# Supplementary Appendix

Supplement to: Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med 2022;386:437-48. DOI: 10.1056/NEJMoa2108330

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

# Supplementary Appendix

## Table of Contents

**List of Countries, Sites and Investigators**

| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| Argentina | Hospital Alemán | Gonzalo Gomez Abuin | 3 |
| Argentina | Centro de Oncologia e Investigacion Buenos Aires COIBA | Mirta S Varela | 2 |
| Argentina | Instituto de Oncologia Angel H. Roffo | Maria Valeria Caceres | 2 |
| Argentina | Instituto Medico Especializado Alexander Fleming | Mauro Orlando | 5 |
| Argentina | Hospital Privado de Comunidad | Pablo Hugo Capellino | 3 |
| Argentina | Centro Oncologico Riojano Integral | Diego Lucas Kaen | 4 |
| Argentina | Instituto de Investigaciones Metabolicas | Juan Cundom | 3 |
| Argentina | IDIM Instituto de Diagnostico e Investigaciones Metabolicas | Margarita Sonia Alfie | 1 |
| Australia | Peter MacCallum Cancer Centre | Linda Mileshkin | 7 |
| Australia | Royal Brisbane and Women's Hospital | Jeffrey Goh | 3 |
| Australia | St John of God Medical Clinic | Andrew Dean | 3 |
| Australia | Royal North Shore Hospital | Sally Baron-Hay | 10 |
| Brazil | Hospital Araújo Jorge Associação de Cobate ao Câncer de Goiás | Ruffo de Freitas Junior | 2 |
| Brazil | União Brasileira de Educação e Assistência Hospital São Lucas da PUCRS | Fernanda Bronzon Damian | 4 |
| Brazil | Faculdade de Medicina da Universidade Federal de Minas Gerais | Angélica Nogueira Rodrigues | 6 |
| Brazil | Fundação Dr. Amaral Carvalho | Patrícia Medeiros Milhomem Beato | 4 |
| Brazil | Hospital de Clínicas de Porto Alegre da UFRGS | Pedro Emanuel Rubini Liedke | 1 |
| Brazil | Instituto Nacional do Câncer, Hospital do Câncer – II | Andréia Cristina de Melo | 8 |
| Brazil | Instituto do Câncer do Estado de São Paulo - ICESP | Maria Del Pilar Estevez Diz | 5 |
| Brazil | Clínica de Pesquisa e Centro de Estudos em Oncologia Ginecológica e Mamária Ltda. | Roberto Hegg | 7 |
| Canada | Centre hospitalier de l'Université de Montréal - CHUM | Diane Provencher | 4 |
| Canada | Sunnybrook Health Sciences Centre | Helen MacKay | 9 |
| Canada | London Health Sciences Centre | Stephen Welch | 3 |
| Canada | Tom Baker Cancer Centre | Prafull Ghatage | 4 |
| Canada | Jewish General Hospital | Susie Kit Sze Lau | 6 |
| Canada | CHU de Québec-Université Laval - Hôtel-Dieu de Québec | Alexandra Sebastianelli | 7 |

| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| Canada | CIUSSS de l'Est-de-l'Île-de-Montréal - Hôpital Maisonneuve-Rosemont | Suzanne Fortin | 4 |
| Canada | Cancer Care Manitoba | Shaundra Popowich | 5 |
| Canada | CIUSSS de l'Estrie-CHUS | Paul Bessette | 4 |
| Canada | Ottawa General Hospital | Johanne Weberpals | 1 |
| Canada | Princess Margaret Cancer Centre | Amit Oza | 11 |
| Colombia | Oncomedica S.A. | Edwin Alberto Hoyos | 4 |
| Colombia | Fundacion Colombiana de Cancerologia Clinica Vida | Andres Yepes/Tomas Sanchez | 6 |
| Colombia | Clinica del Country | Luis Leonardo Rojas | 3 |
| Colombia | Rodrigo Botero SAS | Jorge Salinas | 1 |
| Colombia | Clinica Colsanitas S.A. Sede Clinica Universitaria Colombia | Marc Edy Pierre | 4 |
| Colombia | Fundacion Valle del Lili | Juan Guillermo Restrepo | 3 |
| Colombia | Biomelab S A S | Oscar Madiedo | 0 |
| Colombia | Clinica de la Costa Ltda. | Ivan José Bustillo | 1 |
| France | Groupe Hospitalier Diaconesses Croix Saint-Simon | Frederic Selle | 8 |
| France | Institut Gustave Roussy | Emeline Colomba | 9 |
| France | Centre Léon Bérard | Isabelle Ray-Coquard | 10 |
| France | Institut Régional du Cancer de Montpellier – ICM | Michel Fabbro | 9 |
| France | Institut Bergonié | Anne Floquet | 8 |
| France | Centre Oscar Lambret | Annick Chevalier-Place/Cyril Abdeddaim | 6 |
| France | Centre Eugène Marquis | Thibault de la Motte Rouge | 3 |
| France | Centre de Lutte Contre le Cancer François Baclesse | Florence Joly-Lobbedez | 6 |
| France | Hôpital privé du Confluent | Alain Lortholary | 2 |
| France | Centre Hospitalier Lyon-Sud | Benoit You | 4 |
| France | Groupe Hospitalier Broca Cochin Hotel Dieu | Jerome Alexandre | 3 |
| France | Centre Armoricain de Radiothérapie, d'Imagerie Médicale et d'Oncologie (CARIO) | Anne-Claire Hardy-Bessard | 2 |
| Germany | Universitaetsklinikum Erlangen | Alexander Hein | 5 |
| Germany | Universitaetsklinikum Carl Gustav Carus | Pauline Wimberger | 3 |
| Germany | Charite Campus Virchow | Jalid Sehouli | 3 |
| Germany | UniversitaetsklInikum Tuebingen | Andreas Hartkopf | 0 |
| Germany | Universitaetsklinikum Hamburg-Eppendorf | Barbara Schmalfeldt | 1 |
| Ireland | Mater Misericordiae University Hospital | Austin Duffy/Catherine Margaret Kelly | 3 |

| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| Israel | Chaim Sheba Medical Center | Ronnie Shapira Frommer | 10 |
| Israel | Rabin Medical Center | Ram Eitan | 5 |
| Israel | Rambam Medical Center | Amnon Amit | 7 |
| Israel | Edith Wolfson Medical Center | Talia Levy | 2 |
| Israel | Soroka Medical Center | Mihai Meirovitz | 3 |
| Israel | Hadassah Medical Center. Ein Kerem | Amichay Meirovitz | 2 |
| Italy | IRCCS Ospedale San Raffaele | Giorgia Mangili | 4 |
| Italy | Azienda Ospedaliera per l'Emergenza Cannizzaro | Paolo Scollo | 5 |
| Italy | Fondazione IRCCS Istituto Nazionale dei Tumori di Milano | Domenica Lorusso/ Francesco Raspagliesi | 4 |
| Italy | Istituto Nazionale Tumori IRCCS Fondazione Pascale | Carmela Pisano | 4 |
| Italy | Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori | Ugo de Giorgi | 1 |
| Italy | Istituto Europeo di Oncologia | Nicoletta Colombo | 16 |
| Italy | Policlinico Universitario Agostino Gemelli | Giovanni Scambia/Domenica Lorusso | 26 |
| Japan | Saitama Medical University International Medical Center | Kosei Hasegawa | 4 |
| Japan | Shizuoka Cancer Center Hospital and Research Institute | Yasuyuki Hirashima | 3 |
| Japan | Niigata University Medical & Dental Hospital | Takayuki Enomoto | 5 |
| Japan | Iwate Medical University Hospital | Hiroaki Itamochi | 1 |
| Japan | Kurume University Hospital | Kimio Ushijima | 11 |
| Japan | The Jikei University Hospital | Aikou Okamoto | 3 |
| Japan | National Hospital Organization Shikoku Cancer Center | Kazuhiro Takehara | 5 |
| Japan | Hyogo Cancer Center | Koji Matsumoto | 2 |
| Japan | Aichi Cancer Center Hospital | Mika Mizuno/Jun Sakata | 10 |
| Japan | Keio University Hospital | Wataru Yamagami | 4 |
| Japan | National Hospital Organization Hokkaido Cancer Center | Shinichiro Minobe | 8 |
| Japan | National Cancer Center Hospital | Kan Yonemori | 13 |
| Japan | The Cancer Institute Hospital of JFCR | Nobuhiro Takeshima/Mayu Yunokawa | 13 |
| Japan | Tohoku University Hospital | Hideki Tokunaga | 3 |
| Japan | Ehime University Hospital | Takashi Matsumoto | 7 |

| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| Japan | Kagoshima University Hospital | Hiroaki Kobayashi | 2 |
| Japan | University of Tsukuba Hospital | Toyomi Satoh | 9 |
| Japan | The Jikei University Kashiwa Hospital | Hirokuni Takano | 0 |
| Japan | Tokai University Hospital | Masae Ikeda | 1 |
| Mexico | Centro Hemato Oncológico Privado | Ángel Gómez Villanueva | 2 |
| Mexico | Investigación Onco Farmacéutica S de RL de CV | Juan Paulo Ceja García | 7 |
| Mexico | Christus Muguerza Clínica Vidriera | Jorge Luis Martínez Rodríguez | 9 |
| Mexico | Faicic S de RL de CV | Erika Castillo | 3 |
| Mexico | Grupo Medico Camino SC | María de la Luz García | 9 |
| New Zealand | Auckland City Hospital | Michelle Wilson | 1 |
| Poland | Narodowy Instytut Onkologii - Oddzial w Gliwicach | Rafal Tarnawski | 9 |
| Poland | Narodowy Instytut Onkologii im. Marii Sklodowskiej-Curie | Iwona Glogowska/Mariusz Bidzinski | 5 |
| Poland | Szpitale Pomorskie Sp. z o.o. | Joanna Pikiel | 1 |
| Poland | Beskidzkie Centrum Onkologii im. Jana Pawla II | Malgorzata Okreglicka Lewandowska | 7 |
| Poland | Instytut Centrum Zdrowia Matki Polki | Igor Jacek Symonowicz | 0 |
| Poland | Szpital Kliniczny im Ks Anny Mazowieckiej | Anna Danska - Bidzinska | 4 |
| Poland | Pomorski Uniwersytet Medyczny w Szczecinie | Aneta Cymbaluk-Ploska | 1 |
| Russia | Mordovia Republican Oncological Dispensary | Pavel Igorevich Skopin | 3 |
| Russia | SPb SBHI City Clinical Oncological Dispensary | Alla Sergeevna Lisyanskaya | 6 |
| Russia | Republican Clinical Oncology Dispensary of Tatarstan MoH | Alfiya Irekovna Khasanova | 4 |
| Russia | Altay Regional Oncology Dispensary | Sergey Alexandrovich Lazarev | 6 |
| Russia | Tomsk National Research Medical Center of Russian Academy of Sciences | Larisa Aleksandrovna Kolomiets | 3 |
| Russia | FSBI National Medical Oncology Research Center n.a. N.N. Blokhina | Alexander Alexandrovich Fedenko | 0 |
| Russia | Moscow Research Oncology Institute named after P.A. Hertsen | Alexander Alexandrovich Fedenko | 5 |
| Russia | Republican Clinical Oncology Dispensary of Republic of Bashkortostan | Oleg Nikolaevich Lipatov | 8 |
| Russia | Leningrad Regional Oncology Center | Olga Nikolaevna Mikheeva | 2 |

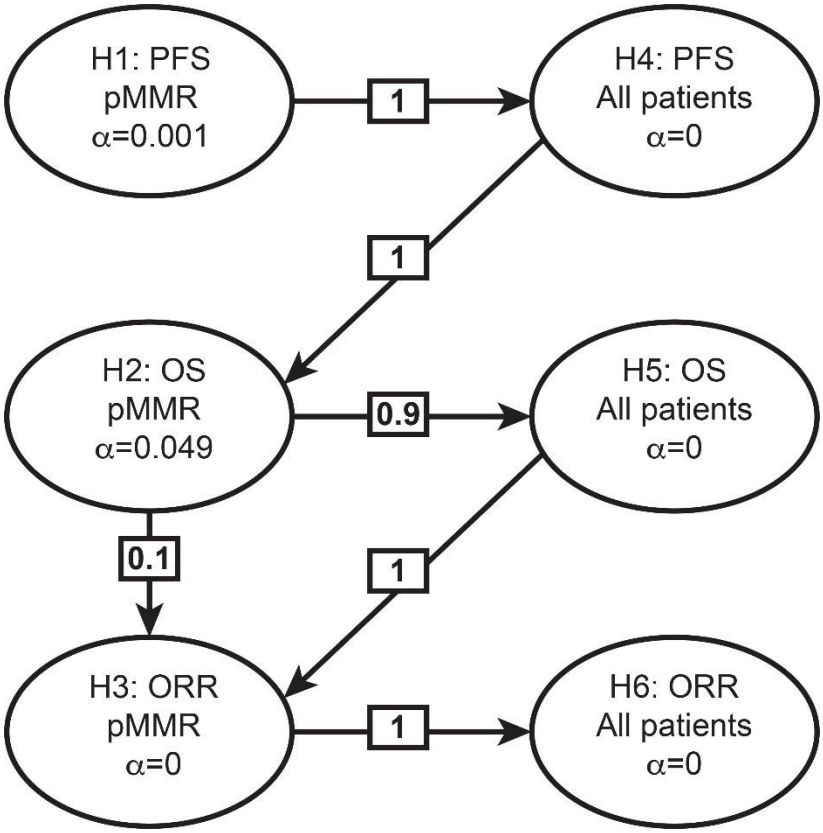
| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| Russia | FSBI-FRCC of Special Types Med. Care and Technologies FMBA of Russia | Anna Genrikhovna Kedrova | 3 |
| South Korea | National Cancer Center | Sang Yoon Park/Myong Cheol Lim | 6 |
| South Korea | Seoul National University Hospital | Jae-Weon Kim | 6 |
| South Korea | Asan Medical Center | Yong Man Kim | 11 |
| South Korea | Samsung Medical Center | Byoung-Gie Kim | 6 |
| Spain | Hospital General Universitari Vall d' Hebron | Ana Oaknin Benzaquen | 5 |
| Spain | Instituto Catalán de Oncología ICO - Hospital Duran i Reynals | Marta Gil Martín | 2 |
| Spain | Hospital Universitario Gregorio Marañón | José Ángel Arranz Arija | 5 |
| Spain | Hospital Universitario Ramón y Cajal | Eva María Guerra Alía | 11 |
| Spain | Hospital Clínico San Carlos | Antonio Casado Herráez | 8 |
| Spain | Clínica Universitaria Navarra – Madrid | Antonio González Martín | 3 |
| Spain | Hospital Universitario y Politécnico La Fe de Valencia | Ana Santaballa Bertrán | 4 |
| Taiwan | Taipei Veterans General Hospital | Peng-Hui Wang | 5 |
| Taiwan | National Taiwan University Hospital | Wen-Fang Cheng | 2 |
| Taiwan | Taichung Veterans General Hospital | Chien-Hsing Lu | 4 |
| Taiwan | Kaohsiung Chang Gung Memorial Hospital | Chen-Hsuan Wu | 1 |
| Taiwan | Mackay Memorial Hospital | Chih-Long Chang | 3 |
| Taiwan | Chang Gung Medical Foundation. Linkou | Jian-Tai Qiu/Ting-Chang Chang | 6 |
| Taiwan | Kaohsiung Veterans General Hospital | Wen-Shiung Liou | 1 |
| Turkey | Baskent Universitesi Ankara Hastanesi | Ozden Altundag | 2 |
| Turkey | Hacettepe University Medical Faculty | Zafer Arik | 8 |
| Turkey | Acibadem Bursa Hastanesi | Bulent Orhan/Hatice Doruk/Ozkan Kanat | 2 |
| Turkey | Acibadem Universitesi Atakent Hastanesi | Ali Arican | 8 |
| Turkey | Florence Nightingale Gayrettepe Hastanesi | Cetin Ordu | 7 |
| Turkey | Baskent Universitesi Adana Dr.Turgut Noyan Uygulama ve Arastirma Merkezi | Huseyin Mertsoylu | 7 |
| Turkey | Ege Universitesi Tip Fakultesi | Ulus Ali Sanli | 12 |
| UK | Imperial College Healthcare NHS Trust | Jonathan Krell | 6 |
| UK | Addenbrookes Hospital | Christine Parkinson | 6 |
| UK | Royal Marsden NHS Foundation Trust | Susana Banerjee | 3 |
| UK | Royal Marsden NHS Foundation Trust | Susana Banerjee | 4 |
| UK | University College Hospital | Mary McCormack | 4 |

| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| UK | University Hospital Southampton NHS Foundation Trust | Clare Green | 4 |
| UK | Barts Health NHS Trust - St Bartholomew s Hospital | Melanie Powell | 3 |
| UK | Royal Sussex County Hospital | Rebecca Herbertson | 1 |
| UK | Guy's & St Thomas' NHS Foundation Trust | James Wilson/Ana Montes/Rebecca Kristeleit | 8 |
| USA | Florida Hospital Cancer Institute | Robert W. Holloway | 1 |
| USA | Sanford Gynecology Oncology | Maria Bell | 1 |
| USA | Greater Baltimore Medical Center | Paul Celano | 1 |
| USA | University of California San Francisco - Helen Diller Family Comprehensive Cancer Center | Edwin Alvarez | 4 |
| USA | The West Clinic, PC dba West Cancer Center | Adam ElNaggar | 3 |
| USA | University Medical Center New Orleans | Agustin A. Garcia | 1 |
| USA | Georgia Cancer Center at Augusta University | Sharad Ghamande | 9 |
| USA | John Theurer Cancer Center at Hackensack University Medical Center | Deena M. Graham | 1 |
| USA | North Shore University Health System | Mary Tilley Jenkins Vogel | 4 |
| USA | Utah Cancer Specialists | Stephan DiSean Kendall | 2 |
| USA | UCLA Hematology and Oncology Clinic (Westwood) | Gottfried E Konecny | 3 |
| USA | Holy Name Medical Center | Sharyn Lewin | 2 |
| USA | UT Southwestern Medical Center | David Scott Miller | 3 |
| USA | Parkland Health & Hospital System | David Scott Miller | 1 |
| USA | Stephenson Cancer Center | Debra L. Richardson | 1 |
| USA | University of Rochester Medical Center | Richard G. Moore | 11 |
| USA | Massachusetts General Hospital | David R. Spriggs | 0 |
| USA | Duke University Medical Center | Angeles Secord | 5 |
| USA | University of Miami Health System - Sylvester Cancer Center | Brian Slomovitz/Jonathan Trent | 5 |
| USA | Smilow Cancer Hospital at Yale - New Haven | Alessandro Santin | 11 |
| USA | Memorial Sloan Kettering Cancer Center | Vicky Makker | 21 |
| USA | Memorial Sloan Kettering Cancer Center - Monmouth | Vicky Makker | 0 |
| USA | Memorial Sloan Kettering Cancer Center – Monmouth - West Harrison | Vicky Makker | 1 |

| Country | Site Name | Principal Investigator | Patients Randomized, n |
|---|---|---|---|
| USA | Maryland Oncology Hematology, P.A. | Cheryl A. Aylesworth | 1 |
| USA | Willamette Valley Cancer Institute and Research Center | Charles Anderson | 5 |
| USA | Texas Oncology - San Antonio Medical Center | Joseph de la Garza | 3 |
| USA | Arizona Oncology Associates, PC- HAL | Bradley Monk | 7 |
| USA | Texas Oncology - South Austin | Lynne Knowles | 7 |

**Supplementary Figure S1.** Multiplicity graph for type I error control of study hypotheses.

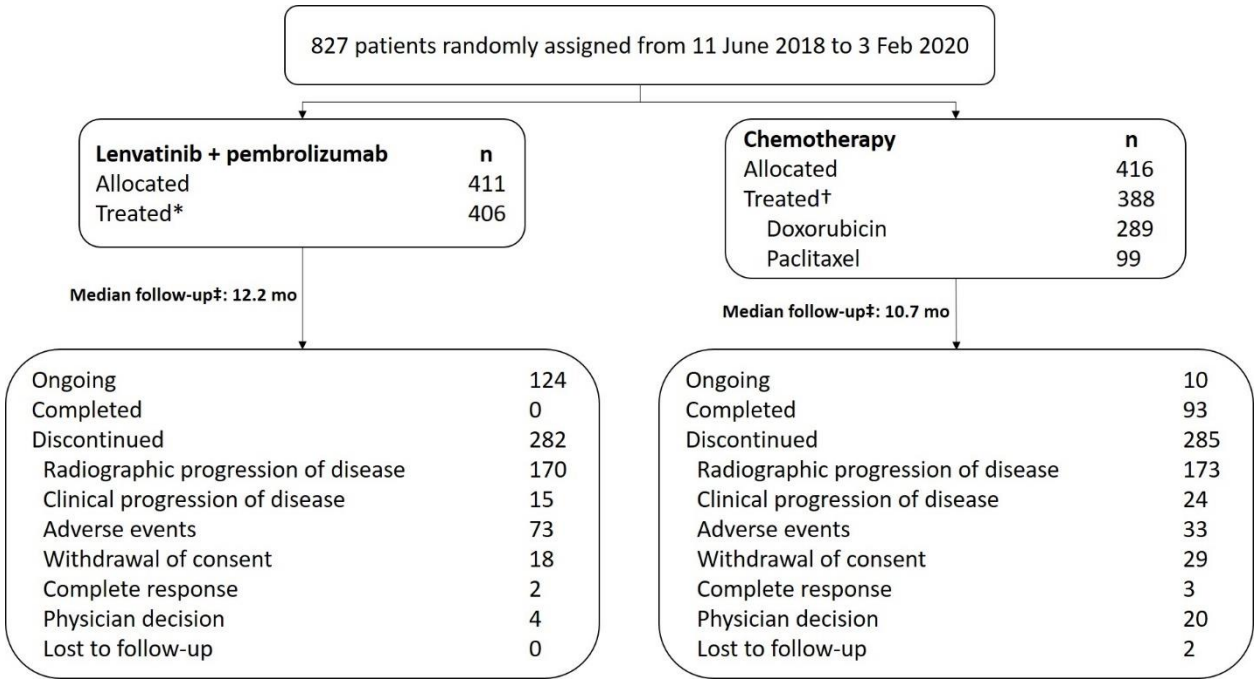
Initial two-sided alpha allocation for each hypothesis is represented in the ellipse representing the hypothesis.* The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. The multiplicity strategy followed the graphical approach of Maurer and Bretz (Maurer W, Bretz F. *Biopharm Res* 2013;5[4]:311-20).




*One-sided alpha allocation was originally planned per the protocol.

H, hypothesis; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

**Supplementary Figure S2.** Disposition of patients in Study 309/KEYNOTE-775.



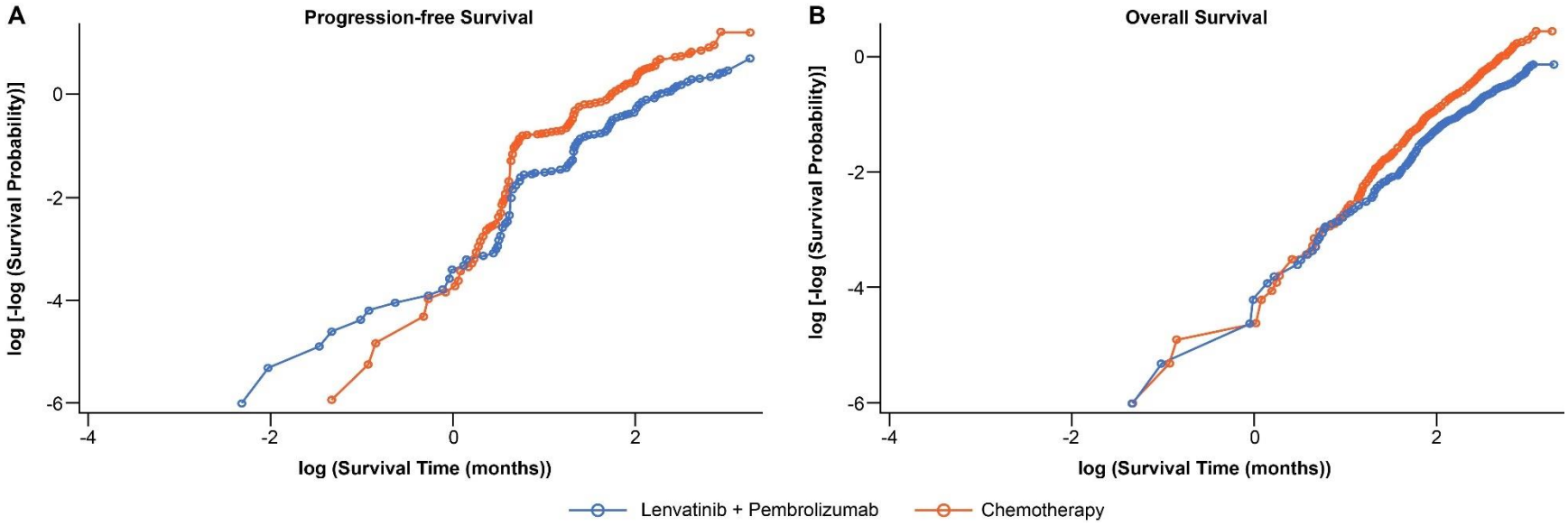

*A total of 342 pMMR patients started treatment with lenvatinib plus pembrolizumab.

†A total of 325 pMMR patients started treatment with doxorubicin (n=239) or paclitaxel (n=86).

‡Defined as the time from randomization to the date of death or database cutoff date of 26 October, 2020, if the patient was alive.

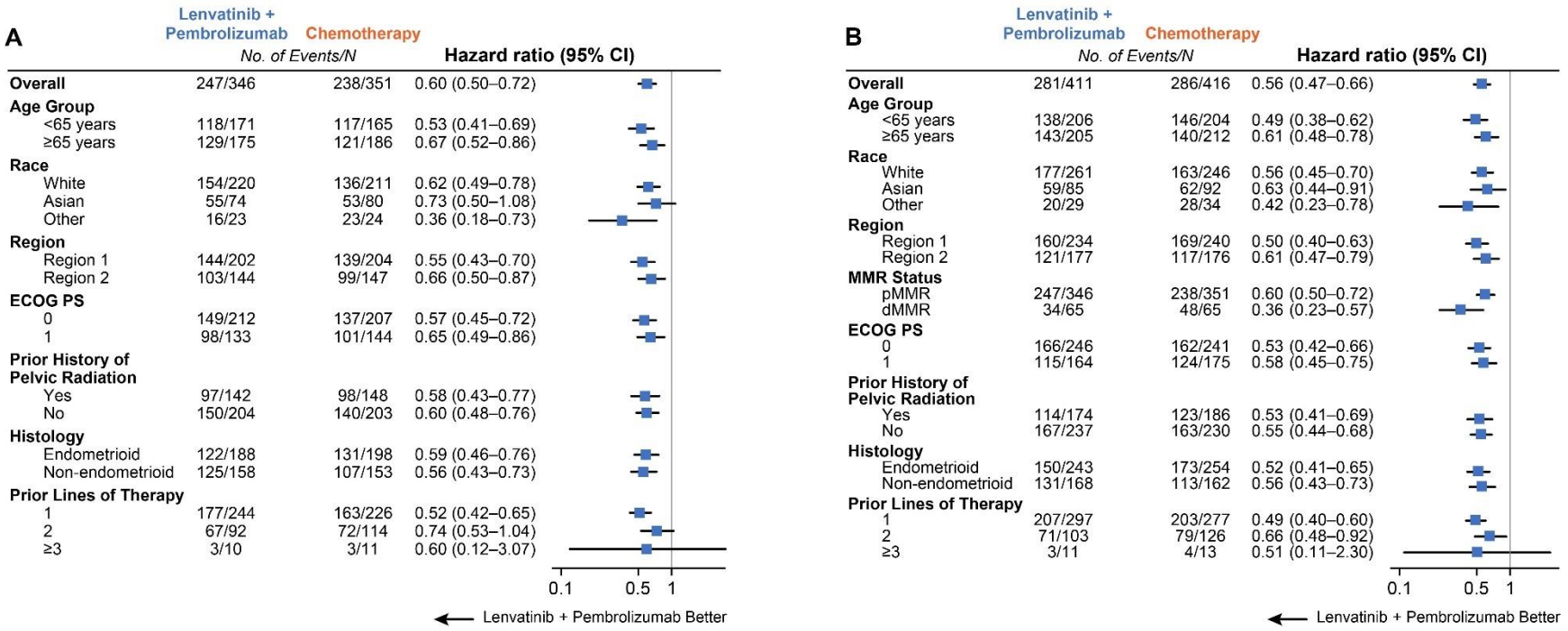
**Supplementary Figure S3.** Plots of log(-log(survival probability)) vs log(survival time) to check for proportional hazards in all patients.

Panel A shows the proportional hazard evaluation of progression-free survival; Panel B shows the proportional hazard evaluation of overall survival. An evaluation supporting proportional hazards was also performed using a statistical test based on scaled Schoenfeld residuals (*P*=0.33 for progression-free survival; *P*=0.18 for overall survival).



**Supplementary Figure S4.** Subgroup analyses of progression-free survival.

Panels A and B show subgroup analyses of progression-free survival in pMMR and all patients, respectively.

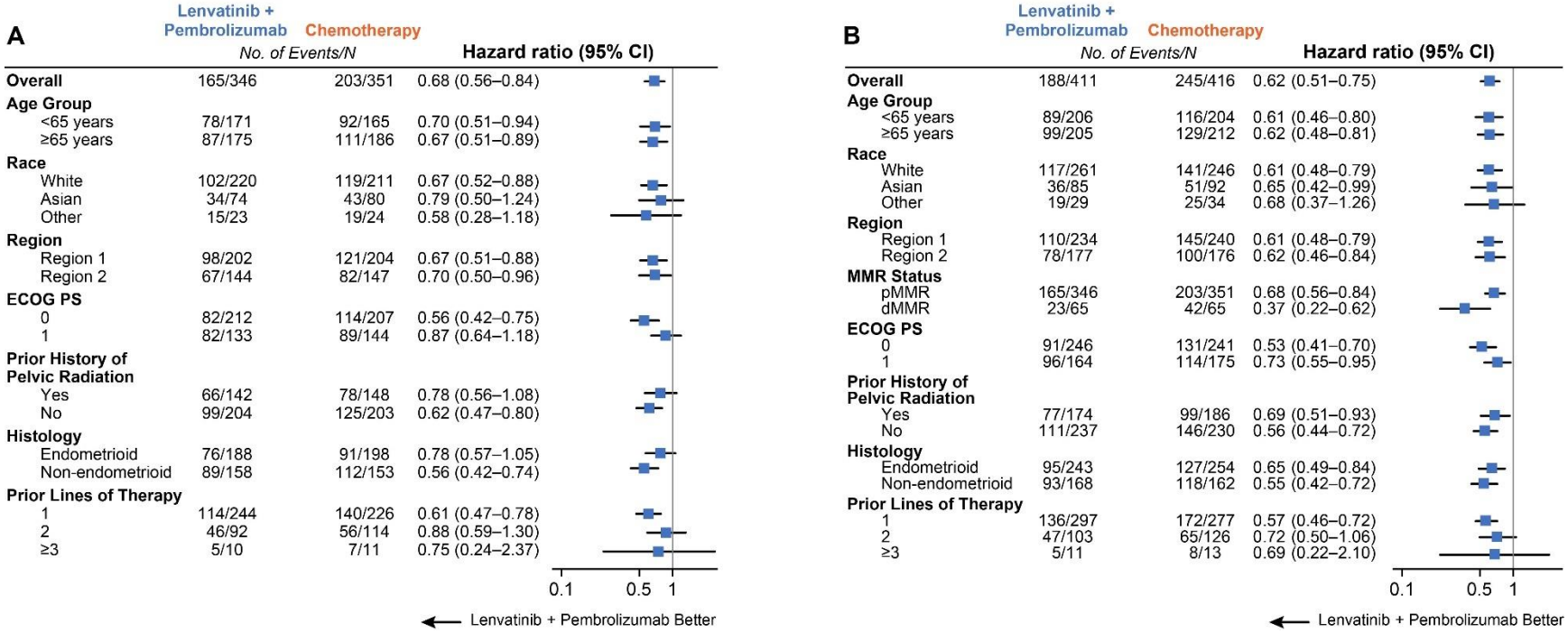



*Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel. Region 2: Rest of the world.

CI, confidence interval; dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; pMMR, mismatch repair-proficient.

**Supplementary Figure S5.** Subgroup analyses of overall survival.

Panels A and B show subgroup analyses of overall survival in pMMR and all patients, respectively.

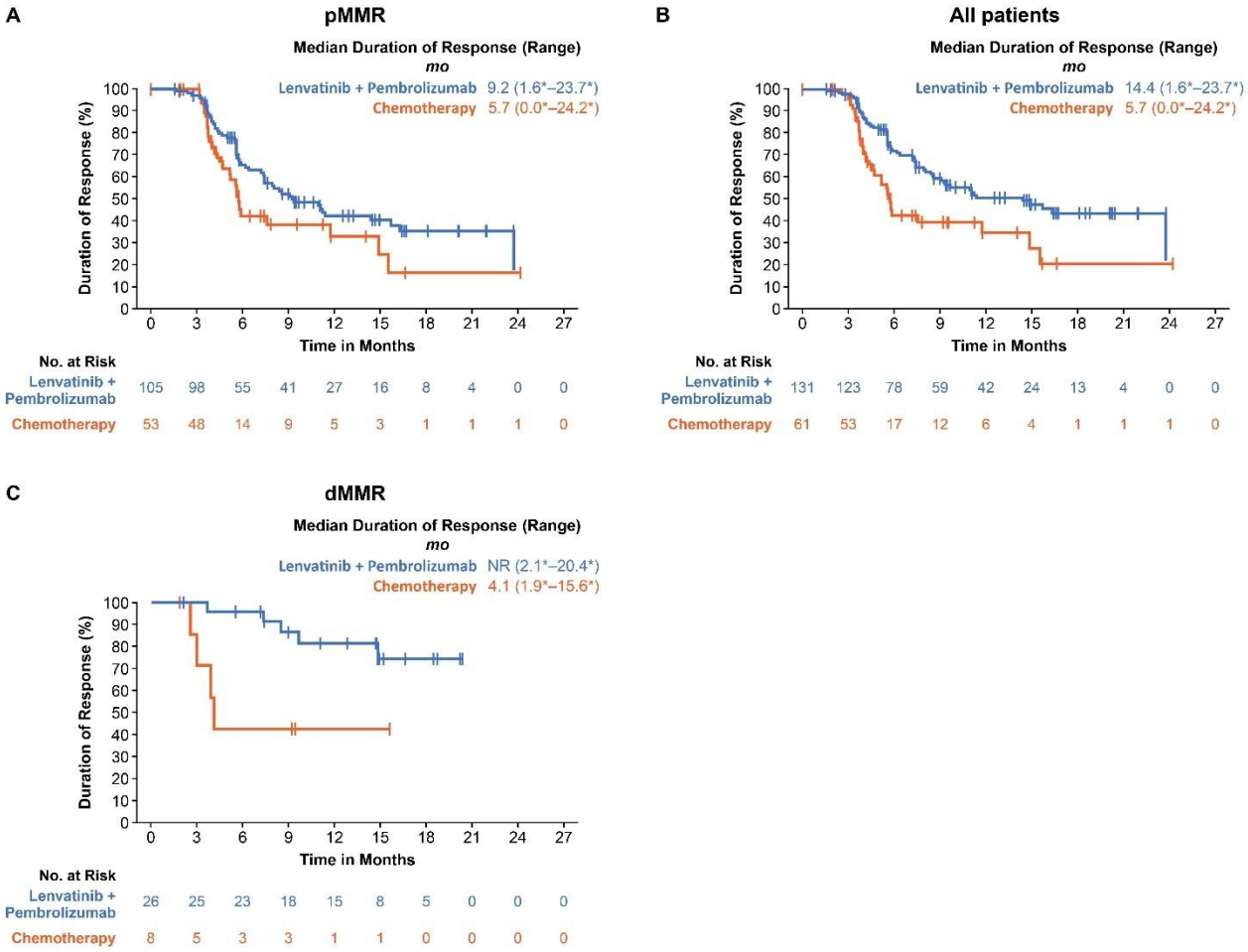



*Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel. Region 2: Rest of the world.

CI, confidence interval; dMMR, mismatch repair-deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; pMMR, mismatch repair-proficient.

**Supplementary Figure S6.** Duration of response.

Panel A shows duration of response for pMMR patients. Panel B shows duration of response for all patients. Panel C shows duration for response for dMMR patients. Duration of response was calculated using the product-limit (Kaplan–Meier) method for censored data.

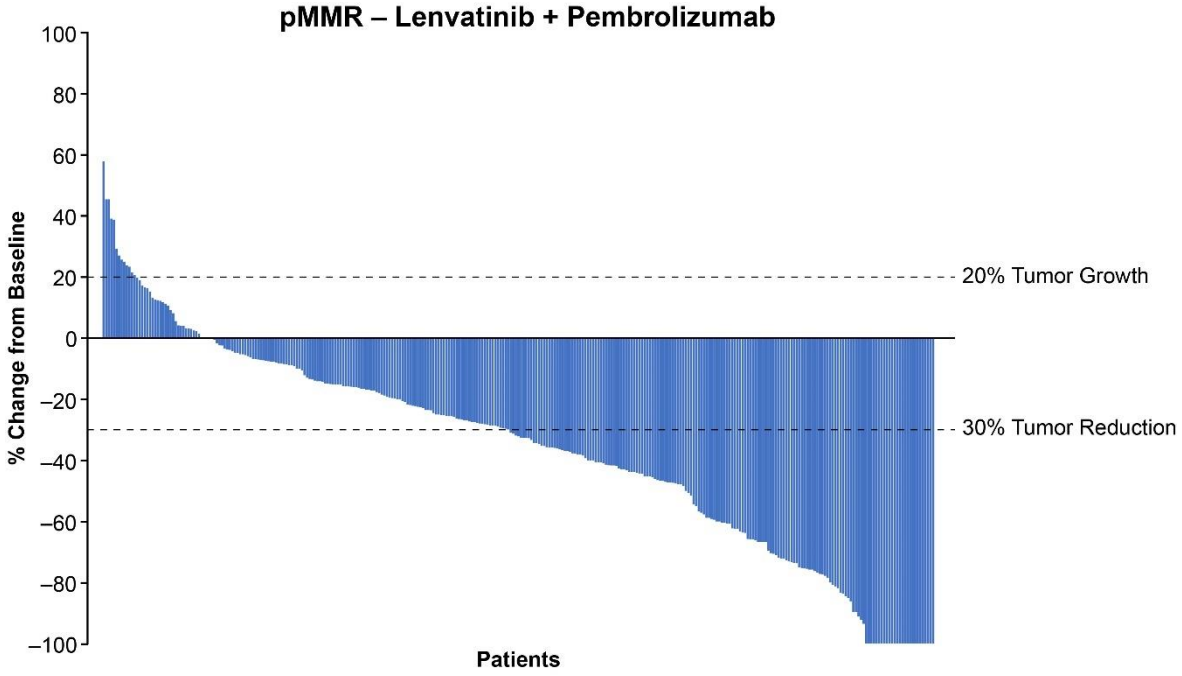



*No progressive disease by the time of last disease assessment.

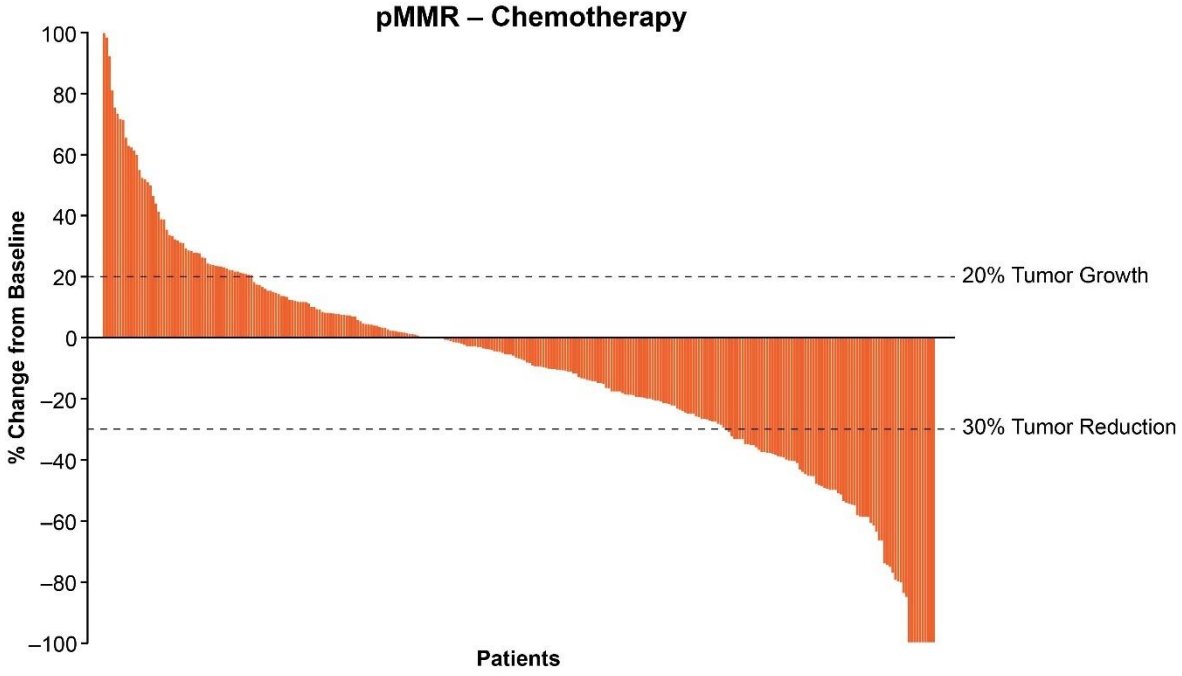
dMMR, mismatch repair-deficient; NR, not reached; pMMR, mismatch repair-proficient.

**Supplementary Figure S7.** Waterfall plots of best percentage change from baseline for target lesions based on BICR assessment per RECIST v1.1 in patients with measurable disease.
Panels A and B show results for pMMR patients in the lenvatinib plus pembrolizumab and chemotherapy groups, respectively. Panels C and D show results for all patients in the lenvatinib plus pembrolizumab and chemotherapy groups, respectively.

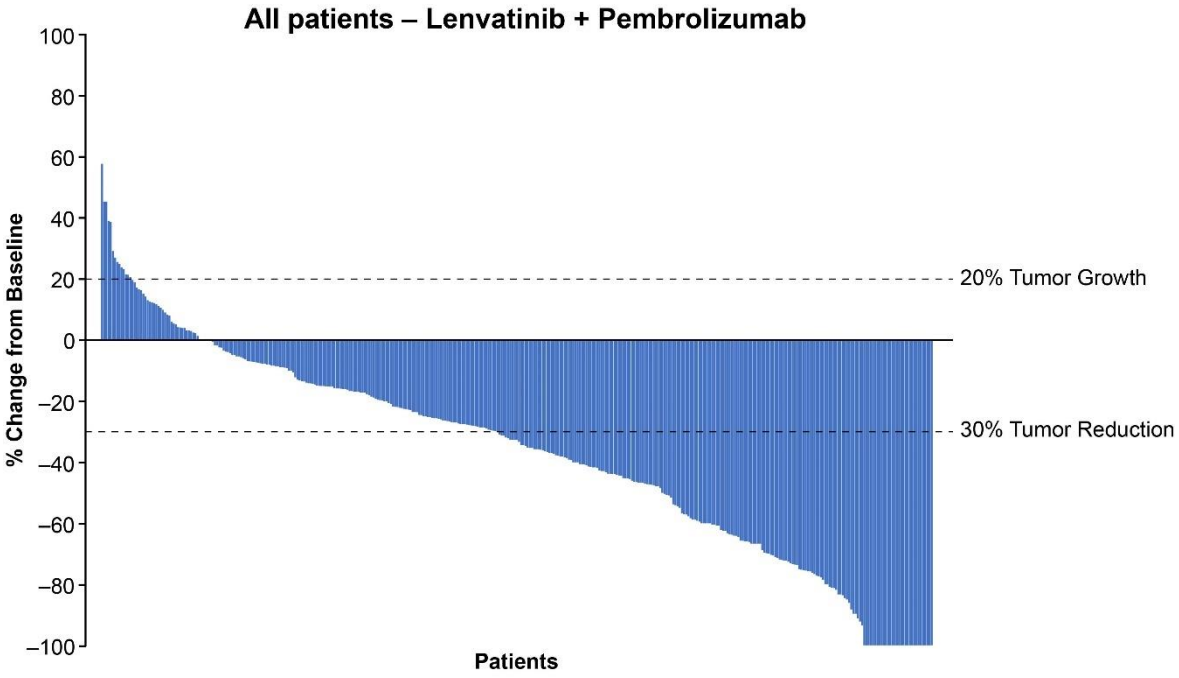
**A**



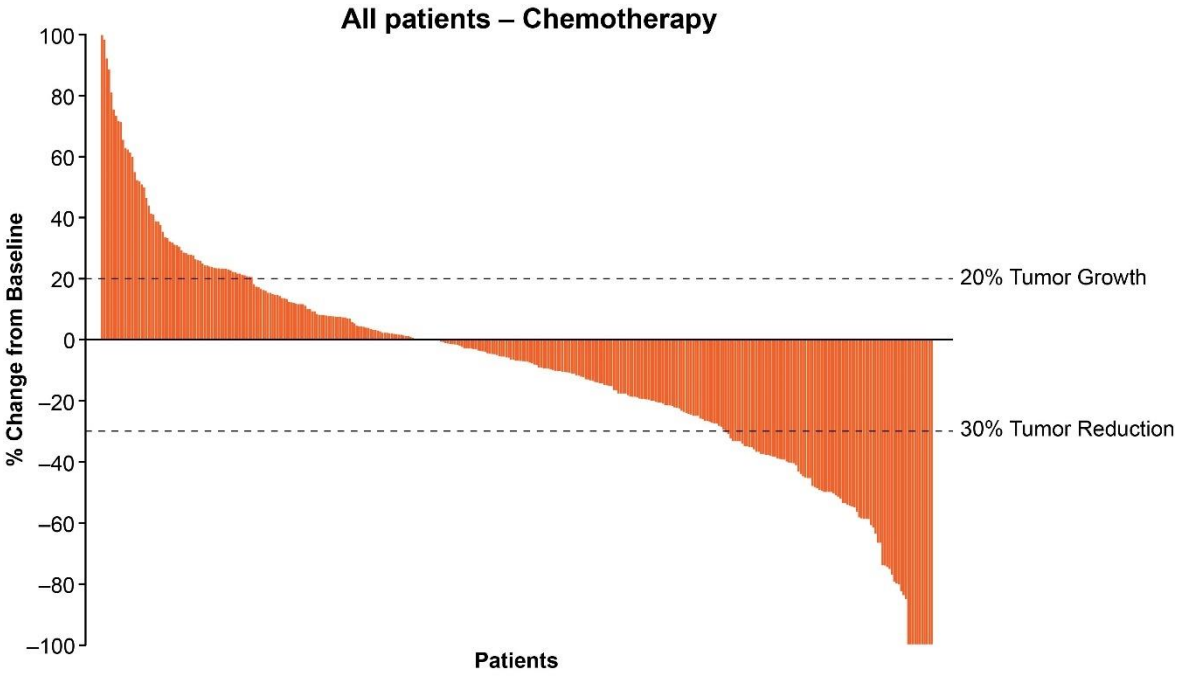

**B**



**C**

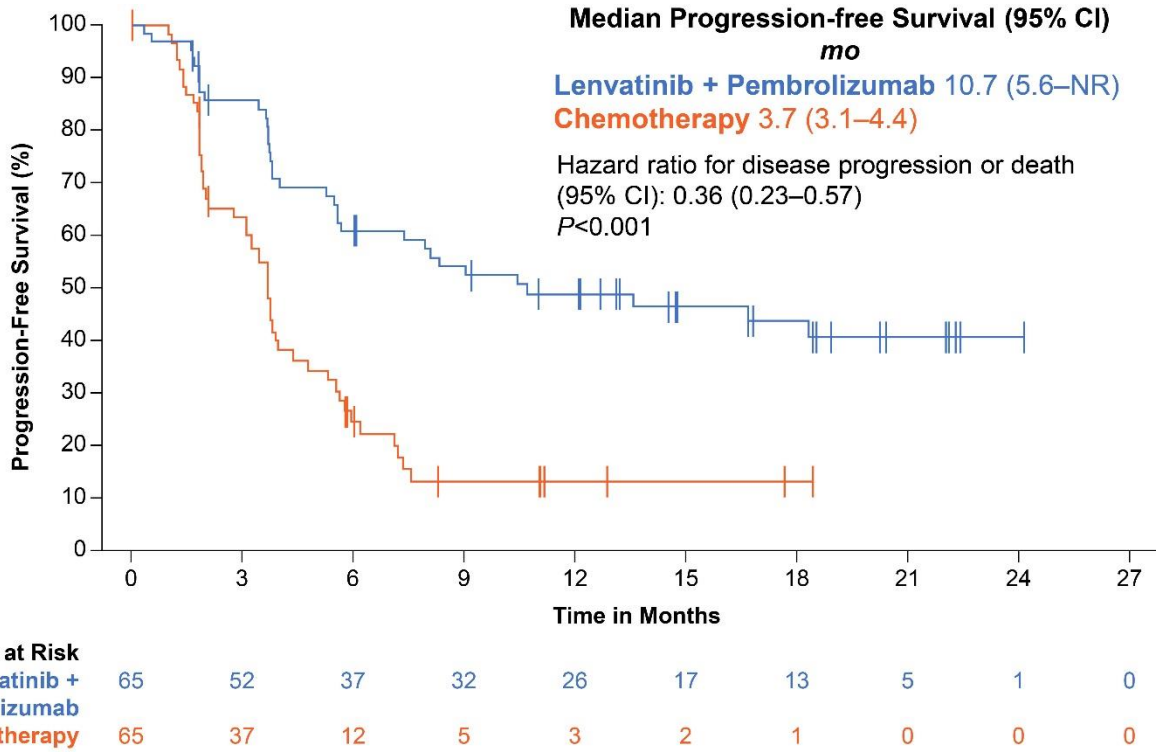



**D**



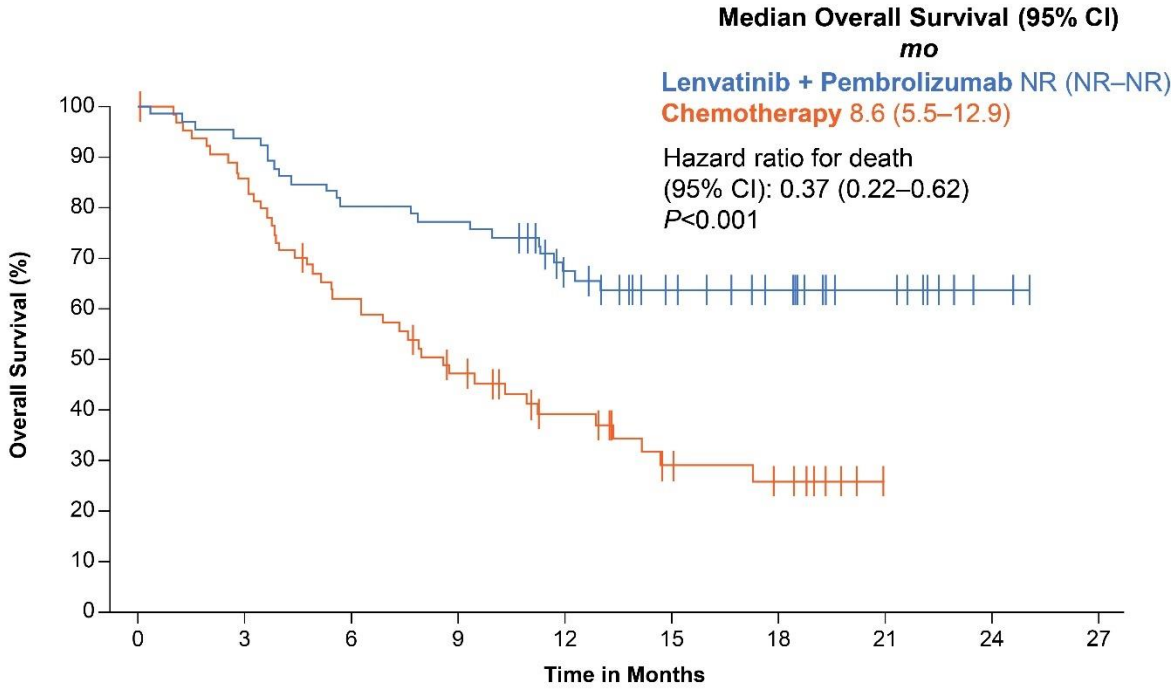

BICR, blinded independent central review; pMMR, mismatch repair-proficient; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

**Supplementary Figure S8.** Progression-free survival in DNA mismatch repair-deficient patients.



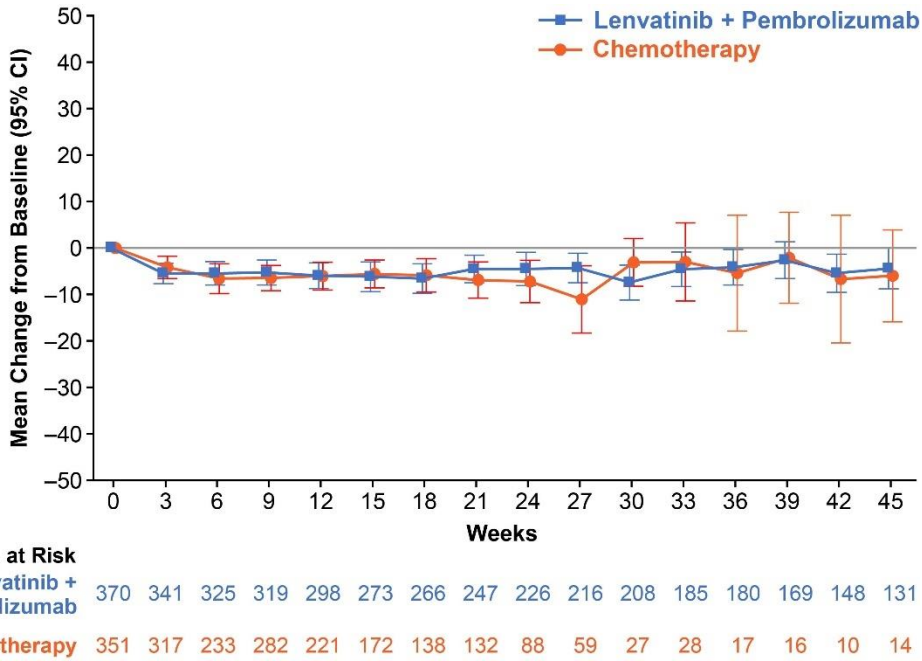

CI, confidence interval; NR, not reached.

**Supplementary Figure S9.** Overall survival in DNA mismatch repair-deficient patients.




CI, confidence interval; NR, not reached.

**Supplementary Figure S10.** Empirical mean change from baseline and 95% CI for the European Organisation for Research and Treatment of Cancer QLQ-C30 Global Health Status/QoL over time by treatment group in all patients.




| No. at Risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lenvatinib + Pembrolizumab | 370 | 341 | 325 | 319 | 298 | 273 | 266 | 247 | 226 | 216 | 208 | 185 | 180 | 169 | 148 | 131 |
| Chemotherapy | 351 | 317 | 233 | 282 | 221 | 172 | 138 | 132 | 88 | 59 | 27 | 28 | 17 | 16 | 10 | 14 |

CI, confidence interval.

**Supplementary Table S1.** Demographics and disease characteristics at baseline for pMMR patients.*

| Characteristic | Lenvatinib + Pembrolizumab (n = 346) | Chemotherapy (n = 351) |
|---|---|---|
| Median age (range) — yr | 65 (30–82) | 66 (35–86) |
| Age <65 yr — no. (%) | 171 (49.4) | 165 (47.0) |
| Race — no. (%)† | | |
| White | 220 (63.6) | 211 (60.1) |
| Black or African American | 15 (4.3) | 9 (2.6) |
| Asian | 74 (21.4) | 80 (22.8) |
| Geographic region — no. (%)‡ | | |
| Region 1 | 202 (58.4) | 204 (58.1) |
| Region 2 | 144 (41.6) | 147 (41.9) |
| ECOG performance status — no. (%)§ | | |
| 0 | 212 (61.3) | 207 (59.0) |
| 1 | 133 (38.4) | 144 (41.0) |
| Prior history of pelvic radiation — no. (%) | | |
| Yes | 142 (41.0) | 148 (42.2) |
| No | 204 (59.0) | 203 (57.8) |
| Histology of initial diagnosis — no. (%) | | |
| Endometrioid carcinoma<br>High-grade<br>Low-grade<br>Not specified‖ | <br>73 (21.1)<br>50 (14.5)<br>65 (18.8) | <br>77 (21.9)<br>41 (11.7)<br>80 (22.8) |
| Serous carcinoma | 99 (28.6) | 112 (31.9) |
| Clear cell carcinoma | 29 (8.4) | 17 (4.8) |
| Mixed | 18 (5.2) | 13 (3.7) |
| Mucinous | 1 (0.3) | 1 (0.3) |
| Neuroendocrine | 2 (0.6) | 0 (0.0) |
| Undifferentiated histology | 4 (1.2) | 2 (0.6) |
| Other | 5 (1.4) | 6 (1.7) |
| Unclassified | 0 (0.0) | 2 (0.6) |

*Percentage totals may not be 100 due to rounding.

†8.4% of patients in the lenvatinib plus pembrolizumab group and 10.3% of patients in the chemotherapy group were missing information on race. Other races (2.3% in the lenvatinib plus

pembrolizumab group and 4.3% in the chemotherapy group) include American Indian or Alaska native, native Hawaiian or other Pacific Islander and multi-racial patients.

‡Region 1: Europe, USA, Canada, Australia, New Zealand, Israel. Region 2: Rest of the world.

§1 patient in the lenvatinib plus pembrolizumab group had an ECOG score deviation of 3.

‖The “not specified” category includes endometrioid (grade not specified) and endometrioid with squamous differentiation.

ECOG, Eastern Cooperative Oncology Group; pMMR, mismatch repair-proficient.

**Supplementary Table S2.** Histology at initial diagnosis for those categories totaling less than 5% of all patients.

| **Characteristic** | **Lenvatinib + Pembrolizumab (n = 411)** | **Chemotherapy (n = 416)** |
|---|---|---|
| Histology of initial diagnosis — no. (%) | | |
| Mucinous | 1 (0.2) | 1 (0.2) |
| Neuroendocrine | 2 (0.5) | 0 |
| Undifferentiated histology | 4 (1.0) | 3 (0.7) |
| Other | 6 (1.5) | 7 (1.7) |
| Unclassified | 0 | 3 (0.7) |

**Supplementary Table S3.** Statement of study population representation.

| Category | Example |
|---|---|
| Disease, problem, or condition under investigation | Advanced or recurrent endometrial cancer that has failed prior platinum based therapy in any setting. |
| Special considerations related to: | |
| Sex and gender | Endometrial cancer, as a malignancy of the uterus, affects women. |
| Age | The incidence of endometrial cancer increases steeply with age.[1] While the average age at diagnosis is 63 years, the incidence of cases in women under the age of 50 years has been rising.[2] |
| Race or ethnic group | While an increased frequency of endometrial cancer and associated mortality has been noted in women from multiple backgrounds, this rise has been most dramatic in black women over the previous decade.[2] |
| Geography | Endometrial cancer incidence is increasing globally, most notably in Asia, Europe, and North America.[3] |
| Other considerations | Endometrial cancer includes several histologies that at a high level can be subset into endometroid and non-endometroid. In general, non-endometroid endometrial carcinomas are considered to be the most aggressive and have been shown to occur at higher rates in black women.[2] Molecular classification, including Mismatch Repair Status (MMR), is an important biomarker in endometrial cancer. Endometrial cancer in this setting is expected to be deficient in mismatch repair proteins (dMMR) in approximately 25% of patients and predominantly comprised of endometroid histologies,[4,5] with the remaining cases being proficient in mismatch repair proteins (pMMR). |
| Overall representativeness of this trial | The participants in this study demonstrated the expected sex, gender, and age for this type of disease and treatment setting. The study was global with enrollment including North America, Latin America, Europe, Russia, and Asia Pacific. Patients were not enrolled from Africa. The overall proportion of Black patients randomized globally was 3.7%, and the proportion of study patients randomized in United States was 14% which is consistent with the proportion in the United States (per most recent census [2020], 13.4% of individuals identified as Black or African American).[6] The percentage of endometroid histologies was 60% and non-endometroid 40%, while 16% of participants had tumors that were dMMR and 84% were pMMR which is consistent with what is expected in this setting for histology and MMR status respectively. |

[1]Felix AS and Brinton LA. Cancer Epidemiol Biomarkers Prev 2018;27(9):985-994; [2]Lu KH and Broaddus RR. N Engl J Med 2020; 383:2053-64; [3]Lortet-Tieulent J, et al. J Natl Cancer Inst. 2018;110:354-361; [4]Lorenzi M, et al J Oncol 2020;2020:1807929; [5]Kommoss S, et al. Ann Oncol. 2018;29(5):1180-1188; [6]United States Census QuickFacts. (https://www.census.gov/quickfacts/fact/table/US/RHI225219).

**Supplementary Table S4.** Prespecified and multiple imputation analysis of objective response.

| Characteristic | Lenvatinib + Pembrolizumab | Chemotherapy | Lenvatinib + Pembrolizumab | Chemotherapy | Lenvatinib + Pembrolizumab | Chemotherapy |
|---|---|---|---|---|---|---|
| | *pMMR patients* | | *All patients* | | *dMMR patients* | |
| No. of patients | 346 | 351 | 411 | 416 | 65 | 65 |
| **Prespecified Analysis** | | | | | | |
| Objective response — % | 30.3 | 15.1 | 31.9 | 14.7 | 40 | 12 |
| Difference vs chemotherapy — % (95% CI) | 15.2 (9.1–21.4) | -- | 17.2 (11.5–22.9) | -- | 28 (13–42) | -- |
| *P*-value | <0.001 | -- | <0.001 | -- | <0.001 | -- |
| **Multiple Imputation Analysis** | | | | | | |
| Objective response — % | 31.8 | 17.2 | 33.5 | 17.0 | 43 | 15 |
| Difference vs chemotherapy — % (95% CI) | 14.6 (8.2–20.9) | -- | 16.6 (10.7–22.4) | -- | 27 (12–42) | -- |
| Nominal *P*-value | <0.001 | -- | <0.001 | -- | 0.001 | -- |

CI, confidence interval; dMMR, mismatch repair-deficient; pMMR, mismatch repair-proficient.

**Supplementary Table S5.** Summary of drug exposure in all patients in the safety analysis population.

| | **Lenvatinib + Pembrolizumab (n = 406)** | **Chemotherapy (n = 388)** |
|---|---|---|
| Duration on Therapy — days* | | |
| Mean | 271.9 | 108.9 |
| Median | 231.0 | 104.5 |
| Standard deviation | 194.6 | 90.4 |
| Range | 1.0 to 817.0 | 1.0 to 785.0 |
| Duration on Both Lenvatinib and Pembrolizumab — days† | | |
| Mean | 231.5 | NA |
| Median | 191.0 | NA |
| Standard deviation | 185.4 | NA |
| Range | 1.0 to 784.0 | NA |
| Duration on Lenvatinib — days‡ | | |
| Mean | 251.8 | NA |
| Median | 211.5 | NA |
| Standard deviation | 191.3 | NA |
| Range | 1.0 to 817.0 | NA |
| Duration on Pembrolizumab — days§ | | |
| Mean | 251.6 | NA |
| Median | 211.0 | NA |
| Standard deviation | 190.9 | NA |
| Range | 1.0 to 784.0 | NA |

*Duration on therapy is calculated as the days between first dose date and last dose date in each treatment arm.

+For lenvatinib plus pembrolizumab, defined as from the first date when both drugs were taken until the date when one of the two drugs was first discontinued.

‡For lenvatinib plus pembrolizumab, defined as from the first date when lenvatinib was taken until the date when lenvatinib was discontinued.

§For lenvatinib plus pembrolizumab, defined as from the first date when pembrolizumab was taken until the date when pembrolizumab was discontinued.

**Supplementary Table S6.** Summary of exposure by duration in the safety analysis population.

| Duration of Exposure, months | Lenvatinib + Pembrolizumab (n = 406) | | Chemotherapy (n = 388) | |
|---|---|---|---|---|
| | n | Person-time (months) | n | Person-time (months) |
| > 0 | 406 | 3627.1 | 388 | 1388.6 |
| ≥ 1 | 376 | 3611.2 | 323 | 1358.3 |
| ≥ 3 | 325 | 3505.7 | 213 | 1163.3 |
| ≥ 6 | 243 | 3143.4 | 42 | 403.5 |
| ≥ 12 | 110 | 1939.7 | 10 | 151.7 |
| ≥ 18 | 48 | 1017.5 | 1 | 25.8 |
| ≥ 24 | 5 | 128.2 | 1 | 25.8 |

Each patient is counted once on each applicable duration category row.

Duration of exposure is the time from the first dose date to the last dose date.

**Supplementary Table S7.** Summary of dose reduction of lenvatinib in all patients.*

| | Lenvatinib + Pembrolizumab (n = 406) |
|---|---|
| Patients with a dose reduction — no. (%) | 288 (70.9) |
| Number of dose reductions — no. (%) | |
| 0 | 118 (29.1) |
| 1 | 103 (25.4) |
| 2 | 105 (25.9) |
| 3 | 54 (13.3) |
| 4 | 26 (6.4) |
| Time to first dose reduction — months | |
| n | 288 |
| Mean (standard deviation) | 2.7 (2.69) |
| Median | 1.9 |
| Range | 0.1 to 22.8 |

*The starting dose of lenvatinib was 20 mg/day for patients enrolled in the lenvatinib plus pembrolizumab group. Dose reductions of lenvatinib occurred in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day was to be discussed with sponsors. Once the lenvatinib dose was reduced, it was not to be increased at a later date, unless the dose was mistakenly decreased; in this situation, sponsor approval was required to increase the dose. Please check the protocol included with the **Supplementary Materials** for further details.

**Supplementary Table S8.** Most frequent adverse events (≥5%) leading to dose reductions in either treatment group.

| **Event** | **Lenvatinib + Pembrolizumab (n = 406)**<br>**n (%)** | **Chemotherapy (n = 388)**<br>**n (%)** |
|---|---|---|
| Hypertension | 72 (17.7) | 0 |
| Diarrhea | 45 (11.1) | 1 (0.3) |
| PPES | 33 (8.1) | 0 |
| Proteinuria | 32 (7.9) | 0 |
| Decreased appetite | 25 (6.2) | 1 (0.3) |
| Fatigue | 24 (5.9) | 4 (1.0) |
| Weight decreased | 22 (5.4) | 0 |

For lenvatinib plus pembrolizumab, dose reductions were for lenvatinib only.

PPES, palmar-plantar erythrodysesthesia syndrome.

**Supplementary Table S9.** Most frequent adverse events (≥5%) leading to treatment interruptions in either treatment group.

| Event | Lenvatinib + Pembrolizumab (n = 406) n (%) | | | | Chemotherapy (n = 388) n (%) |
|---|---|---|---|---|---|
| | Lenvatinib or pembrolizumab interruption | Lenvatinib and pembrolizumab interruption* | Lenvatinib interruption† | Pembrolizumab interruption‡ | |
| Diarrhea | 54 (13.3) | 20 (4.9) | 43 (10.6) | 33 (8.1) | 0 |
| Hypertension | 50 (12.3) | 6 (1.5) | 45 (11.1) | 14 (3.4) | 0 |
| Proteinuria | 30 (7.4) | 2 (0.5) | 24 (5.9) | 8 (2.0) | 0 |
| Decreased appetite | 27 (6.7) | 2 (0.5) | 20 (4.9) | 9 (2.2) | 0 |
| Vomiting | 24 (5.9) | 5 (1.2) | 22 (5.4) | 7 (1.7) | 3 (0.8) |
| Fatigue | 21 (5.2) | 4 (1.0) | 17 (4.2) | 9 (2.2) | 2 (0.5) |

*Interruption of lenvatinib and pembrolizumab due to the same adverse event.

†Interruption of lenvatinib, regardless of action taken for pembrolizumab.

‡Interruption of pembrolizumab, regardless of action taken for lenvatinib.

**Supplementary Table S10.** Most frequent adverse events (≥1%) leading to treatment discontinuations in either treatment group.

| Event | Lenvatinib + Pembrolizumab (n = 406) n (%) | | | | Chemotherapy (n = 388) n (%) |
|---|---|---|---|---|---|
| | Lenvatinib or pembrolizumab discontinuation | Lenvatinib and pembrolizumab discontinuation* | Lenvatinib discontinuation† | Pembrolizumab discontinuation‡ | |
| Hypertension | 8 (2.0) | 0 | 8 (2.0) | 0 | 0 |
| Asthenia | 7 (1.7) | 1 (0.2) | 7 (1.7) | 1 (0.2) | 1 (0.3) |
| Decreased appetite | 7 (1.7) | 3 (0.7) | 7 (1.7) | 3 (0.7) | 0 |
| Diarrhea | 7 (1.7) | 2 (0.5) | 5 (1.2) | 4 (1.0) | 1 (0.3) |
| Weight decreased | 6 (1.5) | 1 (0.2) | 6 (1.5) | 1 (0.2) | 0 |
| Proteinuria | 5 (1.2) | 0 | 5 (1.2) | 0 | 0 |
| Alanine aminotransferase increased | 4 (1.0) | 1 (0.2) | 1 (0.2) | 4 (1.0) | 0 |
| Intestinal obstruction | 4 (1.0) | 4 (1.0) | 4 (1.0) | 4 (1.0) | 0 |
| Vomiting | 4 (1.0) | 0 | 4 (1.0) | 0 | 0 |

*Discontinuation of lenvatinib and pembrolizumab due to the same adverse event.

†Discontinuation of lenvatinib, regardless of action taken for pembrolizumab.

‡Discontinuation of pembrolizumab, regardless of action taken for lenvatinib.

**Supplementary Table S11.** Summary of adverse events, dose modifications and discontinuations for all patients.

| | Lenvatinib + Pembrolizumab | Chemotherapy |
|---|---|---|
| | n (%) | |
| Patients in population | 406 | 388 |
| with one or more adverse events | 405 (99.8) | 386 (99.5) |
| with no adverse event | 1 (0.2) | 2 (0.5) |
| with drug-related* adverse events | 395 (97.3) | 364 (93.8) |
| with toxicity grade 3–5 adverse events | 361 (88.9) | 282 (72.7) |
| with toxicity grade 3–5 drug-related adverse events | 316 (77.8) | 229 (59.0) |
| with serious adverse events | 214 (52.7) | 118 (30.4) |
| with serious drug-related adverse events | 135 (33.3) | 55 (14.2) |
| with dose modification† due to an adverse event | 380 (93.6) | 161 (41.5) |
| with dose interruption‡ due to an adverse event | 281 (69.2) | 105 (27.1) |
| interruption of pembrolizumab | 203 (50.0) | 0 |
| interruption of lenvatinib | 238 (58.6) | 0 |
| interruption of both pembrolizumab and lenvatinib | 125 (30.8) | 0 |
| with dose reduction§ due to an adverse event | 270 (66.5) | 50 (12.9) |
| who died | 23 (5.7) | 19 (4.9) |
| who died due to a drug-related adverse event | 6 (1.5) | 8 (2.1) |
| discontinued‖ due to an adverse event | 134 (33.0) | 31 (8.0) |
| discontinued pembrolizumab | 76 (18.7) | 0 |
| discontinued lenvatinib | 125 (30.8) | 0 |
| discontinued both pembrolizumab and lenvatinib | 57 (14.0) | 0 |
| discontinued due to a drug-related adverse event | 108 (26.6) | 22 (5.7) |
| discontinued pembrolizumab | 40 (9.9) | 0 |
| discontinued lenvatinib | 92 (22.7) | 0 |
| discontinued both pembrolizumab and lenvatinib | 20 (4.9) | 0 |
| discontinued due to a serious adverse event | 88 (21.7) | 14 (3.6) |
| discontinued pembrolizumab | 60 (14.8) | 0 |
| discontinued lenvatinib | 81 (20.0) | 0 |
| discontinued both pembrolizumab and lenvatinib | 50 (12.3) | 0 |
| discontinued due to a serious drug-related adverse event | 61 (15.0) | 8 (2.1) |

| | | |
|---|---|---|
| discontinued pembrolizumab | 28 (6.9) | 0 |
| discontinued lenvatinib | 50 (12.3) | 0 |
| discontinued both pembrolizumab and lenvatinib | 17 (4.2) | 0 |

*Determined by the investigator to be related to the drug.

†Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

‡For lenvatinib + pembrolizumab, the dose interruption of either pembrolizumab or lenvatinib.

§For lenvatinib + pembrolizumab, the dose reduction for only lenvatinib.

‖For lenvatinib + pembrolizumab, the discontinuation of either pembrolizumab or lenvatinib.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.

MedDRA preferred terms "neoplasm progression," "malignant neoplasm progression" and "disease progression" not related to the drug are excluded.

Grades are based on NCI CTCAE version 4.03.

CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute.

**Supplementary Table S12.** Treatment-related adverse events that occurred in 10% or more patients in any group in all patients.

| Preferred Term | Lenvatinib + Pembrolizumab (n = 406) n (%) | | Chemotherapy (n = 388) n (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3* | Any Grade | Grade ≥3* |
| Patients with any treatment-emergent adverse events | 395 (97.3) | 316 (77.8) | 364 (93.8) | 229 (59.0) |
| Hypertension† | 248 (61.1) | 146 (35.9) | 4 (1.0) | 1 (0.3) |
| Hypothyroidism†‡ | 221 (54.4) | 4 (1.0) | 0 | 0 |
| Diarrhea | 171 (42.1) | 25 (6.2) | 42 (10.8) | 3 (0.8) |
| Nausea | 158 (38.9) | 12 (3.0) | 157 (40.5) | 4 (1.0) |
| Decreased appetite | 149 (36.7) | 24 (5.9) | 64 (16.5) | 0 |
| Fatigue | 113 (27.8) | 15 (3.7) | 92 (23.7) | 12 (3.1) |
| Proteinuria† | 102 (25.1) | 18 (4.4) | 4 (1.0) | 0 |
| Vomiting | 99 (24.4) | 10 (2.5) | 59 (15.2) | 6 (1.5) |
| Weight decreased | 90 (22.2) | 24 (5.9) | 7 (1.8) | 0 |
| Palmar-plantar erythrodysesthesia syndrome† | 84 (20.7) | 11 (2.7) | 3 (0.8) | 0 |
| Arthralgia | 84 (20.7) | 4 (1.0) | 17 (4.4) | 0 |
| Dysphonia | 76 (18.7) | 0 | 2 (0.5) | 0 |
| Asthenia | 75 (18.5) | 17 (4.2) | 76 (19.6) | 9 (2.3) |
| Stomatitis | 70 (17.2) | 8 (2.0) | 46 (11.9) | 2 (0.5) |
| Alanine aminotransferase increased | 63 (15.5) | 13 (3.2) | 14 (3.6) | 2 (0.5) |
| Aspartate aminotransferase increased | 58 (14.3) | 13 (3.2) | 12 (3.1) | 2 (0.5) |

| Preferred Term | Lenvatinib + Pembrolizumab (n = 406) n (%) | | Chemotherapy (n = 388) n (%) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3* | Any Grade | Grade ≥3* |
| Anemia | 58 (14.3) | 8 (2.0) | 150 (38.7) | 43 (11.1) |
| Myalgia | 54 (13.3) | 3 (0.7) | 13 (3.4) | 0 |
| Headache | 53 (13.1) | 1 (0.2) | 14 (3.6) | 0 |
| Rash | 47 (11.6) | 2 (0.5) | 6 (1.5) | 0 |
| Mucosal inflammation | 45 (11.1) | 6 (1.5) | 35 (9.0) | 3 (0.8) |
| Platelet count decreased | 43 (10.6) | 7 (1.7) | 20 (5.2) | 3 (0.8) |
| Blood thyroid stimulating hormone increased | 40 (9.9) | 0 | 1 (0.3) | 0 |
| Constipation | 36 (8.9) | 0 | 51 (13.1) | 0 |
| Neutropenia | 22 (5.4) | 4 (1.0) | 127 (32.7) | 95 (24.5) |
| Leukopenia | 20 (4.9) | 0 | 47 (12.1) | 27 (7.0) |
| Alopecia | 17 (4.2) | 0 | 117 (30.2) | 2 (0.5) |
| Neutrophil count decreased | 17 (4.2) | 7 (1.7) | 93 (24.0) | 82 (21.2) |
| White blood cell count decreased | 15 (3.7) | 4 (1.0) | 58 (14.9) | 40 (10.3) |

*Treatment-related adverse events led to death in 1.5% in the lenvatinib plus pembrolizumab group (cardiac disorder [n=1]; gastrointestinal disorder [n=1]; general disorders and administration site conditions [n=2]; benign, malignant and unspecified neoplasms [n=1]; nervous system disorders [n=1]), and 2.1% in the chemotherapy group (cardiac disorders [n=3]; infections and infestations [n=3]; respiratory, thoracic, mediastinal disorders [n=2]).

†Clinically significant adverse events for lenvatinib in all patients (**Supplementary Table S14**).

‡Adverse event of interest for pembrolizumab in all patients (**Supplementary Table S13**).

**Supplementary Table S13.** Adverse events of interest for pembrolizumab in all patients.*

| **Preferred Term** | **Lenvatinib + Pembrolizumab (n = 406) n (%)** | **Chemotherapy (n = 388) n (%)** |
|---|---|---|
| Hypothyroidism | 234 (57.6) | 3 (0.8) |
| Hyperthyroidism | 47 (11.6) | 4 (1.0) |
| Colitis | 19 (4.7) | 1 (0.3) |
| Severe skin reactions | 13 (3.2) | 1 (0.3) |
| Infusion reactions | 12 (3.0) | 6 (1.5) |
| Thyroiditis | 8 (2.0) | 0 |
| Hepatitis | 6 (1.5) | 0 |
| Adrenal insufficiency | 5 (1.2) | 0 |
| Pancreatitis | 5 (1.2) | 0 |
| Pneumonitis | 5 (1.2) | 1 (0.3) |
| Type I diabetes mellitus | 4 (1.0) | 0 |
| Uveitis | 3 (0.7) | 0 |
| Encephalitis | 2 (0.5) | 0 |
| Hypophysitis | 2 (0.5) | 0 |
| Myositis | 2 (0.5) | 0 |
| Nephritis | 2 (0.5) | 0 |
| Myasthenic syndrome | 1 (0.2) | 0 |
| Myocarditis | 1 (0.2) | 0 |
| Vasculitis | 1 (0.2) | 2 (0.5) |

*Please see **Definitions of Select Terms**.

**Supplementary Table S14.** Clinically significant adverse events for lenvatinib in all patients.*

| **Preferred Term** | **Lenvatinib + Pembrolizumab (n = 406) n (%)** | **Chemotherapy (n = 388) n (%)** |
|---|---|---|
| Hypothyroidism | 277 (68.2) | 4 (1.0) |
| Hypertension | 264 (65.0) | 21 (5.4) |
| Hepatotoxicity | 137 (33.7) | 44 (11.3) |
| Proteinuria | 120 (29.6) | 12 (3.1) |
| Hemorrhage | 99 (24.4) | 51 (13.1) |
| Palmar-plantar erythrodysesthesia syndrome | 90 (22.2) | 4 (1.0) |
| Renal events | 74 (18.2) | 23 (5.9) |
| Gastrointestinal perforation | 16 (3.9) | 1 (0.3) |
| Hypocalcemia | 16 (3.9) | 14 (3.6) |
| QT prolongation | 16 (3.9) | 8 (2.1) |
| Arterial thromboembolic events | 15 (3.7) | 3 (0.8) |
| Fistula formation | 10 (2.5) | 4 (1.0) |
| Cardiac dysfunction | 4 (1.0) | 12 (3.1) |
| Posterior reversible encephalopathy syndrome | 1 (0.2) | 0 |

*Please see **Definitions of Select Terms**.

**Supplementary Table S15.** Serious adverse events occurring in ≥1% of all patients.

| **Preferred Term** | **Lenvatinib + Pembrolizumab (n = 406) n (%)** | **Chemotherapy (n = 388) n (%)** |
|---|---|---|
| Hypertension | 17 (4.2) | 0 |
| Urinary tract infection | 13 (3.2) | 2 (0.5) |
| Diarrhea | 10 (2.5) | 3 (0.8) |
| Decreased appetite | 9 (2.2) | 0 |
| Vomiting | 9 (2.2) | 3 (0.8) |
| Acute kidney injury | 8 (2.0) | 3 (0.8) |
| Pyrexia | 8 (2.0) | 3 (0.8) |
| Cholecystitis | 7 (1.7) | 0 |
| Colitis | 7 (1.7) | 1 (0.3) |
| Pneumonia | 6 (1.5) | 3 (0.8) |
| Death | 5 (1.2) | 3 (0.8) |
| Dehydration | 5 (1.2) | 1 (0.3) |
| Intestinal obstruction | 5 (1.2) | 3 (0.8) |
| Sepsis | 5 (1.2) | 5 (1.3) |
| Abdominal pain | 4 (1.0) | 1 (0.3) |
| Ileus | 4 (1.0) | 0 |
| Pulmonary embolism | 4 (1.0) | 5 (1.3) |
| Febrile neutropenia | 2 (0.5) | 16 (4.1) |
| Anemia | 1 (0.2) | 9 (2.3) |
| Neutropenia | 1 (0.2) | 7 (1.8) |

Every patient is counted a single time for each applicable row and column.

## Definitions of Select Terms

**Dual-primary Endpoints**

- Progression-free survival by blinded independent central review (BICR): defined as the time from the date of randomization to the date of the first documentation of disease progression, as determined by blinded BICR of objective radiographic disease progression per RECIST v1.1 or death due to any cause (whichever occurs first). See Section 9.6.1 – Statistical Methods for Efficacy Analyses for definition of censoring.
- Overall survival: defined as the time from the date of randomization to the date of death due to any cause. Patients who are lost to follow-up and those who are alive at the date of data cut-off will be censored at the date the patient was last known alive, or date of data cut-off, whichever occurs first.

**Secondary Endpoints**

- Objective response rate: defined as the proportion of patients who have best overall response of either complete response or partial response as determined by BICR per RECIST v1.1.

**Serious Adverse Event**

A serious adverse event is defined as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly or birth defect.

**Adverse Event of Interest for Pembrolizumab**

Adverse events of interest for pembrolizumab were determined based on a list of terms specified by the sponsor and were considered regardless of relationship to treatment by investigator. Please note that these definitions may include a grouping of different adverse event terms versus a single preferred term.

**Clinically Significant Adverse Event for Lenvatinib**

Clinically significant adverse events for lenvatinib were identified based on a prespecified list of preferred terms maintained by Eisai and Merck & Co., Inc., Kenilworth, NJ, USA to consistently characterize the safety of lenvatinib across the clinical programs. Please note that these definitions may include a grouping of different adverse event terms versus a single preferred term.

## Supplementary Methods:

**MMR Testing**

Archived tumor tissue from the most recent surgery/biopsy or from a fresh biopsy (if there was no archival tumor tissue available), was collected from all enrolled patients for determination of MMR status by central assessment prior to randomization. Mouse and rabbit antibodies against MMR proteins were used to perform automated immunohistochemistry staining and chromogenic labeling of the MLH1, MSH2, MSH6, and PMS2 proteins on the Ventana Benchmark Ultra (Roche Diagnostics, Tucson Arizona). The MLH1 (clone M1, mouse monoclonal, Ventana, Cat# 790-5091), PMS2 (clone A16-4, mouse monoclonal, Ventana, Cat# 790-5094), MSH2 (clone G219-1129, mouse monoclonal, Ventana, Cat# 790-5093) and MSH6 (clone SP93, rabbit monoclonal, Ventana, Cat# 790-5092) antibodies were used to perform immunohistochemistry staining. The MMR status was determined by pathologist evaluation.

When available, a tissue sample collected after the latest systemic treatment was preferred. Recruiment was to stop once fully enrolled for pMMR patients (n=660); the number of patients with dMMR was to be capped at n=120 or 15% of the entire study population in order to reflect the expected prevalence of dMMR tumors in this treatment setting.

**Treatment Duration**

Patients could continue to receive study treatment until disease progression was confirmed by blinded independent central review, development of unacceptable toxicity, withdrawal of consent, receipt of 35

administrations of pembrolizumab (approximately two years), or a lifetime cumulative dose of 500 mg/m² of doxorubicin. Patients who completed treatment with pembrolizumab for 35 cycles could continue receiving lenvatinib alone until disease progression, unacceptable toxicity, or withdrawal of consent. Patients received study treatment as continuous 21-day cycles (for patients treated with lenvatinib plus pembrolizumab and doxorubicin), or continuous 28-day cycles (for patients receiving weekly paclitaxel). Further details regarding discontinuation of study drugs are included in the protocol supplied with the **Supplementary Materials**.

**Assessments**

Tumor assessments based on chest, abdomen and pelvis computed tomography or magnetic resonance imaging were obtained at screening and every 8 weeks from randomization, or sooner if clinically indicated, until disease progression. Patients were also monitored via regular performance of physical examinations and laboratory evaluation for hematology, blood chemistry, and urine values; as well as, periodic measurement of vital signs and electrocardiograms.

**Safety Analyses**

Parameters identified a priori constituted Tier 1; there were no Tier 1 events in this study. Tier 2 required that ≥10% of patients in any treatment group exhibited the event; Tier 2 also included patients with Grade 3–5 adverse events (≥5% of patients in 1 of the treatment groups) and serious adverse events (≥1% of patients in 1 of the treatment groups). Tier 2 parameters were assessed via point estimates with 95% confidence intervals provided for differences in the proportion of patients with events using the Miettinen and Nurminen method. All other adverse events and predefined limits of change belonged to Tier 3. Only point estimates by treatment group were provided for Tier 3 safety parameters.

**Health-related Quality-of-Life**

The health-related quality-of-life analyses were based on all randomized patients who had at least one health-related quality-of-life assessment available and had received at least one dose of the study intervention.

**Statistical Methods**

Assuming an accrual period of 19 months and a follow-up period of 24 months, a total of 660 patients were required to observe 526 death events by the time of 43 months after the first patient was randomized (19 months enrollment plus 24 months follow-up period).

**Multiple Imputation Analysis of Objective Response Rate**

To account for the missing response data (best overall response of 'Not Assessed' [**Table 2**]), objective response rates were analyzed using multiple imputation (Little R, Rubin D. Statistical Analysis with Missing Data, Third Edition. Hoboken, NJ: John Wiley & Sons, Inc.; 2019). This considered pre-specified stratification factors including MMR status (either proficient [pMMR] or deficient [dMMR]), Eastern Cooperative Oncology Group performance status (0 or 1), geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: Rest of the world), and prior history of pelvic radiation (yes or no). Following the generation of the 200 imputed data sets, each dataset was analyzed separately using the stratified Miettinen and Nurminen's method to yield a difference in objective response rates between treatment groups, standard error, and 95% confidence interval. This information was combined to obtain a single difference and nominal *P*-value.

Regarding the missing at random (MAR) assumption, because more participants in the chemotherapy arm withdrew consent in this open-label setting compared to the lenvatinib + pembrolizumab arm, more participants in the chemotherapy arm were designated as "not assessed" due to not having a

postbaseline assessment available for response evaluation. After accounting for the treatment arm in the imputation model, the missing data due to withdrawal of consent is unlikely dependent on the future outcome of response.