Kidney Cancer Research Summit KCRS21

Pembrolizumab vs Placebo As Post Nephrectomy Adjuvant Therapy For Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

Toni K. Choueiri[1]; Piotr Tomczak[2]; Se Hoon Park[3]; Balaji Venugopal[4]; Thomas Ferguson[5]; Yen-Hwa Chang[6]; Jaroslav Hajek[7]; Stefan N. Symeonides[8]; Jae Lyun Lee[9]; Naveed Sarwar[10]; Antoine Thiery-Vuillemin[11]; Marine Gross-Goupil[12]; Mauricio Mahave[13]; Naomi Haas[14]; Piotr Sawrycki[15]; Todd L. Saretsky[16]; Rodolfo F. Perini[16]; Pingye Zhang[16]; Kentaro Imai[16]; Jaqueline Willemann-Rogerio[16]; David Quinn[17]; Thomas Powles[18]*.

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Poznań University of Medical Sciences, Poznań, Poland; [3]Sungkyunkwan University, Samsung Medical Center, Seoul, South Korea; [4]Beatson West of Scotland Cancer Centre and University of Glasgow, Glasgow, UK; [5]Fiona Stanley Hospital, Perth, Australia, [6]Taipei Veterans General Hospital, Taipei, Taiwan, [7]Fakultni Nemocnice Ostrava, Ostrava, Czech Republic, [8]Edinburgh Cancer Centre and University of Edinburgh, UK, [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [10]Imperial College Healthcare NHS Trust, London, UK, [11]University Hospital Jean Minjoz, Besançon, France, [12]University Hospital Bordeaux-Hôpital Saint-André, Bordeaux, France, [13]Fundacion Arturo Lopez Perez FALP, Santiago, Chile, [14]Abramson Cancer Center, Philadelphia, PA, USA, [15]Wojewodzki Szpital Zespolony im. L. Rydygiera w Toruniu, Torun, Poland, [16]Merck & Co., Inc., Kenilworth, NJ, USA, [17]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA, [18]Royal Free Hospital NHS Trust, University College London, London, UK.

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Disclosures

- Tom Powles
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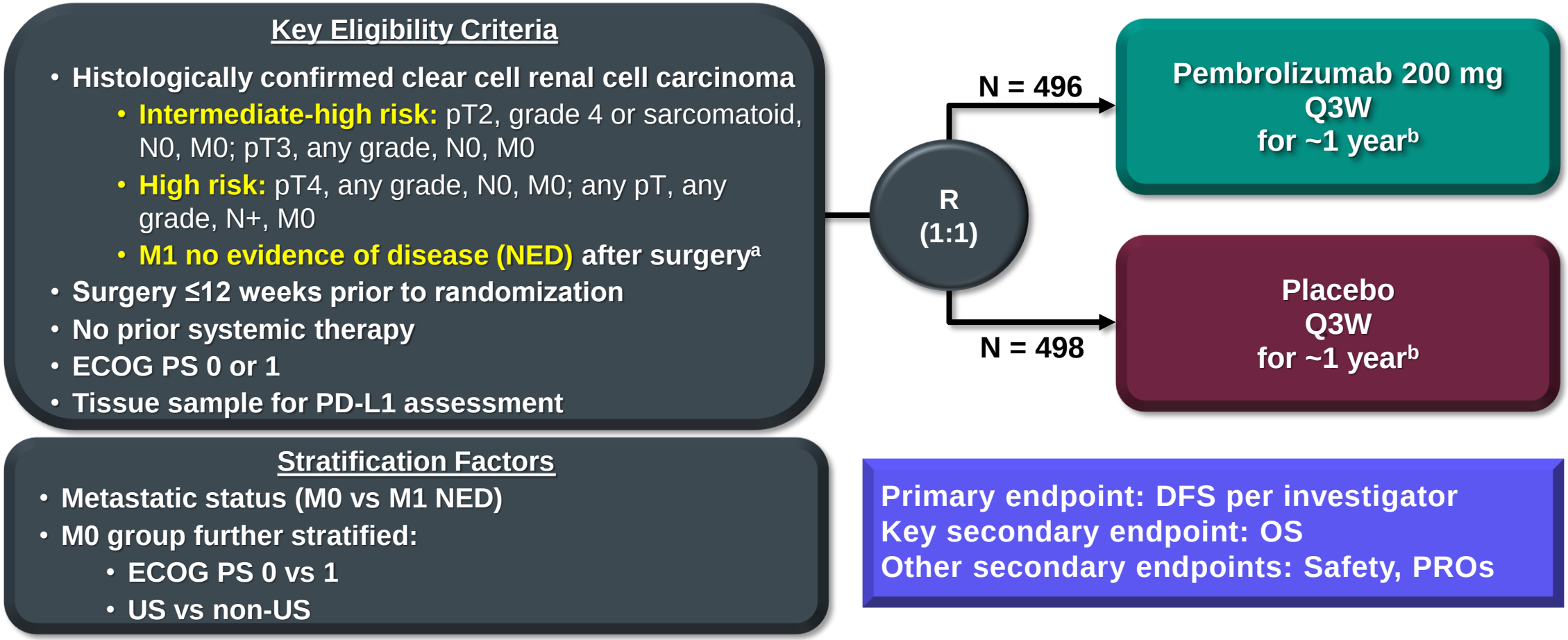
Adjuvant Therapy for Renal Cell Carcinoma

- 2020: Kidney cancer was responsible for nearly 180,000 deaths worldwide[1]
- Nephrectomy is the standard of care treatment for locoregional RCC[2,3]
  - No globally accepted standard adjuvant therapy supported by high levels of evidence
  - Studies of adjuvant immunotherapy with cytokines have yielded negative results[4]
  - VEGF-targeted therapy has not shown a consistent benefit in the adjuvant setting[5]
- Nearly half of patients eventually experience disease recurrence after surgery[4-6]
  - Risk factors include tumor stage/size, nodal involvement, and nuclear grade
  - Patients with M1 stage and no evidence of disease (NED) after resection of oligometastatic sites are also at high risk of relapse[7]
- **KEYNOTE-564** (NCT03142334) is a phase 3, double-blind, multicenter trial of pembrolizumab vs placebo following nephrectomy in participants with RCC

1. Sung et al. *CA Cancer J Clin* 2021;71:209-49; 2. NCCN. Kidney cancer (version 2.2022); 3. Escudier et al. *Ann Oncol* 2019;30:706-20; 4. Smaldone et al. *Hematol Oncol Clin North Am* 2011;25:765-91; 5. Sun et al. *Eur Urol* 2018;74:611-20; 6. Correa et al. *J Clin Oncol* 2019;37:2062-71; 7. Appleman et al. *J Clin Oncol* 37, 2019 (suppl; abstr 4502).

KEYNOTE-564 Study Design



Median (range) time from randomization to cutoff: 24.1 (14.9–41.5) months

DFS, disease-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks.
[a]M1 NED: no evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy; [b]≤17 cycles of treatment were equivalent to ~1 year.

Statistical Considerations

- First prespecified interim analysis planned after ~265 DFS events and minimum follow-up of 12 months from last participant enrolled
  - After 15 months minimum follow-up, 260 DFS events had occurred (78% of planned for final analysis)
  - 51 OS events had occurred (26% of planned for final analysis)
- 95% power to detect HR 0.67 at α = 2.5% (one-sided) for the primary endpoint of DFS for ~990 participants
  - The overall type I error rate was strongly controlled at 2.5%[a]
  - DFS tested first at α = 2.5%, then α passed to OS if null DFS hypothesis was rejected
- DFS and OS were estimated by the Kaplan-Meier method
  - HRs and 95% CIs were estimated using a stratified Cox proportional hazard model
  - Between-arm differences assessed with stratified log-rank test
  - Subgroup analyses were nominal and descriptive; no formal comparisons were performed
- The PRO analysis population included all randomized participants with ≥1 dose study treatment and ≥1 completed assessment for the specific outcome
  - No adjustments for multiple testing or estimation were used for PROs

[a]Maurer and Bretz graphical method.

Baseline Characteristics

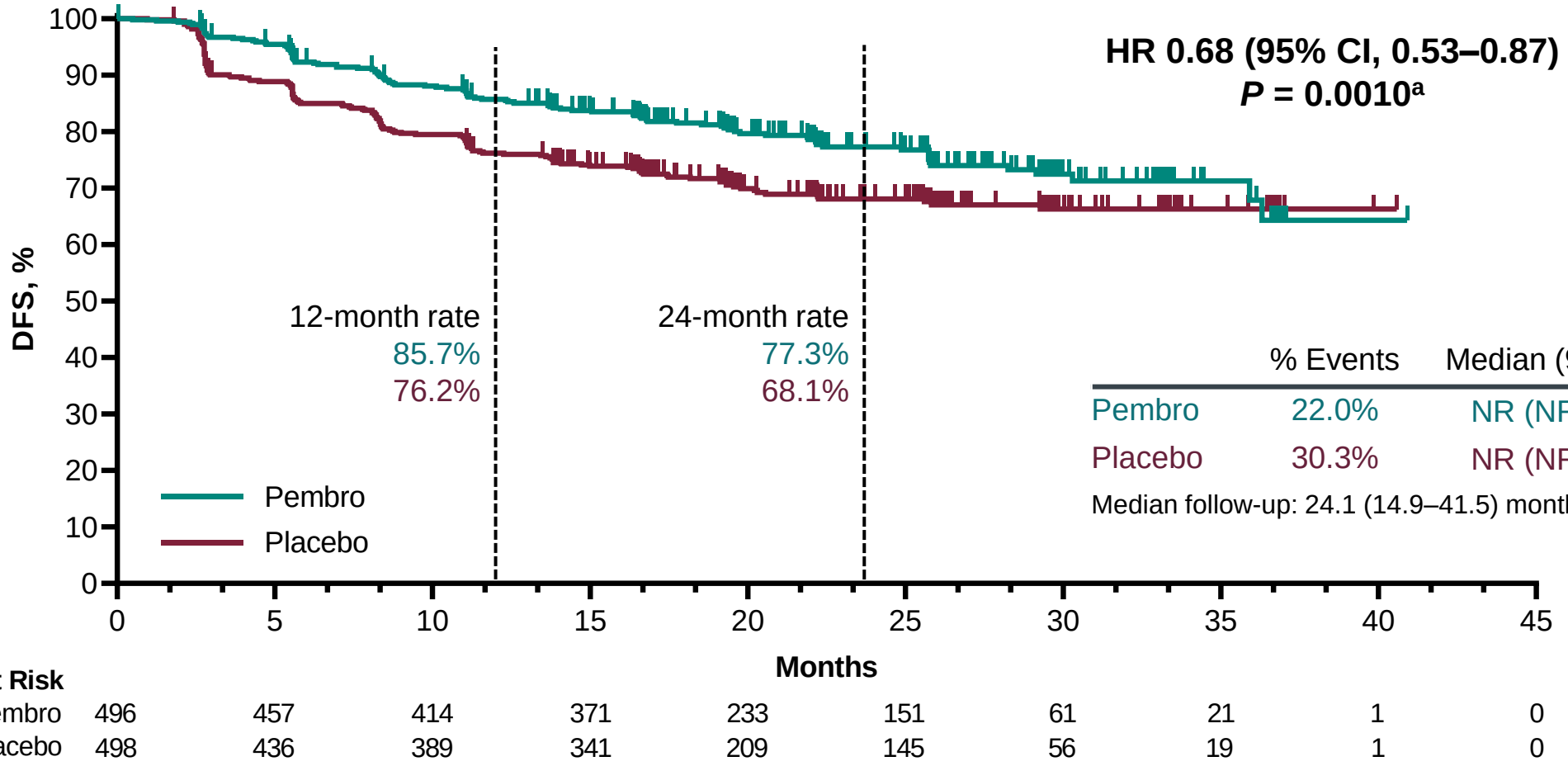
Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Age, median (range), yrs	60 (27−81)	60 (25−84)
Male	347 (70.0)	359 (72.1)
ECOG PS		
0	421 (84.9)	426 (85.5)
1	75 (15.1)	72 (14.5)
Geographic location		
North America	133 (26.8)	125 (25.1)
European Union	188 (37.9)	187 (37.6)
Rest of the world	175 (35.3)	186 (37.3)
Sarcomatoid features		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)
Disease risk category		
M0 intermediate-high risk	427 (86.1)[a]	433 (86.9)
M0 high risk	40 (8.1)	36 (7.2)
M1 NED	29 (5.8)	29 (5.8)

Characteristic, n (%)	Pembro N = 496	Placebo N = 498
Primary tumor stage		
T1	11 (2.2)	15 (3.0)
T2	27 (5.4)	33 (6.6)
T3	444 (89.5)	437 (87.8)
T4	14 (2.8)	13 (2.6)
Tumor grade[b]		
1	19 (3.8)	16 (3.2)
2	153 (30.8)	150 (30.1)
3	219 (44.2)	213 (42.8)
4	103 (20.8)	119 (23.9)
Lymph node stage		
N0	465 (93.8)	467 (93.8)
N1	31 (6.3)	31 (6.2)
PD-L1 status[c]		
CPS <1	124 (25.0)	113 (22.7)
CPS ≥1	365 (73.6)	383 (76.9)
Missing	7 (1.4)	2 (0.4)

Intermediate-high risk: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0; **High risk:** pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0; **M1 NED:** No evidence of disease after primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy.

[a]Included 5 participants with T2, grade ≤3, N0, M0 or T1, N0, M0. [b]2 additional participants in the pembro group had missing tumor grade. [c]Assessed using the PD-L1 IHC 22C3 pharmDx assay. CPS (combined positive score) is the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. Data cutoff date: December 14, 2020.

DFS by Investigator, ITT Population

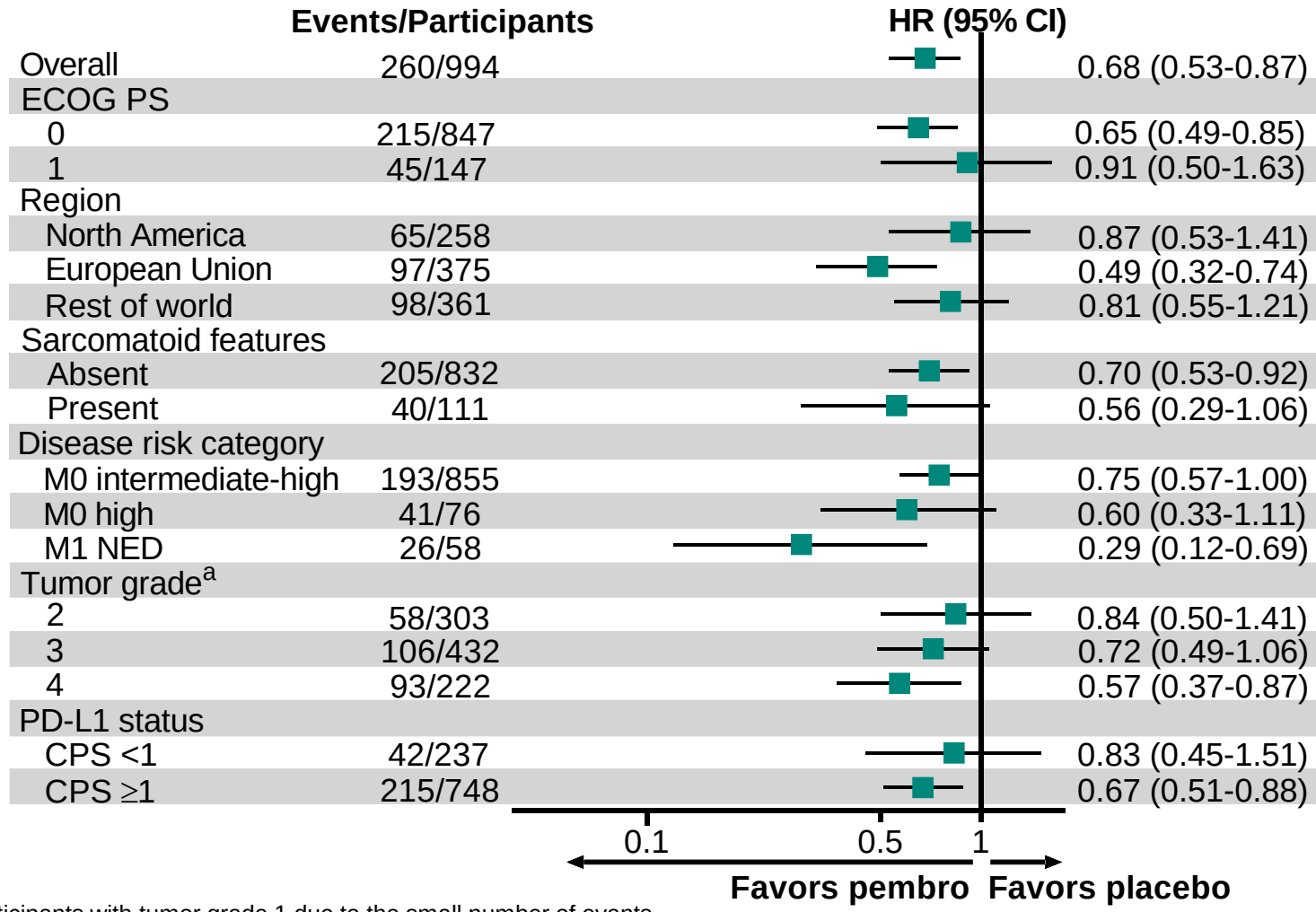


	% Events	Median (95% CI)
Pembro	22.0%	NR (NR–NR)
Placebo	30.3%	NR (NR–NR)

Median follow-up: 24.1 (14.9–41.5) months.

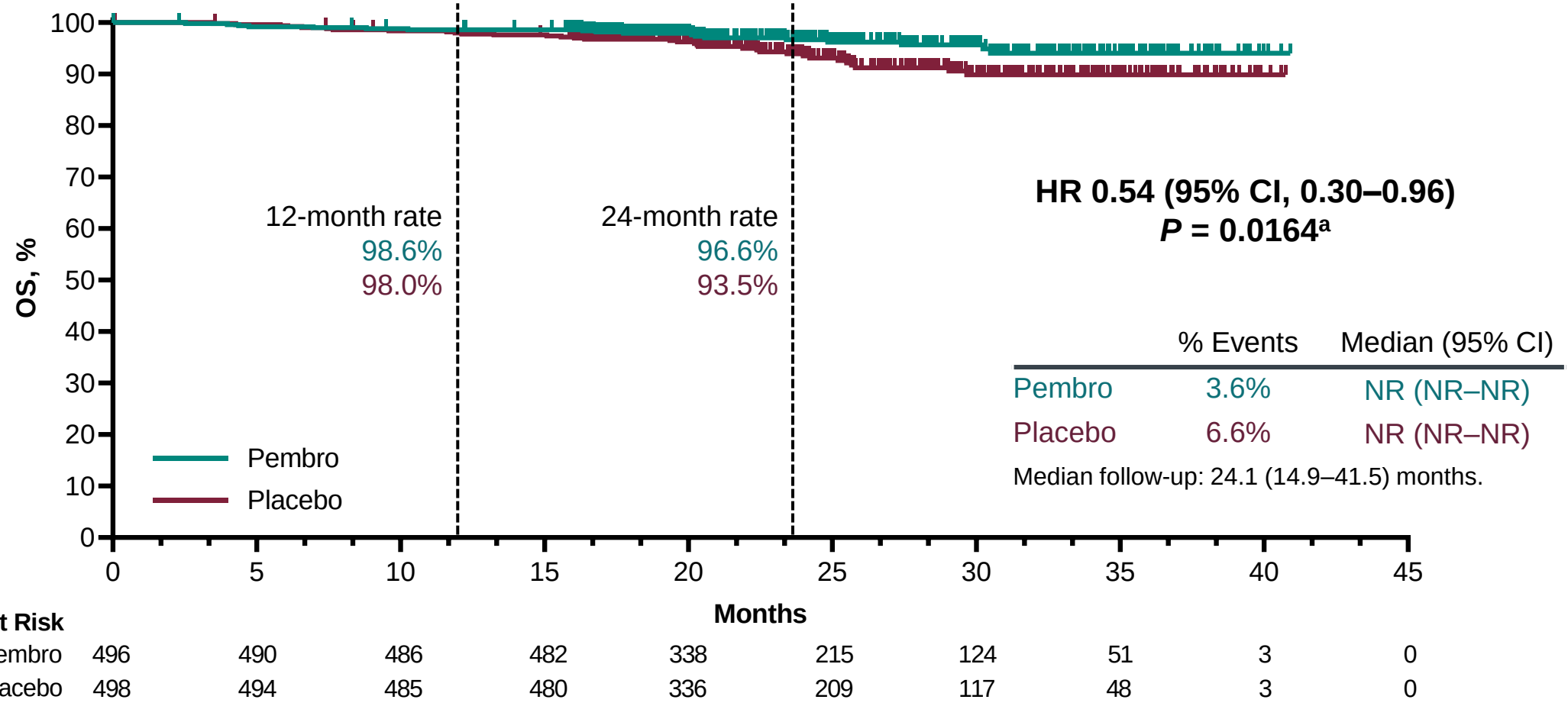
[a]Crossed prespecified p-value boundary for statistical significance of 0.0114. DFS was estimated by the Kaplan-Meier method; HRs and 95% CIs were estimated using a stratified Cox proportional hazard model. Between-arm differences assessed with stratified log-rank test.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

DFS by Investigator in Subgroups, ITT Population



[a]Subgroup analysis was not performed for participants with tumor grade 1 due to the small number of events.
ITT population included all randomized participants. Data cutoff date: December 14, 2020.

Interim OS Results, ITT Population



HR 0.54 (95% CI, 0.30–0.96)
***P* = 0.0164[a]**

	% Events	Median (95% CI)
Pembro	3.6%	NR (NR–NR)
Placebo	6.6%	NR (NR–NR)

Median follow-up: 24.1 (14.9–41.5) months.

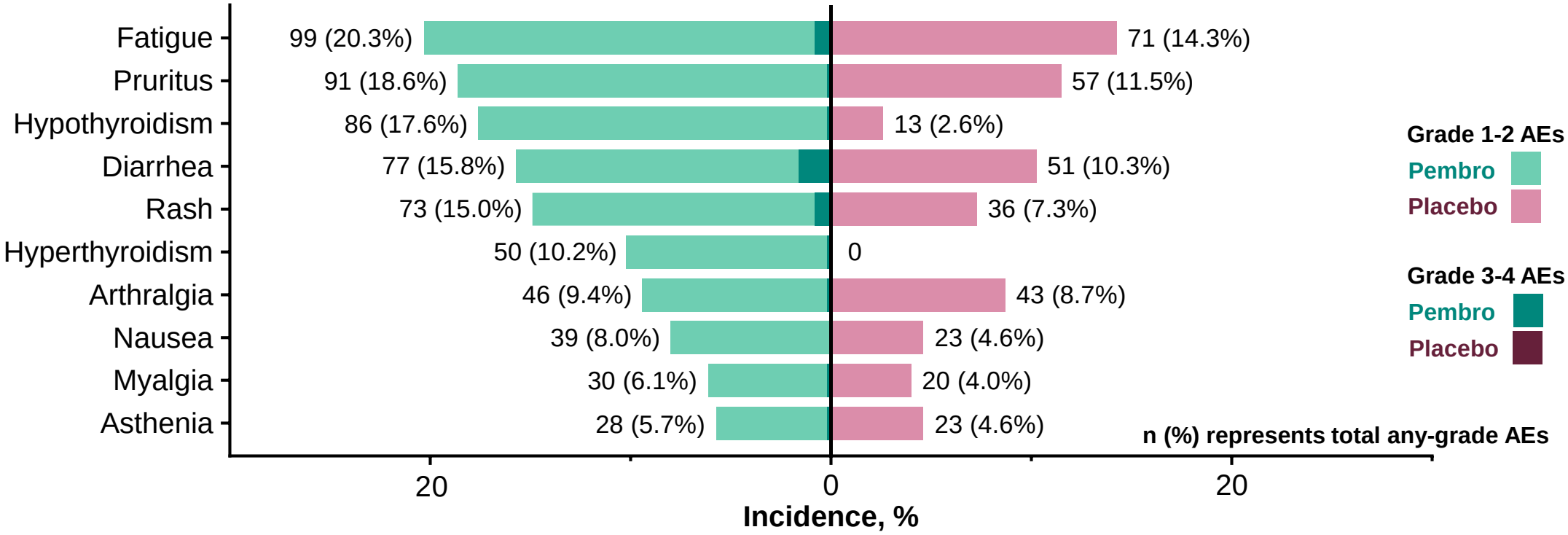
[a]Did not cross prespecified p-value boundary for statistical significance of 0.0000093 for 51 events. Final analysis for OS to occur after approximately 200 OS events.
ITT population included all randomized participants. NR, not reached. Data cutoff date: December 14, 2020.

Summary of Safety Results, As-Treated Population

Participants with ≥1 AE, n (%)	Pembro N = 488	Placebo N = 496
All-cause AEs	470 (96.3)	452 (91.1)
Grade 3–5	158 (32.4)	88 (17.7)
Led to treatment discontinuation	101 (20.7)	10 (2.0)
Led to death	2 (0.4)	1 (0.2)
Serious all-cause AEs[a]	100 (20.5)	56 (11.3)
Led to treatment discontinuation	49 (10.0)	5 (1.0)
Treatment-related AEs	386 (79.1)	265 (53.4)
Grade 3–5	92 (18.9)	6 (1.2)
Led to treatment discontinuation	86 (17.6)	3 (0.6)
Led to death	0	0

[a]Serious AEs were AEs that were life-threatening, required hospitalization, resulted in death or persistent/significant disability/incapacity, or were judged as serious per investigator.
As-treated population included all participants who received ≥1 dose of study treatment. Median duration (range) of treatment was 11.1 (0.0–14.3) months with pembro and 11.1 (0.0–15.4) months with placebo.
Data cutoff date: December 14, 2020.

Treatment-Related AEs with Incidence ≥5%, As-Treated Population



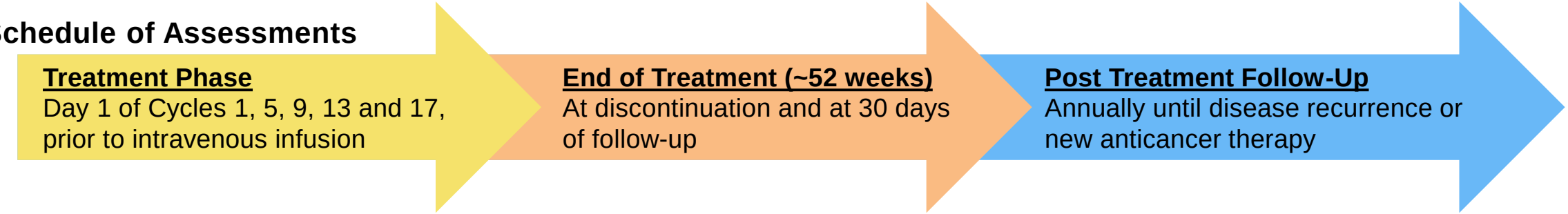
High-dose (≥40 mg/day) systemic corticosteroid treatment for AEs prespecified to be immune-mediated[a], n (%)	
Pembro	**Placebo**
36 (7.4)	3 (0.6)

[a]Based on a prespecified list of terms included regardless of attribution to study treatment by investigator. No deaths due to immune-mediated AEs occurred.
As-treated population included all participants who received ≥1 dose of study treatment. No treatment-related deaths occurred. Data cutoff date: December 14, 2020.

PRO Assessment Schedule and Instruments

- **Secondary endpoint:** Longitudinal least squares (LS) mean change analysis from baseline to week 52 in each treatment group by FKSI-DRS and QLQ-C30 GHS/QoL

Schedule of Assessments



PRO Instruments	Focus	Items	Recall Period
FKSI-DRS	• Most important symptoms associated with advanced kidney cancer • Total score ranges from 0 to 36 • Higher scores represent better symptom status • Estimated threshold for clinically meaningful change from baseline: 3 points[1]	9	Past 7 days
EORTC QLQ-C30	• 9 multiple item scales (5 functional scales, 3 symptom scales, 1 GHS/QoL scale) • 6 single-item symptom scales • Scores for all scales range from 0 to 100 • For GHS/QoL and functional scales, a higher score corresponds to better HRQoL • For symptom scales, a higher score represents worse symptoms • Estimated threshold for clinically meaningful change from baseline: 10 points[2]	30	Past 7 days

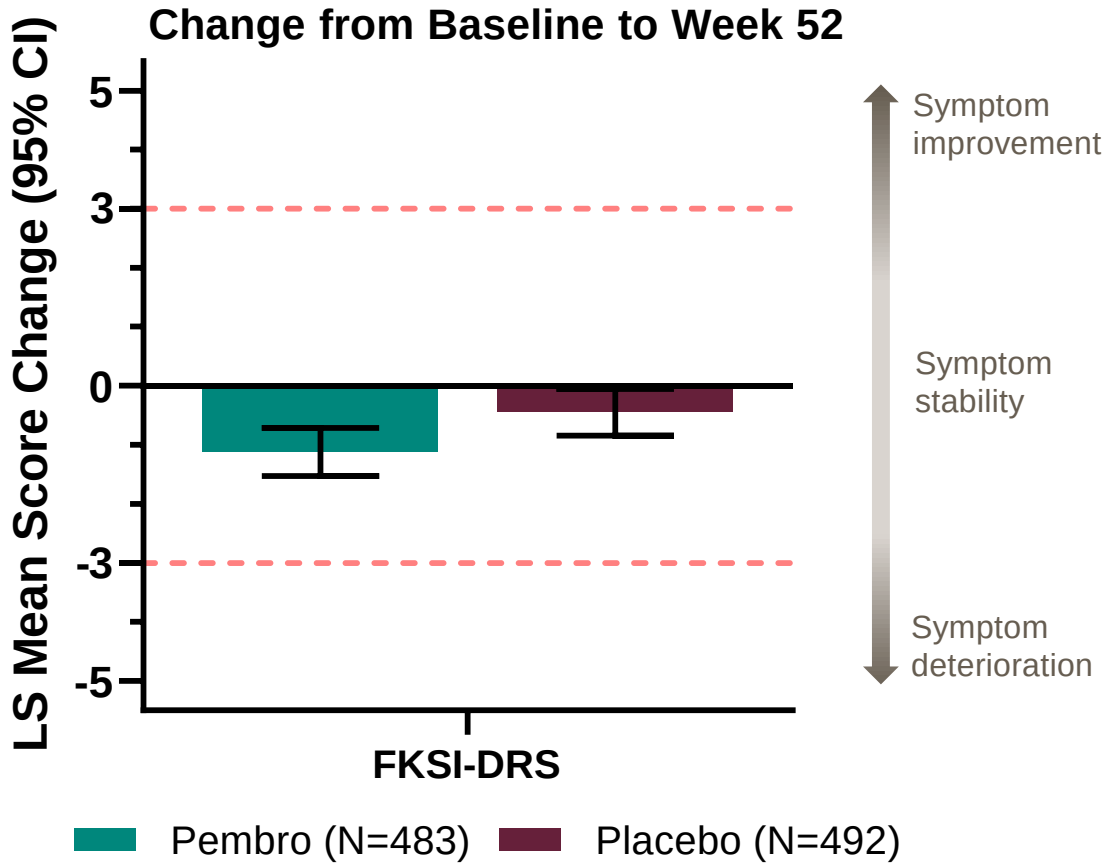
1. Cella D, et al. *Value Health* 2007;10:285-93; 2. Snyder CF, et al. *Qual Life Res* 2015;24:1207-16.
EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms; GHS, global health status; HRQoL, health-related quality of life; QoL, quality of life.

Summary of FKSI-DRS Scores

- At week 52 (planned end of treatment), completion rate was >60% and compliance was >80% for all PRO measures

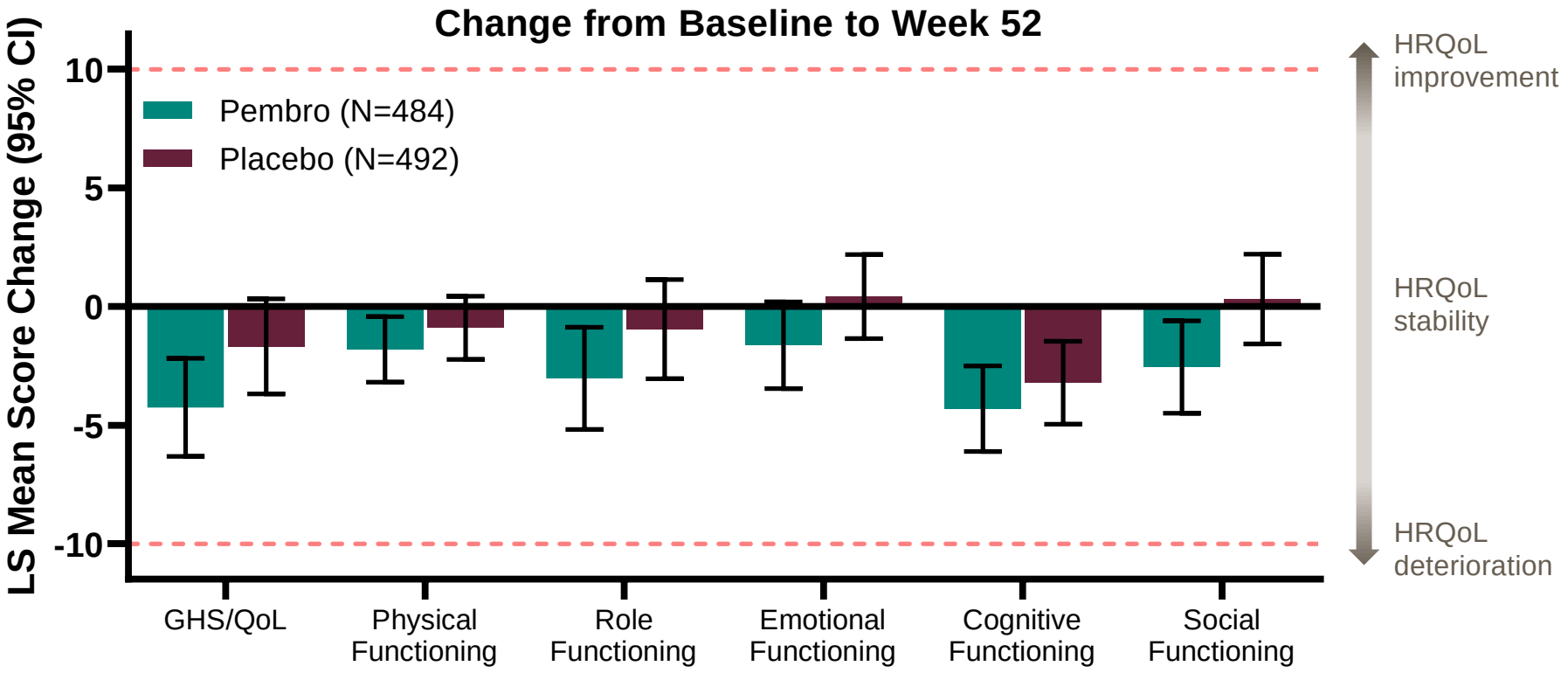
Treatment	Change from Baseline to Week 52	
	N	LS Mean (95% CI)
Pembro	483	−1.12 (−1.53 to −0.71)
Placebo	492	−0.45 (−0.84 to −0.05)

- Scores did not meet the estimated threshold for meaningful change from baseline[1] (dotted line) in either trial arm, and the confidence intervals overlapped



1. Cella D, et al. *Value Health* 2007;10:285-93.
PRO analysis population included all randomized participants who received ≥1 dose of treatment and completed ≥1 PRO assessment. Data cutoff date: December 14, 2020.

Summary of QLQ-C30 HRQoL Scale Scores

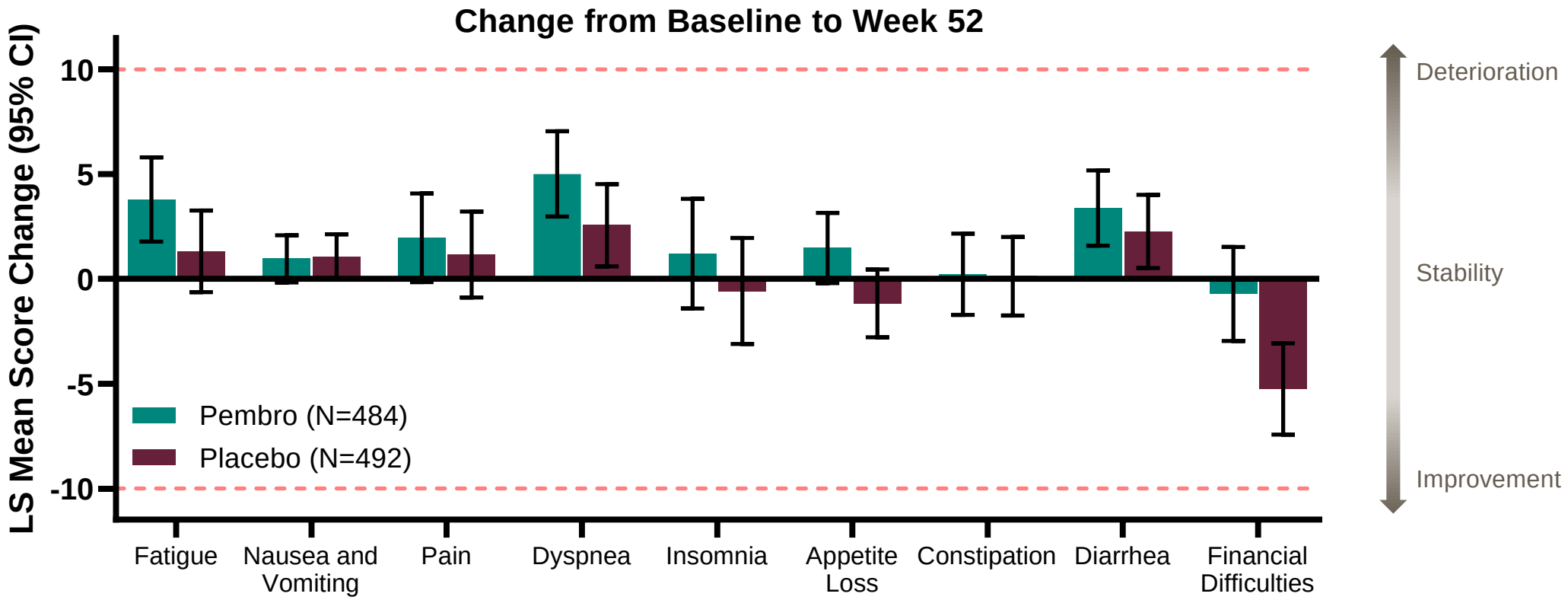


- At week 52 (planned end of treatment), completion rate was >60% and compliance was >80% for all PRO measures
- Scores did not meet the estimated threshold for meaningful change from baseline[1] (dotted line) in either trial arm, and the confidence intervals overlapped

1. Snyder CF, et al. *Qual Life Res* 2015;24:1207-16.

PRO analysis population included all randomized participants who received ≥1 dose of treatment and completed ≥1 PRO assessment. Data cutoff date: December 14, 2020.

Summary of QLQ-C30 Symptom Scale Scores



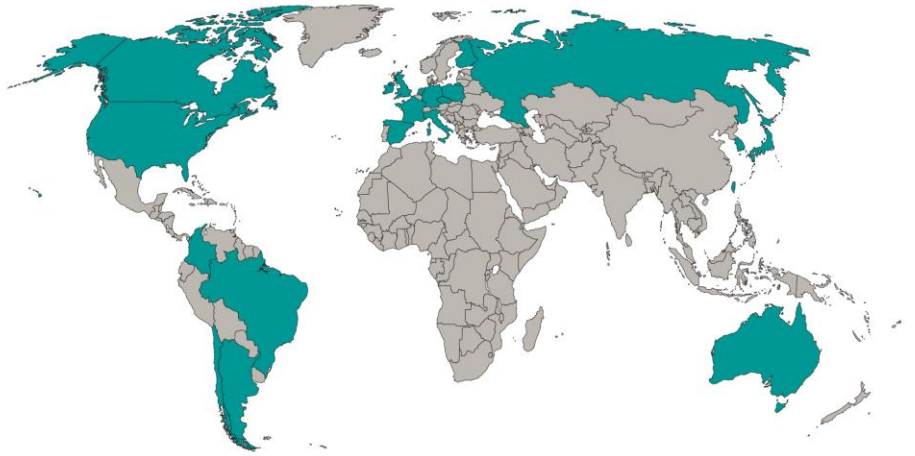
- Overall, scores did not meet the estimated threshold for meaningful change from baseline[1] (dotted line) in either trial arm, and the confidence intervals generally overlapped

1. Snyder CF, et al. *Qual Life Res* 2015;24:1207-16.
PRO analysis population included all randomized participants who received ≥1 dose of treatment and completed ≥1 PRO assessment. Data cutoff date: December 14, 2020.

Summary and Conclusions

- Pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS vs placebo in patients with RCC at high risk of recurrence after surgery
- Fewer OS events occurred in the pembrolizumab vs placebo arm although statistical significance was not met at this prespecified interim analysis, and follow up is ongoing for the key secondary endpoint of OS
- Safety results were in line with expectations and no new safety signals were observed
  - Low incidence of high-dose corticosteroid treatment for immune-mediated AEs
- No clinically meaningful changes from baseline in health-related QoL or symptom scores were observed with adjuvant pembrolizumab or placebo
  - Disease-related symptoms are rarely severe at this disease stage
- KEYNOTE-564 is the first positive phase 3 study with immunotherapy in adjuvant RCC and these results support pembrolizumab as a potential new standard of care for patients with RCC in the adjuvant setting

Acknowledgements



PARTICIPANTS AND THEIR FAMILIES

Investigators and site personnel from 213 sites in 21 countries

Argentina: LE Fein, DL Kaen, RD Kowalyszyn, A Dri, JP Sade, MD Tatangelo, JJ Zarba, VE Leiva, GA Mendez, MS Alfie; Australia: HP Gurney, ID Davis, TR Ferguson, M Khattak, F Parnis, SJ Harris, M Warren, SJ Brown, C Harris; Brazil: J de Janoski Menezes, AP Fay, JN Antonio Jr, R de Cassia Costamilan, PMM. Beato, RO Rocha, D Muniz, AG e Silva, SC Sales, FM Barbosa, S Silvio, J Silva, L Brust, L Rapatoni; Canada: G Faucher, N Iqbal, S Ghedira, EW Winquist, G Lo, C Yeung, D Marceau, N Martel, J-B Paradis, HJ Conter, M Salim, A-K Lalani, N Hanna, J Graham, V Torri, M Levesque; Chile: A Acevedo, F Orlandi, C Caglevic, JL Leal, M Mahave, C Ibanez, L Villanueva, MA Ojeda, P Galaz, P Fernandez, P Carvajal, F Flores, EY Ruiz, A Estay; Colombia: GA Rojas-Uribe, MEG Fernandez, JC Ospina, CMA Castro, IC Durango, JA Rubiano, AF Cardona, R Manneh; Czech Republic: Z Kral, B Melichar, P Holeckova, J Prausova, T Buchler, R Kotasek, H Perkova, J Hajek; Finland: P Bono, K Peltola, K Kankaanranta, P-L Kellokumpu-Lehtinen, P Bostrom, H Hakkarainen, J Kononen, H Ronkainen; France: A Thiery-Vuillemin, C Chevreau, M Gross-Goupil, D Topart, JL Deville, S Oudard, F Rolland, S Abadie-Lacourtoisie, B Laguerre, D Borchiellini, S Tartas; Germany: J Bedke, PJ Goebell, M-O Grimm, A Lorch, A Merseburger, S Hauser, T Hoefner, C Thomas, M Wirth, S Feyerabend, C Niedworok, A Panic, H Kirchen, A Neisius, M Rink, F Adams, W Schultze-Seemann, J Busch, T Schlomm, A Becker, F Roos, P Reichardt; Ireland: R McDermott, O Breathnach, E Jordan; Italy: F Nole, G Facchini, S Pignata, S Bracarda, A Hamzaj, G Procopio, R Sabbatini, G Ferretti, M Milella, C Buttigliero, M Tucci, U de Giorgi; Japan: G Kimura, K Nishimura, A Yamaguchi, A Yokomizo, M Oyama, H Matsumoto, H Matsuyama, Y Yamamoto, R Mizuno, H Uemura, M Eto, S Anai, M Tsujihata, H Tsunemori, Y Tomita, N Masumori, Y Miura, T Takano, M Kato, S Tamada, H Kato, N Ioritani, Y Matsukawa, N Sassa, H Kitamura, K Numakura, Y Murakami; Netherlands: H Westgeest, M Aarts, P Hamberg; Poland: C Szczylik, P Langiewicz, I Danielewicz, KL Kmak, J Wojcik-Tomaszewska, P Sawrycki, B Karaszewska, EM Nowakowska-Zajdel, D Sawka, BC Stopa, M Ziobro, P Tomczak, T Kubiatowski, A Chaladaj-Kujawska, AC Lesikow, B Sikora-Kupis, M Marczewska-Skrodzka, M Sobala, W Bal; Russia: BY Alekseev, RA Gafanov, A Izmailov, A Semenov, MI Shkolnik, VB Matveev, SG Afanasyev, E Kopyltsov, R Zukov, EA Fomin, ON Lipatov; South Korea: JL Lee, SH Park, B Keam, M Kim, SY Rha, J Chung; Spain: PG Borau, E Grande, JA Arranz, JLP Gracia, MAC Duran, I Delgado, NS Gonzalez, PJM Rey, AM Pino, RG Sarrio, JM Langa; Taiwan: C-H Chang, Y-H Chang, T-P Lin, T-C Wei, C-H Chen, S-T Pang, K-Y Chiu; UK: SN Symeonides, S Vengalil, R Hawkins, TS Waddell, R Jones, B Venugopal, AC Humphreys, N Sarwar, M Afshar, L Pickering, TB Powles; US: R Amato, J Rowe, MB Atkins, H-J Hammers, A Chaudhry, TK Choueiri, PW Cobb, B Gartrell, N Haas, R Hauke, E Heath, S McCune, P Jiang, C Kyriakopoulos, DM Anderson, E Gunderson, D Martincic, P Schlegel, H McKean, DM Prow, J Sarantopoulos, S Srinivas, S Tykodi, Y Zakharia, C Hwang, T Gourdin, F Senecal, P Varadarajan, A Koletsky, L Nadeau, T Zhang, DI Quinn, AK Miller, B Kumar, S Agarwala, G Lu, N Hashemi-Sadraei, R Lauer, D McDermott, A Alva, K Chen, SW Cole, J Fuloria, SDS Kendall, A Desai, EA Singer, G Jayram, JA Karam, G Keogh, R Galamaga, S Kochuparambil, JT Yorio, S Prakash, DA Richards, ID Schnadig, D Waterhouse, JM Burke, M Fleming, CG Chakmakjian, O Goodman Jr, M Gupta, G Doshi, S Jain, T Giever, A Flaherty, TE Hutson, M Agrawal, R Owera.

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Twitter: @DrChoueiri
Twitter: @TomPowles1

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