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Age, tumor biology and treatment outcomes in advanced renal cell carcinoma: a post hoc analysis of JAVELIN Renal 101

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Abstract

Whether age affects the relative efficacy of treatments for advanced clear-cell renal cell carcinoma remains unclear. We conducted a post hoc analysis of individual patient data from the final analysis of the phase III JAVELIN Renal 101 trial, which randomized 886 patients to avelumab plus axitinib or sunitinib. We assessed progression-free survival (PFS) and overall survival (OS) using a 65-year age cutoff, with 60- and 70-year cutoffs in sensitivity analyses and examined age-related tumor gene-expression patterns in 726 participants. Among 885 evaluable patients, the PFS hazard ratio for avelumab plus axitinib versus sunitinib was 0.64 (95% confidence interval 0.53–0.78) in patients aged <65 years and 0.79 (0.61–1.01) in those aged ≥65 years. The treatment-by-age interaction was not statistically significant (*P* for interaction = 0.080), and no OS interaction was observed. In exploratory analyses within each treatment group, older patients receiving sunitinib had longer PFS at the 65- and 70-year cutoffs, whereas PFS with avelumab plus axitinib was similar across age groups. Younger age was associated with enrichment of proliferative, inflammatory, and immune-infiltrated tumor gene-expression signatures. Chronological age did not significantly modify relative treatment efficacy at the primary cutoff; these exploratory clinical and biological findings require independent validation.

Keywords: clear-cell renal cell carcinoma; avelumab plus axitinib; immune checkpoint inhibitor; age factors; transcriptome.

Introduction

Renal cell carcinoma (RCC) represents approximately 2–3% of all adult malignancies worldwide, and approximately 20–30% of patients have metastatic disease at the initial diagnosis, with a 5-year survival rate of approximately 12% [1]. The treatment of metastatic RCC has changed substantially with the development of immune checkpoint inhibitor (ICI)-based combination therapies. Several phase III randomized trials have established ICI plus tyrosine kinase inhibitor (TKI) combinations as first-line treatment for advanced clear-cell RCC [2]. Avelumab plus axitinib, evaluated in the phase III JAVELIN Renal 101 trial, also

demonstrated a significant and durable progression-free survival (PFS) benefit over sunitinib at the final analysis with a minimum follow-up of 68 months, representing the longest follow-up among ICI plus TKI phase III trials reported to date [3].

The number of RCC cases in older adults is steadily increasing in parallel with an increase in the elderly population [4]. Immunosenescence, which encompasses impaired effector T-cell responses, contraction of the naïve T-cell pool, and reduced T-cell receptor repertoire diversity, is a well-characterized consequence of aging [5]. Aging also modifies tumor biology through inflammaging, altered tumor-infiltrating immune cell composition, and metabolic reprogramming within the tumor microenvironment [6]. Recent transcriptomic profiling of clear-cell RCC has further revealed age-dependent molecular signatures and distinct clinical stratification patterns, indicating that tumors from younger and older patients can differ in their underlying biology [7]. These observations have raised questions regarding whether aging influences the relative efficacy of ICI-based therapy [8,9]. Accumulating evidence suggests that the clinical benefit of ICI therapy is largely preserved in elderly patients across multiple tumor types, although heterogeneity exists across settings and treatment lines [10,11]. A previous subgroup analysis from this trial reported that the clinical benefit of avelumab plus axitinib was maintained in older patients. However, that analysis was limited to descriptive comparisons without formal treatment-by-age interaction testing and was conducted at a timepoint when overall survival (OS) data were still immature and follow-up was ongoing [12].

In the present study, we performed a post hoc analysis using individual patient data from the final analysis of the phase III JAVELIN Renal 101 trial to evaluate whether age modifies the treatment effect of avelumab plus axitinib versus sunitinib on PFS and OS. In addition, we applied Gene Set Enrichment Analysis (GSEA) to characterize age-associated differences in tumor transcriptomic profiles. To our knowledge, no prior study has directly integrated transcriptomic profiling with differential treatment effects of ICI-based versus vascular endothelial growth factor receptor (VEGFR)-TKI therapy within a randomized phase III clinical trial.

Patients and Methods

Study design and data sources

This study was a post hoc analysis of the JAVELIN Renal 101 trial (NCT02684006), a phase III, open-label, randomized controlled trial comparing first-line avelumab plus axitinib with sunitinib in patients with previously untreated advanced clear-cell RCC. The original trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The trial protocol, amendments, and informed consent forms were approved by the institutional review board or independent ethics committee at each participating site, and all participants provided written informed consent. Details of the trial design and eligibility criteria have been reported previously [13]. Anonymized individual patient data from the final analysis, with a minimum follow-up of 68 months and a data cutoff consistent with the final publication, were obtained from Merck, following a formal data request. Due to anonymization procedures, continuous age data were not available. Age was provided in anonymized categories, typically as single-year age bands where numbers were sufficient and as broader age ranges where numbers were small. Binary age groups were subsequently constructed using 60-, 65-, and 70-year cutoffs. Separately, exploratory bulk RNA-sequencing analyses were conducted using data from 726 trial participants obtained from a previously published dataset [14]. These data included continuous age values but could not be linked to the Merck-provided individual patient data or to individual PFS/OS outcomes; therefore, the transcriptomic analyses were independent of the clinical age-effect analyses and were used to provide biological context only.

Patient population

The original trial enrolled 886 patients randomized 1:1 to avelumab plus axitinib (n = 442) or sunitinib (n = 444), stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and geographic region (United States vs Canada/Western Europe vs rest of the world) [3]. The present analysis included all randomized patients with available age group data. One patient in the avelumab plus axitinib arm was excluded due to missing age information, resulting in an analytic cohort of 885 patients (avelumab plus axitinib, n=441; sunitinib, n=444).

Age grouping and analysis thresholds

The primary analysis compared outcomes between patients <65 years of age and those ≥65 years of age, in accordance with the definition of elderly patients established by the

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E7 guideline [15]. Sensitivity analyses were performed using age thresholds of 60 and 70 years, which are commonly employed in geriatric oncology and RCC studies, to assess the robustness of the findings across alternative, clinically relevant cutoffs.

Clinical endpoints

The primary endpoint of this analysis was PFS, defined as the time from randomization to the first occurrence of disease progression, as assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause. The secondary endpoint was OS, defined as the time from randomization to death from any cause, consistent with the original trial definitions [16].

Statistical analysis

PFS and OS were estimated using the Kaplan-Meier method, and differences between subgroups were assessed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. To evaluate whether the relative treatment effect of avelumab plus axitinib versus sunitinib differed by age group, a treatment-by-age interaction term was included in Cox models stratified by geographic region and ECOG performance status, and the likelihood ratio test was used to calculate *P* values for interaction. Sensitivity analyses incorporated clinically relevant covariates, including International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score, sex, and programmed death ligand 1 (PD-L1) expression [17,18]. The proportional hazards assumption was assessed for the primary Cox models using Schoenfeld residual tests. Models that violated the assumption were interpreted with appropriate caution and supplemented by a restricted mean survival time (RMST) analysis, which was performed as a sensitivity analysis. This study was a post hoc, exploratory analysis, and no adjustment for multiple comparisons was performed given its hypothesis-generating nature. Statistical significance for all analyses, including treatment-by-age interaction tests, was defined as a two-sided *P* value <0.05, consistent with the threshold used in the primary trial analysis. Differences in baseline characteristics between age groups were assessed using the chi-square test or Fisher's exact test when expected cell counts were <5. All statistical analyses were performed using R (ver. 4.5.0,

R Foundation for Statistical Computing, Vienna, Austria).

Gene set enrichment analysis

GSEA was performed in a preranked framework, using continuous age as the ranking variable by computing gene-wise Spearman correlation coefficients with age, against two gene set collections from the Molecular Signatures Database (MSigDB) v7.4: the Hallmark collection (H) and the immunologic signature gene sets (C7). Normalized enrichment scores and false discovery rate (FDR) q-values were calculated; gene sets with FDR <0.25 were considered significantly enriched, in accordance with standard GSEA methodology. This analysis was conducted to explore whether age-associated differences in immune-related transcriptomic pathways may provide biological context for the observed clinical findings.

Results

1. Patient Characteristics

A total of 885 patients were included in this analysis: 441 in the avelumab plus axitinib arm (age <65 years, n = 270; age ≥65 years, n = 171) and 444 in the sunitinib arm (age <65 years, n = 275; age ≥65 years, n = 169). In the overall cohort, combining both treatment arms, baseline clinical and disease characteristics were generally comparable between patients aged <65 years and those aged ≥65 years (Table 1).

2. Efficacy of Avelumab Plus Axitinib Versus Sunitinib by Age Group: PFS and OS

In the primary analysis using a 65-year age threshold, avelumab plus axitinib demonstrated a statistically significant PFS benefit over sunitinib in patients <65 years of age (HR 0.64, 95% CI 0.53–0.78; $P < 0.001$), whereas the magnitude of benefit was attenuated in those ≥65 years of age (HR 0.79, 95% CI 0.61–1.01; $P = 0.065$). The P value for the treatment-by-age interaction was 0.080 (Table 2). Sensitivity analyses using 60- and 70-year thresholds showed a nominal treatment-by-age interaction at the 70-year cutoff (P for interaction = 0.029). However, the ≥70-year subgroup was small, and the treatment-effect estimate was imprecise (HR 1.10, 95% CI 0.71-1.70). This exploratory finding should be interpreted as hypothesis-generating rather than

confirmatory because analyses across overlapping age cutoffs were not adjusted for multiple comparisons. Kaplan–Meier curves for PFS by age subgroup are shown in Fig. 1A and 1B, and forest plots of treatment effects across age thresholds in Fig. 1C. Sensitivity analyses at 60- and 70-year cutoffs are provided in Supplementary Figs. S1–S2 and S3–S4, respectively. In contrast, no age threshold yielded a statistically significant treatment-by-age interaction for OS. At the primary 65-year cutoff, the HR for OS was 0.88 (95% CI 0.71–1.08; $P = 0.219$) in patients <65 years of age and 0.97 (95% CI 0.75−1.27; $P = 0.851$) in those ≥65 years of age (P for interaction = 0.585). Although a directionally consistent trend favoring avelumab plus axitinib in younger patients was observed across all cutoffs, none reached statistical significance for the OS interaction. Kaplan–Meier curves for OS by age subgroup are shown in Figs. 1D and 1E, and forest plots of treatment effects across age thresholds in Fig. 1F. The proportional hazards assumption was satisfied across all age thresholds and endpoints (Supplementary Table S1). Additional adjustment for IMDC risk category, sex, and PD-L1 expression status did not materially change the overall pattern of treatment-by-age interaction estimates for PFS or OS (Supplementary Table S2). This analysis used complete-case data and was stratified by ECOG performance status and geographic region.

3. Age-Dependent PFS Outcomes with Sunitinib

To explore the impact of age on outcomes within each treatment arm, we performed Kaplan–Meier analyses and fitted Cox proportional hazards models stratified by ECOG performance status and geographic region. As these within-arm comparisons were not based on randomization, baseline characteristics were assessed for potential confounding. Baseline clinical and disease characteristics were generally comparable between younger and older patients in both treatment arms (Supplementary Table S3). In the primary analysis using a 65-year age cutoff, younger patients treated with sunitinib (age <65 years) had significantly shorter PFS than older patients (age ≥65 years) (HR 0.77, 95% CI 0.62–0.97; $P = 0.028$; median PFS, 7.9 vs 11.1 months) (Fig. 2A). In contrast, no meaningful age-related difference in PFS was observed among patients receiving avelumab plus axitinib (HR 1.01, 95% CI 0.81–1.27; $P = 0.905$; median PFS 12.9 vs 14.1 months) (Fig. 2B). These findings were consistent across alternative cutoffs, with the most pronounced difference observed at the 70-year threshold and no significant difference at the 60-year cutoff (Table 3). The proportional hazards assumption

was satisfied in the avelumab plus axitinib arm but violated in the sunitinib arm (Supplementary Table S4). RMST analysis supported the age-related PFS difference with sunitinib, with the RMST difference (age <65 years minus age ≥65 years) increasing from −1.5 months at 12 months to −3.5 months at 36 months (Supplementary Table S5). For OS, no significant age-dependent difference was observed in either arm (sunitinib: HR 0.99, 95% CI 0.78–1.26, *P* = 0.957; avelumab plus axitinib: HR 1.08, 95% CI 0.84–1.37, *P* = 0.551; Fig. 2C–D), and the proportional hazards assumption was satisfied in both comparisons (Supplementary Table S4). As these within-arm comparisons are not based on randomization and were derived from a post hoc, exploratory framework, they should be interpreted as hypothesis-generating rather than as evidence of a causal age-by-treatment effect within the sunitinib arm.

4. Transcriptomic Features Associated with Patient Age

To explore the biological basis underlying the age-dependent differences in treatment outcomes, we performed exploratory GSEA, using continuous age as a preranked variable, without applying a predefined age cutoff, against the Hallmark and immunologic signature (C7) gene set collections in MSigDB v7.4. Accordingly, enrichment is described in relation to lower or higher age rather than predefined age groups. In the Hallmark collection, gene sets associated with aggressive tumor biology were prominently enriched at lower age. Proliferation-related pathways, including MYC_TARGETS_V1, G2M_CHECKPOINT, E2F_TARGETS, and MTORC1_SIGNALING, were among the most significantly enriched, and EPITHELIAL_MESENCHYMAL_TRANSITION was also enriched at lower age. TNFA_SIGNALING_VIA_NFKB and INFLAMMATORY_RESPONSE were likewise enriched at lower age. In contrast, higher age was associated with enrichment of metabolic gene sets, including BILE_ACID_METABOLISM, FATTY_ACID_METABOLISM, and XENOBIOTIC_METABOLISM (Fig. 3A; Supplementary Table S6). In the C7 ImmuneSigDB collection, gene sets corresponding to effector and activated $CD8^+$ T-cell states were the most prominently enriched signatures at lower age, with the two top-ranked gene sets representing effector $CD8^+$ T cells at day 6 versus day 10 of differentiation. The enrichment pattern extended across multiple immune cell lineages, including $CD4^+$ T-cell activation, regulatory T-cell signatures, natural killer (NK)-cell stimulation states, B-cell receptor signaling, and myeloid cell activation gene sets, all of which were enriched at lower age. None of the top 20 gene sets was enriched at higher age (Fig. 3B; Supplementary Table S7).

Discussion

In this post hoc analysis of the JAVELIN Renal 101 trial, we investigated whether patient age modifies the relative treatment benefit of avelumab plus axitinib versus sunitinib in previously untreated advanced clear-cell RCC, using individual patient data from the final analysis. A previous age subgroup analysis from JAVELIN Renal 101 suggested that avelumab plus axitinib maintained efficacy in older patients. However, that analysis was conducted at an earlier data cutoff when OS data were still immature and did not include formal treatment-by-age interaction testing [12]. At the prespecified 65-year threshold, the PFS point estimate numerically favored avelumab plus axitinib more strongly in younger patients than in older patients. However, the treatment-by-age interaction did not reach statistical significance (*P* for interaction = 0.080), and no significant interaction was observed for OS at any cutoff. These primary analyses therefore do not provide statistically significant evidence that chronological age modifies the relative efficacy of avelumab plus axitinib versus sunitinib. Sensitivity analyses across the 60- and 70-year thresholds showed a numerically weaker relative benefit of avelumab plus axitinib in the older subgroups, reaching nominal significance only at the 70-year cutoff (*P* for interaction = 0.029). Because three age cutoffs were examined without adjustment for multiplicity, this finding should be regarded as hypothesis-generating rather than confirmatory. Consistent with the PFS results, exploratory analyses of objective response rate showed that avelumab plus axitinib achieved higher response rates than sunitinib across all age cutoffs, with treatment benefits evident in both younger and older patients (Supplementary Fig. S5). In exploratory within-arm analyses, PFS with avelumab plus axitinib was similar between age groups across the examined cutoffs, whereas PFS with sunitinib was longer in the older subgroup at the 65- and 70- year cutoffs. This within-arm association was more robust when assessed using restricted mean survival time, given that the proportional hazards assumption was violated in the sunitinib arm. These within-arm comparisons are not based on randomization and should be interpreted as hypothesis-generating rather than as evidence of a causal age-by-treatment effect within the sunitinib arm. Taken together, our results do not suggest that avelumab plus axitinib is less effective in older patients. Rather, they suggest that sunitinib may perform relatively better with increasing age, an observation that requires independent validation.

Subgroup analyses from randomized phase III trials of ICI-based combinations versus sunitinib have generally suggested preserved survival benefits across age categories, consistent with the notion of age-independent efficacy of ICI-based regimens [12,19-21]. However, these prior analyses have relied mainly on age-stratified HRs and forest plots without formal testing of treatment-by-age interactions, which limits their ability to determine whether chronological age truly modifies the relative benefit of ICI-based combinations versus VEGFR-targeted TKI monotherapy. From a methodological standpoint, explicit interaction analyses are essential to distinguish superficially similar subgroup results across age strata from genuine effect modification by age. In this context, our exploratory post hoc analysis using individual patient data from the final JAVELIN Renal 101 dataset formally evaluated treatment-by-age interactions for both PFS and OS across multiple prespecified age cutoffs. This approach provides a more transparent framework for assessing age effects than descriptive subgroup comparisons alone, although the post hoc nature of the work and the absence of multiplicity adjustment across the three cutoffs warrant cautious interpretation of the nominal *P* values. Overall, our findings support the view that ICI-based combinations, including avelumab plus axitinib, can be appropriately used in older adults, and highlight the need for formal interaction testing when interpreting age subgroup data from randomized trials.

The following transcriptomic observations offer biological context for the clinical findings above rather than direct proof of a causal pathway, because the clinical and RNA-sequencing datasets could not be linked at the individual-patient level. In the exploratory GSEA, lower age was associated with significant enrichment of proliferative gene sets, including MYC targets, E2F targets, and G2M checkpoint pathways, consistent with a highly proliferative tumor phenotype [22]. In addition, mTORC1 and PI3K/AKT/mTOR signaling pathways were enriched at lower age, consistent with a metabolically and biosynthetically activated state that supports sustained tumor growth [23]. NF-κB-driven inflammatory pathways, along with downstream IL-6/JAK/STAT3 signaling, were also enriched at lower age. NF-κB activation has been implicated in resistance to VEGFR-targeted therapy in clear-cell RCC, partly through IL-6-mediated upregulation of compensatory angiogenic signaling, which may contribute to alternative proangiogenic cascades that circumvent sunitinib blockade [24]. Furthermore, enrichment of epithelial-mesenchymal transition (EMT)-related gene sets suggests a more invasive, mesenchymal tumor phenotype associated with lower age, consistent with prior reports that EMT-related transcriptomic alterations are associated with TKI resistance and enhanced invasiveness in clear-cell RCC [25,26]. ImmuneSigDB (C7)-based analyses provide

complementary insight, demonstrating broad enrichment across multiple immune cell lineages (including effector and memory $CD8^+$ T-cell signatures, activated $CD4^+$ T-cell signatures, NK cell-related gene sets, regulatory T-cell signatures, and inflammatory myeloid cell signatures) at lower age. This pattern mirrors broadly immune-infiltrated clear-cell RCC tumor microenvironments, where robust T-cell infiltration coexists with abundant regulatory T cells and tumor-associated macrophages, rather than a purely activated antitumor immune state. This highly proliferative and broadly immune-infiltrated landscape may render tumors associated with lower age relatively less sensitive to VEGFR-targeted monotherapy [27]. Avelumab acts primarily through PD-L1 blockade and NK cell-mediated antibody-dependent cellular cytotoxicity [28]. These effects may be preserved, potentially explaining the greater relative benefit of avelumab plus axitinib observed in younger subgroups across the examined age cutoffs. This interpretation is consistent with biomarker analyses from JAVELIN Renal 101, in which a 26-gene immune signature encompassing T-cell and NK cell function, as well as high $CD8^+$ infiltration, was significantly associated with prolonged PFS in the avelumab plus axitinib arm but not in the sunitinib arm [14].

In contrast, higher age was associated with enrichment of xenobiotic and lipid-related metabolic programs, including fatty acid and bile acid metabolism, with relatively few proliferation-associated and immune-infiltration signatures. In other words, at higher age, the transcriptomic profile did not display the highly proliferative, inflammatory, and EMT-enriched transcriptomic features that have been linked to VEGFR-TKI resistance in clear-cell RCC [23-25]. These observations are consistent with reports that aging is accompanied by coordinated changes in immune surveillance, metabolic homeostasis, and the tumor microenvironment [7]. This pattern is compatible with the longer PFS with sunitinib in the older subgroup at the 65- and 70-year cutoffs in our exploratory within-arm analysis. Importantly, PFS with avelumab plus axitinib was similar between age groups across the examined cutoffs in the present analysis, and we did not observe age-dependent loss of activity. One possible interpretation is that the narrowing of relative benefit observed in exploratory older-patient subgroups reflects more favorable sunitinib outcomes in the older subgroups, rather than diminished activity of the ICI-based combination. This exploratory pattern, together with the transcriptomic observations above, supports further evaluation of age-associated tumor biology as a potential complement to chronological age for guiding first-line regimen selection in clear-cell RCC. Independent validation using patient-level linked clinical and molecular data will be needed to confirm this hypothesis.

This study has several limitations. First, this study was a post hoc, exploratory analysis, and the treatment-by-age interactions were not prespecified in the original JAVELIN Renal 101 trial protocol. The findings should therefore be regarded as hypothesis-generating rather than confirmatory. Second, the transcriptomic analyses were performed in a subset of patients with available tumor RNA sequencing data and may not fully represent the overall trial population. Third, bulk RNA sequencing does not allow discrimination between tumor-intrinsic transcriptomic signals and those derived from stromal or immune cell populations within the tumor microenvironment. The age-associated metabolic gene set enrichment observed at high age may therefore reflect compositional differences in the tumor microenvironment rather than tumor cell-intrinsic biological changes. Furthermore, because transcriptomic analyses were performed using tumor tissue rather than peripheral blood samples, the observed immune-related signatures reflect the tumor microenvironment and cannot be used to infer systemic host immune status or age-related immune dysfunction. Although both the clinical and transcriptomic analyses were conducted in patients enrolled in JAVELIN Renal 101, they were derived from different data sources and could not be unequivocally linked at the individual-patient level. Fourth, the use of 60-, 65-, and 70-year chronological age cutoffs to define age subgroups is inherently arbitrary, and chronological age is an imperfect surrogate for biological aging. Factors such as functional status, comorbidities, and frailty, which were not systematically assessed in this trial, may more precisely capture the biological heterogeneity attributed to age in this analysis. Finally, the relatively small number of patients in some age subgroups, particularly those ≥70 years of age, limits the statistical power of subgroup-specific analyses and precludes definitive conclusions regarding treatment outcomes in the oldest patients.

Conclusion

In this post hoc analysis of JAVELIN Renal 101, chronological age at the primary 65-year cutoff did not significantly modify the relative treatment effect of avelumab plus axitinib versus sunitinib. In exploratory within-arm analyses, PFS with sunitinib was longer in the older subgroup at the 65- and 70-year cutoffs, whereas PFS with avelumab plus axitinib was similar between age groups across the examined cutoffs. Age-associated transcriptomic patterns, including enrichment of proliferative and immune-infiltrated signatures at lower age and

metabolic signatures at higher age, provide biological context for these exploratory findings. Independent validation using linked clinical and molecular data is required.

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Author contributions

Y. Sekino conceived the study, acquired the data, and critically revised the manuscript for important intellectual content. N. Nomura performed the statistical analyses with A. Takamori and Y. Orihashi and drafted the manuscript. Y. Kohada, M. Naito, S. Miyamoto, K. Kobatake, H. Kitano, K. Goto, and K. Hieda interpreted the results. N. Hinata supervised the study. All authors reviewed and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from Merck, but restrictions apply to the availability of these data, which were used under license for the current study and are therefore not publicly available. Qualified researchers may request access to the individual participant data from Merck, subject to review and approval in accordance with its data-sharing policy.

Competing Interests

The authors declare no competing interests.

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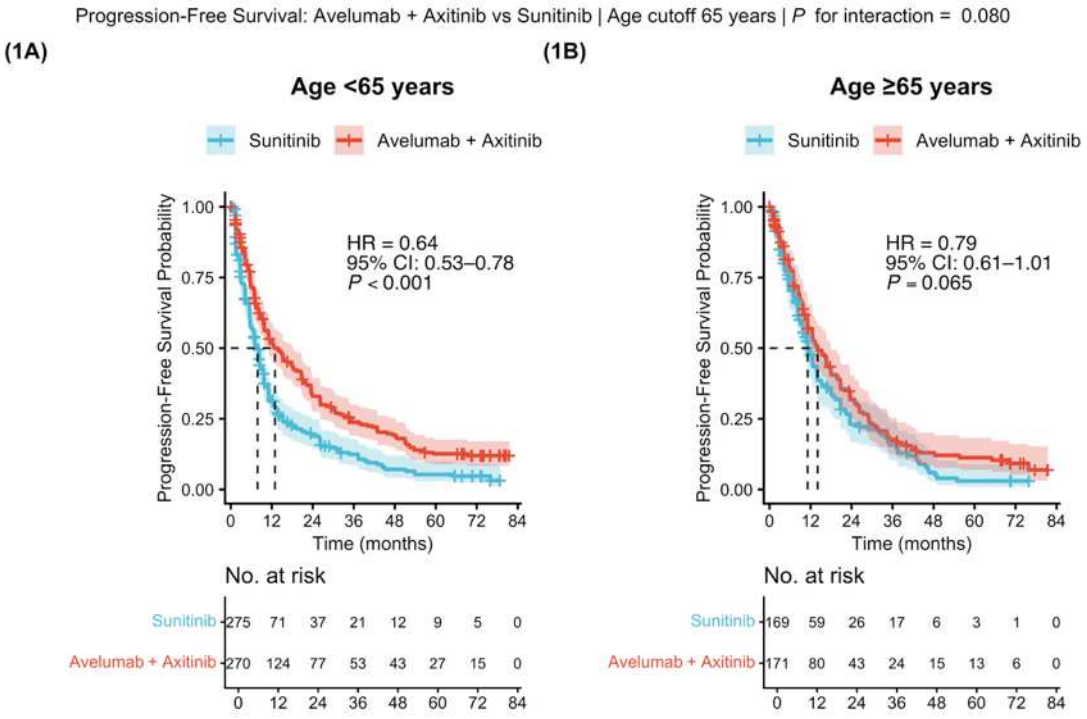


Figure 1A–B. Progression-free survival (PFS) by age subgroup (age cutoff 65 years) in patients with advanced renal cell carcinoma treated with avelumab plus axitinib or sunitinib.

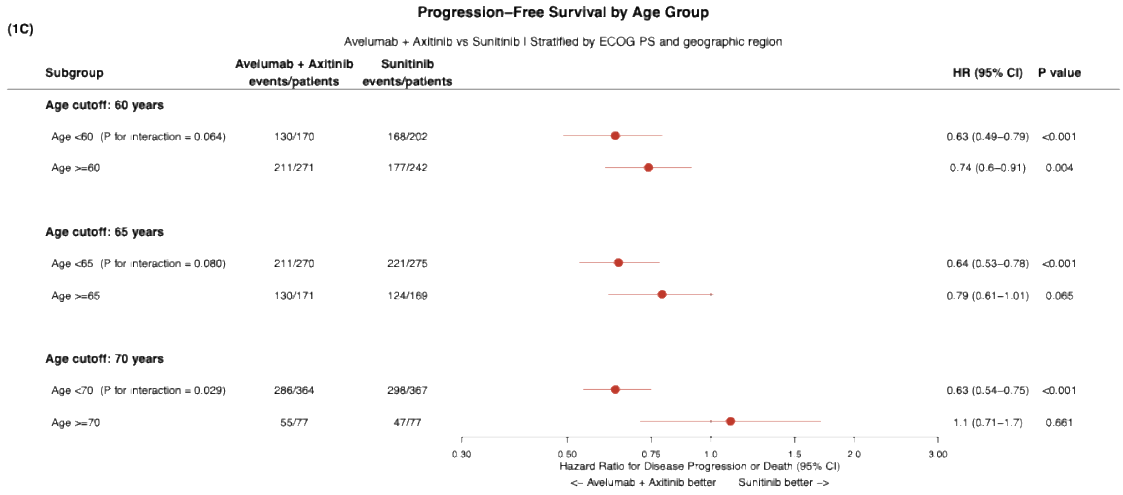
(A) PFS in patients aged <65 years. (B) PFS in patients aged ≥65 years. Curves were estimated

505 by the Kaplan–Meier method; hazard ratios (HRs, 95% confidence intervals) were derived
506 from Cox proportional hazards models stratified by ECOG performance status and
507 geographic region. The *P* value for treatment-by-age interaction was 0.080.
508 (B)

509 Figure 1C. Forest plot of progression-free survival (PFS) by age cutoffs (60, 65, and 70
510 years) in patients with advanced renal cell carcinoma treated with avelumab plus
511 axitinib versus sunitinib.

512 Hazard ratios (HRs, 95% confidence intervals) for disease progression or death were
513 estimated from Cox proportional hazards models stratified by ECOG performance
514 status and geographic region. HR < 1 favors avelumab plus axitinib; *P* values for
515 treatment-by-age interaction are shown for each age cutoff.

516



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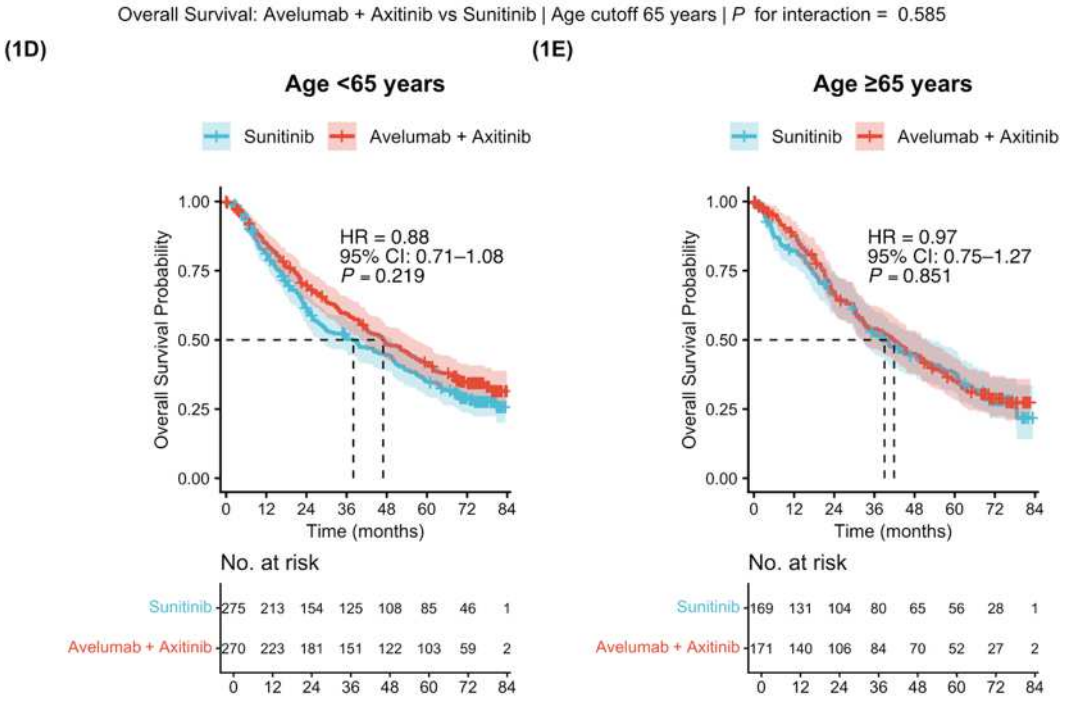
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519 Figure 1C. Forest plot of progression-free survival (PFS) by age cutoffs (60, 65, and 70
520 years) in patients with advanced renal cell carcinoma treated with avelumab plus
521 axitinib versus sunitinib.

522 Hazard ratios (HRs, 95% confidence intervals) for disease progression or death were
523 estimated from Cox proportional hazards models stratified by ECOG performance
524 status and geographic region. HR < 1 favors avelumab plus axitinib; *P* values for
525 treatment-by-age interaction are shown for each age cutoff.

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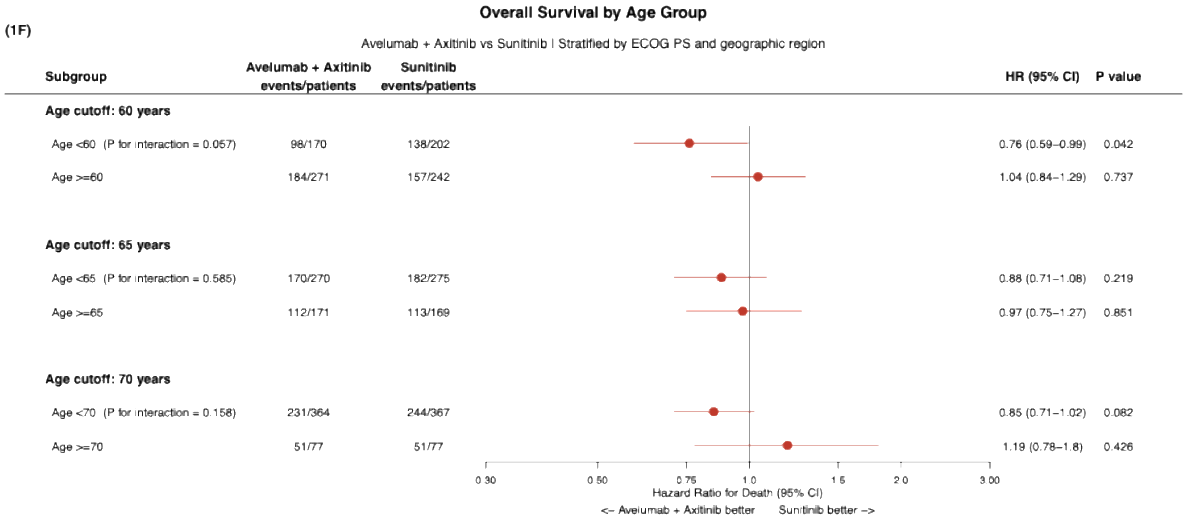
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529 Figure 1D–E. Overall survival (OS) by age subgroup (age cutoff 65 years) in patients
530 with advanced renal cell carcinoma treated with avelumab plus axitinib or sunitinib.
531 (D) OS in patients aged <65 years. (E) OS in patients aged ≥65 years. Curves were
532 estimated by the Kaplan–Meier method; hazard ratios (HRs, 95% confidence intervals)
533 were derived from Cox proportional hazards models stratified by ECOG performance
534 status and geographic region. The *P* value for treatment-by-age interaction for OS at
535 the 65-year cutoff was 0.585.

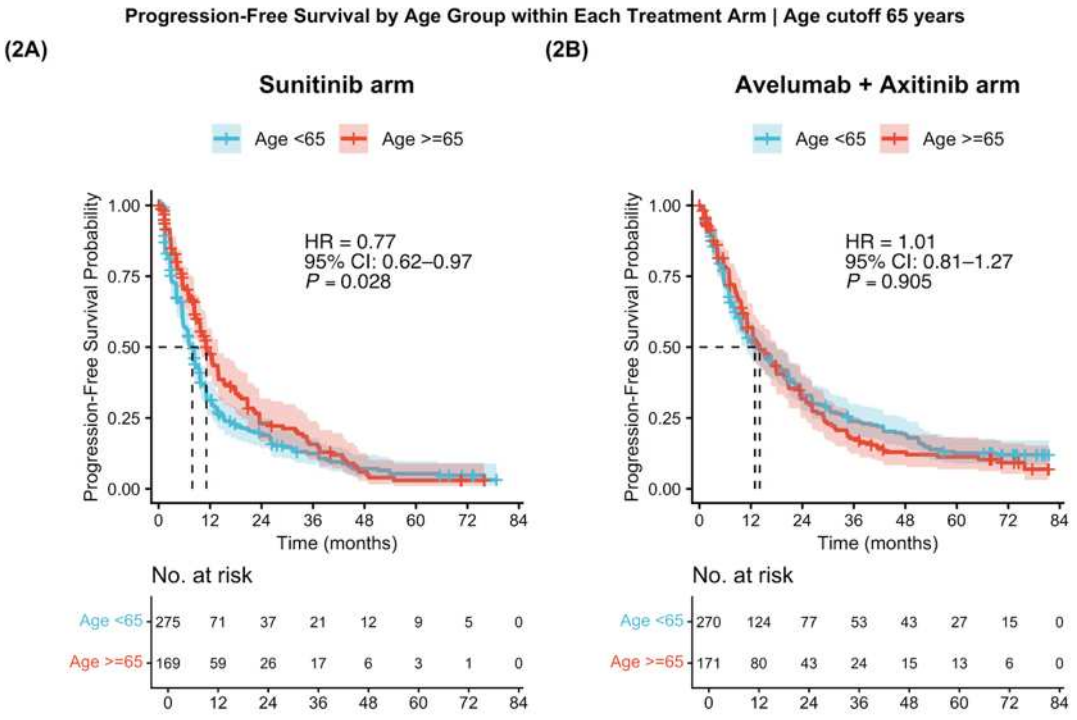
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537

538 Figure 1F. Forest plot of overall survival (OS) by age cutoffs (60, 65, and 70 years) in
539 patients with advanced renal cell carcinoma treated with avelumab plus axitinib versus
540 sunitinib.

541 Hazard ratios (HRs, 95% confidence intervals) for death were estimated using Cox
542 proportional hazards models stratified by ECOG performance status and geographic
543 region. HR < 1 favors avelumab plus axitinib. *P* values for the treatment-by-age
544 interaction are presented for each age cutoff.



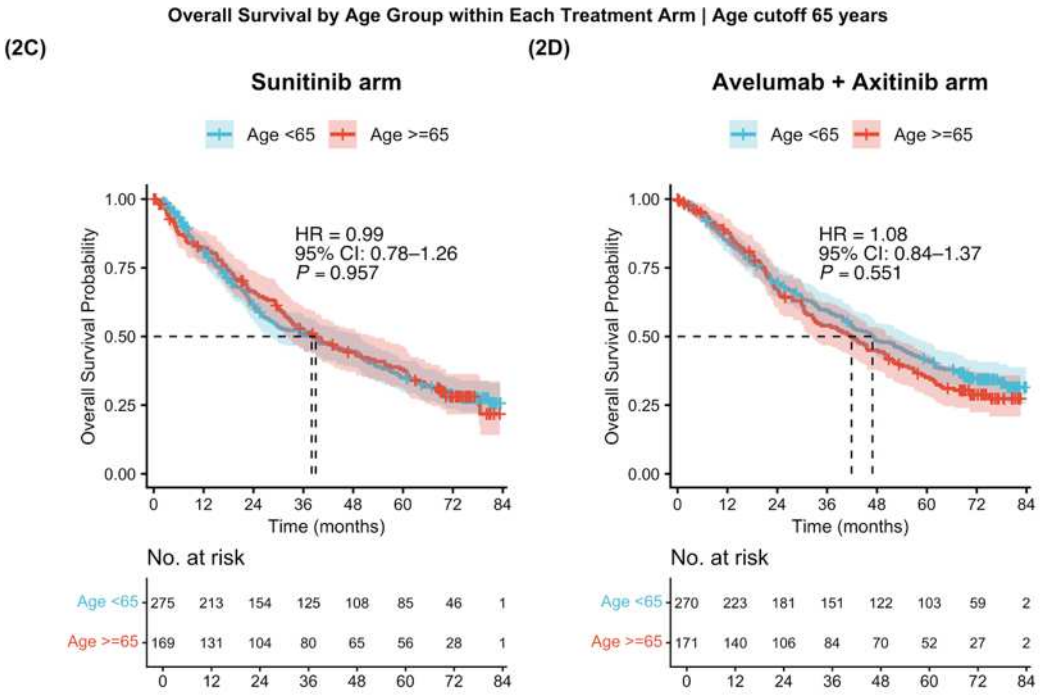
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546 Figure 2A–B. Progression-free survival (PFS) by age subgroup within each treatment
547 arm (age cutoff 65 years) in patients with advanced renal cell carcinoma.

548 (A) PFS in patients treated with sunitinib, comparing age <65 versus ≥65 years. (B)
549 PFS in patients treated with avelumab plus axitinib, comparing age <65 versus ≥65
550 years. Curves were estimated by the Kaplan–Meier method; hazard ratios (HRs, 95%
551 confidence intervals) for older versus younger patients were derived from Cox

552 proportional hazards models stratified by ECOG performance status and geographic

553 region. HR <1 indicates a lower hazard in older patients.



554

555 Figure 2C–D. Overall survival (OS) by age subgroup within each treatment arm (age

556 cutoff 65 years) in patients with advanced renal cell carcinoma.

557 (C) OS in patients treated with sunitinib, comparing age <65 versus ≥65 years. (D) OS

558 in patients treated with avelumab plus axitinib, comparing age <65 versus ≥65 years.

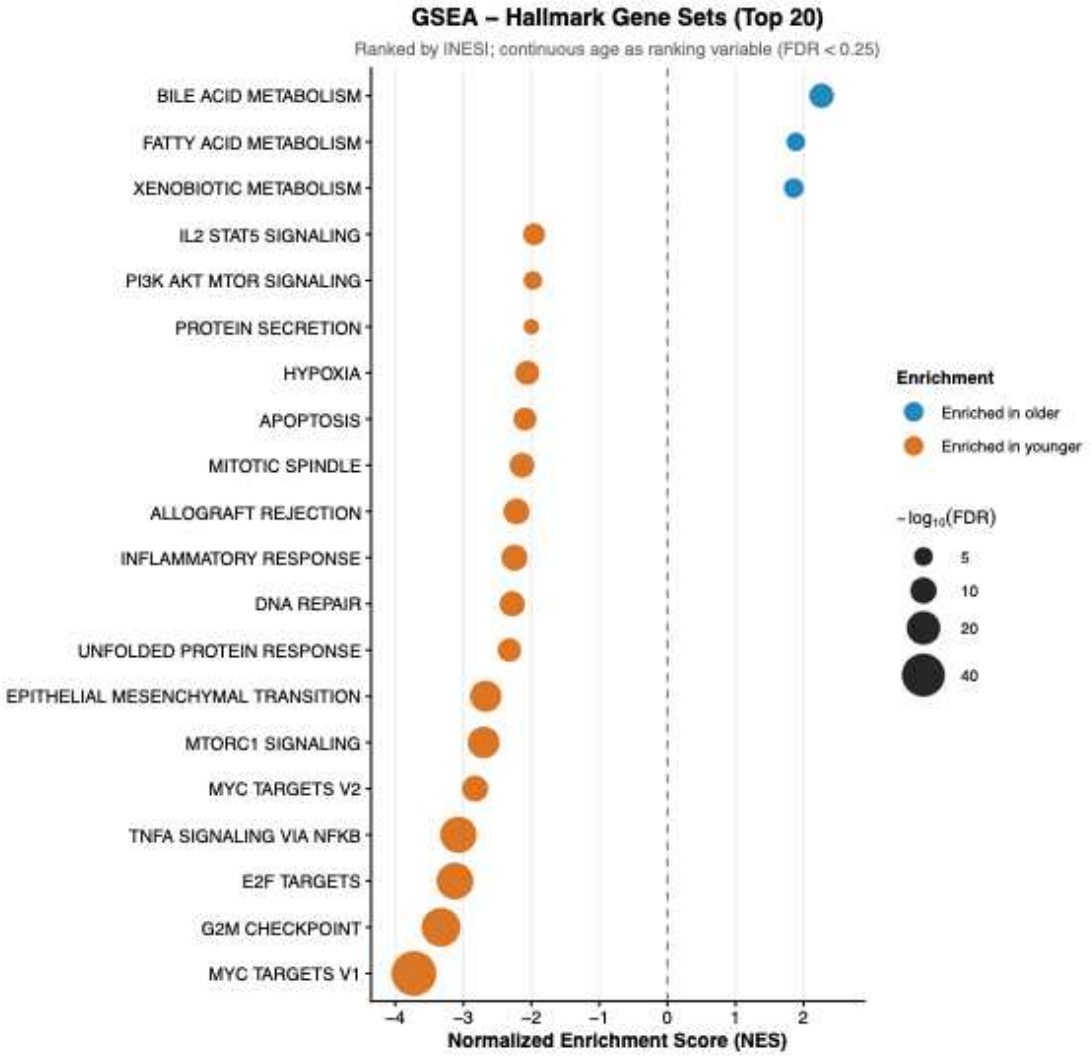
559 Curves were estimated by the Kaplan–Meier method; hazard ratios (HRs, 95%

560 confidence intervals) for older versus younger patients were derived from Cox

561 proportional hazards models stratified by ECOG performance status and geographic

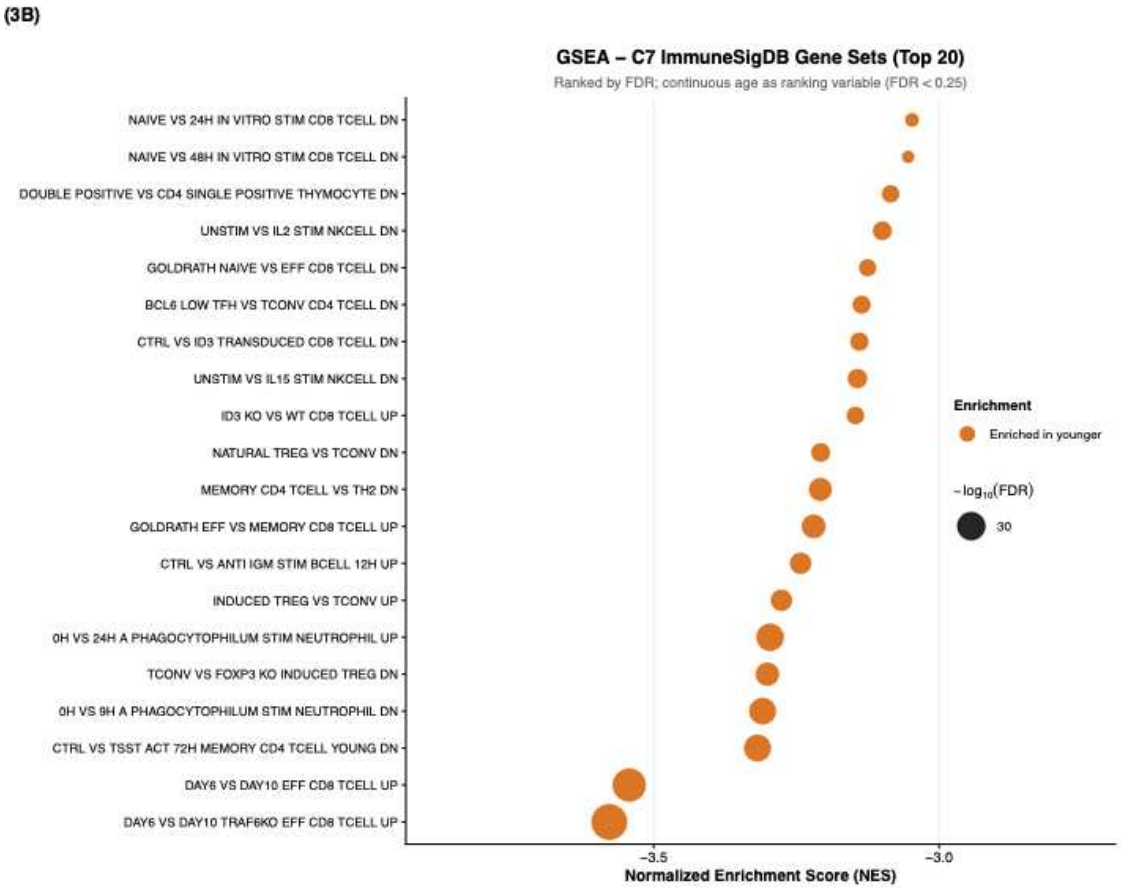
562 region. HR <1 indicates a lower hazard in older patients.

(3A)


GSEA – Hallmark Gene Sets (Top 20)
Ranked by INESI; continuous age as ranking variable (FDR < 0.25)
BILE ACID METABOLISM
FATTY ACID METABOLISM
XENOBIOTIC METABOLISM
IL2 STAT5 SIGNALING
PI3K AKT MTOR SIGNALING
PROTEIN SECRETION
HYPOXIA
APOPTOSIS
MITOTIC SPINDLE
ALLOGRAFT REJECTION
INFLAMMATORY RESPONSE
DNA REPAIR
UNFOLDED PROTEIN RESPONSE
EPITHELIAL MESENCHYMAL TRANSITION
MTORC1 SIGNALING
MYC TARGETS V2
TNFA SIGNALING VIA NFKB
E2F TARGETS
G2M CHECKPOINT
MYC TARGETS V1
−4
−3
−2
−1
0
1
2
Normalized Enrichment Score (NES)
Enrichment
Enriched in older
Enriched in younger
−log10(FDR)
5
10
20
40

563

564



565

566 Figure 3A–B. Gene set enrichment analysis (GSEA) of age-related transcriptional

567 programs in advanced renal cell carcinoma.

568 (A) Hallmark gene sets: top 20 pathways ranked by the absolute normalized enrichment score
569 (|NES|) among gene sets with FDR < 0.25. (B) C7 ImmuneSigDB gene sets: top 20 pathways
570 ranked by false discovery rate (FDR) among gene sets with FDR < 0.25. Continuous age was
571 used as the ranking variable in both analyses. In each panel, bubble position on the x-axis
572 represents the normalized enrichment score (NES), bubble size represents $-\log_{10}(\mathrm{FDR})$, and
573 bubble color indicates the direction of enrichment.

574

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577

578

	avelumab plus axitinib		sunitinib		*P* value
Characteristics	Age <65	Age ≥65	Age <65	Age ≥65	Age <65 vs ≥65
	N = 270	N = 171	N = 275	N = 169	pooled treatment arms
Male	197 (73.0%)	118 (69.0%)	219 (79.6%)	125 (74.0%)	0.107
ECOG PS					0.759
0	172 (63.7%)	107 (62.6%)	175 (63.6%)	106 (62.7%)	
1	98 (36.3%)	64 (37.4%)	100 (36.4%)	63 (37.3%)	
Geographic region					0.924
United States	75 (27.8%)	53 (31.0%)	84 (30.5%)	46 (27.2%)	
Canada/Western Europe	75 (27.8%)	52 (30.4%)	79 (28.7%)	48 (28.4%)	
Rest of the World	120 (44.4%)	66 (38.6%)	112 (40.7%)	75 (44.4%)	
IMDC risk classification					0.253
Favorable	52 (19.3%)	42 (24.6%)	56 (20.4%)	40 (23.7%)	
Intermediate	165 (61.1%)	104 (60.8%)	175 (63.6%)	102 (60.4%)	
Poor	50 (18.5%)	23 (13.5%)	44 (16.0%)	27 (16.0%)	
Not evaluated	3 (1.1%)	2 (1.2%)	0 (0.0%)	0 (0.0%)	
PD-L1 expression status					0.325
Positive (≥1%)	164 (60.7%)	105 (61.4%)	189 (68.7%)	101 (59.8%)	
Negative (<1%)	80 (29.6%)	52 (30.4%)	70 (25.5%)	50 (29.6%)	
Not evaluated	26 (9.6%)	14 (8.2%)	16 (5.8%)	18 (10.7%)	
Prior nephrectomy	217 (80.4%)	135 (78.9%)	228 (82.9%)	129 (76.3%)	0.147

579 Table 1. Baseline clinical and disease characteristics by age group and treatment arm in patients
580 with advanced clear-cell renal cell carcinoma treated with avelumab plus axitinib or sunitinib.

581 For each treatment arm, baseline characteristics are summarized for patients aged <65 years and
582 ≥65 years; *P* values represent comparisons of baseline clinical and disease characteristics

Endpoint	Age cutoff	Age group	avelumab plus axitinib n (events)	sunitinib n (events)	HR (95% CI)	*P* value	*P* interaction
PFS	60	Age <60	170 (130)	202 (168)	0.63 (0.49–0.79)	<0.001	0.064
		Age ≥60	271 (211)	242 (177)	0.74 (0.6–0.91)	0.004	
	65	Age <65	270 (211)	275 (221)	0.64 (0.53–0.78)	<0.001	0.08
		Age ≥65	171 (130)	169 (124)	0.79 (0.61–1.01)	0.065	
	70	Age <70	364 (286)	367 (298)	0.63 (0.54–0.75)	<0.001	0.029
		Age ≥70	77 (55)	77 (47)	1.1 (0.71–1.7)	0.661	
OS	60	Age <60	170 (98)	202 (138)	0.76 (0.59–0.99)	0.042	0.057
		Age ≥60	271 (184)	242 (157)	1.04 (0.84–1.29)	0.737	
	65	Age <65	270 (170)	275 (182)	0.88 (0.71–1.08)	0.219	0.585
		Age ≥65	171 (112)	169 (113)	0.97 (0.75–1.27)	0.851	
	70	Age <70	364 (231)	367 (244)	0.85 (0.71–1.02)	0.082	0.518
		Age ≥70	77 (51)	77 (51)	1.19 (0.78–1.8)	0.426	

between age groups (<65 vs ≥65 years), with the two treatment arms pooled. Values are n (%). Chi-square tests or Fisher's exact tests were used. ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1, programmed death-ligand 1.

Table 2. Subgroup analyses of progression-free survival (PFS) and overall survival (OS) by age group in patients treated with avelumab plus axitinib or sunitinib.

For each endpoint and age cutoff (60, 65, and 70 years), the table shows the number of patients and events in each age subgroup by treatment arm, hazard ratios (HRs) with 95% confidence intervals (CIs) for avelumab plus axitinib versus sunitinib, and *P* values within each subgroup, together with the *P* value for the treatment-by-age interaction. HR <1 favors avelumab plus axitinib. Cox proportional hazards models were stratified by ECOG performance status and

geographic region, and *P* interaction values were derived from likelihood ratio tests comparing models with and without the interaction term.

		avelumab plus axitinib				sunitinib			
Endpoint	Age cutoff	Younger group n (events)	Older group n (events)	HR (95% CI)	*P* value	Younger group n (events)	Older group n (events)	HR (95% CI)	*P* value
PFS	60	170 (130)	271 (211)	1.08 (0.87–1.36)	0.477	202 (168)	242 (177)	0.84 (0.67–1.05)	0.123
	65	270 (211)	171 (130)	1.01 (0.81–1.27)	0.905	275 (221)	169 (124)	0.77 (0.62–0.97)	0.028
	70	364 (286)	77 (55)	1 (0.75–1.35)	0.985	367 (298)	77 (47)	0.64 (0.46–0.87)	0.005
OS	60	170 (98)	271 (184)	1.25 (0.98–1.6)	0.076	202 (138)	242 (157)	0.92 (0.73–1.16)	0.476
	65	270 (170)	171 (112)	1.08 (0.84–1.37)	0.551	275 (182)	169 (113)	0.99 (0.78–1.26)	0.957
	70	364 (231)	77 (51)	1.25 (0.91–1.7)	0.164	367 (244)	77 (51)	0.91 (0.67–1.24)	0.543

Table 3. Within-treatment-arm comparisons of progression-free survival (PFS) and overall survival (OS) between younger and older age subgroups among patients receiving avelumab plus axitinib or sunitinib.

For each treatment arm, baseline characteristics are summarized for patients aged <65 years and ≥65 years, and P values represent comparisons between age groups within the same treatment arm. Values are n (%). Pearson's chi-square test without continuity correction was used; Fisher's exact test was used when any expected cell count was <5. For IMDC risk classification and PD-L1 expression status, P values were calculated among patients with evaluable data. ECOG PS,

613 Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic
614 Renal Cell Carcinoma Database Consortium; PD-L1, programmed death-ligand 1.

615

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