THE EMBO JOURNAL

CDK8 remodels the tumor microenvironment and promotes resistance to KRASG12D inhibitors and daraxonrasib in PDAC

Kathleen McAndrews, Krishnan Mahadevan, Bingrui Li, Anais Comptdaer, Amari Sockwell, Sami Morse, Patience Kelly, Sarah Patel, Michelle Kirtley, Barbara Moreno Diaz, Hengyu Lyu, David Peng, Sima Khazaei, Aislyn Schalck, Xunian Zhou, Hikaru Sugimoto, Aaron Bickert, Lakshmi Kavitha Sthanam, Meagan Taylor, Shreyasee Kumbhar, Kent Arian, Yasaman Barekatain, Francesca Paradiso, Paola Guerrero, Vincent Bernard, Navid Sobhani, Alondra Camacho-Acevedo, Kiara Bornes, Phuong Thao Tran, Anirban Maitra, Timothy Heffernan, and Raghu Kalluri

Corresponding author: Raghu Kalluri (rkalluri@mdanderson.org)

Review Timeline:

Submission Date:	30th Mar 26
Editorial Decision:	4th May 26
Editor's Correspondence:	8th May 26
Revision Received:	23rd Jun 26
Accepted:	26th Jun 26

Editor: Daniel Klimmeck

Transaction Report:

Please note that the manuscript was previously reviewed at another journal. As EMBO Press has a transfer agreement (including the identities of the referees) with that journal, revision was invited based on the reports from that previous external review.

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Reviewer #3 (Remarks to the Author):

Summary

The additional work done using RAS inhibitors currently being clinically tested in additional PDX models is appreciated. The inability to analyze human samples due to the companies not allowing reporting is understandable. Addition of this limitation in the discussion, as well as modifying the title, is noted. However, questions remain.

Answer: Thank you for the acknowledging our revisions and that as of today, samples from patients with PDAC are not available from any clinical trials for analyses by independent research groups like ours. Therefore, PDXs are only option for any human correlates analyses, as done here. In this regard, the included analyses using RMC6236, which is currently the most advanced inhibitor in clinical testing with impressive response rates for a single agent targeted therapy, and RMC9805, a $KRAS^{G12D}$(ON) inhibitor currently in phase 3 trials. The reviewer commented that MRTX1133 is not relevant in human PDX experiments because clinical testing has been discontinued to due formulation and bioavailability issues; therefore, we removed that data in the previous revised version.

Major Points

1. Regarding expression of CDK8 levels in Reviewer Fig 1A, it would be striking to see if tumors that were more resistant to RAS inhibitor therapy all had higher levels at baseline or if baseline level is not predictive of response. This comparison would potentially strengthen translatability and the central premise of the manuscript. Across several PDXs, baseline CDK8 levels are higher in sensitive tumors compared to resistant ones. This directly contradicts with the proposed model in which CDK8 promotes resistance and is not adequately addressed. The data more appropriately position CDK8 as a correlatively enriched marker in some resistant contexts, not a validated driver.

Answer: We analyzed baseline CDK8 levels and the correlation is similar to the data at endpoint that is included in the manuscript (**Reviewer Fig. 1**). The reviewer raises the question regarding whether CDK8 is an inherent driver of resistance vs. an acquired driver of resistance, which was addressed in the previous version. While higher baseline CDK8 expression correlating with response may be indicative of its role as an inherent resistance driver, it is more suggestive of clonal selection of $CDK8^{+}$ cells when $KRAS^{G12D}$ targeting resistance is encountered resulting in

Figure for reviewers removed

overall increased CDK8 expression and functional dependency only in response to KRAS inhibitor treatment and ensuing resistance. Importantly, if that was not the case, then treatment of original PDAC tumors in mouse models with CDK8 inhibitors should have led to efficacy when oncogenic $KRAS^{G12D}$ mediated pathways are active and operational (**Reviewer Figure 2**). In addition, the role of CDK8 is not just relevant to cancer cell autonomous functions but also impacts the TME to induce therapy resistance. Treatment with a CDK8 inhibitor overcomes the negative impact on immune microenvironment and enables the efficacy of immunotherapy in $KRAS^{G12D}$ inhibitor resistant tumors (**Figure 5** in the revised manuscript).

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2. With respect to murine CDK8 levels in the orthotopic experiment (Reviewer Figs 1E-F), the authors need to include expression of CDK8 levels in the vehicle group, especially since they list vehicle pERK expression (Reviewer Fig 1D). Without this, it is not possible to discern is the increase in CDK8 a return to baseline or the increase is only in response to continued pressure from pan-RAS inhibition. The authors have not shown that CDK8 decreases early and increases with the emergence of resistance, as one of the reviewers explicitly recommended. The added timepoints appear selected but not temporally linked to the development of resistance.

Answer: We thank the reviewer for raising this point. We have now included analysis of vehicle treated mice and show that the abundance of $CDK8^{+}$ cells is similar between vehicle and RMC6236 sensitive tumors which increases in RMC6236 resistant tumors (**Reviewer Fig. 3, Supplemental Fig. 5E-G**).

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Answer: We agree that MRTX1133, RMC6236, and RMC9805 have different mechanisms of action, but all act to suppress $KRAS^{G12D}$ signaling in this context. Despite such differences, CDK8 is a conserved mechanism of resistance across distinct modalities of RAS inhibition, which we view as a strength of our findings and provides rationale for future studies evaluating whether CDK8 upregulation is a conserved immune remodeling driven mechanism of resistance with alternate KRAS* targeting strategies. We revised the discussion to address this point.

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Dear Raghu,

Thank you again for the submission of your amended manuscript (EMBOJ-2026-124254) to The EMBO Journal, as well as for your patience with our feedback from the arbitration process. We have carefully assessed your manuscript, and the point-by-point response provided to the referee concerns that were raised during peer-review at a different journal. In addition, and as mentioned before, we decided to send the revised version of your work back to seek original reviewer input with respect to technical robustness, conceptual advance and overall suitability of your work for publication in The EMBO Journal. We have now received the re-report by referee #2 which I enclose below. As you will see from the expert's comments, s/he is now in favour of the work and supportive of publication at The EMBO Journal, pending satisfactory minor revision.

We are thus pleased to inform you that we can offer to swiftly move forward towards acceptance of this work at The EMBO Journal, pending minor revision of the following remaining issues, which need to be adjusted in a re-submitted version.

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Thank you again for giving us the chance to consider your manuscript for The EMBO Journal, I look forward to hearing from you and receiving your final revised version of the manuscript.

Best regards,

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Senior Editor
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Please remember: Digital image enhancement is acceptable practice, as long as it accurately represents the original data and conforms to community standards. If a figure has been subjected to significant electronic manipulation, this must be noted in the figure legend or in the 'Methods' section. The editors reserve the right to request original versions of figures and the original images that were used to assemble the figure.

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I served as a reviewer for this manuscript submitted to another venue previously.

In summary, I valued the scientific significance and translational potential of the study, but less enthusiasm on the causal role of CDK8 levels on the development of drug resistance, and its direct human relevance (difficulty in testing human PDAC samples).

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@Arbitrating comment Ref#2: Justified and agreed.

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@Arbitrating comment Ref#2: The results largely support the conclusion. The point on "whether CDK8 is an inherent driver of resistance vs. an acquired driver of resistance" should be discussed in the Discussion section, as argued here.

2. With respect to murine CDK8 levels in the orthotopic experiment (Reviewer Figs 1E-F), the authors need to include expression of CDK8 levels in the vehicle group, especially since they list vehicle pERK expression (Reviewer Fig 1D). Without this, it is not possible to discern is the increase in CDK8 a return to baseline or the increase is only in response to continued pressure from pan-RAS inhibition. The authors have not shown that CDK8 decreases early and increases with the emergence of resistance, as one of the reviewers explicitly recommended. The added timepoints appear selected but not temporally linked to the development of resistance.

Answer: We thank the reviewer for raising this point. We have now included analysis of vehicle treated mice and show that the abundance of CDK8+ cells is similar between vehicle and RMC6236 sensitive tumors which increases in RMC6236 resistant tumors (Reviewer Fig. 3, Supplemental Fig. 5E-G).

@Arbitrating comment Ref#2: The point was fully addressed.

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@Arbitrating comment Ref#2: The argument is not well supported by the data. The authors claimed that "CDK8 is not significantly increased in PATX155 following RMC9805 treatment". However, the data showed two-fold increase on average in treatment group, as compared to vehicle control. The lack of statistically significant difference is largely due to sample variations. What is the sample size in each group?

4. The additional PDX data remain correlative and do not demonstrate that CDK8 is mechanistically required for resistance to KRAS inhibitors. No CDK8 perturbation studies (inhibition, knockdown, overexpression) were performed and no functional rescue experiments are provided. So how could they claim that CDK8 drives resistance if they didn't knock it down?

Answer: Knockdown and other perturbation studies in patient-derived models are difficult to pursue as these are tumor transplant models and not cell line-derived models. Our data suggests that CDK8 acts cancer cell-extrinsic driver in resistant tumors to remodel the immune microenvironment. PDXs require an immunodeficient background lacking T cells to grow in mice and such studies are not possible.

@Arbitrating comment Ref#2: I agree with both reviewer and the authors. If this critical experiment cannot be done, the authors should tone down their strong conclusion.

5. They merged data from MRTX1133, RMC6236, and RMC9805 without addressing major mechanistic differences between these agents. Resistance pathways differ widely across these inhibitors, yet the authors treat CDK8 as a unified node without justification.

Answer: We agree that MRTX1133, RMC6236, and RMC9805 have different mechanisms of action, but all act to suppress KRASG12D signaling in this context. Despite such differences, CDK8 is a conserved mechanism of resistance across distinct modalities of RAS inhibition, which we view as a strength of our findings and provides rationale for future studies evaluating whether CDK8 upregulation is a conserved immune remodeling driven mechanism of resistance with alternate KRAS* targeting strategies. We revised the discussion to address this point.

@Arbitrating comment Ref#2: I largely agree. This important issue needs to be raised and thoroughly discussed.

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Answer: We appreciate that clinical biopsy data or large-scale transcriptomics would strengthen our hypotheses; however, TCGA, CPTAC, and other large-scale transcriptomics datasets are not relevant for our studies as they do not include patients treated with RAS inhibitors. Currently, there are no publicly available datasets from KRASG12D PDAC patients that were treated with RAS inhibitors and the companies sponsoring current RAS inhibitor trials have not approved the publication of any patient data or correlative biopsy data (See answer to comment # 1). As a result, we included data from cell lines and PDXs and have tempered conclusions related to human relevance in the revised manuscript.

@Arbitrating comment Ref#2: Again, I agree with both the reviewer and the authors. Thus, the strong conclusion on human relevance should be tune down, given lack of strong supporting data.

Minor Points

1. Tumors resistant to RMC-6236 had sustained suppression of pERK expression (Reviewer Figs 1C-D). This is interesting since bypass signaling and return of pERK occurs in response to sustained RAS inhibition, as shown by the authors in Main Fig 1F where resistant tumors treated with MRTX1133 had pERK expression return to baseline in the same orthotopic model system (Main Fig 1F). Including tumor volumes/mass at time of tumor excision for all samples would be appreciated.

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@Arbitrating comment Ref#2: OK

Editor's Correspondence **8th May 2026**

Dear Raghu,

Further to below, I attach the mentioned list of formatting changes required for your final resubmission.

Please let us know any time should you have additional questions related.

Best regards,

Daniel

Daniel Klimmeck PhD
Senior Editor
The EMBO Journal

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Formatting changes required for the revised version of the manuscript:

>> Please provide the main manuscript text as .docx file.

>> Figures in separate files: Figures should be removed from the manuscript text and uploaded as individual, high resolution figure files. Legends should be placed after the References.

>> Author Contributions: Remove the author contributions information from the manuscript text. Note that CRediT has replaced the traditional author contributions section as of now because it offers a systematic machine-readable author contributions format that allows for more effective research assessment. and use the free text boxes beneath each contributing author's name to add specific details on the author's contribution.

More information is available in our guide to authors.
https://www.embopress.org/page/journal/14602075/authorguide

>> Provide a completed Author Checklist.

>> Adjust the title of the 'Declaration of Interests' section to 'Disclosure and Competing Interests Statement'.

>> Section order should be corrected as follows: title page with complete author information, abstract, keywords, introduction, results, discussion, methods, data availability section, acknowledgements, disclosure and competing interests statement, references, main figure legends, tables, expanded view figure legends.´.

>> Figure callouts: Please ensure that the figures and panels are called out in sequential order. In addition, currently, a callout for Supplemental Table 1 needs to be added.

>> References: please adjust reference format to EMBO Journal format, 10 authors et al.

>> Please recheck references for the bioRxiv entries Mahadevan et al 2025a, 2025b and update the citations if in the meantime published as regular article.

>> Please add a Reagents and Tools table to the Methods section, as a separate file using the existing template in the Guide

For Authors, listing key reagents, experimental models, software and relevant equipment.

Please compare also our Guide-to-Authors instructions:
https://www.embopress.org/page/journal/14602075/authorguide#structuredmethods

>> Funding: add the 'Sid W. Richardson Foundation' to the list of funders indicated in our online system.

>>Appendix file with ToC: Appendix file needs to be in PDF format; title page with "Appendix for + manuscript title" (author and affiliation list not necessary) and ToC with page numbers of listed items missing; nomenclature should be Appendix Figure Sx throughout the manuscript and Appendix PDF

>> Dataset EV legends: source file name, title, legend and manuscript callout all need to be updated to Dataset EV1 instead of Table S1, legend should be removed from Appendix ("Supplementary Information") and uploaded as a separate tab/sheet in the Excel file.

>> Please provide source data for the study as to the separate request e-mail. Source data should be uploaded as one (zipped) file per figure.

>> Data availability section: specify all databases and datsets used adding hyperlinks.
Remove referee tokens and make sure datasets are made publicly accessible.

>> Consider additional changes and comments from our production team as indicated below:

DATA CHECK: PASS: Please note that the specific URLs for GSE269679, GSE269680, PRJNA1124144 datasets are not provided in the data availability statement.

- Data citations: no comments
- Figure Legends (main + EV):
1. Please note that the exact p values are not provided in the legends of figures 1B, D, F, I, M, Q; 2H, J, L, Q; 3B, E, G, J, K, L, M, O; 4B, C, E, F, G, H, J, L; 5C, E, G, H, K, L
2. Please note that the box plot needs to be defined in terms of minima, maxima, centre, bounds of box and whiskers, and percentile in the legends of figure 3G

Further information is available in our Guide For Authors: https://link.springer.com/journal/44318/submission-guidelines

Please use the link below to submit your revision:

https://emboj.msubmit.net/cgi-bin/main.plex

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Answer: We thank the reviewer for raising this point. We have now included analysis of vehicle treated mice and show that the abundance of CDK8+ cells is similar between vehicle and RMC6236 sensitive tumors which increases in RMC6236 resistant tumors (Reviewer Fig. 3, Supplemental Fig. 5E-G).

@Arbitrating comment Ref#2: The point was fully addressed.

3. Regarding PDX data, making comparisons regarding CDK8+ cells between samples (Reviewer Fig 1J) needs to be complimented by making comparisons between each of these and the respective vehicle group as done in Reviewer Fig 1H. This is necessary due to the discrepancy where PDXs PATX124 and PATX155 had similar levels of CDK8 expression after RAS inhibitor treatment (Reviewer Fig 1A) but then different responses to RAS inhibitor therapy (PATX124-Resistance and PATX155-Partial Response, Figs 1G-J). This potentially suggests differing levels at baseline, which could be determinative of response.

Answer: We revised the manuscript to include comparisons to vehicle and observe that CDK8 is not significantly increased in PATX155 following RMC9805 treatment (Reviewer Fig. 4, Supplemental Fig. 5J-K). This suggests that baseline levels of CDK8 may be indicative of responses; however, as detailed in our response to major point 1, CDK8 dependency is only encountered resistance to KRASG12D targeting occurs.

@Arbitrating comment Ref#2: The argument is not well supported by the data. The authors claimed that "CDK8 is not significantly increased in PATX155 following RMC9805 treatment". However, the data showed two-fold increase on average in treatment group, as compared to vehicle control. The lack of statistically significant difference is largely due to sample variations. What is the sample size in each group?

4. The additional PDX data remain correlative and do not demonstrate that CDK8 is mechanistically required for resistance to KRAS inhibitors. No CDK8 perturbation studies (inhibition, knockdown, overexpression) were performed and no functional rescue experiments are provided. So how could they claim that CDK8 drives resistance if they didn't knock it down?

Answer: Knockdown and other perturbation studies in patient-derived models are difficult to pursue as these are tumor transplant models and not cell line-derived models. Our data suggests that CDK8 acts cancer cell-extrinsic driver in resistant tumors to remodel the immune microenvironment. PDXs require an immunodeficient background lacking T cells to grow in mice and such studies are not possible.

@Arbitrating comment Ref#2: I agree with both reviewer and the authors. If this critical experiment cannot be done, the authors should tone down their strong conclusion.

5. They merged data from MRTX1133, RMC6236, and RMC9805 without addressing major mechanistic differences between these agents. Resistance pathways differ widely across these inhibitors, yet the authors treat CDK8 as a unified node without justification.

Answer: We agree that MRTX1133, RMC6236, and RMC9805 have different mechanisms of action, but all act to suppress KRASG12D signaling in this context. Despite such differences, CDK8 is a conserved mechanism of resistance across distinct modalities of RAS inhibition, which we view as a strength of our findings and provides rationale for future studies evaluating whether CDK8 upregulation is a conserved immune remodeling driven mechanism of resistance with alternate KRAS* targeting strategies. We revised the discussion to address this point.

@Arbitrating comment Ref#2: I largely agree. This important issue needs to be raised and thoroughly discussed.

6. Human relevance is still limited. Despite added PDX data, no human primary tissue, clinical biopsy, or large-scale transcriptomic correlation is included. Public datasets (TCGA, CPTAC) are not leveraged. The claim of improved human relevance remains overstated.

Answer: We appreciate that clinical biopsy data or large-scale transcriptomics would strengthen our hypotheses; however, TCGA, CPTAC, and other large-scale transcriptomics datasets are not relevant for our studies as they do not include patients treated with RAS inhibitors. Currently, there are no publicly available datasets from KRASG12D PDAC patients that were treated with RAS inhibitors and the companies sponsoring current RAS inhibitor trials have not approved the publication of any patient data or correlative biopsy data (See answer to comment # 1). As a result, we included data from cell lines and PDXs and have tempered conclusions related to human relevance in the revised manuscript.

@Arbitrating comment Ref#2: Again, I agree with both the reviewer and the authors. Thus, the strong conclusion on human relevance should be tune down, given lack of strong supporting data.

Minor Points
1. Tumors resistant to RMC-6236 had sustained suppression of pERK expression (Reviewer Figs 1C-D). This is interesting since bypass signaling and return of pERK occurs in response to sustained RAS inhibition, as shown by the authors in Main Fig 1F where resistant tumors treated with MRTX1133 had pERK expression return to baseline in the same orthotopic model system (Main Fig 1F). Including tumor volumes/mass at time of tumor excision for all samples would be appreciated.

Answer: We believe that the lack of pERK rebound in RMC6236 treated tumors vs. MRTX1133 treated tumors is due to differences in the mechanism of action of each drug. RMC6236 binds to the active RAS-GTP complex, meaning that it can act to suppress both amplified wildtype RAS signaling and mutant RAS signaling. In contrast, MRTX1133 non-covalently binds to KRASG12D with high specificity, which still allows for wildtype KRAS signaling which could drive pERK rebound. We revised the manuscript to address differences in the mechanisms of action of the drugs in response to this point and major point 5.

@Arbitrating comment Ref#2: Agreed.

2. What are the treatment durations for each of the PDXs? Is the classification of PD, PR, SD made at the same time point post initiation of treatment or is this the best response observed?

Answer: We apologize for the insufficient experimental details provided for PDX experiments. The treatment duration for the PDXs varied depending on the growth kinetics of each PDX, and the classification reported is the best response observed. We updated the revised manuscript to include this information.

@Arbitrating comment Ref#2: Agreed.

3. Uninterpretable supplementary data. Gene-level expression tables (Cdk8, Nras, Kras, Myc, Yap1, Abcb1a, etc.) show inconsistent changes and are not integrated into any mechanistic interpretation. Their relevance is unclear.

Answer: We appreciate the opportunity to clarify the supplementary data table. Supplementary Table 1 includes a list of copy number variations (CNVs) and their location in the genome identified in tumors and cell lines as opposed to gene expression. The data is a more detailed explanation of the plots included in Supplemental Fig. 5A and 7G-H. We analyzed 3 individual tumors per treatment group, and inconsistent changes reflect heterogeneity in the amplifications/deletions that are present. We revised the text to clarify these points.

@Arbitrating comment Ref#2: OK

Dear Daniel: Thank you for providing us with the reassessment of our revised manuscript. We appreciate the opportunity to see this work published in the EMBO J. Please see our pointwise response below.

Referee #2, arbitrating re-comments:

I served as a reviewer for this manuscript submitted to another venue previously.

In summary, I valued the scientific significance and translational potential of the study, but less enthusiasm on the causal role of CDK8 levels on the development of drug resistance, and its direct human relevance (difficulty in testing human PDAC samples).

For this review, I have made comments one-by-one on the authors' rebuttal letter as detailed below. I support the publication of this paper in EMBO, if the authors would address my minor critiques, and are willing to tune down the strong statement on causal role of CDK8 in drug resistance and human relevance.

Answer: Thank you for the assessment of our work.

Referee #2, arbitrating re-comments on Author rebuttal response:

Reviewer #3 (Remarks to the Author):

Summary: The additional work done using RAS inhibitors currently being clinically tested in additional PDX models is appreciated. The inability to analyze human samples due to the companies not allowing reporting is understandable. Addition of this limitation in the discussion, as well as modifying the title, is noted. However, questions remain.

@Arbitrating comment Ref#2: Justified and agreed.

Major Points
1. Regarding expression of CDK8 levels in Reviewer Fig 1A, it would be striking to see if tumors that were more resistant to RAS inhibitor therapy all had higher levels at baseline or if baseline level is not predictive of response. This comparison would potentially strengthen translatability and the central premise of the manuscript. Across several PDXs, baseline CDK8 levels are higher in sensitive tumors compared to resistant ones. This directly contradicts with the proposed model in which CDK8 promotes resistance and is not adequately addressed. The data more appropriately position CDK8 as a correlatively enriched marker in some resistant contexts, not a validated driver.

@Arbitrating comment Ref#2: The results largely support the conclusion. The point on "whether CDK8 is an inherent driver of resistance vs. an acquired driver of resistance" should be discussed in the Discussion section, as argued here.

Answer: We revised the discussion section to include these points.

2. With respect to murine CDK8 levels in the orthotopic experiment (Reviewer Figs 1E-F), the authors need to include expression of CDK8 levels in the vehicle group, especially since they list

vehicle pERK expression (Reviewer Fig 1D). Without this, it is not possible to discern is the increase in CDK8 a return to baseline or the increase is only in response to continued pressure from pan-RAS inhibition. The authors have not shown that CDK8 decreases early and increases with the emergence of resistance, as one of the reviewers explicitly recommended. The added timepoints appear selected but not temporally linked to the development of resistance.

@Arbitrating comment Ref#2: The point was fully addressed.

3. Regarding PDX data, making comparisons regarding CDK8+ cells between samples (Reviewer Fig 1J) needs to be complimented by making comparisons between each of these and the respective vehicle group as done in Reviewer Fig 1H. This is necessary due to the discrepancy where PDXs PATX124 and PATX155 had similar levels of CDK8 expression after RAS inhibitor treatment (Reviewer Fig 1A) but then different responses to RAS inhibitor therapy (PATX124-Resistance and PATX155-Partial Response, Figs 1G-J). This potentially suggests differing levels at baseline, which could be determinative of response.

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Answer: 4 tumors per condition were included in the analysis. We revised the text to reflect that PATX155, which has a PR to RMC9805, shows a trend towards increased CDK8, albeit not statistically significant (P=0.1099).

4. The additional PDX data remain correlative and do not demonstrate that CDK8 is mechanistically required for resistance to KRAS inhibitors. No CDK8 perturbation studies (inhibition, knockdown, overexpression) were performed and no functional rescue experiments are provided. So how could they claim that CDK8 drives resistance if they didn't knock it down?

@Arbitrating comment Ref#2: I agree with both reviewer and the authors. If this critical experiment cannot be done, the authors should tone down their strong conclusion.

Answer: We revised the text to temper conclusions about human relevance.

5. They merged data from MRTX1133, RMC6236, and RMC9805 without addressing major mechanistic differences between these agents. Resistance pathways differ widely across these inhibitors, yet the authors treat CDK8 as a unified node without justification.

Answer: We agree that MRTX1133, RMC6236, and RMC9805 have different mechanisms of action, but all act to suppress KRASG12D signaling in this context because the model is driven by oncogenic KrasG12D. Despite such differences, CDK8 is a conserved mechanism of resistance across distinct modalities of RAS inhibition, which we view as a strength of our findings and provides rationale for future studies evaluating whether CDK8 upregulation is a conserved immune remodeling driven mechanism of resistance with alternate KRAS* targeting strategies. Our conclusions are driven the collected data. We revised the discussion to address this point.

@Arbitrating comment Ref#2: I largely agree. This important issue needs to be raised and thoroughly discussed.

Answer: We revised the discussion to further discuss this point.

6. Human relevance is still limited. Despite added PDX data, no human primary tissue, clinical biopsy, or large-scale transcriptomic correlation is included. Public datasets (TCGA, CPTAC) are not leveraged. The claim of improved human relevance remains overstated.

@Arbitrating comment Ref#2: Again, I agree with both the reviewer and the authors. Thus, the strong conclusion on human relevance should be tune down, given lack of strong supporting data.

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@Arbitrating comment Ref#2: Agreed.

2. What are the treatment durations for each of the PDXs? Is the classification of PD, PR, SD made at the same time point post initiation of treatment or is this the best response observed?

Answer: We apologize for the insufficient experimental details provided for PDX experiments. The treatment duration for the PDXs varied depending on the growth kinetics of each PDX, and the classification reported is the best response observed. We updated the revised manuscript to include this information.

@Arbitrating comment Ref#2: Agreed.

3. Uninterpretable supplementary data. Gene-level expression tables (Cdk8, Nras, Kras, Myc, Yap1, Abcb1a, etc.) show inconsistent changes and are not integrated into any mechanistic interpretation. Their relevance is unclear.

@Arbitrating comment Ref#2: OK

Thank you for your patience and the time.

Regards,

Raghu

Dear Raghu,

Thank you for submitting the revised version of your manuscript. I have now evaluated your amended manuscript and concluded that the remaining minor concerns have been sufficiently addressed.

I am thus pleased to inform you that your manuscript has been accepted for publication in the EMBO Journal.

Your manuscript will be processed for publication by EMBO Press. It will be copy edited and you will receive page proofs prior to publication. Please note that you will be contacted by Springer Nature Author Services to complete licensing and payment information.

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Thank you again for this contribution to The EMBO Journal and congratulations on a successful publication! Please consider us again in the future for your most exciting work.

Best regards,

Daniel

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The data shown in figures should satisfy the following conditions:
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- plots include clearly labeled error bars for independent experiments and sample sizes. Unless justified, error bars should not be shown for technical
- if n<5, the individual data points from each experiment should be plotted. Any statistical test employed should be justified.
- Source Data should be included to report the data underlying figures according to the guidelines set out in the authorship guidelines on Data

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Each figure caption should contain the following information, for each panel where they are relevant:
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- the exact sample size (n) for each experimental group/condition, given as a number, not a range;
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