ASCO GU 2018: Melhores Resumos – Câncer de Bexiga Metastático

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Declaração de Conflitos de Interesse

De acordo com a Resolução 1931/2009 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

- Honorários por aulas ministradas: Astellas, Bayer, Ferring, Zodiac
- Auxílio para congressos: Bayer, Janssen, Pfizer, Sanofi, Zodiac, Roche
- Subinvestigadora de estudos clínicos: AstraZeneca, BMS, Janssen, MSD, Roche

Two-year follow-up from the phase 3 KEYNOTE-045 trial of pembrolizumab versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer

Joaquim Bellmunt,[1] Ronald de Wit,[2] David J. Vaughn,[3] Yves Fradet,[4] Jae Lyun Lee,[5] Lawrence Fong,[6] Nicholas J. Vogelzang,[7] Miguel A. Climent,[8] Daniel P. Petrylak,[9] Toni K. Choueiri,[1] Andrea Necchi,[10] Winald Gerritsen,[11] Howard Gurney,[12] David I. Quinn,[13] Stéphane Culine,[14] Cora N. Sternberg,[15] Kijoeng Nam,[16] Tara Frenkl,[16] Rodolfo F. Perini,[16] Dean F. Bajorin[17]

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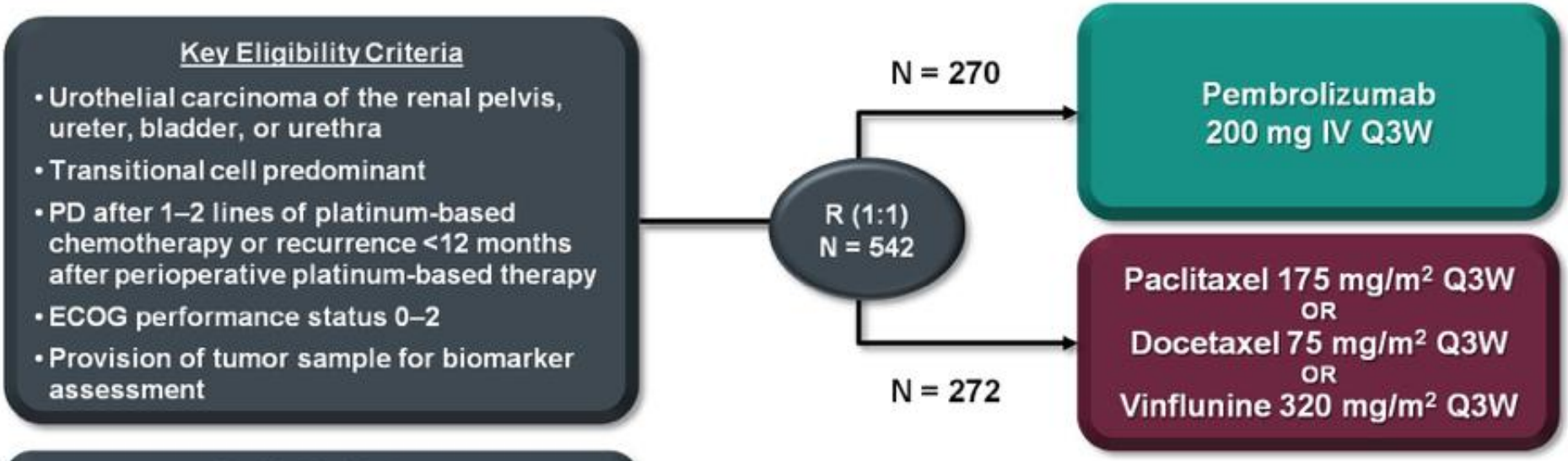
KEYNOTE-045 Study Design (NCT02256436)



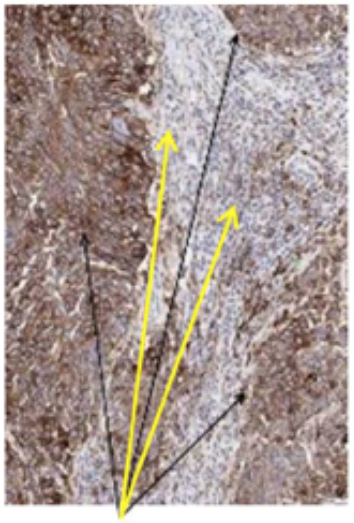
- Dual primary end points: OS and PFS[a]
- Key secondary end points: ORR, DOR, safety
- Response: RECIST v1.1 by blinded, independent central review
- Both unselected and biomarker-selected patients

[a]In total ITT population and in patients with combined positive score ≥10%.

Assessments

- Tumor imaging: week 9, then every 6 weeks for year 1, and every 12 weeks thereafter
- Data cutoff date for updated analysis: **October 26, 2017**
  - Actual OS events: **417** (400 previously[1])
  - Median follow-up: **27.7** months (median, 22.5 months previously[1])
- PD-L1: assessed centrally using PD-L1 IHC 22C3 pharmDx (Dako)
  - Expression scored using combined positive score (CPS)

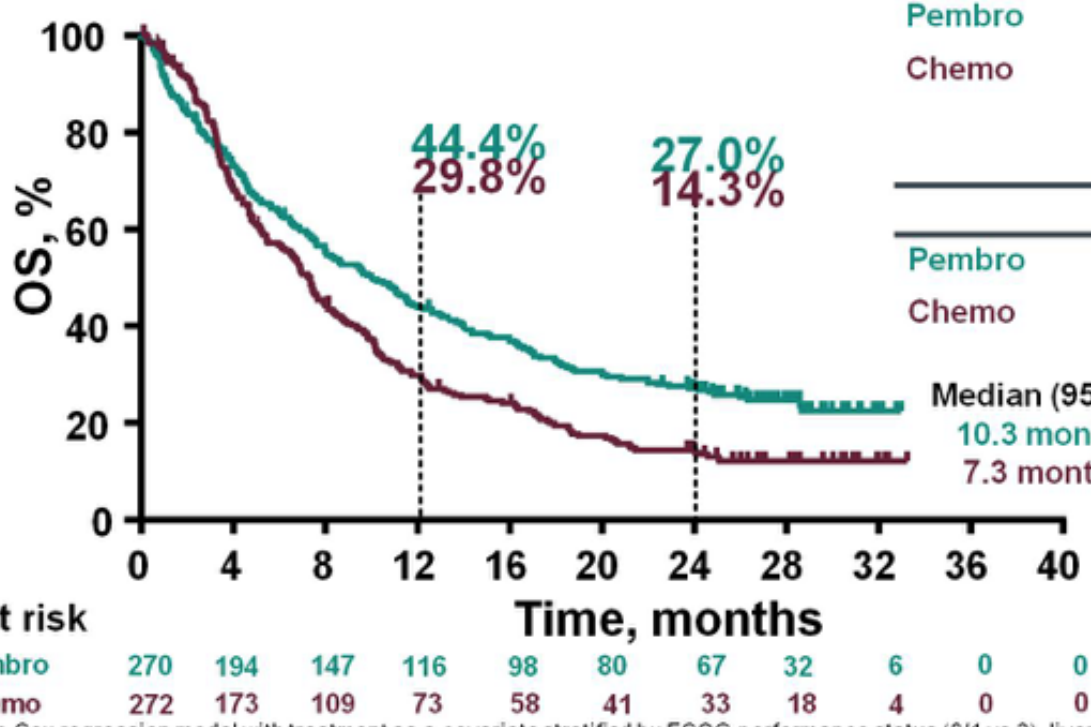
$$\text{CPS} = \frac{\#\text{ PD-L1–staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}}$$



PD-L1–positive cells (tumor cells, macrophages, lymphocytes)

1. de Wit R et al. *Ann Oncol*. 2017;28 (suppl 5):v605-v649.

Overall Survival: Total



14.1 months of follow-up[1]

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

27.7 months of follow-up

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

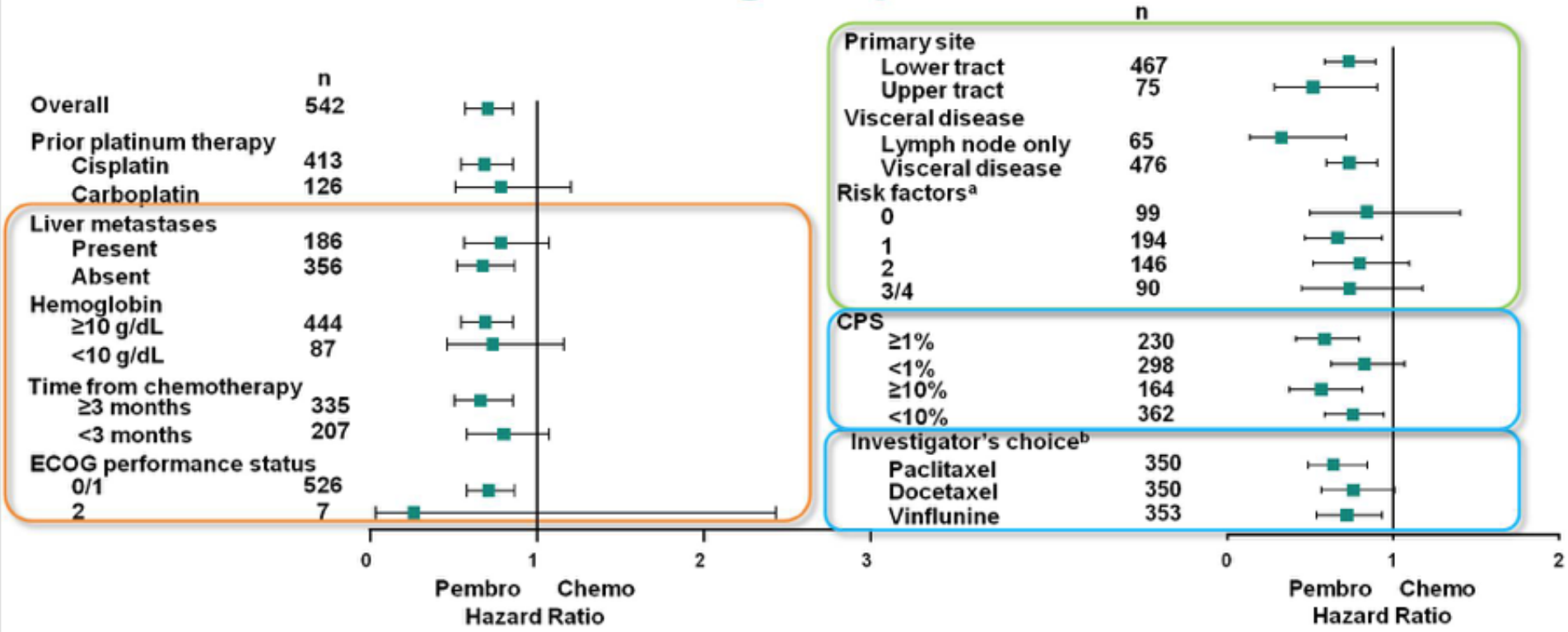
Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.

1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

Overall Survival: Subgroups



[a]Includes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol*. 2010;27:1850-1855) + time from prior chemotherapy <3 months (*Eur Urol*. 2013;63:717-723). [b]N is shown for the chemotherapy arm only. All comparisons were to all patients in the pembrolizumab arm.
Data cutoff date: October 26, 2017.

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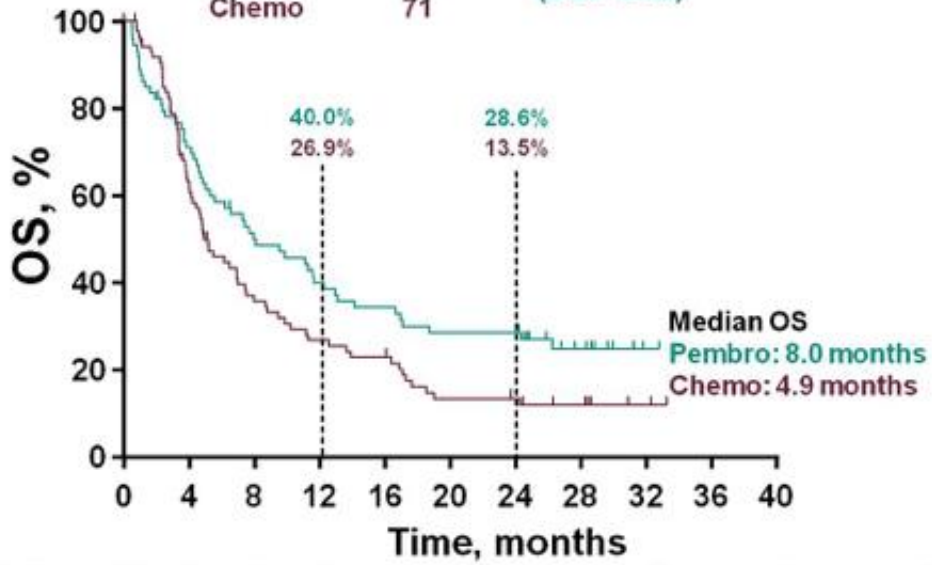
Overall Survival: CPS ≥10 and CPS <10

CPS ≥10

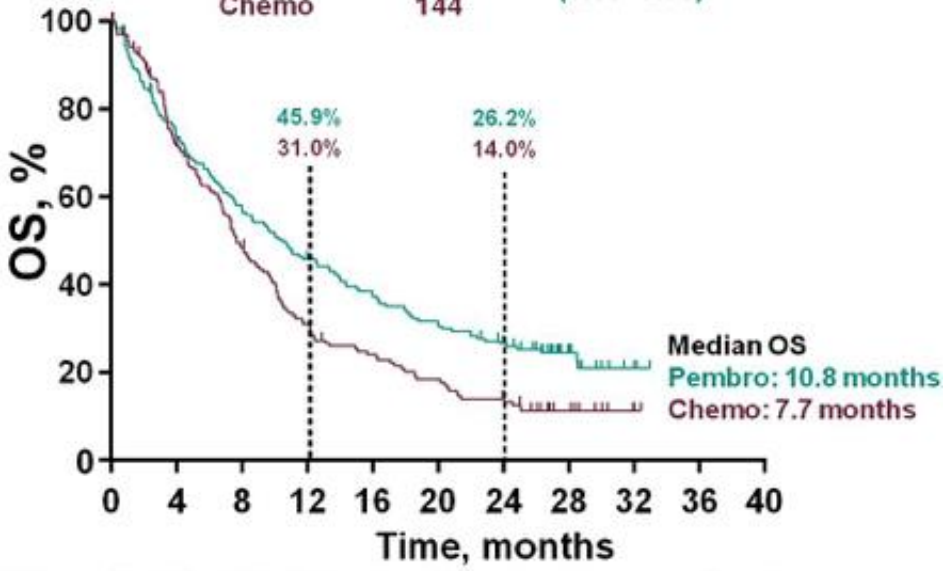
	Events, n	HR (95% CI)[a]	P[b]
Pembro	53	0.56 (0.38–0.82)	0.00153
Chemo	71		



Pembro	74	51	35	28	24	20	20	9	1	0	0
Chemo	90	52	28	21	18	10	9	6	2	0	0

CPS <10

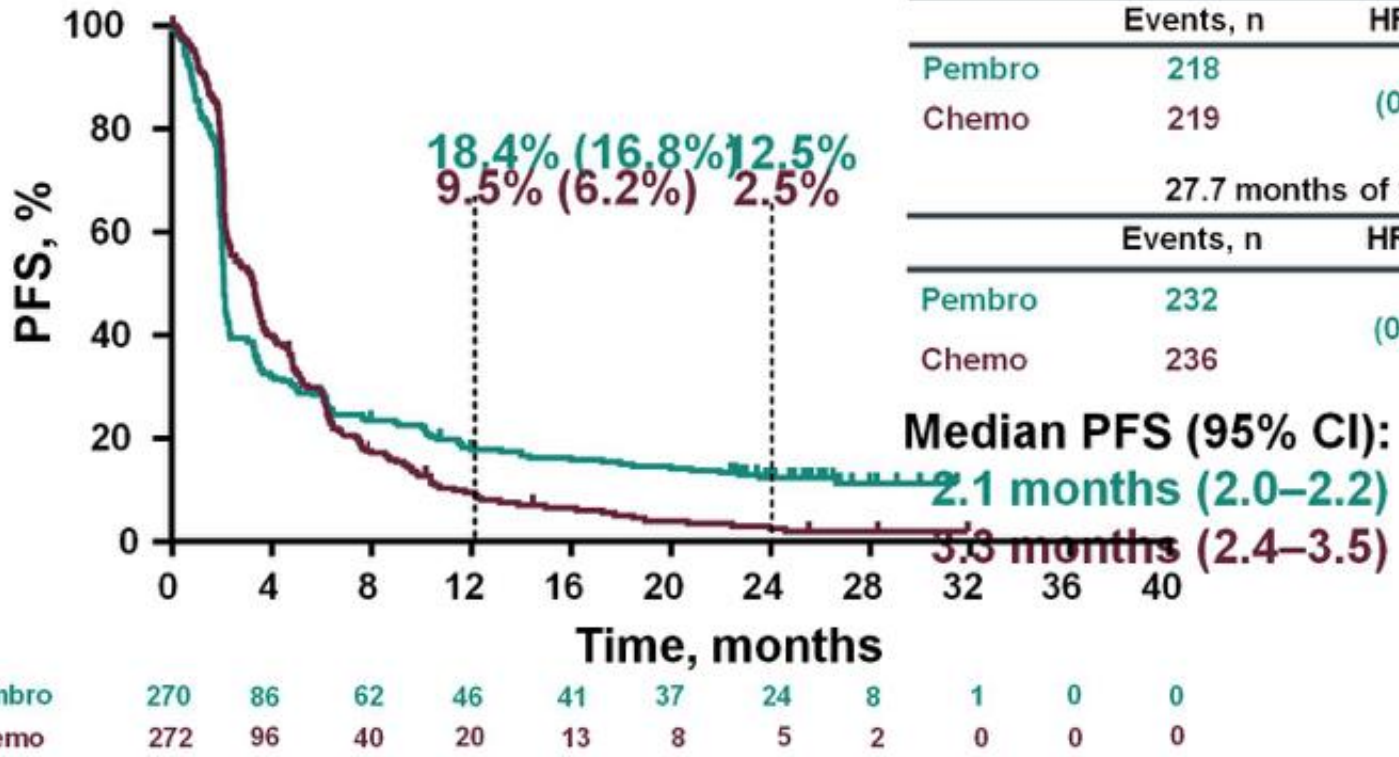
	Events, n	HR (95% CI)[a]	P[b]
Pembro	139	0.75 (0.59–0.95)	0.00859
Chemo	144		



Pembro	186	135	105	83	69	57	44	21	5	0	0
Chemo	176	118	79	50	38	29	22	10	2	0	0

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.

Progression-Free Survival: Total



14.1 months of follow-up[1]

	Events, n	HR (95% CI)	*P*
Pembro	218	0.98 (0.81–1.19)	0.420
Chemo	219		

27.7 months of follow-up

	Events, n	HR (95% CI)	*P*
Pembro	232	0.96 (0.79–1.16)	0.31714
Chemo	236		

Median PFS (95% CI):

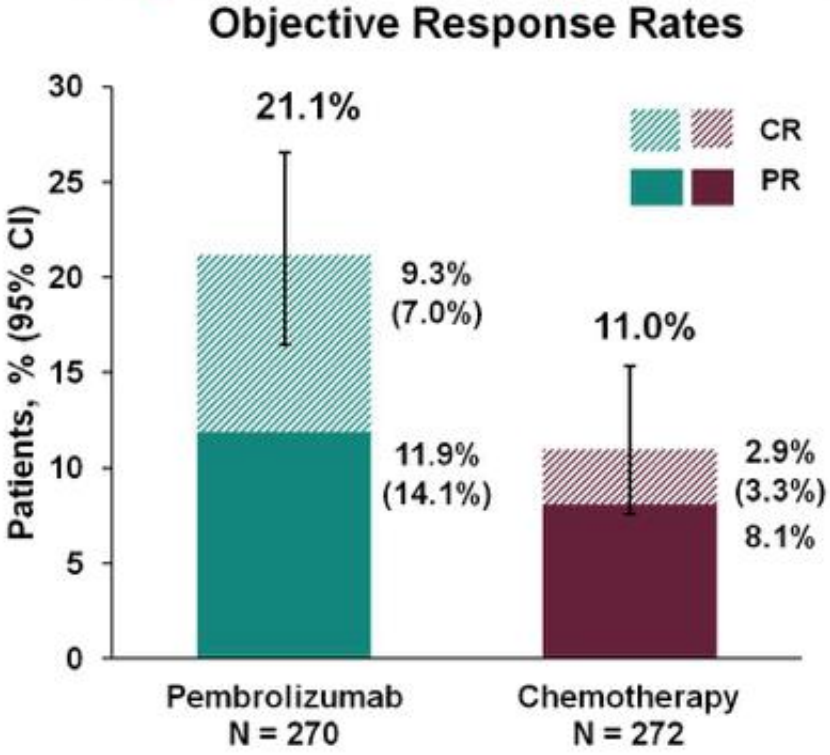
2.1 months (2.0–2.2)

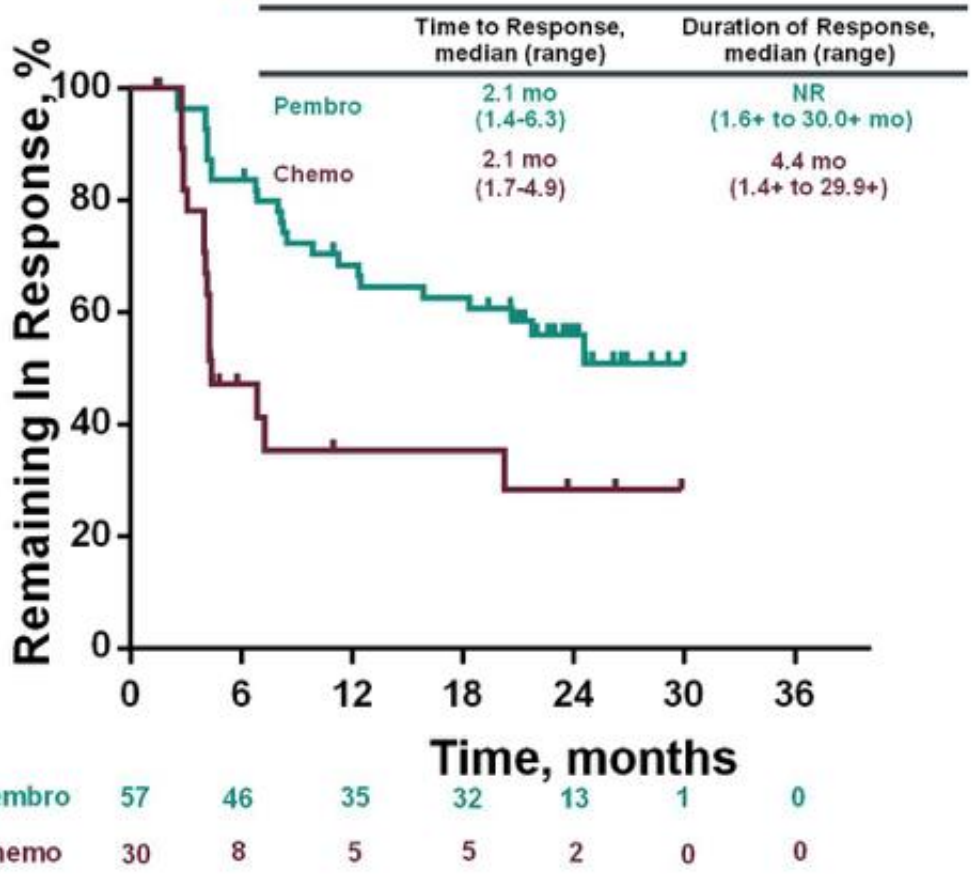
3.5 months (2.4–3.5)

Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: October 26, 2017.

1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

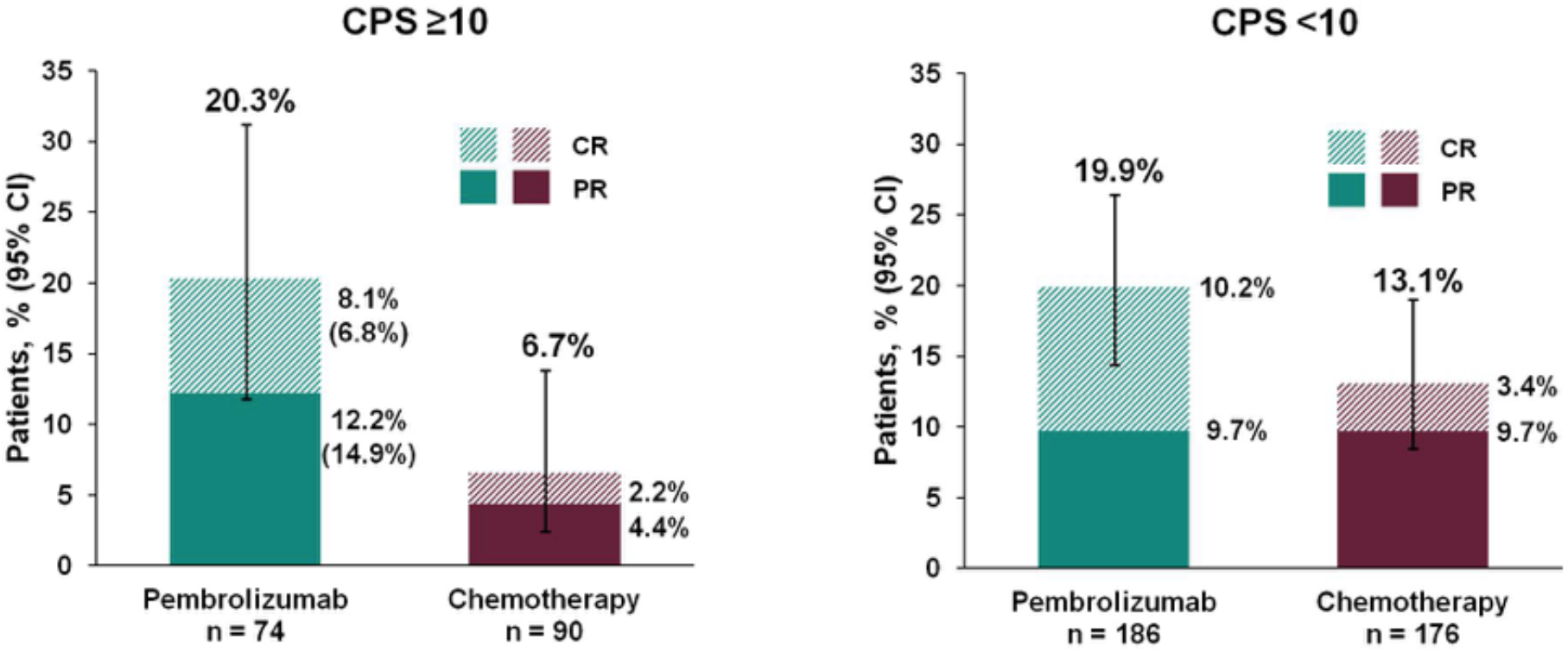
Objective Response and Response Duration





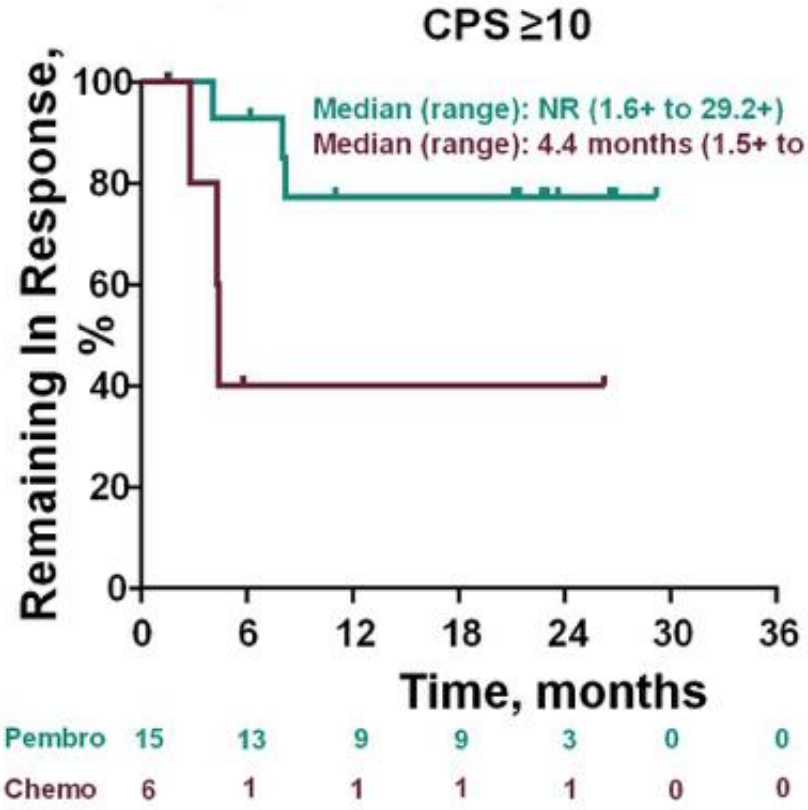
Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: October 26, 2017.

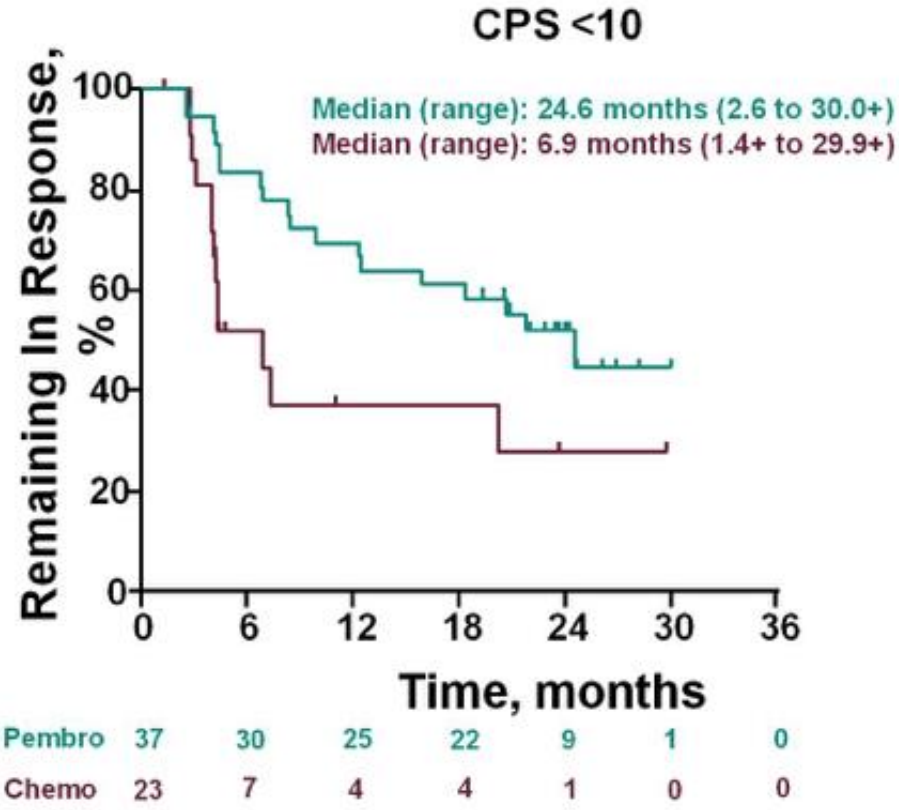
Objective Response by PD-L1 Status



Data cutoff date: October 26, 2017.

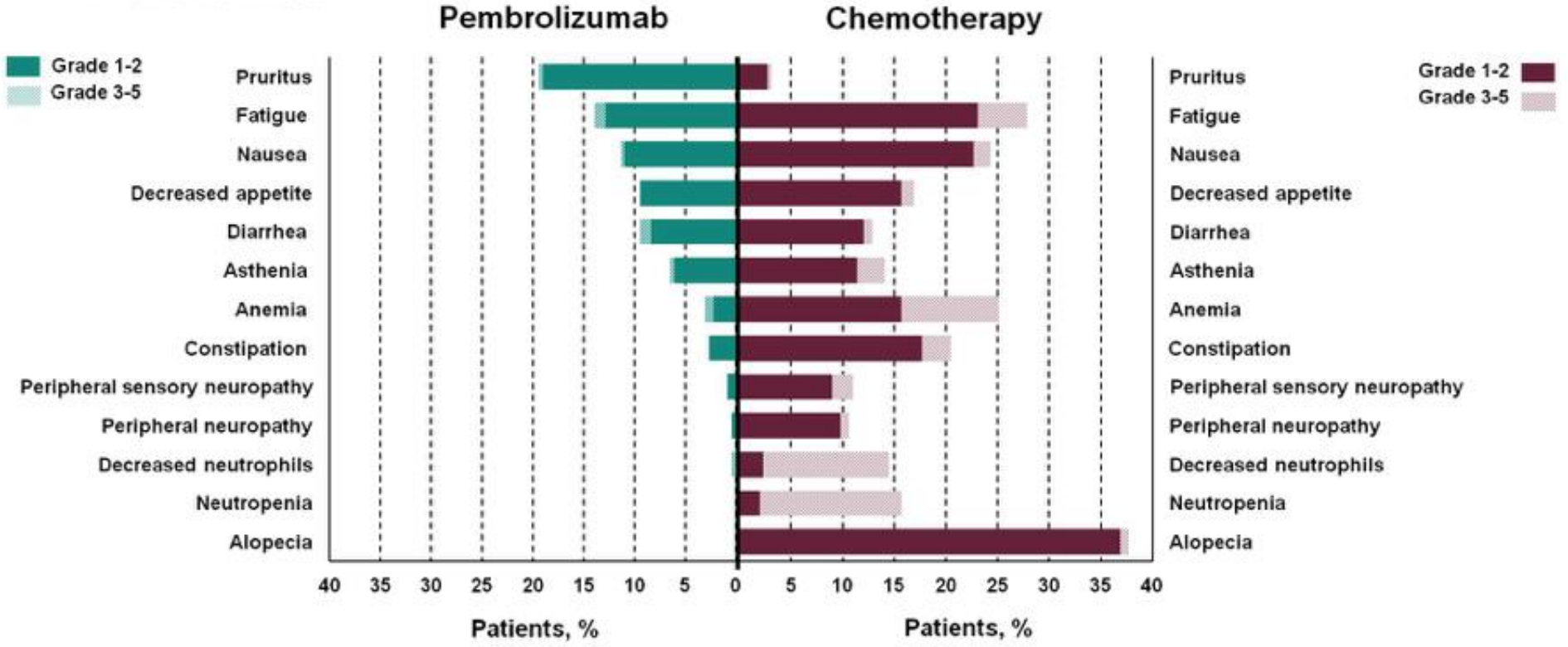
Response Duration by PD-L1 Status





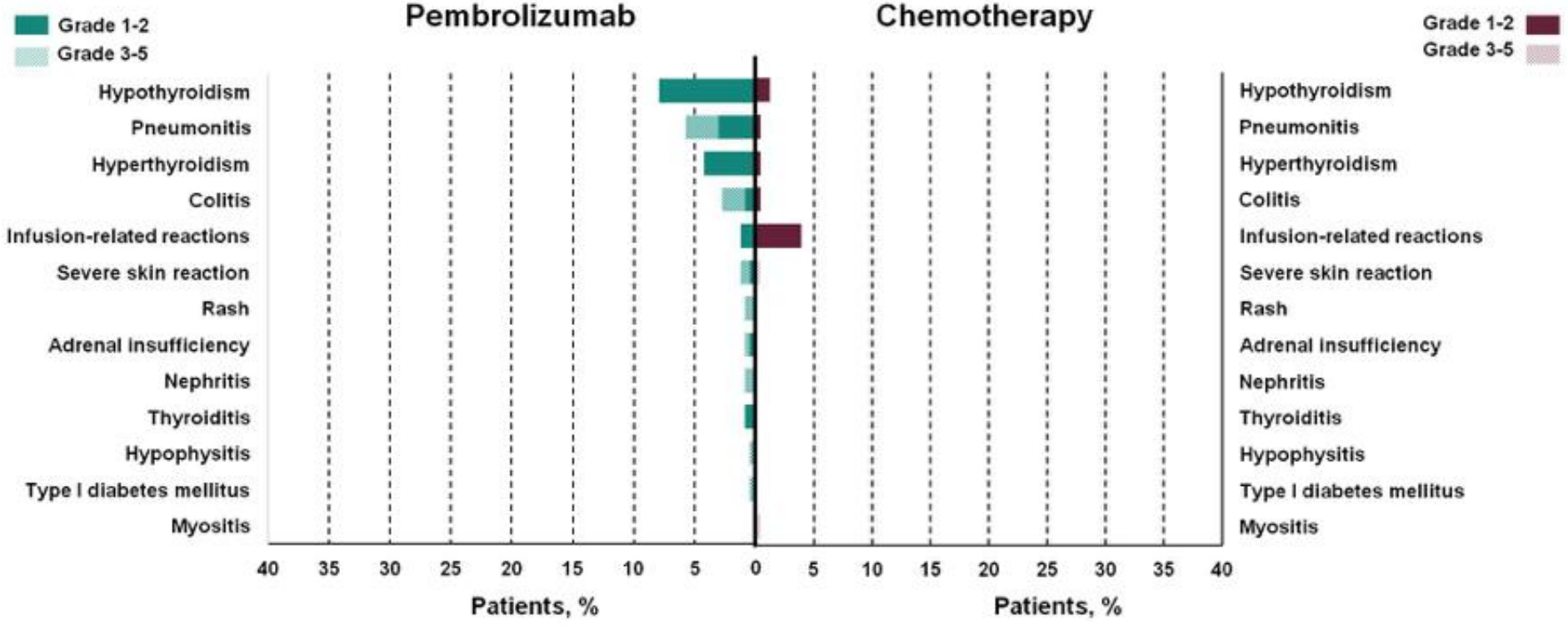
Data cutoff date: October 26, 2017.

Treatment-Related AEs Occurring in ≥10% of Patients[a]



[a]Of patients in either treatment arm.
7.5% febrile neutropenia in the chemotherapy arm.
Data cutoff date: October 26, 2017.

AEs of Interest Occurring in ≥1 Patient[a,b]



[a]Based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included.
[b]In either treatment arm.
Data cutoff date: October 26, 2017.

Conclusions

- Pembrolizumab is the first immunotherapy to demonstrate superior survival over chemotherapy in patients with advanced urothelial carcinoma after failure of platinum-based therapy
- Level 1 evidence supports the use of pembrolizumab as a standard of care for this patient population
- These data have led to the approvals by the FDA, the EMA, and the Japanese Ministry of Health, Labor, and Welfare of pembrolizumab for the treatment of advanced, platinum-resistant/refractory urothelial carcinoma irrespective of PD-L1 status[1]
  - Data obtained after over 2 years of follow-up are consistent with those that led to the approval of pembrolizumab for these patients

1. Merck Sharp & Dohme Corp (pembrolizumab) injection, for intravenous use. Whitehouse Station, NJ USA; 09/2017.

Atezolizumab vs Chemotherapy in Platinum-Treated Locally Advanced or Metastatic Urothelial Carcinoma: Immune Biomarkers, Tumor Mutational Burden and Clinical Outcomes From the Phase III IMvigor211 Study

Thomas Powles,[1] Yohann Loriot,[2] Alain Ravaud,[3] Nicholas J. Vogelzang,[4] Ignacio Duran,[5] Margitta Retz,[6] Ugo De Giorgi,[7] Stephane Oudard,[8] Aristotelis Bamias,[9] Hartmut Koeppen,[10] Ning Leng,[10] Edward E. Kadel III,[10] Priti S. Hegde,[10] Na Cui,[10] Xiaodong Shen,[10] Christina L. Derleth,[10] Marjorie Green,[10] Romain Banchereau,[10] Sanjeev Mariathasan,[10] Michiel S. van der Heijden[11]

[1]Barts Cancer Institute, Queen Mary University of London, London, UK; [2]Gustave Roussy, Villejuif, France; [3]Hôpital Saint-André CHU, Bordeaux, France; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [5]Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain; [6]Technische Universität München, Munich, Germany; [7]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Istituto di Ricovero e Cura a Carattere Scientifico, Meldola, Italy; [8]Hôpital Européen Georges-Pompidou, Paris, France; [9]National and Kapodistrian University of Athens Alexandra Hospital, Athens, Greece; [10]Genentech, Inc., South San Francisco, CA, USA; [11]Netherlands Cancer Institute, Amsterdam, the Netherlands

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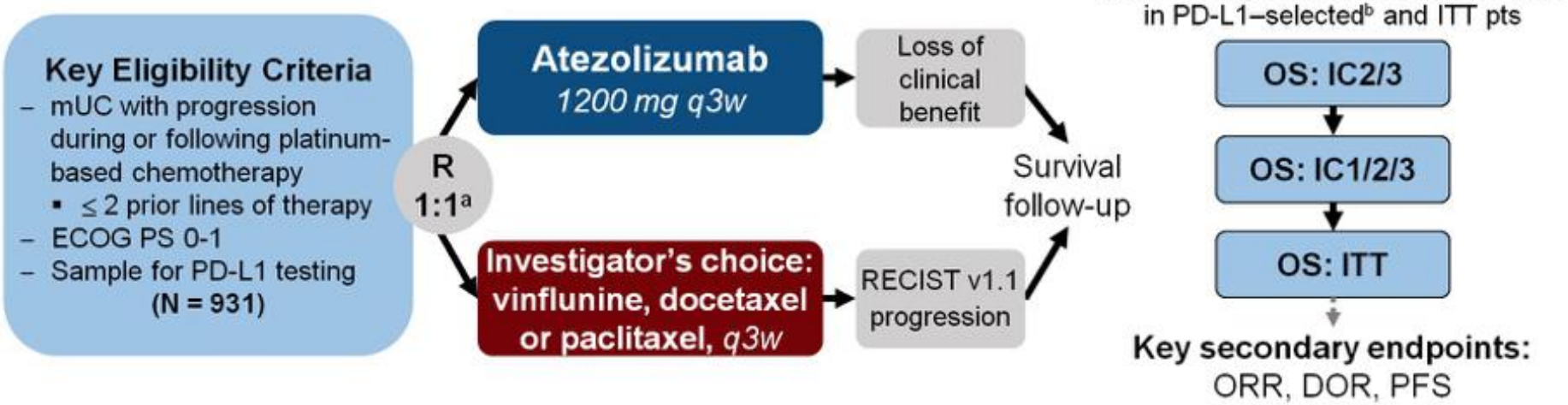
Phase III IMvigor211 Trial Design



- **Key exploratory endpoint:** relationship between tumor immune specific– or disease-related biomarkers and efficacy
- ***Objectives of this analysis:*** *compare clinical outcomes in ITT and PD-L1 subgroups vs those defined by tumor gene expression (tGE) signatures and tumor mutational burden (TMB)*

ClinicalTrials.gov ID, NCT02302807. IC, tumor-infiltrating immune cell.
[a] Stratification factors: 0 vs 1/2/3 risk factors (time from prior chemotherapy < 3 mo, ECOG PS > 0 and hemoglobin < 10 g/dL), yes vs no liver metastases, PD-L1 IC0/1 vs IC2/3 status, vinflunine vs taxane selection. [b] PD-L1 expression on IC assessed per VENTANA SP142 IHC assay: scored as IC3 (≥ 10%), IC2 (≥ 5% and < 10%).

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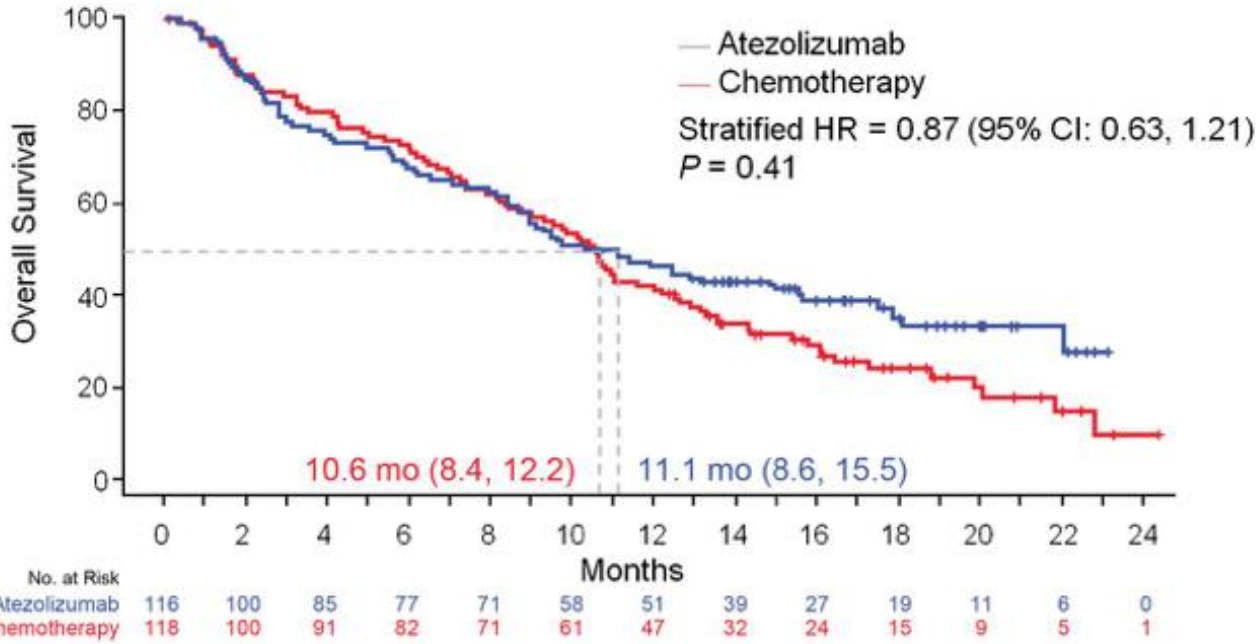
OS Analysis in PD-L1 IC2/3 Population



Powles *Lancet*. 2017. Median follow-up duration: 17.3 mo (range 0-24.5 mo).

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OS: IC2/3

OS: IC1/2/3

OS: ITT

- Based on OS results in the PD-L1 IC2/3 population, the primary endpoint was not met

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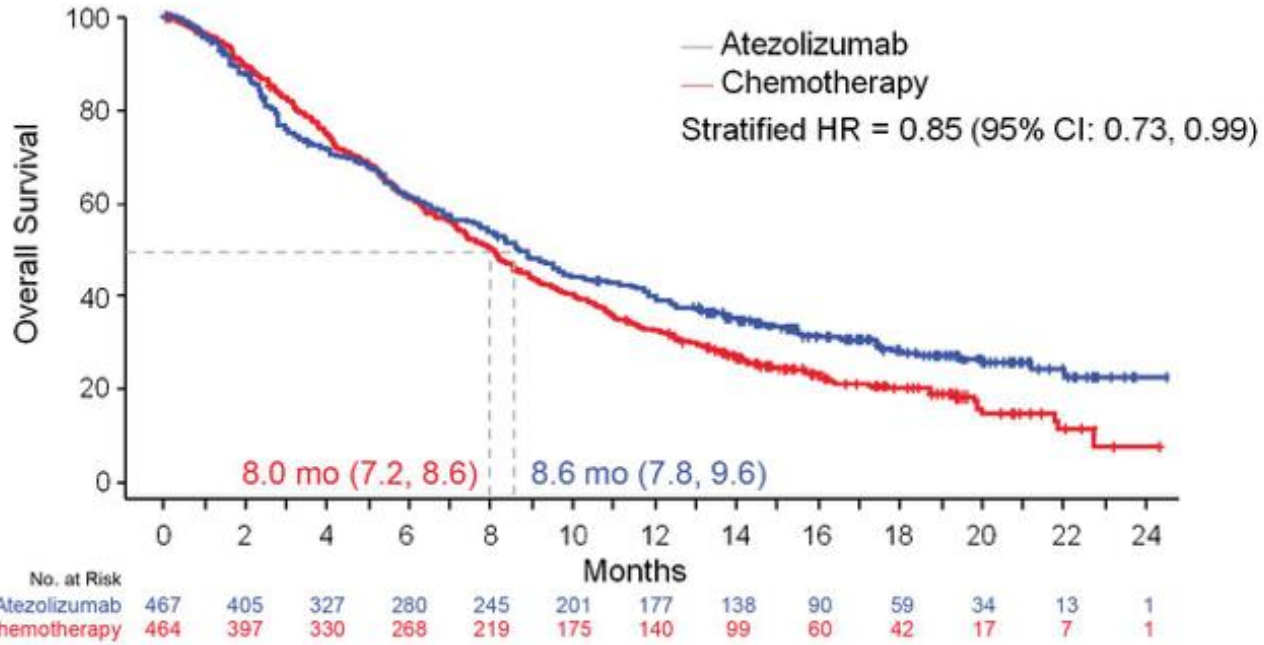
OS Analysis in ITT Population



OS: IC2/3
↓
OS: IC1/2/3
↓
OS: ITT

- Exploratory analyses in the ITT population demonstrated improved OS with atezolizumab vs chemotherapy

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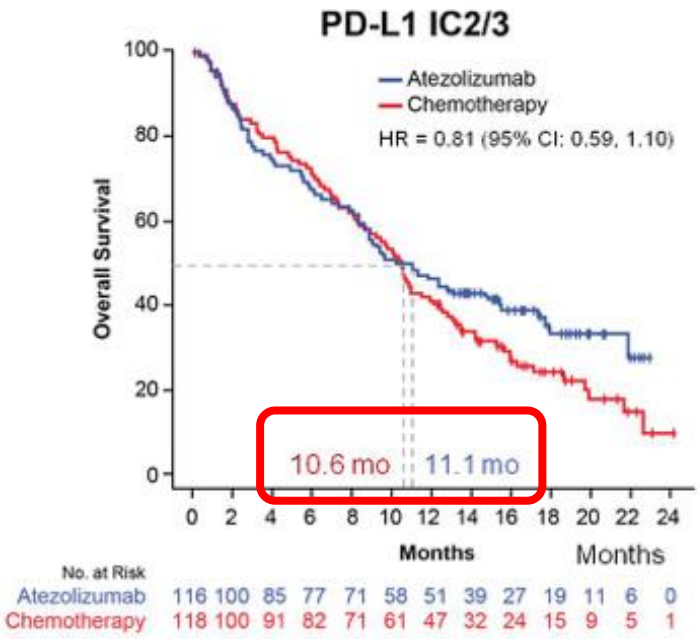
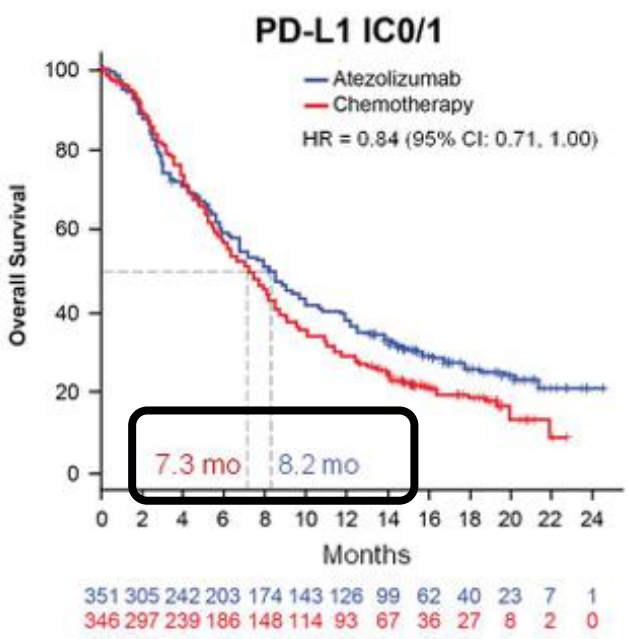
OS by PD-L1 IC Status





- In our study design, we hypothesized that efficacy was associated with PD-L1 status
- Unexpectedly, PD-L1 overexpression resulted in favorable outcomes in both arms
- Subsequent biomarker analyses focused on the ITT population

Unstratified HRs are displayed. Reprinted in part from *The Lancet*, Powles T, et al. 2017 Dec 18. [Epub]. © 2017, with permission requested from Elsevier.

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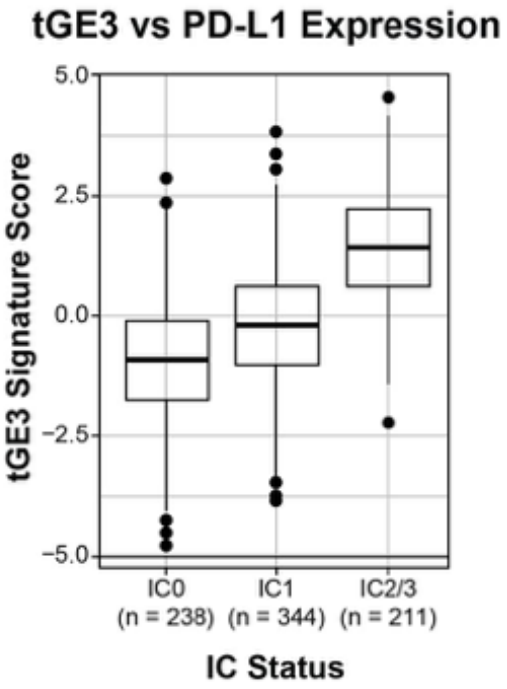
Additional Biomarker Analyses: tGE3

- The 3-gene "tGE3" signature was developed as a surrogate of PD-L1 IHC expression and pre-existing immunity[1-5]
  - *IFNG* encodes interferon gamma
  - *CXCL9* encodes C-X-C motif chemokine ligand 9
  - *CD274* encodes PD-L1
- RNA sequencing was used, and 793 patients were tGE3 evaluable



1. Rosenberg *Lancet* 2016. 2. Balar *Lancet* 2017. 3. Rusinova *Nucleic Acids Res* 2013. 4. Kowanetz WCLC 2017. 5. Mariathasan *Nature* in press.

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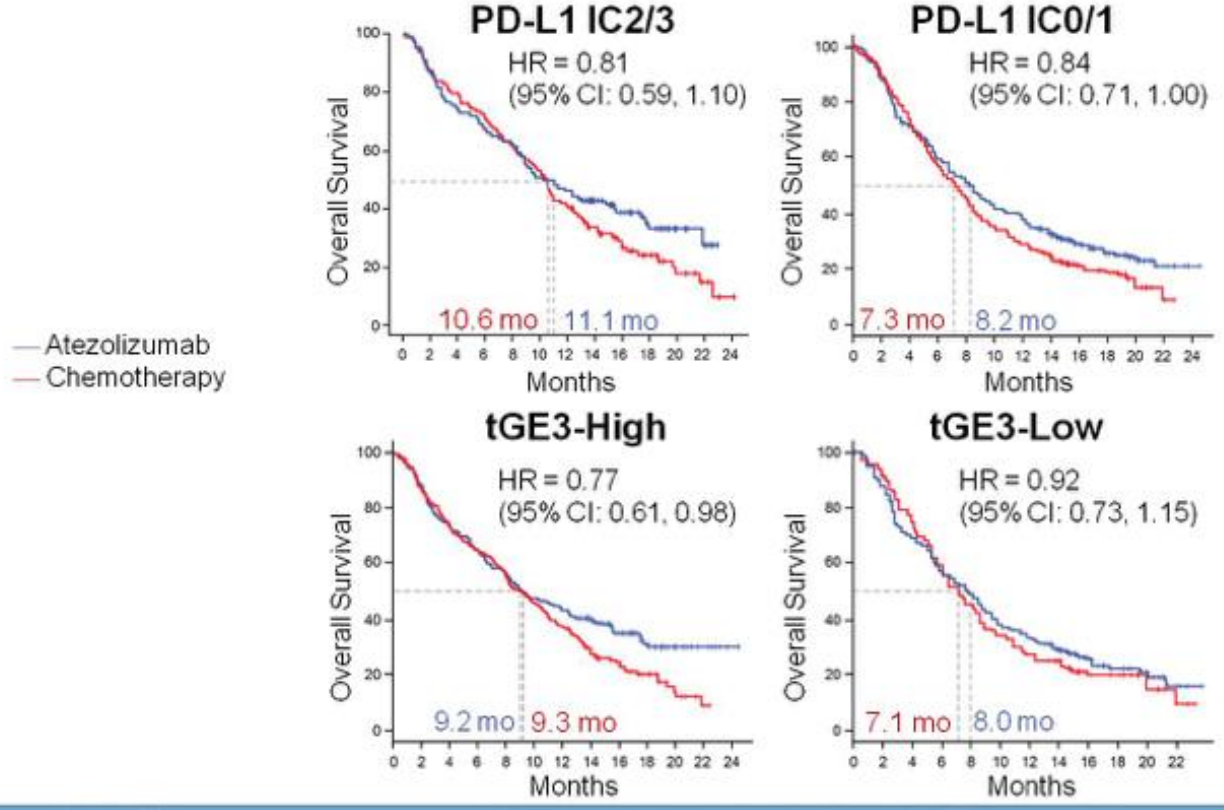
Similar OS Trend in tGE3 and PD-L1 IC Subgroups



- tGE3 results were comparable to results based on PD-L1 IC
- tGE3-high tumor status was associated with better prognosis in both arms
- PD-L1 IC enriches for tumors with higher pre-existing T-effector immunity

Unstratified HRs are displayed.
[a] Assessment cutoffs were defined by median scores for tGE.
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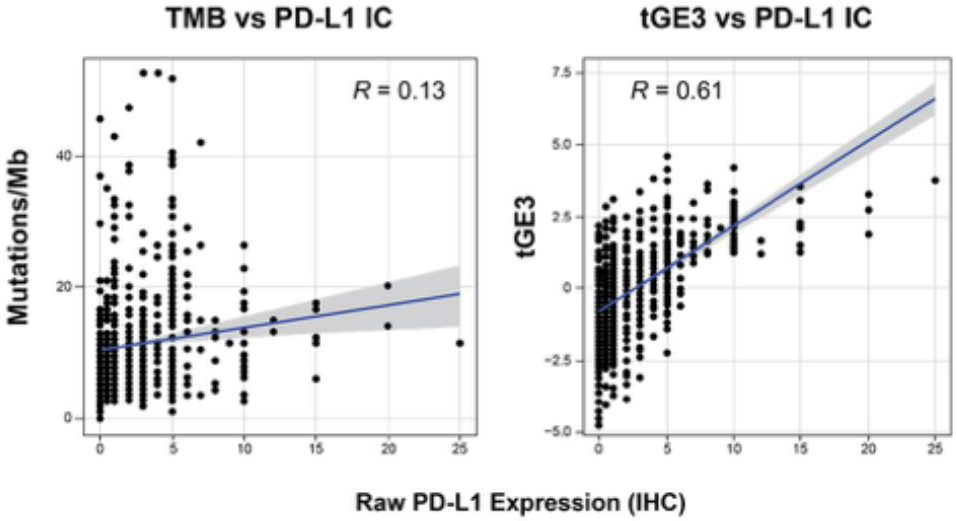
Additional Biomarker Analyses: TMB (cont)

- mUC has high mutation burden that may contribute to increased immunogenicity[1-3]
  - PD-L1 IC does not correlate with TMB (FoundationOne panel)[4]
  - By contrast, PD-L1 IC correlates with tGE3
- PD-L1 IC (tGE3) and TMB measure distinct biological features
- OS in 544 TMB-evaluable patients recapitulated ITT data (n = 931)
  - Baseline characteristics (e.g., PD-L1 IC status,[4] histology and liver metastases) were balanced between arms



Mb, megabase. 1. Lawrence *Nature* 2013. 2. Kandoth *Nature* 2013. 3. TCGA *Nature* 2014. 4. Powles *Lancet* 2017.

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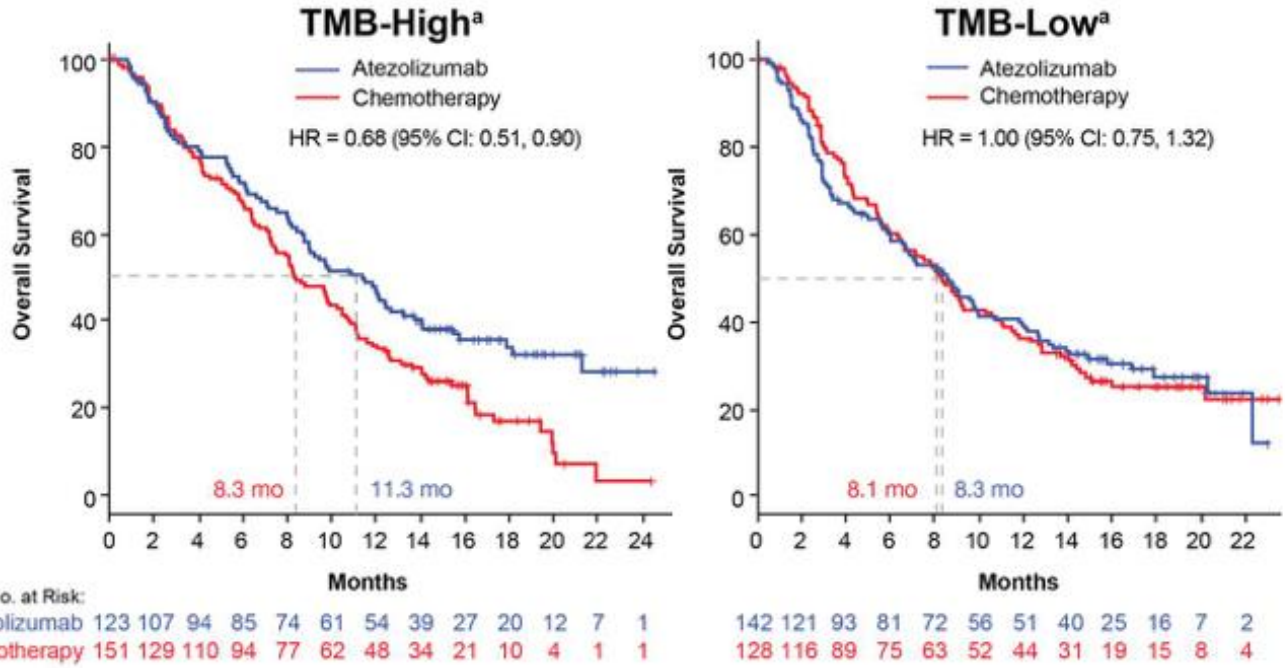
OS by TMB



- In the TMB-high subgroup, mOS was numerically longer with atezolizumab
- Complete and partial responses and prolonged OS were observed in subgroups of patients with TMB-low tumors in both arms

Unstratified HRs are displayed. [a] Median scores were used to define assessment cutoffs: TMB-high (≥ median) or TMB-low (< median). Median TMB in the biomarker-evaluable population was 9.65 mutations/Mb. Reprinted from *The Lancet*, Powles T, et al. 2017 Dec 18. [Epub]. © 2017, with permission requested from Elsevier.

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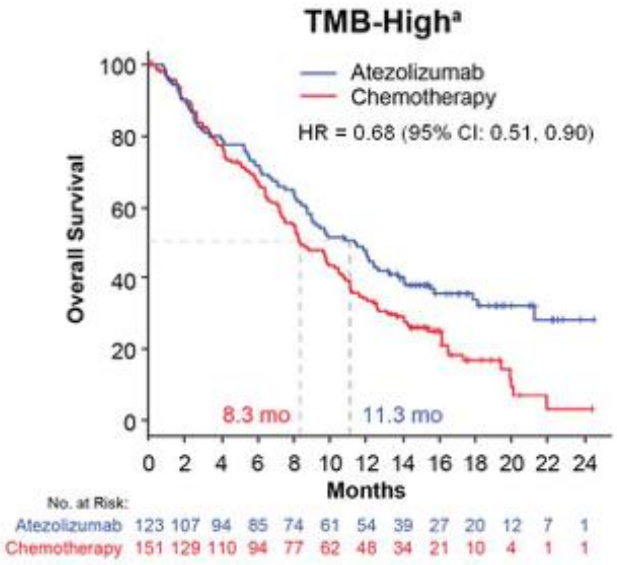
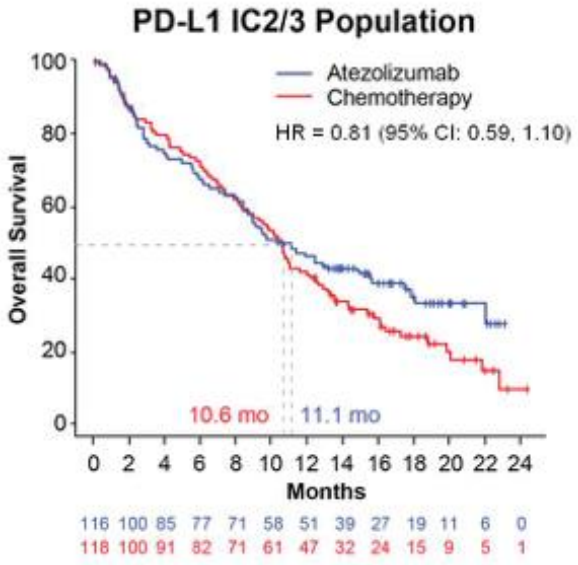
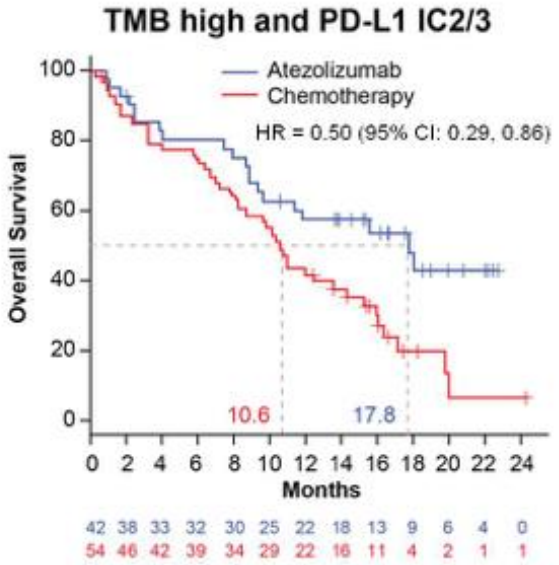
OS by TMB and PD-L1 Status







- Improved OS benefit was observed in patients with high TMB as well as high PD-L1 IC scores

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Conclusions

- The primary endpoint of OS in PD-L1–selected patients was not met in IMvigor211, but OS advantage was observed with atezolizumab in the ITT population in exploratory analysis
- tGE3 was used to further investigate unexpected PD-L1 results, and like PD-L1, it selected for good outcomes in both arms
- High TMB was associated with OS favoring atezolizumab but not chemotherapy, suggesting that it may be an independent predictor of clinical benefit
- DDR mutations correlated with increased TMB but did not enrich for increased efficacy in the atezolizumab arm
- Combinations of distinct biomarkers should be explored in prospective studies

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