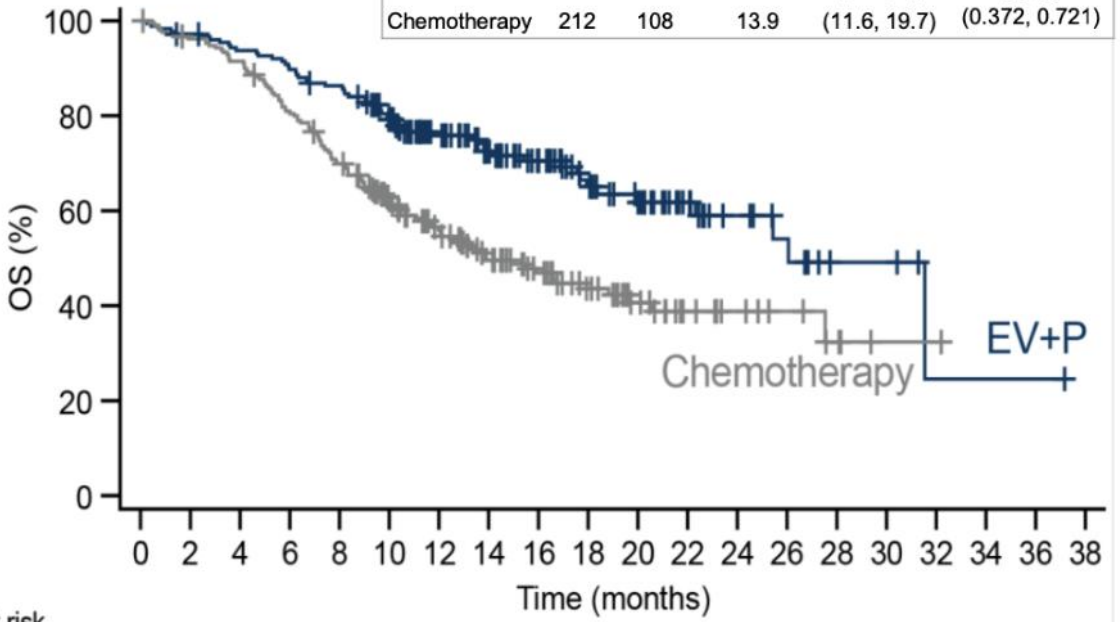
Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

Powles, 1966M0, ESMO 2024

#4: A NEED OF A BIOMARKER?

Nectin-4 H-score <275[a]

	N	Events	Median (months)	95% CI	Stratified HR (95% CI)
EV+P	177	57	26.1	(22.3, –)	0.518 (0.372, 0.721)
Chemotherapy	212	108	13.9	(11.6, 19.7)	

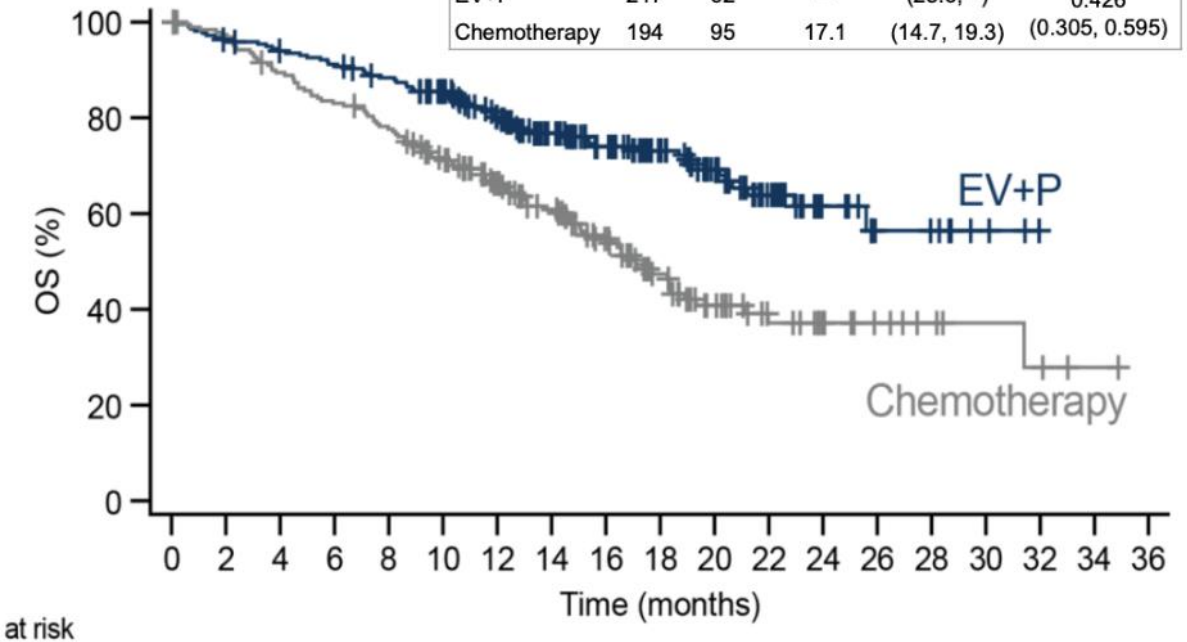


No. at risk

EV+P	177	171	164	157	150	128	102	81	64	46	36	24	15	11	4	4	1	1	1
Chemotherapy	212	202	192	169	145	114	87	66	50	36	24	15	10	7	4	1	1		

Nectin-4 H-score ≥275[a]

	N	Events	Median (months)	95% CI	Stratified HR (95% CI)
EV+P	217	62	–	(25.6, –)	0.426 (0.305, 0.595)
Chemotherapy	194	95	17.1	(14.7, 19.3)	

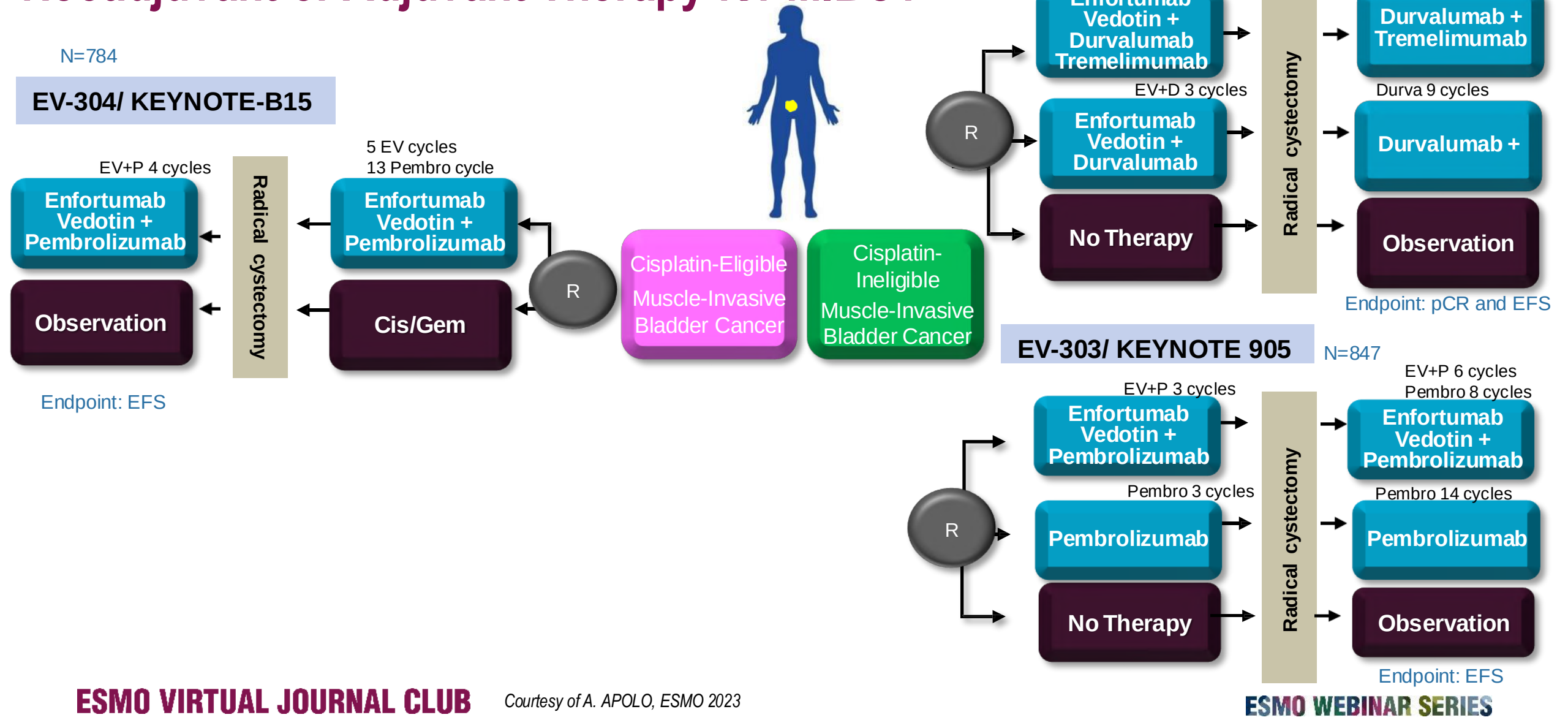


No. at risk

EV+P	217	208	201	195	186	169	144	121	103	81	59	35	17	8	7	3			
Chemotherapy	194	184	168	156	145	126	103	86	65	46	30	19	13	9	6	4	3	1	

NECTIN-4 IHC IS NOT ASSOCIATED WITH EVP RESPONSE

#5: DEFINING THE BEST SETTING
Neoadjuvant or Adjuvant Therapy for MIBC?



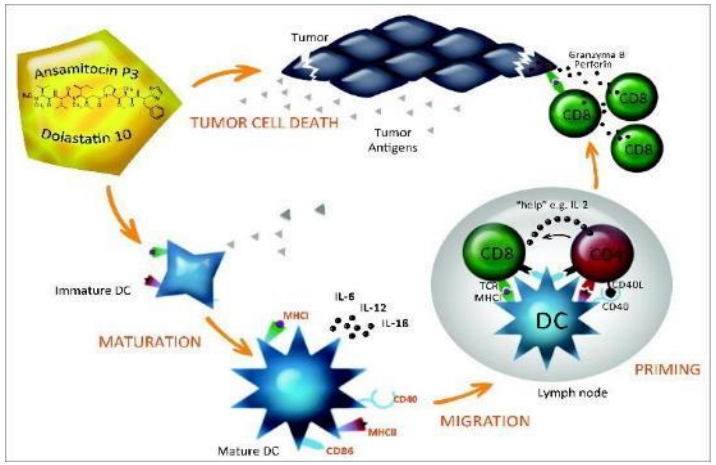
Courtesy of A. APOLO, ESMO 2023

OTHER REMAINING OPEN QUESTIONS

#6: IMPACT ON SEQUENCE (L2): What treatment becomes the best second-line therapy?

#7: COST : How can we afford this treatment? Can we better select our patients?

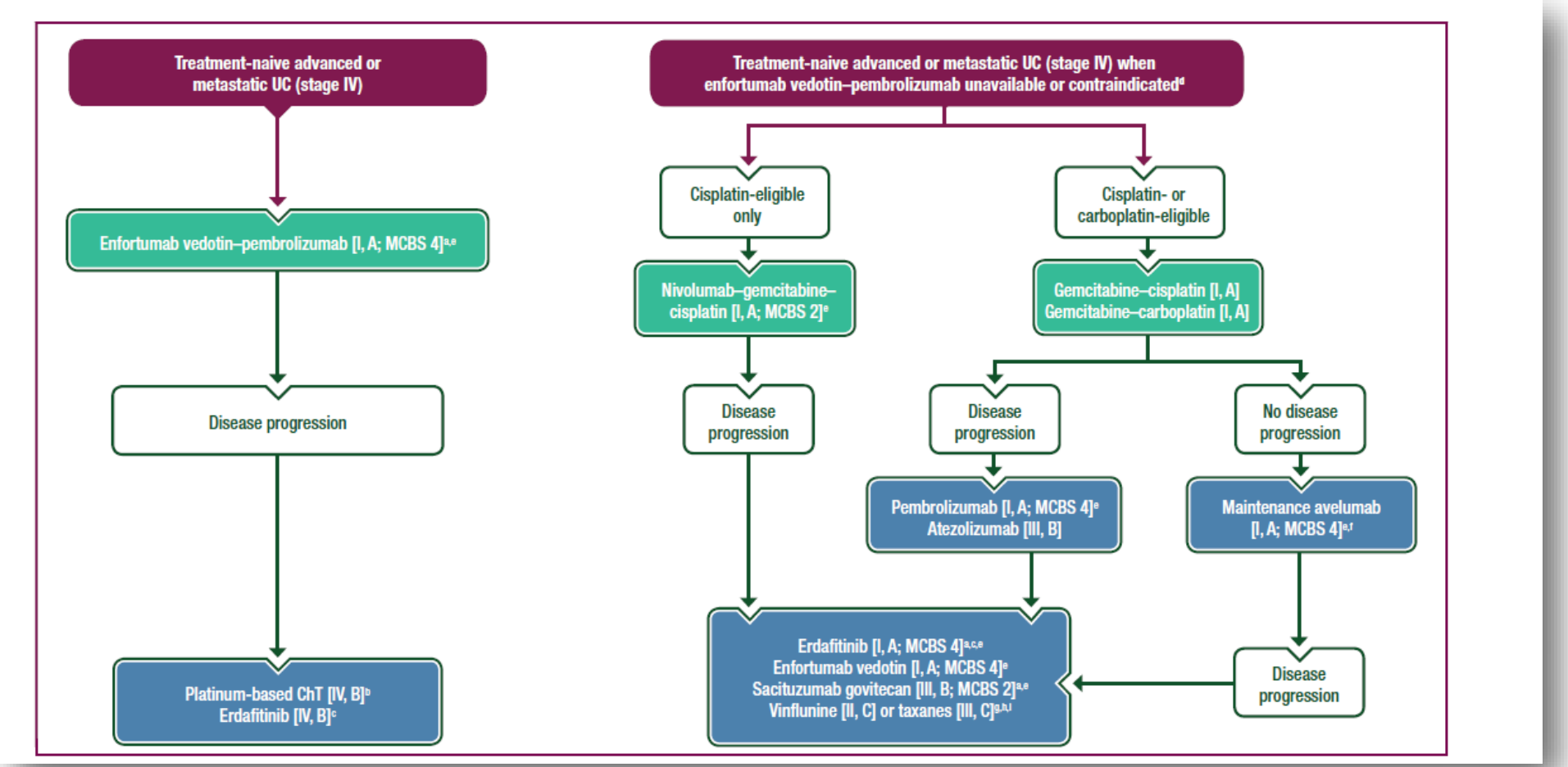
#8: UNDERSATNDING THE BIOLOGY OF SYNERGY TODEFINE THE BEST COMBO



- Human dendritic cells exposed to MMAE upregulate costimulatory molecules and display enhanced T cell-stimulatory capacity
- Preclinical studies have shown that EV:
  - Induces early hallmarks of immunogenic cell death in vitro
  - Induces immunomodulatory changes in mouse xenografts
  - Induces gene expression patterns associated with immunogenic cell death

Muller et al. OncoImmunology 2014 Rosenberg J ESMO Immuno-Oncology 2021 Boshuizen et al. Cancer Research 2021 Olson, Younan et al., SITC 2022

CONCLUSION – A NEW SOC



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