IN BRIEF

BREAST CANCER

Ribociclib effective in HR$^+$, HER2$^-$ breast cancer

Newly published data from the MONALEESA-3 trial demonstrate that ribociclib is effective in patients with HR$^+$/HER2$^-$ breast cancer. In this trial, 726 postmenopausal women with disease relapse >12 months after completion of endocrine therapy were randomized in a 2:1 ratio to receive fulvestrant plus ribociclib or fulvestrant alone. Patients in the ribociclib plus fulvestrant group had a median progression-free survival (PFS) duration of 20.5 months versus 12.8 months (hazard ratio 0.59, 95% CI 0.48–0.73; $P < 0.001$). Improvements in PFS in the ribociclib group were accompanied by increased risks of several grade 3 adverse events including neutropenia (46.6% versus 0%) and leukopenia (13.5% versus 0%), in addition to grade 4 neutropenia (6.8% versus 0%). These findings demonstrate the superiority of the addition of ribociclib to fulvestrant monotherapy in this setting.

ORIGINAL ARTICLE Slamon, D. J. et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2018.78.9909 (2018)

PROSTATE CANCER

PARP inhibitors synergize with abiraterone

Poly(ADP-ribose) polymerase (PARP) inhibitors have been previously shown to improve the outcomes of patients with *BRCA*-mutant prostate cancer. Now, data from a phase II study demonstrate that the PARP inhibitor olaparib, in combination with abiraterone, provides benefit even in the absence of homologous recombination (HRR) deficiency. 142 patients were randomly assigned to receive abiraterone plus olaparib or abiraterone plus placebo regardless of HRR status. Patients receiving olaparib plus abiraterone had significantly improved median radiographic progression-free survival relative to those in the abiraterone plus placebo group (13.8 months versus 8.2 months; HR 0.65, 95% CI 0.44–0.97; $P = 0.034$). Patients in the olaparib group had an increased risk of grade ≥3 adverse events (41% versus 27%); however, grade 1–2 adverse events were more frequent in patients receiving abiraterone alone.

ORIGINAL ARTICLE Clarke, N. et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(18)30365-6 (2018)

HAEMATOLOGICAL CANCER

Quizartinib tested in patients with high-risk AML

In a phase II single-arm trial, patients with high-risk acute myeloid leukaemia (AML) received the FLT3 inhibitor quizartinib: patients >60 years of age with relapsed (within 1 year) and/or refractory AML were assigned to cohort 1, while patients >18 years of age with relapsed and/or refractory AML following salvage chemotherapy or haemopoietic stem cell transplantation were assigned to cohort 2. The majority (74.4%) of patients had detectable *FLT3*-internal tandem duplications, which are typically associated with an inferior prognosis. Similar response rates of 77% and 74% were observed in cohorts 1 and 2, respectively, with similar frequencies of composite complete remissions (56% and 46%) and complete remission (3% and 4%) also observed. Quizartinib is currently under further investigation in phase III trials.

ORIGINAL ARTICLE Cortes, J. et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(18)30240-7 (2018)

TARGETED THERAPIES

Redefining *KRAS* activation

Oncogenic mutations in *KRAS* are considered to 'lock' the protein in a constitutively active state, which therefore results in ligand-independent activation of KRAS signalling. Two separate preclinical studies now challenge this paradigm, indicating that, in order to drive lung tumorigenesis, mutant *KRAS* requires the activation of ERBB receptors.

Emilio Casanova and his team found that genetic deletion of *Egfr* (a member of the ERBB family) reduced the growth of *Kras*-mutated lung adenocarcinomas in mice. "Previous clinical trials had shown that the EGFR inhibitors erlotinib and gefitinib were not effective in patients with *KRAS*-mutated lung adenocarcinomas," explains Casanova, who adds "We confirmed this effect in our experimental model, in which these inhibitors triggered a tumour-escape mechanism. However, the pan-ERBB inhibitor afatinib blocked the escape mechanism leading to impaired lung tumorigenesis."

In their study, Daniel Murphy and collaborators developed a mouse model combining mutant *Kras* with a modest overexpression of *Myc*. "We initially observed low-grade adenocarcinomas that were uniform in appearance, but 6 weeks after tumour initiation, we saw discrete regions with altered histology in individual tumours," explains Murphy. These regions were isolated, and their transcriptomes were compared with those of low-grade regions, revealing increased expression of multiple ligands from the ERBB family along with other genes that enhance EGFR and/or ERBB signalling. Treatment with the pan-ERBB inhibitor neratinib enhanced the antitumour effect of the MEK inhibitor trametinib in mice harbouring *Kras*-mutant tumours.

"From the clinical perspective, the most important finding is that *Kras*-driven lung tumours are sensitive to ERBB inhibition in mice. These drugs now need to be evaluated in clinical trials. Substantial toxicities will need to be overcome, likely through lung-restricted delivery of the drugs or biomarker-guided treatment scheduling," explains Murphy. Likewise, Casanova considers that "a clinical trial with afatinib, an FDA-approved drug, in patients with *KRAS*-mutated lung adenocarcinoma should be straightforward, although patient stratification based on the presence of biomarkers predicting response to afatinib will likely be needed."

Comparing both studies, Murphy comments "In our experiments, no survival benefit was derived from monotherapy with neratinib, whereas Casanova and colleagues report efficacy using a different pan-ERBB inhibitor (afatinib) as a single agent. The difference is likely to be derived from the different dosing schedules or mouse models used." Casanova adds "We are very excited that we arrived independently at the same conclusion, which makes us very confident of the robustness of these findings."

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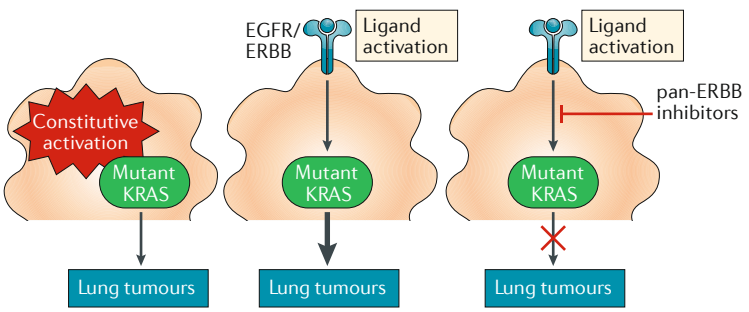

Credit: Simon Bradbrook/ Springer Nature Limited

ORIGINAL ARTICLES Moll, H. P. et al. Afatinib restrains K-RAS–driven lung tumorigenesis. *Sci. Transl Med.* **10**, eaao2301 (2018) | Kruspig, B. et al. The ERBB network facilitates KRAS-driven lung tumorigenesis. *Sci. Transl Med.* **10**, eaao2565 (2018)