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# Ceralasertib plus Durvalumab in Ras Mutant and Ras Wild-Type Advanced Non-Small Cell Lung Cancer: Two Cohorts of the Phase II Platform National Lung Matrix Trial

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## ABSTRACT

**Purpose:** Preclinical data suggest that ceralasertib, a potent ATR inhibitor, might reverse resistance to anti-PD-(L)1 in KRAS-mutant lung adenocarcinoma (LUAD). Activity of ceralasertib/durvalumab was, therefore, assessed in 2 prospective, parallel immune checkpoint blockade-resistant cohorts, 1 harboring KRAS mutations (J1) and the other without (NAJ), within the National Lung Matrix Trial.

**Patients and Methods:** Oral ceralasertib was administered (240 mg twice daily on days 15–28) with durvalumab (1,500 mg i.v., on day 1 of every 28-day cycle) until disease progression. Coprimary outcomes were objective response (OR) and 24-week durable clinical benefit (DCB). Biological impacts of ceralasertib were assessed in a human BJ-hTERT KRASV12<sup>ER-TAM</sup> model. Immunologic impact of KRAS mutation was assessed using gene-level processed LUAD The Cancer Genome Atlas Pan-Cancer data.

**Results:** Between July 2, 2020, and October 31, 2021, 43 patients were registered, 19 and 18 of whom were evaluable for outcome analysis in cohorts J1 and NAJ, respectively. Cohort target recruitment (30 participants each) was not reached due to trial closure at the preplanned end of funding. Bayesian estimates of DCB rates (95% credible intervals) were 37.7% (19.1–59.2) for J1 and 29.3% (12.6–51.2) for NAJ. Two participants demonstrated OR, both KRAS mutant, 1 of whom had KEAP1/STK11 co-mutation. KRAS mutation significantly increased the proportion of cells harboring ceralasertib-induced micronuclei. Ceralasertib blunted KRAS-mediated STAT1 downregulation.

**Conclusions:** Although outcome measures on ceralasertib/durvalumab in anti-PD-(L)1-resistant patients with LUAD are modestly higher in KRAS-mutant participants, these differences are not significant, a result likely related to the modest impact of KRAS mutation alone on the immunobiology of LUAD.

## Introduction

KRAS is commonly mutated in lung adenocarcinoma (LUAD), and success in targeting this alteration with genotype-matched targeted therapy attests to its importance as an oncogenic driver in this common disease (1). Data derived from inducible cell line

models show that KRAS mutation seems to instruct an immunosuppressive program in the tumor microenvironment (TME) through 2 principal mechanisms. Activation of oncogenic KRAS induces the secretion of multiple cytokines and chemokines that drive recruitment and polarization of protumorigenic myeloid and myeloid-associated cell populations (2). In KRAS-induced lung

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## Translational Relevance

Multiple anti-PD-(L)1 combinations are being trialed to reverse anti-PD-(L)1 resistance in lung cancer. Identifying appropriate biomarkers is essential to triage patients to the combination most likely to reverse the main driver of resistance in their cancer. Preclinically, KRAS mutation instructs an immunosuppressive program driven by downregulation of IFN signaling and upregulation of myeloid cell recruitment/polarization. Ceralasertib, a potent ATR inhibitor, increases genomic instability in KRAS-mutant cells, driving formation of immunogenic micronuclei, and can synergize with anti-PD-L1. In this analysis of 2 prospective, parallel cohorts within the National Lung Matrix Trial, we show that although clinical outcomes resulting from ceralasertib/durvalumab in anti-PD-(L)1-resistant participants with lung adenocarcinoma (LUAD) were modestly higher in those with KRAS mutations compared with those without, these differences were nonsignificant. This result potentially relates to the modest impact of KRAS mutation alone on the immunobiology of LUAD, which we also demonstrate.

cancer models, Th17 cells and neutrophils are both significantly induced by KRAS activation, with the myeloid component having the characteristics of granulocytic myeloid-derived suppressor cells (G-MDSC; ref. 3). IL17 mediates their tumoral recruitment, and depletion of G-MDSC retards tumor growth. Ablation of IL17C significantly reduces tumoral neutrophil recruitment, and knockout of IL17C significantly enhances the efficacy of anti-PD-1 compared with wild-type (WT) animals (4). Second, mutant KRAS significantly downregulates both type I and type II interferon (IFN) signaling (2). As such, pharmacologic KRAS inhibition reverses both the expression of protumoral cytokines and chemokines, significantly reducing monocyte and neutrophil tumoral infiltration in vivo, and upregulates IFN responses both in vitro and in vivo. Despite the significant resultant remodeling of the TME, KRAS inhibition is insufficient to sensitize immune resistant lung cancers to immune checkpoint blockade (ICB; ref. 2).

We hypothesized that an alternative approach to that of direct RAS inhibition to reverse resistance to ICB in KRAS-mutant LUAD would be to combine ATR inhibition with ICB. Ceralasertib is a potent and specific orally available ATR inhibitor, which in mouse models enhances the activity of anti-PD-L1 (5). Interestingly, the monotherapy efficacy of ceralasertib is dependent on CD8<sup>+</sup> T cells and is attenuated by blockade of type I IFN signaling.

Ceralasertib decreases the number of monocytic myeloid-derived suppressor cells (5), which mediate resistance to ICB in lung cancer (6, 7) and the number of tumor-associated macrophages while increasing the number of activated dendritic cells (DC). Ceralasertib significantly reduces the immunosuppressive activity of G-MDSC, an effect associated with upregulation of type I IFN signaling in these cells. Ceralasertib increases intratumoral type I IFN signaling, including STING-mediated type I IFN production by cancer cells. In anti-PD-L1 monotherapy- and ceralasertib monotherapy-resistant models, the addition of ceralasertib to anti-PD-L1 results in significant reductions of tumor growth. Importantly, this synergy with anti-PD-L1 and the associated proimmunogenic effects, including an increase in tumoral antigen-specific CD8<sup>+</sup> T cells, is

abrogated by blockade of type I IFN. Ceralasertib causes the formation of acentric micronuclei in cancer cells (8, 9), which have defective nuclear lamina which are prone to rupture, shedding DNA into the cytosol, and activating cytosolic DNA sensors, thus driving a type I IFN response with resultant enhanced immunogenicity (10).

Mutant KRAS also causes DNA damage via transcription replication conflicts and the formation of R-loops (11, 12). Replication stress (RS) occurs when DNA replication forks slow or stall and which occur when the replication and transcription machinery collide due to hypertranscription or collision of the replication machinery with R-loops (13). Replication fork slowing results in the subsequent collapse of forks into double-strand breaks (DSB) as well as mitotic entry with under-replicated DNA, which can lead to the formation of micronuclei. RAS-induced fork slowing activates the RS response factor CHK1, and accordingly, ATR deficiency leads to an enhanced accumulation of DSB and increased genomic instability in a murine Ras-transformed background compared with nontransformed counterparts (14). An RS response defect signature (RSDR) predicts outcome with ICB across diverse nonhypermethylated cancers, including lung cancer, and RSDR-high cell lines exhibit increased ATR activation and accumulate DSB and cytosolic DNA (15).

Based on the strong supporting preclinical data and as part of the phase II development of ceralasertib plus durvalumab, we tested and report here the activity of the combination in 2 preplanned, prospective, parallel ICB-resistant non-small cell lung cancer (NSCLC) cohorts from the phase II platform National Lung Matrix Trial (NLMT). The cohorts included patients previously treated with anti-PD-(L)1 whose cancers harbored KRAS mutations and patients whose cancers were KRAS WT.

Finally, it is important not to consider KRAS-mutant LUAD as a biologically homogeneous entity. Downstream signaling from the different KRAS subtypes is quite distinct: for example, G12D preferentially activates Akt signaling whereas RalA/B signaling dominates in G12C LUAD cells and suppresses Akt via activation of S6 kinase (16). High PD-L1-expressing G12C-mutant lung cancer treated with pembrolizumab have significantly improved survival compared with non-G12C cancers, and G12C-mutant patients have higher numbers of tumor-infiltrating lymphocytes and greater activation of IFN $\gamma$  signaling pathway genes than non-G12C cases (17). G12C KRAS-mutant cancers have significantly improved survival versus G12D with both single-agent anti-PD-1 and combination chemoimmunotherapy regardless of PD-L1 tumor proportion score, and G12D cancers have significantly fewer infiltrating T cells than non-G12D KRAS-mutant lung cancers (18). These data highlight the criticality of assessing the differential impacts of therapeutically targeting KRAS according to KRAS mutational subtype.

## Patients and Methods

### Trial design

Patients included in this study were recruited as part of the NLMT [ClinicalTrials.gov NCT02664935 (19), ISRCTN38344105 (20), EudraCT 2014-000814-73 (21); trial protocol available in Supplementary Study S1]. In summary, this is an umbrella phase II platform trial in advanced NSCLC run in the United Kingdom and investigating 9 experimental targeted drug interventions in 23 different actionable biomarker cohorts and 2 further interventions in 2 sequential cohorts of patients with no actionable biomarkers (the NA cohorts; Supplementary Fig. S1; ref. 22). Arm J (cohorts J1 and NAJ) was added to the trial in protocol v9.0 (January 22, 2020) by

substantial amendment 19, which received full regulatory approval on April 1, 2020. Additional details are included in Supplementary Methods S1.

Patients included here are the 2 cohorts of patients who received ceralasertib plus durvalumab: 1 cohort with *KRAS* mutations (cohort J1) and 1 with no actionable biomarkers and, in particular, *KRAS* WT (cohort NAJ). Both cohorts required a successful Stratified Medicine Programme 2 (SMP2) test result available for *STK11/LKBI* and a pass rate of 90% > of the core genes. Target recruitment for each cohort was 30 patients. At the time the initial results were published (22), which provided an overview of the entire trial, cohorts J1 and NAJ had not yet been opened.

The NLMT complied with all regulatory requirements; ethical approval was obtained from South Central-Oxford C Research Ethics Committee; clinical trial authorization was granted by the UK Medicines and Healthcare products Regulatory Agency. The trial was sponsored by the University of Birmingham and run by the Cancer Research UK Clinical Trials Unit. The trial was submitted and published to ISRCTN (20) on June 10, 2015.

### Trial participants

Eligible patients had histologically or cytologically confirmed NSCLC stage III (not suitable for radical radiotherapy or surgery) or stage IV with measurable disease according to Response Evaluation Criteria in Solid Tumors [RECIST v1.1 (23)] and needed to have received previous anticancer treatment or refused standard-of-care first-line therapy; full eligibility criteria can be found in the trial protocol in Supplementary Study S1.

Supplementary Table S1 provides background information on the cancer under study and the representativeness of the study population.

All patients gave written informed consent in accordance with Good Clinical Practice and the Declaration of Helsinki's ethical principles for medical research.

### Trial procedures

Ceralasertib (AZD6738) was administered orally at a dose of 240 mg twice daily on days 15 to 28, with durvalumab (1,500 mg i.v.) on day 1 of every 28-day cycle until confirmed disease progression.

Patients could continue trial treatment after progression if tolerated, and there was clinical benefit. Blood for ctDNA was collected before dosing before the first cycle of treatment and then every 8 weeks (every other cycle).

### Trial outcomes

For cohorts J1 and NAJ, the coprimary outcome measures were objective response (OR), defined as the incidence of confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 (23), and durable clinical benefit (DCB), defined as the incidence of remaining free of disease progression at the fourth protocol-defined CT assessment at approximately 24 weeks from commencing treatment. Participants who were lost to follow-up after discontinuing before the 24-week time point were counted as not having met the threshold for successful DCB. Secondary outcomes are included in Supplementary Methods S1.

### Trial statistical analysis

A Bayesian adaptive trial design was used to screen each experimental targeted drug intervention in the NLMT for signals of efficacy in each selected molecularly defined cohort. The statistical

analysis plan is available at ISRCTN38344105 (20) and briefly explained in Supplementary Methods S1.

A per-protocol analysis population (which includes patients who received sufficient protocol treatment) was used for analysis of OR, DCB, progression-free survival (PFS), and overall survival (OS). It was also used for the descriptive analysis of the best percentage change in the sum of target lesion diameters. An intention-to-treat population (all registered participants) was used for reporting serious adverse events (SAE).

### Trial patient and public involvement

Patient and public involvement (PPI) was provided throughout the trial setup and delivery through membership of the Trial Management Group (S. Hayton and T. Haswell), providing document review and input at meetings. PPI representation was also present on the independent Trial Steering Group (M. Baker), providing oversight of trial governance, conduct and results, and input into interim analysis decisions.

### ctDNA extraction and library preparation

DNA was extracted from plasma at baseline and at the end of treatment (progression or treatment discontinuation) using the QIAamp Circulating Nucleic Acid Kit (QIAGEN, 55114). Additional details are included in Supplementary Methods S1.

### Bioinformatics

Gene-level processed (level 3) "LUAD TCGA PanCancer" mutation (excluding silent mutations) and RSEM normalized RNA sequencing (RNA-seq) data were used. The Cancer Genome Atlas (TCGA) patient LUAD tumor samples were grouped by mutation status, focusing on 5 important driver genes in NSCLC: EGFR, *KRAS*, TP53, *STK11*, and *KEAP1* genes. Additional details are included in Supplementary Methods S1.

### Singleplex immunohistochemistry

Formalin-fixed, paraffin-embedded tumor sections were sourced from TRACERx NSCLC tumors with and without *KRAS* mutations (24). Sections were immunohistochemistry (IHC)-stained with anti-retinoid-related orphan receptor  $\gamma$  t (ROR $\gamma$ T; Merck 6F3.1, RRID: AB\_11205416, 1:700) by Leica BOND RX (RRID: SCR\_025548) using a pH 9.0 heat-induced epitope retrieval protocol and 3,3'-diaminobenzidine (DAB) chromogenic development. Additional details are included in Supplementary Methods S1.

### Multiplex IHC

Using the Opal IHC Kit (Akoya, NEL821001KT, RRID: SCR\_023774), a Leica BOND RX performed a sequential pH 9.0 heat-induced epitope retrieval protocol, with antibody removal steps and a final 4',6-diamidino-2-phenylindole (DAPI) counterstain. Additional details are included in Supplementary Methods S1.

### Cell culture

Human BJ-hTERT *KRAS*V12ER-TAM cells were generated by lentiviral transduction. Additional details are included in Supplementary Methods S1.

### Micronuclei

Cells were fixed with 4% paraformaldehyde for 10 minutes, and DNA was counterstained with DAPI. Images were acquired on a Nikon E600 microscope with a Nikon Plan Apo 60 $\times$  (1.3 NA) oil lens, an Andor Zyla sCMOS digital camera, and Nikon NIS

elements BR 5.41.01 software. Micronuclei were counted using ImageJ (RRID: SCR\_003070; refs. 25, 26).

### RNA-seq

Cells were harvested in TRI Reagent (Zymo Research), and RNA extraction was performed using the Direct-zol RNA Miniprep Kit (Zymo Research), including DNase I treatment, according to the manufacturer's instructions. Additional details are included in Supplementary Methods S1.

### Western blot

Cells were extracted in a urea-tris- $\beta$ -mercaptoethanol (UTB) buffer (50 mmol/L Tris-HCl, pH 7.5, 150 mmol/L  $\beta$ -mercaptoethanol, and 8 mol/L urea) and sonicated, and protein concentration was determined by Bradford assay. Primary antibodies are listed in Supplementary Methods S1.

## Results

In a model system, *KRAS* mutation significantly increases ceralasertib-induced micronuclei formation and ceralasertib blunts *KRAS*-mediated STAT1 downregulation.

We previously reported that *HRAS* activation in the absence of any other oncogenic drivers (using the human BJ-hTERT fibroblast model) leads to increased micronuclei formation, which would be expected to activate cGAS-STING signaling (27). However, recent preclinical data show that acute *KRAS* G12V induction causes downregulation of type I IFN (and type II) signaling (2). We therefore queried whether, like *HRAS* activation, *KRAS* G12V activation in this model also generates micronuclei and demonstrate that it does, albeit nonsignificantly (Fig. 1A–C). As expected, ceralasertib, in the absence of *RAS* activation, results in a dose-dependent increase in micronuclei formation up to a dose of 1  $\mu$ mol/L. Importantly, the activation of *KRAS* G12V results in a significant increase in the proportion of cells with micronuclei induced by ceralasertib alone up to the 1  $\mu$ mol/L dose, demonstrating that the impact of ceralasertib and *KRAS* activation on micronuclei formation is at least additive. Beyond this dose, it is likely that the cell toxic effects will eliminate cells that are cycling faster, thereby reducing the cell number with micronuclei. Figure 1D shows that there is no impact on viability of BJ-hTERT cells with or without *KRAS* G12V activation up to a ceralasertib dose of 1  $\mu$ mol/L.

In line with previous data (2, 28), acute *KRAS* activation in our system activates Myc target expression and results in significant downregulation of key genes associated with type I IFN responses (2), including the critical pathway sensor STAT1 (Fig. 2A and B). The type I antiviral response is dependent on the ISGF3 complex containing STAT1/STAT2 heterodimers and type I IFN-induced inflammatory responses are dependent on STAT1 homodimers binding to  $\gamma$ -activated sequences (29, 30). MYC binds the *STAT1* locus and represses its expression, resulting in downregulation of IFN pathway gene expression (2). However, the addition of ceralasertib dose-dependently blunts the significant *KRAS*-mediated STAT1 downregulation such that following the addition of ceralasertib, the *RAS*-mediated STAT1 downregulation is no longer significant, although there is no appreciable effect of the addition of ceralasertib on pSTAT1 levels in *RAS*-activated cells (Fig. 2C and D). In summary, ceralasertib on a mutant *KRAS* G12V-activated background generates potentially more immunogenic micronuclei than on a WT background, and ceralasertib blunts the *KRAS*-mediated downregulation of the critical IFN pathway signaling gene

STAT1, suggesting that ceralasertib has the potential to, in part, reverse this inherently immunosuppressive mechanism of *KRAS* mutation.

Clinical outcomes in patients with anti-PD-(L)1-resistant advanced lung cancer with or without *KRAS* mutation were treated with a combination of ceralasertib and durvalumab.

Between July 2, 2020, and October 31, 2021 (when the trial closed), 43 patients were registered from 17 UK hospitals to receive ceralasertib plus durvalumab within arm J of the NLMT, 20 with *KRAS* mutation (cohort J1) and 23 with no actionable alteration suitable for treatment in 1 of the other arms of the NLMT, and, by definition, all *KRAS* WT (cohort NAJ). All study participants were naive to *KRAS* G12C inhibitors. Cohorts passed their interim analyses but did not reach their target recruitment of 30 due to the trial closing at the preplanned trial closure date at the end of the funding period. All 43 patients were included in the safety analysis of the treatment. Six patients were excluded from the per-protocol population (1 nontreated in J1; 4 nontreated and 1 inadmissible/ineligible in NAJ), resulting in 19 and 18 patients evaluable for outcome analysis in cohorts J1 and NAJ, respectively (Fig. 3).

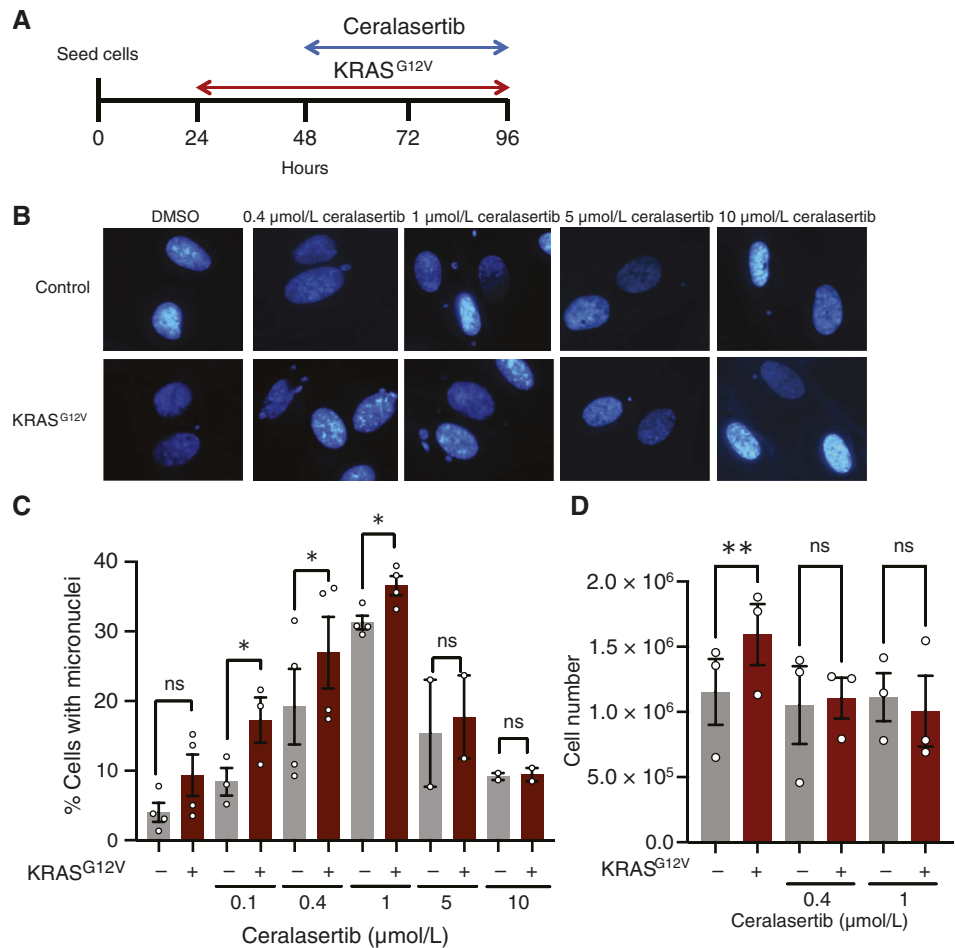
In the 43 registered patients, the median age was 67 years (range, 49–84), with 56% females, 86% adenocarcinoma pathology, 79% with metastases, and 19% PS0 and 81% PS1, with a similar distribution of baseline characteristics across the 2 cohorts (Supplementary Table S2). The screening data from the SMP2 showed few concomitant genetic aberrations to the *KRAS* mutation in the J1 cohort, with the most common being a *CDKN2A* mutation present in 6 patients, also present in 10 patients in the NAJ cohort (Supplementary Fig. S2). Three concomitant *STK11* mutations were present in both arms. At the time of data lock (October 15, 2025), all participants in the per-protocol (analysis) population had been followed up until death.

Of the 37 per-protocol participants, the median number of cycles received was 5, with participants receiving between 1 and 36 cycles of treatment; the main reason for treatment discontinuation was progressive disease (PD; Figs. 3 and 4A). There were 3,556 AE and 1,651 adverse reactions (AR; those related to trial treatment) in 42 and 39 of the registered patients, respectively, but only 178 (5%) and 115 (7%) of these events were reported as grade 3 or above, with platelet count decrease being the most common (Supplementary Table S3). There were 34 SAE reported in 20 participants; 7 of which were categorized as related [serious AR (SAR)] and 8 as related and unexpected (suspected unexpected SAR) in 5 and 6 patients, respectively.

The Bayesian estimated DCB rates [95% credible interval (CrI)] were 37.7% (19.1–59.2), 7 of 19 participants in the *KRAS*-mutant cohort J1, and 29.3% (12.6–51.2), 5 of 18 participants in NAJ (Fig. 4A; Supplementary Table S4). The PPoS of 0.92 for J1 showed that if recruitment had continued to the target of 30 patients, there was a very high probability of a “GO” decision directing further investigation of this combination in the *KRAS*-mutant population. Two per-protocol patients achieved OR, both in J1 ( $n = 19$ ), giving a Bayesian estimated true OR rate (95% CrI) of 13.1% (3.2–31.7) in that cohort (Fig. 4B; Supplementary Table S4) showing a very low probability of a clinically relevant true OR rate (PP = 0.04). There were no responders in NAJ. In terms of best percentage change in the sum of target lesion diameters, the waterfall plot shows no clear segregation between J1 and NAJ, with participants from both cohorts distributed across the full range of values (Fig. 4B).

**Figure 1.**

Ceralasertib-dependent micronuclei formation in the absence of KRAS activation. **A**, Strategy for cell treatments. KRAS<sup>G12V</sup> was induced in BJ-hTERT-KRAS<sup>G12V</sup>ERTAM fibroblasts for 72 hours by adding 500 nmol/L 4-hydroxytamoxifen (4-OHT). Ethanol (EtOH) was used for the no KRAS<sup>G12V</sup> control. Ceralasertib was added for 48 hours after the first 24 hours of KRAS<sup>G12V</sup> induction at the concentrations indicated. **B**, Representative images of micronuclei after 72 hours of KRAS<sup>G12V</sup> induction or EtOH control with and without ceralasertib at the concentrations indicated. Cells were stained with DAPI. **C**, Percentages of cells with micronuclei as on **B**. **D**, Cells were all seeded at equal densities, treated as in **A**, and counted in a hemocytometer after 96 hours. Means and standard errors of the mean (SEM) of  $n = 2-4$  are shown. Paired  $t$  test. \*,  $P \leq 0.05$ ; \*\*,  $P \leq 0.01$ ; ns, not significant.



Recent data in genetically engineered mouse models (GEMM) show that, although the addition of ceralasertib to anti-PD-1 does not provide benefit in KRAS-mutant models with *STK11* loss, it does in a GEMM with KRAS, *STK11*, and *KEAP1* mutations (31). *KEAP1* mutation significantly activates ATR signaling. In an exploratory analysis of HUDSON, the benefit of ceralasertib/durvalumab against the other 3 combinations seems to be greatest in the KRAS-mutant patients harboring co-mutations in *KEAP1* and/or *STK11*. Therefore, we evaluated these co-mutations in the 19 evaluable participants reported here in cohort J1. Of those classified as KRAS-mutant by tissue sequencing (an eligibility criteria used for trial entry), only 2 had *STK11* loss detected on tissue sequencing. This relatively low figure was due to 2 other arms open at the time in the NLMT platform specifically recruiting KRAS-mutant patients with concomitant *STK11* loss. Although *KEAP1* was not on the original parsimonious panel used for tissue sequencing, there were 15 KRAS-mutant samples from evaluable participants with an available baseline ctDNA sample, which passed analytic quality control. Of these, 3 had concomitant *KEAP1* mutations. One of these concomitantly harbored 1 of the 2 *STK11* mutations identified. This sample corresponded to 1 of the 2 participants in the cohort achieving PR with a durable OR rate >12 months who remained on treatment for >18 months (Fig. 4A). The second KRAS/*KEAP1* double mutation was from a participant who, while classified as having PD as best response to

treatment, remained on treatment for >12 months, and the third while again being classified as having PD received treatment for around 9 months (Fig. 4A). By protocol, patients with progression were allowed to remain on treatment if it was felt that they were deriving clinical benefit. These data suggest that the patients with concomitant *KEAP1* mutations derived meaningful clinical benefit from the ceralasertib/durvalumab treatment.

As with the DCB and OR rates, PFS and OS were also numerically superior for cohort J1 compared with NAJ (Fig. 5A and B, respectively; Supplementary Table S4). The median PFS (95% CrI) was Bayesian estimated as 6.4 months (4.2–10.4) and 3.9 months (2.5–6.5) for J1 and NAJ, respectively; the estimated median OS (95% CrI) was 15.7 months (10.3–25.7) and 14.2 months (9.2–23.6) for J1 and NAJ, respectively. Although all outcome measures numerically favor the KRAS mutant over the WT patients, the CrI for PFS, OS, DCB rate, and OR rate for both KRAS mutant and WT cohorts overlap (Fig. 5C).

#### In primary LUAD, KRAS mutation alone has a limited impact on tumoral immunobiology

The impact of adding ceralasertib to postoperative durvalumab after preoperative chemoimmunotherapy in those failing to achieve pathologic CR was being tested in the EA5231/CLEAR trial. We analyzed in the setting of primary resected disease using TCGA data, whether KRAS mutation drives the same immunosuppressive

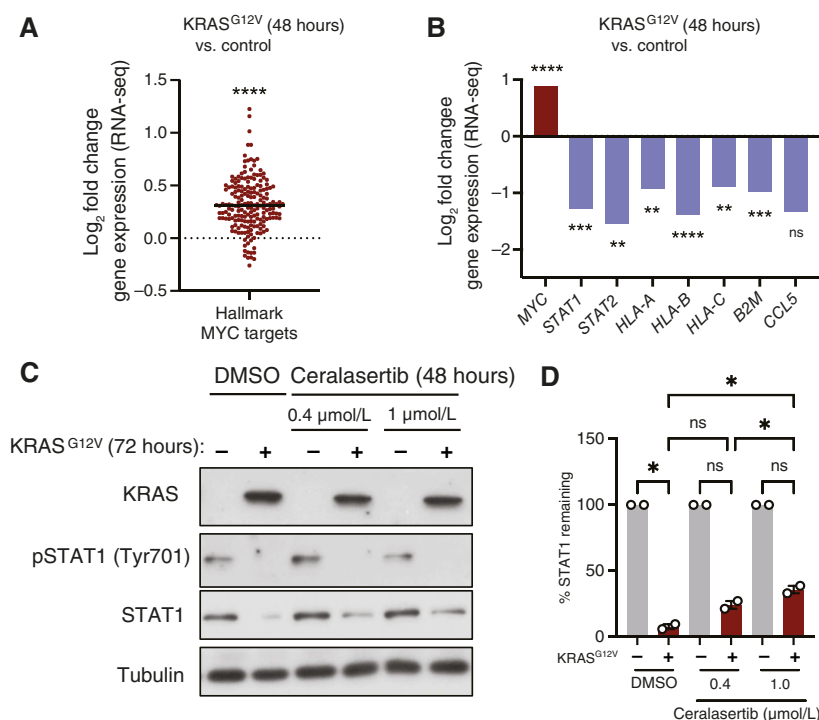


**Figure 2.**

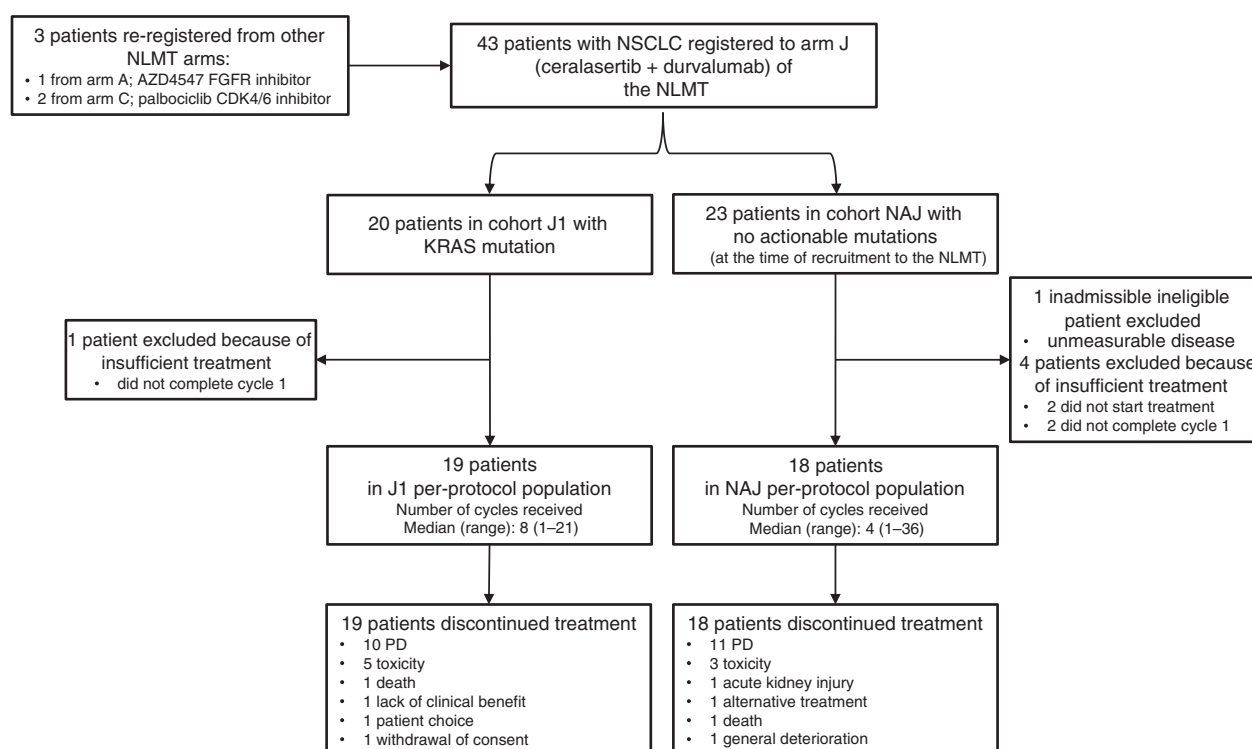
KRAS-dependent MYC activation and downregulation of type I IFN response genes. **A**, Log<sub>2</sub> fold change in Hallmark MYC target (PMID: 26771021) gene expression determined by steady-state RNA-seq after 48 hours of KRAS<sup>G12V</sup> induction (4-OHT) in BJ-hTERT-KRAS<sup>G12V</sup>ERTAM fibroblasts compared with no KRAS<sup>G12V</sup> control (EtOH). Means of *n* = 3 per gene are shown. Line at median. Two-tailed paired *t* test, compared with no KRAS<sup>G12V</sup> control. **B**, Log<sub>2</sub> fold change in expression of the indicated genes determined as in **A**. Means of *n* = 3 are shown. Adjusted *P* values are indicated. **C**, Protein levels of KRAS, phospho-Tyr701-STAT1, STAT1, and tubulin (loading control) after 72 hours of KRAS<sup>G12V</sup> induction or EtOH control in BJ-hTERT fibroblasts. Ceralasertib was added after the first 24 hours of KRAS<sup>G12V</sup> induction at the concentrations indicated. **D**, Quantification of **C**. STAT1 was normalized to the loading control and no KRAS<sup>G12V</sup> (EtOH) control. Means and SEM of *n* = 2 are shown. Repeat-measure (RM) one-way ANOVA with Tukey's multiple comparisons test. \*, *P* ≤ 0.05; \*\*, *P* ≤ 0.01; \*\*\*, *P* ≤ 0.001; \*\*\*\*, *P* ≤ 0.0001; ns, not significant.

programs as reported in preclinical models using a curated 111-gene panel to capture both neutrophil/Th17 cell biology and IFN signaling as highlighted preclinically (2–4), as well as a wider range of T-cell subsets and other immune suppressive cells together with their associated mediators of immunosuppression, multiple immune checkpoints, other important chemokines and their receptors, and antigen processing and presentation genes. Previous studies comprehensively mapped, using LUAD TCGA data, the differentially expressed immune gene pathways in KRAS-mutant LUAD with and without *STK11* and *KEAP1* mutations and in *STK11*-mutant and *KEAP1*-mutant LUAD without concomitant KRAS mutations (32). These analyses explicated many of the immunobiological reasons behind the poor outcome with ICB in KRAS LUAD with *STK11* loss and/or *KEAP1* mutation, in which the deleterious effect of *STK11* and *KEAP1* mutation is only manifested in the context of a concurrent KRAS mutation.

Our KRAS-mutant model system and the immortalized human lung pneumocyte model described above (2) lack mutations in *STK11* and *KEAP1*. To analyze the specific impact of KRAS mutation alone on the immunobiology of LUAD, we compared KRAS mutant/*TP53* WT/*STK11* WT/*KEAP1* WT/*EGFR* WT cancers (rather than all KRAS-mutant cancers, which will include multiple co-mutated samples) with a common reference group—tumors WT for all 5 genes (*KRAS*, *TP53*, *STK11*, *KEAP1*, and *EGFR*). We performed equivalent single-mutation analyses for *EGFR* and *TP53*, in each case comparing against the same WT group. *EGFR* mutation is the most common driver mutation in lung cancer in never-smokers and is rarely found with a concomitant KRAS mutation, and *TP53* is commonly mutated in LUAD and, like KRAS mutation, is another oncogenic driver of genomic instability and has been associated with heightened immune activation. The heatmaps for these 3 mutations are distinct (Fig. 6A). A very limited number of genes are differentially expressed between

KRAS mutation-alone LUAD and KRAS WT LUAD, with only a single gene significantly upregulated in KRAS mutation-alone cancers—RORC. IL17RE and IL17A are upregulated, albeit non-significantly, as are a block of genes associated with neutrophil development, migration, and activation, including CXCL1 and 2, CXCR1 and 2, CSF2, CSF3R, CSF3, IL1B, IL11, and IL8. Upregulation of these genes contrasts with nonstatistical downregulation of most of the other genes. *TP53*-mutant lung cancers exhibit significant upregulation of STAT1, GZMB, IFNG, and CXCL10. These results are in line with earlier data showing that *TP53*-mutant lung cancers lacking *STK11* or *EGFR* co-mutations are immunogenic (33). Finally, we confirm the recently reported significant IFN $\gamma$ -independent upregulation of MHC-class II in *EGFR*-mutant tumors (34), wherein the authors postulate that the lack of co-stimulation on *EGFR*-mutant cancer cells might lead to regulatory T-cell generation and/or T-cell anergy rather than driving CD4<sup>+</sup> effector cell activation. This contrasts starkly with *TP53*-mutant LUAD, in which, despite significant upregulation of IFNG, multiple class II genes are significantly downregulated, along with CIITA (Fig. 6A).

Upregulation of Myc was proposed as a key mechanism for the KRAS mutation-mediated downregulation of IFN gene signaling (2). Using the same pairwise comparisons as above, we show that KRAS mutation alone in the context of established human lung cancer has very little impact on Myc target expression and importantly no effect on the IFN $\alpha$  or  $\gamma$  response, whereas *TP53* mutation significantly increases Myc target expression, and although non-significant, there is an increase in both IFN responses in *TP53* mutant versus WT LUAD (Fig. 6B). In line with the published data showing the immunosuppressive effect of *STK11* and *KEAP1* mutations in the context of KRAS mutation (supported by our CIBERSORTx findings, Supplementary Fig. S3; ref. 31), additional co-mutation of *STK11* and *KEAP1* in KRAS-mutant cancers

**Figure 3.**

Participant flow diagram for arm J. Participant flow diagram for arm J, cohorts J1 and NAJ of the NLMT.

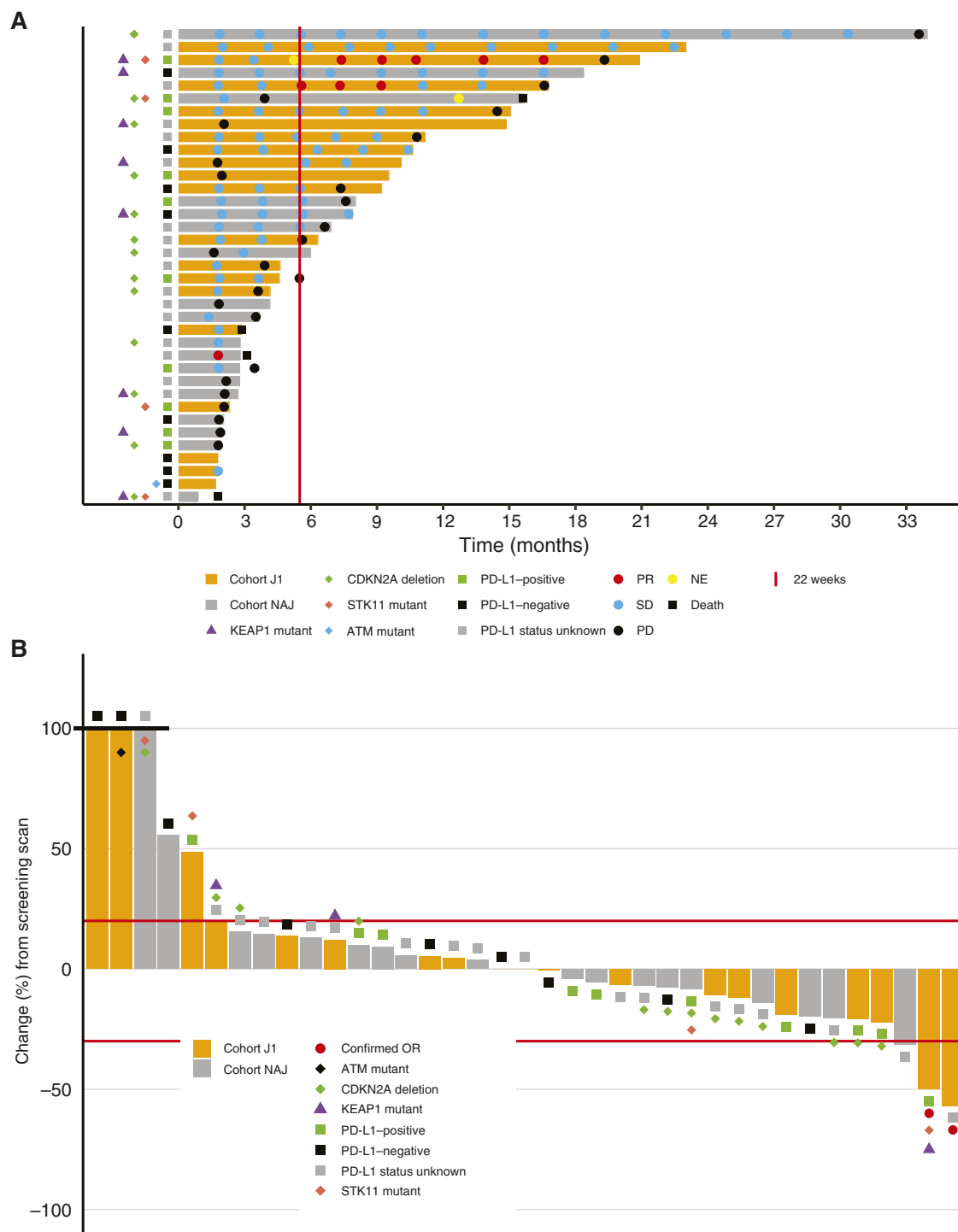
significantly reduces both type I and II IFN pathway activation, and in the case of *KRAS/KEAP1* co-mutation, the Myc targets signature is significantly increased.

Finally, the very modest immunologic impact of *KRAS* mutation alone on a *TP53/STK11/KEAP1/EGFR* background is also seen on pairwise comparison of CIBERSORT signatures of *KRAS* mutant versus WT LUAD with no signature being significantly differentially expressed (Supplementary Fig. S3). The minimal difference in the neutrophil signature expression is notable: this signature is clearly increased by combined *STK11/KEAP1* co-mutation, albeit nonsignificantly. The significant downregulation of monocyte, macrophage, and resting DC signatures in co-mutated cancers versus WT is in keeping with previous data demonstrating downregulation of chemokines and receptors facilitating recruitment of monocytes, myeloid cells, and DCs in *KRAS*-mutant LUAD with these co-mutations (31).

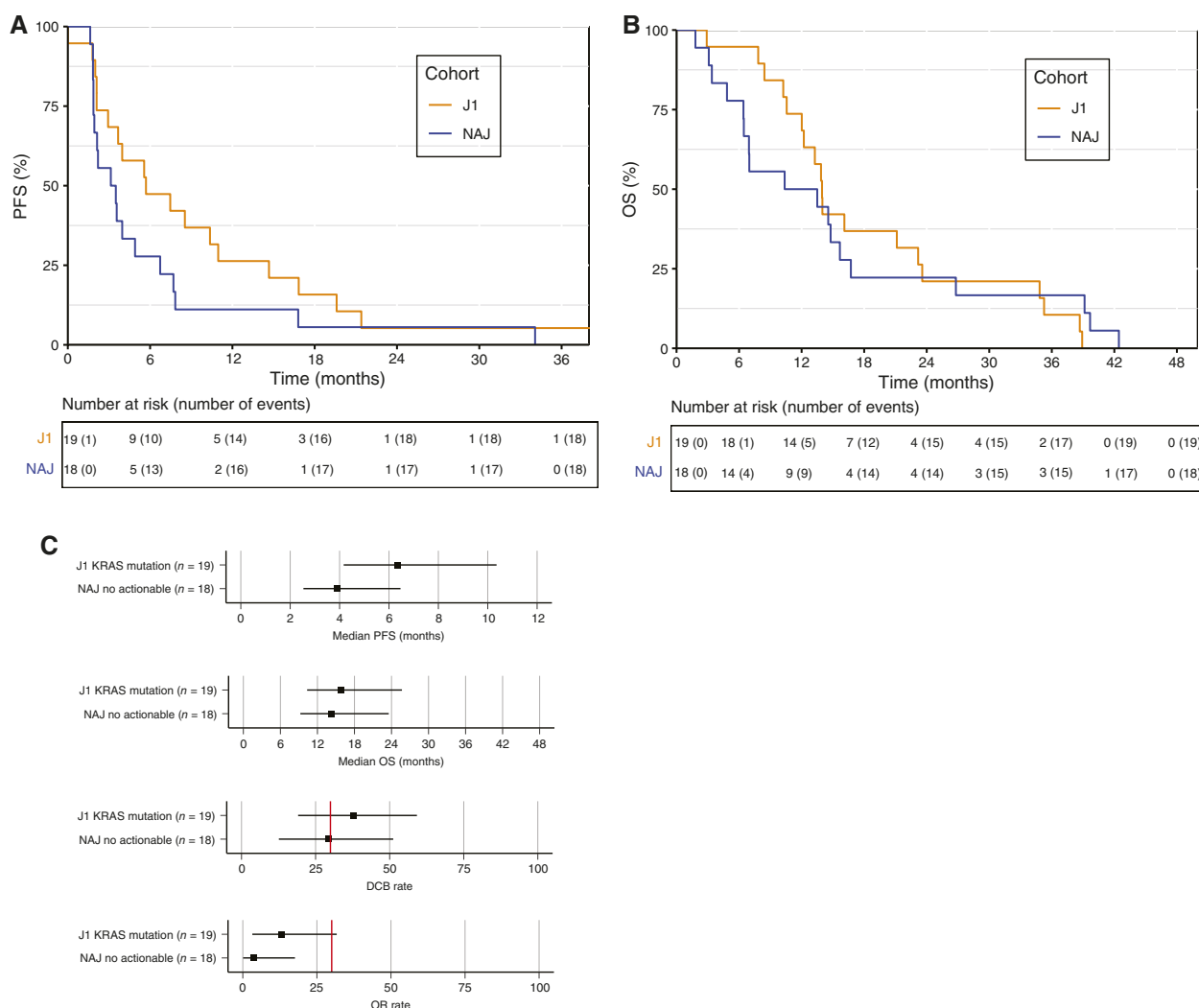
Clinical data show that patients harboring G12C *KRAS* mutations have significantly better outcomes with both anti-PD-1 monotherapy and chemoimmunotherapy compared with patients with G12D-mutated lung cancers (17, 18). Supplementary Figure S4 annotates the swimmer and waterfall plots with the *KRAS* mutational subtype. There are equivalent numbers of G12C and G12D patients in the top and the bottom portions of the swimmer plots of time on treatment. We performed the same immunologic analysis as above this time comparing G12C with G12D *KRAS* mutations with the other genes of interest (*EGFR*, *TP53*, *KEAP1*, and *STK11*) WT (Supplementary Fig. S5). The 111-gene heatmap shows that although G12C cancers are immunologically hotter than G12D cancers, none of the comparisons are significant likely due to relatively

small numbers. Unlike the significant impact of concomitant *KEAP1* and *STK11* mutations on a *KRAS*-mutant background, there is, however, no difference in the expression of the Hallmark MYC targets, IFN $\alpha$  response, or IFN $\gamma$  response signatures in G12C versus G12D lung cancers.

As RORC was the only significantly upregulated immune gene in *KRAS*-mutant tumors from our TCGA gene panel expression analysis, with further upregulation associated with *KEAP1* and/or *STK11* co-mutations (Fig. 6C), we examined tumoral ROR $\gamma$ T protein expression, encoded by RORC, the master transcription factor of Th17 cells, in a panel of TRACERx NSCLC tumors. Similar to TCGA, TRACERx sample tumors are resected primary disease. Due to our limited access to tumor sections with specific co-mutational profiles (Supplementary Table S5), tumors were grouped simply by the presence or absence of *KRAS* mutation. We found a significantly higher abundance of ROR $\gamma$ T+ lymphocytes in *KRAS* mutant compared with *KRAS* WT NSCLC (Supplementary Fig. S6A). We predominantly observed ROR $\gamma$ T+ lymphocytes in lymphoid aggregates, and multiplex staining of lymphoid aggregates detected CD3<sup>+</sup>/CD4<sup>+</sup>/ROR $\gamma$ T+ lymphocytes, consistent with Th17 cells (Supplementary Fig. S6B–S6D). Quantitative analysis by histologic compartment supported our localization observation, showing higher ROR $\gamma$ T+ lymphocytes in lymphoid aggregates compared with tumor bulk regions and consistently higher compartmentalized ROR $\gamma$ T+ lymphocytes in *KRAS* mutant compared with *KRAS* WT tumors (Supplementary Fig. S7A). Interestingly, we did not observe any differences in tumor lymphoid aggregate density, suggesting altered lymphoid aggregate composition in *KRAS*-mutant tumors

**Figure 4.**

Time on treatment and longitudinal responses. **A**, Swimmer plot for participants in cohorts J1 and NAJ ordered by time on treatment. CT assessments are indicated and coded by CR or PR, SD, PD, or NE according to RECIST v1.1. The solid vertical red line indicates 22 weeks, being the minimum time that a participant can be counted as reaching the DCB threshold. Detection of *STK11* mutation and *CDKN2A* deletion from tissue testing are indicated. Detection of *KEAP1* mutation on ctDNA is also indicated (*KEAP1* testing was not included within tissue SMP2 panel). **B**, Waterfall plot indicating the best percentage change in the sum of target lesion diameters for patients in cohorts J1 and NAJ. Per-protocol participants who discontinued without having returned a measurement are included on the left of the plot with a default measurement of +100%. The solid horizontal lines indicate PD (+20%) and PR (−30%), respectively. Detection of tissue *STK11* and *ATM* mutation and *CDKN2A* deletion via SMP2 testing are indicated. Detection of *KEAP1* mutation from blood ctDNA is also indicated, as *KEAP1* testing was not included within the SMP2 panel. NE, not evaluable; SD, stable disease.

**Figure 5.**

PFS and OS. **A**, PFS defined as the time from commencement of trial treatment to the date of CT scan when PD was first recorded or date of death without previously recorded progression. Patients who were alive with no recorded progression at the time of analysis were censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression. **B**, OS defined as the time of commencement of trial treatment to the date of death. Patients who were alive at the time of analysis were censored at the date last seen alive. **C**, Forest plots of Bayesian estimates of median PFS and OS, and DCB and OR rates with 95% CrI. The red vertical line indicates the clinically relevant target rate of 30%.

favoring higher abundance of RORγT+ lymphocytes (Supplementary Fig. S7B).

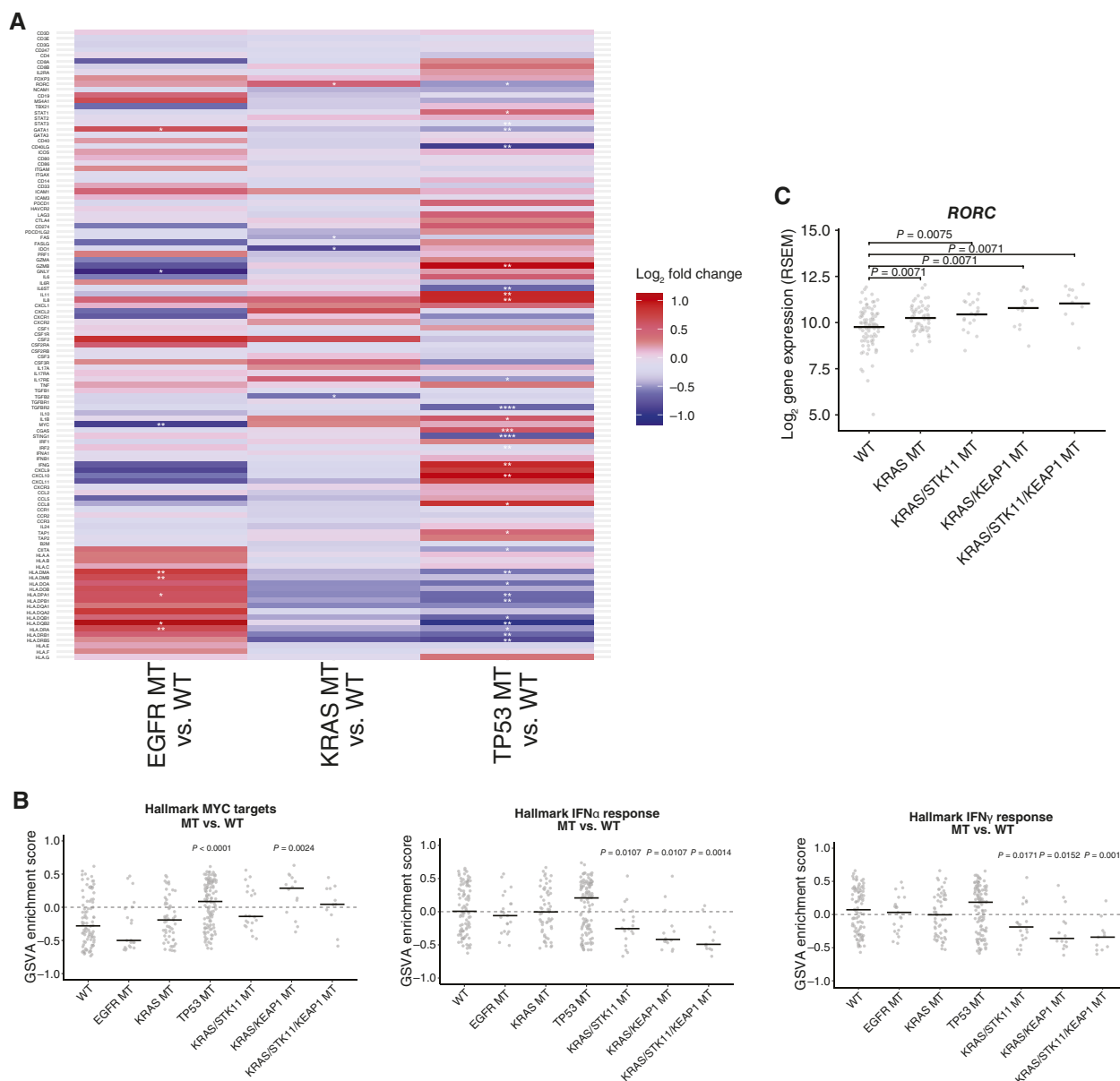
## Discussion

In this prospective evaluation of the impact of the addition of ceralasertib to ICB following ICB failure in patients with LUAD, whereas there are numerical improvements in all outcome measures in favor of *KRAS* mutant compared with *KRAS* WT patients, these differences are modest and nonsignificant. Although our study is limited by the small number of patients recruited, the results are very much in line with retrospective results of the *KRAS* mutant versus WT outcome comparisons with this combination in the HUDSON platform trial (35). Preclinical data, including that presented here, suggested that ceralasertib had the potential to reverse

the inherently immunosuppressive mechanisms of *KRAS* mutation, but we demonstrate that in the setting of human cancer, *KRAS* mutation alone seems to have modest nonsignificant impacts on the immunobiology of LUAD, perhaps explaining the lack of significant differences in outcome according to *KRAS* mutation status. Previous institutional data examining CD8<sup>+</sup> T cell, neutrophil, macrophage, DC-LAMP density, and PD-L1 expression by IHC also demonstrated a lack of impact according to *KRAS* status, unlike the impact of *STK11*, *TP53*, and *EGFR* mutations (33).

A press release in December 2025 announced the termination of the phase III LATIFY trial comparing ceralasertib/durvalumab with docetaxel in the post-ICB setting (36).

Combination ICB trials after ICB failure trials do not tend to preselect on any biomarkers to enrich for those likely to obtain benefit from a given combination simply because there is a paucity

**Figure 6.**

Gene expression across LUAD mutational subgroups. **A**, Log<sub>2</sub> immune gene expression fold changes between groups of LUAD TCGA PanCancer tumors, focusing on single mutation contribution. Tumors with mutations in only *EGFR*, *KRAS*, or *TP53* (WT for the 4 other genes of interest, including *STK11* and *KEAP1*) were compared against a common reference group of tumors WT for all 5 cancer genes (i.e., *EGFR* WT/*KRAS* WT/*TP53* WT/*STK11* WT/*KEAP1* WT tumors, labeled "WT"). *EGFR* MT ( $n = 21$ ) vs. reference WT ( $n = 90$ ), *KRAS* MT ( $n = 55$ ) vs. reference WT, *TP53* MT ( $n = 113$ ) vs. reference WT. Comparisons between groups by unpaired two-tailed  $t$  tests (unequal variances).  $P$  values were adjusted for multiple testing using the Benjamini-Hochberg method. Fold change and adjusted  $P$  values are available in Supplementary Table S6. **B**, Gene set variation analysis (GSVA) enrichment scores for Hallmark MYC targets, IFN $\alpha$ , and IFN $\gamma$  response gene sets in LUAD TCGA PanCancer tumors. Single mutation groups (*EGFR* MT, *KRAS* MT, and *TP53* MT) and co-mutation groups *KRAS*/STK11 MT ( $n = 20$ ), *KRAS*/KEAP1 MT ( $n = 14$ ), and *KRAS*/STK11/KEAP1 MT ( $n = 11$ ) were compared against the reference WT group. Comparisons between groups by unpaired two-tailed  $t$  tests (unequal variances).  $P$  values were adjusted using the Benjamini-Hochberg method. Adjusted  $P$  values are shown where  $P < 0.05$ . **C**, Log<sub>2</sub> gene expression of significantly differentially expressed genes in *KRAS* MT LUAD tumors vs. reference WT heatmap from **A** (i.e., *RORC*, *FAS*, *IDO1*, and *TGFB2*). Here, all pairwise comparisons were analyzed between the reference WT, *KRAS* MT, *KRAS*/STK11 MT, *KRAS*/KEAP1 MT, and *KRAS*/STK11/KEAP1 MT tumor groups. Comparisons between groups by unpaired two-tailed  $t$  tests (unequal variances).  $P$  values were adjusted using the Benjamini-Hochberg method. Adjusted  $P$  values are shown where  $P < 0.05$ . MT, mutant.

of suitable biomarkers. This means that any potential benefit in a particular subgroup of patients will be diluted out by outcomes outside of this subgroup. In this regard, it will be important to see

the separate forest plots of ceralasertib/durvalumab versus docetaxel in LATIFY in *KRAS*-mutant patients whose cancers harbor concomitant *STK11* and/or *KEAP1* mutations versus *KRAS* mutant

alone and *KRAS* WT, given that recent data show these additional co-mutations to be an important biomarker of enhanced sensitivity to ATR inhibition, particularly on a *KRAS*-mutant background (35). These co-mutations have minimal impacts on sensitivity to PARP and ATM inhibition. Although ceralasertib has little impact on colony formation in single *KRAS*-mutant cells, there is a significant reduction in colony formation with *STK11* and/or *KEAP1* co-mutations on a *KRAS*-mutant background (31). In vivo, ceralasertib is more active in *KRAS* co-mutated tumors, particularly when all 3 mutations are present. Importantly, ceralasertib generates more micronuclei and other evidence of genotoxic stress in cells harboring *STK11* and/or *KEAP1* mutations. Mechanistically, *STK11* mutations are associated with defective DNA damage response (DDR) signaling and *KEAP1* mutations activate ATR-CHK1 signaling, making them more sensitive to ATR inhibition. As mentioned, in GEMM, the addition of ceralasertib to anti-PD-1 does not provide benefit in *KRAS*-mutant models with *STK11* loss but does in a GEMM with *KRAS*, *STK11*, and *KEAP1* mutations. In an exploratory analysis of HUDSON, the benefit of ceralasertib/durvalumab against the other 3 combinations seems to be the greatest in the *KRAS*-mutant patients harboring co-mutations in *STK11* and/or *KEAP1* (31). We show here that although numbers are limited, patients with *KRAS/KEAP1* co-mutated cancers seem to derive significant benefit from the addition of ceralasertib to durvalumab in the post-ICB resistance setting. We show that *KEAP1* co-mutation significantly increases Myc target expression and downregulates type I and II IFN signaling, effects not seen with *KRAS* mutation alone.

Much of our knowledge of potential immune-evasion mechanisms, each of which might optimally be treated with specific mechanism-targeted ICB combinations, comes from samples obtained from untreated patients and often from primary tissue. The genomic, transcriptomic, epigenomic, and particularly immunologic landscapes are likely to be different between untreated primary tissue and metastatic cancer resistant to ICB and often chemotherapy. Aligned to this is the broad assumption that reinvigoration of an exhausted TME is likely to be important, but in a comparison of baseline and matched post-ICB resistance samples of patients with NSCLC, there was an upregulation of IFN $\alpha$  and IFN $\gamma$  signatures and notably of DNA repair pathways after therapy, consistent with the concept that acquired resistance to ICB in patients with lung cancer associates with activation of IFN pathways driving retained or increased inflammation rather than being characterized by an immune desert phenotype (37, 38). Tissues from patients receiving neoadjuvant chemoimmunotherapy without appreciable pathologic response could be a rich source to mine the range of immune evasion mechanisms that might suggest candidate biomarkers to select appropriate combination regimens and to select patients likely to benefit from non-ICB-based immunotherapies, such as T-cell therapeutics such as BiTEs and ImmTACs. The outcome for patients with lung cancer without targetable alterations progressing on ICB is unlikely to improve meaningfully without a concerted effort to understand the range of immune evasion mechanisms following exposure to ICB and design and run trials specifically targeting these mechanisms in biomarker-selected patients.

## Data Availability

Participant data and the associated supporting documentation are available upon request to the corresponding author. Details of our data request process is available

on the Cancer Research UK Clinical Trials Unit (CRCTU) website: <https://www.birmingham.ac.uk/research/centres-institutes/cancer-research-uk-clinical-trials-unit/data-sharing-policy>. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The decision to release data will be made by the CRCTU Director's Committee, who will consider the scientific validity of the request, the qualifications and resources of the research group, the views of the Chief Investigator and the trial steering committee, consent arrangements, the practicality of anonymizing the requested data, and contractual obligations. A data sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship, and acknowledgements and obligations for the responsible use of data. An anonymized encrypted dataset will be transferred directly using a secure method and in accordance with the University of Birmingham's IT guidance on encryption of datasets. NLMT statistical analysis code for these arms is available for download from the GitHub repository (39). RNA-seq data generated and analyzed during the current study are available in the Gene Expression Omnibus repository: GSE322525 (40).

## Authors' Disclosures

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## Disclaimer

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## Authors' Contributions

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