HAEMATOLOGICAL CANCER

Uncovering the clonal basis of response and resistance to IDH2 inhibition in AML

Approximately 15–25% of patients with acute myeloid leukaemia (AML) harbour *IDH2* mutations and are candidates for IDH2 inhibition with enasidenib. Now, a longitudinal analysis of the clonal landscape of AML has provided important insights into responsiveness and resistance to enasidenib.

To characterize both differentiation arrest in and the clonal architecture of AML, bone marrow cells from patients included in the pivotal trial of enasidenib were studied using flow cytometry and single-cell genotyping. "We tracked the behaviour of these clones through treatment and at relapse, showing that restored haematopoiesis during remission can be mediated by differentiation of *IDH2*-mutant ancestral clones or progeny subclones," explains Lynn Quek. "We believe that this is the first time the clonal dynamics of AML have been studied at a single-cell level in response to therapy," she adds.

IDH2 mutation-related differentiation arrest might be dependent on the particular co-mutational context, explaining why different populations of clones differentiate upon IDH2 inhibition and potentially also why ~60% of patients have intrinsic resistance to enasidenib. Moreover, "*IDH2*-mutant clones persisting during therapy acquire additional mutations at disease relapse, providing clues to potential mechanisms of acquired enasidenib-resistance," states Quek. No second-site mutations in the mutant *IDH2* allele were detected; however, *IDH2*-mutant subclones with neomorphic mutations in *IDH1* or aberrations affecting components of other potential bypass pathways that restore differentiation arrest, such as cytokine receptors and haematological transcription factors, were clonally selected.

Together, these findings might enable improvements in patient selection in future trials or inform on novel drug combinations.

David Killock

ORIGINAL ARTICLE Quek, L. et al. Clonal heterogeneity of acute myeloid leukemia treated with the IDH2 inhibitor enasidenib. *Nat. Med.* https://doi.org/10.1038/s41591-018-0115-6 (2018)

HAEMATOLOGICAL CANCER

Benefit of nanomedicine confirmed in sAML

Secondary acute myeloid leukaemia (sAML) arising from prior myeloid neoplasia or after anticancer therapy accounts for ~25% of AML cases and has a poor prognosis. Nevertheless, the '7 + 3' cytarabine and daunorubicin regimen has remained the standard induction therapy for >40 years. Now, the improved efficacy of a nanoparticle formulation of cytarabine and daunorubicin, CPX-351, in older patients (aged 60–75 years) with sAML — who have particularly dismal outcomes with 7 + 3 therapy — has been confirmed in a phase III trial.

CPX-351 consists of cytarabine and daunorubicin encapsulated in liposomes at a 5:1 synergistic molar ratio. The phase III trial of this agent was conducted to validate an overall survival (OS) benefit for older patients with newly diagnosed sAML observed in a prior randomized phase II trial. In the phase III trial, the median OS duration in the CPX-351 group ($n = 153$) was 9.6 months versus 6.0 months in the 7 + 3 group ($n = 156$; HR 0.69; 95% CI 0.52–0.90; $P = 0.003$); estimated 2-year OS was 31.1% versus 12.3%. Correspondingly, patients in the CPX-351 group were more likely to achieve remission (47.7% versus 33.3%) and to undergo allogeneic haematopoietic stem cell transplantation (34% versus 25%), with the results of an exploratory analysis of survival after transplantation favouring CPX-351 (HR 0.46, 95% CI 0.24–0.89; $P = 0.009$). Subgroup analyses suggested fairly consistent OS benefits across most subgroups, although prior exposure to hypomethylating agents seemed to reduce the likelihood of benefit from CPX-351.

In agreement with the prolonged plasma circulation and drug exposure of CPX-351, neutrophil and platelet recovery times were delayed relative to those observed with the 7 + 3 regimen. Nevertheless, the overall safety profiles of the two treatments were similar.

In August 2017, CPX-351 became the first FDA-approved treatment for sAML on the basis of these data.

David Killock

ORIGINAL ARTICLE Lancet, J. E. et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2017.77.6112 (2018)

IMMUNOTHERAPY

MHC expression predicts response

The combination of anti-CTLA-4 and anti-PD-1 antibodies in patients with metastatic melanoma provides additive benefits over either modality alone. Now, an analysis of biopsy samples from patients with advanced-stage melanoma receiving sequential immune-checkpoint inhibition as part of the CheckMate 064 or 069 trials provides insight into the mechanisms of each class of agent.

Patterns of MHC expression in non-malignant and malignant skin samples obtained during CheckMate 064 were investigated using immunohistochemistry. MHC I was expressed on all non-malignant skin cells and on the majority of malignant cells, although 34 of 92 samples had MHC I expression on <50% of tumour cells. MHC II was detected in Langerhans cells in non-malignant skin samples, although cellular expression was detectable at the invasive margins in tumour biopsy samples.

In CheckMate 064, patients with MHC I expression on <30% of cells were more likely to have disease progression after 13 weeks of single-agent ipilimumab ($P = 0.02$), whereas a nonsignificant trend was observed between MHC II expression on >1% of cells and response to pembrolizumab ($P = 0.052$). Furthermore, baseline MHC I expression <50% was found to predict inferior overall survival (OS) in those receiving ipilimumab, despite the trial design allowing crossover to pembrolizumab (HR 0.38, 95% CI 0.18–0.82; $P = 0.01$). Conversely, baseline MHC II expression >1% was associated with superior OS in patients who initially received pembrolizumab (HR 0.11, 95% CI 0.02–0.83; $P = 0.01$).

Both associations disappeared in patients receiving concurrent ipilimumab plus nivolumab as part of the CheckMate 069 trial, despite MHC I expression <50% having a 100% negative predictive value for a response to ipilimumab monotherapy in this trial. These findings indicate that MHC I expression is required for a response to ipilimumab, while MHC II expression, likely owing to IFNγ-mediated immune activation, is predictive of a favourable response to pembrolizumab.

Peter Sidaway

ORIGINAL ARTICLE Rodig, S. J. et al. MHC proteins confer differential sensitivity to CTLA-4 and PD-1 blockade in untreated metastatic melanoma. *Sci. Transl Med.* **10**, eaar3342 (2018)