CGG/ERN GENTURIS/ICARE Monthly Journal Round-Up – July 2021

One year of journal round-ups – a look back over the last 12 months!

- **August 2020:** Silvestri *et al*. published data from a retrospective cohort study which showed that men with a *BRCA2* variant were significantly more likely to develop breast, prostate, and pancreatic tumours, as well as multiple primary tumours, compared to men with a *BRCA1* variant.
- **September 2020:** Blair *et al*. published updated clinical practice guidelines for hereditary diffuse gastric cancer, including a change to genetic testing criteria.
- **October 2020:** Greville-Heygate et al. showed that pathogenic variants in *CHEK2* are associated with an adverse prognosis in symptomatic early-onset breast cancer.
- **November 2020:** Mansfield *et al*.'s study showed that the majority of female *BRCA* carriers consider risk-reducing surgery the preferred treatment, but this can be influenced by a woman's experience of cancer and family circumstances. Many women also indicated they would take a hypothetical medicine.
- **December 2020:** Tung *et al*. published data from the TBCRC 048 Phase II study, showing that PARP inhibition is an effective treatment for patients with metastatic breast cancer and germline *PALB2* or *BRCA1/2* mutations, and that there may also be significant implications for treatment of other *PALB2*-associated cancers.
- **January 2021:** Martin *et al*. looked at the uptake of predictive *BRCA* testing in the UK, and showed that age, the proband being unaffected by cancer, and the specific *BRCA* gene significantly affected testing uptake, while other social and demographic variables did not strongly determine uptake of testing.
- **February 2021:** The Breast Cancer Association Consortium and a U.S. study by Hu *et al*. published separate papers about genes associated with breast cancer risk. Both showed that variants in *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *RAD51C*, *RAD51D*, *ATM*, and *CHEK2* – had a significant association with breast cancer risk. Association of BC risk with *MSH6* variants was only seen in the BCAC study, while association of risk with *CDH1* was only seen in the U.S. study.
- **March 2021:** Gaba *et al*. published results from a qualitative study looking at surgical decision making in premenopausal *BRCA* carriers considering RRESDO or RRSO, and factors involved in the decision making included consideration of importance of risk reduction vs early menopause/quality of life, being close to age of menopause, concern about detrimental impact of menopause, strength of family history of BC and/or OC
- **April 2021:** Evans *et al*. showed that there is a high likelihood of finding actionable pathogenic variants in breast cancer genes (particularly *BRCA1, BRCA2, TP53,* and *CHEK2* c.1100delC) in women with very early onset breast cancer (diagnosed ≤30)

- **May 2021:** Tischkowitz *et al*. and the ACMG published key management guidelines for individuals with germline pathogenic variants in *PALB2*, including recommended management of breast, ovarian and pancreatic cancer risk
- **June 2021:** Prof Usha Menon and colleagues published results from the UKCTOCS trial, which showed that USS/MSS screening was not associated with a reduction in deaths from tubal/ovarian cancer, and therefore screening of this nature in women at population risk cannot be recommended.
- **July 2021:** Woodward *et al*. suggest *CHEK2* c.1100delC should be incorporated into diagnostic breast cancer genetic testing panels (see a full summary below!)

Translational science

Combined inhibition of DDR1 and CDK4/6 induces synergistic effects in ER-positive, HER2-negative breast cancer with PIK3CA/AKT1 mutations. Shariati *et al.* (2021). *Oncogene*; 40: 4425-4439. https://www.nature.com/articles/s41388-021-01819-0

Molecular alterations in the PI3K/AKT pathway occur frequently in hormone receptor-positive breast tumours. Patients with ER-positive, HER2-negative metastatic breast cancer are often treated with CDK4/6 inhibitors such as palbociclib in combination with endocrine therapy. Although this is an effective regimen, most patients ultimately progress. The purpose of this study was identifying synthetic lethality partners that can enhance palbociclib's antitumor efficacy in the presence of PIK3CA/AKT1 mutations.

- In this study, the authors performed a human kinome shRNA library screening with ER-positive HER2-negative isogenic MCF7 breast cell lines to identify the genes that, when targeted, sensitize PIK3CA and AKT1 mutant cells to CDK4/6 inhibitor.
- The authors also used isogenic cell lines as a complementary approach to study the influence of genotype on drug sensitivity. This eliminated the effect of other alterations that could impact sensitivity.
- The screening revealed 25–35 hits representing genes putatively synthetic lethal with palbociclib.
- Most of the candidate genes were involved in a variety of cellular growth and signal transduction pathways.
- The screening revealed DDR1 as the only novel target that confirmed synthetic lethal interaction with palbociclib in PIK3CA and AKT1 mutant cell lines.
- They also found that ER-positive breast cancers with PIK3CA/AKT1 mutations were less sensitive to palbociclib monotherapy in vitro in an isogenic panel. This is a novel association that has not been reported clinically.
- In general, the results of this study demonstrated that DDR1 genomic suppression and 7rh inhibition alone markedly reduce cell proliferation, regardless of PI3K pathway activation, and caused tumor regression in vivo.
- The authors also demonstrated that co-inhibition of CDK4/6 and DDR1 in PIK3CA and AKT1 mutant cells caused synergistic inhibition of the cell cycle, accompanied by a reduction in RB phosphorylation and cyclin E2.

- Lastly they also suggested that these results indicate that DDR1 inhibitor induces cell cycle arrest, the mechanism of this synthetic lethal interaction is unknown and further investigation is required.
- In summary, the authors have evaluated a novel combination of CDK4/6 and DDR1 inhibition in PIK3CA/AKT1 mutants ER-positive breast cancer that provides synergistic cell cycle inhibition and tumour growth suppression.

A vaccine targeting mutant IDH1 in newly diagnosed glioma. Platten *et al.* (2021). *Nature*; 592: 463-468. https://www.nature.com/articles/s41586-021-03363-z

- Platten and colleagues now report the results of a phase 1 trial testing an anti-cancer vaccine designed to target neoantigens commonly found in patients with glioma bearing IDH1 mutations.
- Gliomas are the most prevalent primary brain tumours and remain incurable despite extensive molecular characterization and research aimed at identifying viable therapeutic vulnerabilities.
- Among the various glioma subtypes, diffuse gliomas and secondary glioblastomas are driven mostly by gain-of-function oncogenic mutations in genes encoding the metabolic enzymes IDH1 and, less frequently, IDH2, and thus are genetically distinct from primary glioblastomas.
- Mutations in IDH1 are commonly found in heterozygosis and often result in the single-amino-acid substitution of arginine (R) with histidine (H) in the catalytic site of IDH1 at codon 132 (called 'IDH1(R132H)')
- Mutations in IDH1 and IDH2 result in neomorphic enzymatic activities that lead to production of the oncometabolite 2-HG.
- Their results provided proof-of-concept evidence of the feasibility and efficacy of this immunotherapy modality and opened the path for the development of similar therapeutic approaches for the treatment of these lethal tumours.
- Platten and colleagues developed an array of peptides encompassing the R132H substitution within IDH1 and identified the peptide p123–142, which spans the codons 123–142 and includes the R132H substitution, as a potent inducer of specific anti-tumour immune responses to cells expressing mutant IDH1.
- They designed a multi-centre, phase 1 clinical trial (NOA-16; ClinicalTrials.gov identifier NCT02454634) to test the safety, feasibility and efficacy of a vaccine targeting mutant IDH1 in newly diagnosed patients with World Health Organization (WHO) grade III or grade IV glioma.
- They demonstrated that the IDH1-targeting vaccine was safe and immunogenic and could induce both T cell and B cell immune responses across patients bearing a variety of human leukocyte antigen–encoding alleles.
- The authors established a mutation-specificity score to incorporate the duration and level of IDH1-vac-induced T cell immune responses and observed that patients with high scores showed predominant production of the cytokines TNF, IFN-γ and IL-17 by helper T cells, indicative of involvement of the TH1 and TH17 subtypes of helper T cells. The authors also followed up with the patients and assessed the 3-year progression-free and death-free rates, which were 0.63 and 0.84, respectively.

- Treated patients displayed higher rates of pseudoprogression (PsPD), a condition in which patients develop mass lesions that resemble tumour growth by neuroimaging, than those of a molecularly matched cohort that had not been treated with the IDH1-targeting vaccine.
- Overall, these results provide evidence that supports the proposal of the induction of specific anti-tumour immune responses after vaccination with a cancer-specific neoepitope.

In the clinic

A mosaic PIK3CA variant in a young adult with diffuse gastric cancer: case report. Te Paske *et al.* (2021). *European Journal of Human Genetics*. https://doi.org/10.1038/s41431-021-00853-6

- Hereditary diffuse gastric cancer (HDGC) is associated with germline deleterious variants in CDH1 and CTNNA1. The majority of HDGC-suspected patients are still genetically unresolved, raising the need for identification of novel HDGC predisposing genes.
- The authors, under the collaborative environment of the SOLVE-RD consortium, re-analysed whole-exome sequencing data from unresolved gastric cancer cases (n = 83) and identified a mosaic missense variant in PIK3CA in a 25-year-old female with diffuse gastric cancer (DGC) without familial history for cancer.
- The variant, c.3140A>G p.(His1047Arg), a known cancer-related somatic hotspot, was present at a low variant allele frequency (18%) in leukocyte-derived DNA. Somatic variants in PIK3CA are usually associated with overgrowth, a phenotype that was not observed in this patient.
- This report highlights mosaicism as a potential, and understudied, mechanism in the etiology of DGC.

Clinical utility of testing for *PALB2* and *CHEK2* c.1100delC in breast and ovarian cancer. Woodward *et al*. (2021). *Genetics in Medicine.* https://doi.org/10.1038/s41436-021-01234-6

- In the UK, genetic testing for both breast and ovarian cancer now includes *PALB2*, but does not include *CHEK2* c.1100delC
- Study included 3127 women with histologically confirmed diagnoses of invasive breast cancer, carcinoma in situ, or epithelial non-mucinous ovarian cancer, and 1567 female controls
- 35 *PALB2* and 44 *CHEK2* c.1100delC PVs were detected in patients (1% and 1.4% detection rate, respectively, compared with ~7% for *BRCA1/2*)
- Grade 3 ER+ HER2-, grade 3, and triple negative (TN) tumours were enriched in cases with *PALB2* PVs compared with all breast cancers
    - TN tumours occurred in 27.9% of cases with *PALB2* PVs, compared with 11.1% for all breast cancer cases
    - Grade 3 ER+ HER2- BC occurred in 34.9% of cases with *PALB2* PVs, compared with 13.8% for all breast cancer cases
    - Grade 3 phenotype occurred in 75.7% of cases with a *PALB2* PV, compared with 40.7% for all breast cancers that tested negative for *BRCA1/2* and *PALB2*
- *PALB2* PV likelihood increased with increasing Manchester score, but did not for *CHEK2* c.1100delC

    - Interestingly, at very high MS the likelihood of a *PALB2* PV appears to tail off as compared with *BRCA1/2*
- *PALB2* PVs showed perfect segregation in 20/20 FDRs with breast cancer, compared with 7/13 for *CHEK2* c.1100delC
- Authors suggest *CHEK2* c.1100delC should be incorporated into diagnostic breast cancer genetic testing panels

Counselling and ethics

Tumour surveillance for children and adolescents with cancer predisposition syndromes: The psychological impact reported by adolescents and caregivers. Van Engelen *et al.* (2021). *Pediatric Blood & Cancer*; 68(8): e29021. https://doi.org/10.1002/pbc.29021

Introduction

- There are unique challenges for adolescents with hereditary cancer predisposition syndromes, and their parents who may also have the same predisposition
- This study aimed to understand needs of patient population and examine experience of cancer surveillance from perspective of adolescents
- 22 semi-structured interviews were carried out with 9 adolescents with a cancer predisposition syndrome, and 11 parents of children with a cancer predisposition syndrome. Thematic analysis and grounded theory used to analyse data

Summary of key themes

- Benefits of surveillance: majority wanted to take a proactive approach, with surveillance giving a sense of control and some peace of mind. Most felt they would be more worried if they did not attend surveillance
- Challenges of surveillance: There were concerns about the practical aspects of surveillance and potential disruption to daily life. Upsetting for unaffected participants when attending screening in oncology services with unwell patients
- Factors influencing surveillance: Worry associated with surveillance appeared to decrease over time. Parents recognised how their own experience shaped their experience of their child's risks
- Positive factors to manage worries: Positive relationships with family and healthcare providers, and "adjusting state of mind"
- Parents' experience: Parents talked about their worries for their children's futures and expressed a need for further emotional support. They also recognised challenges in communicating with their children about surveillance and risk
- Adolescents' experience: Most reported not thinking about their CPS every day, and they didn't often share their diagnosis with friends but mostly chose to talk to family. Most participants in this group had a good understanding of their condition.

Discussion and conclusion

- The authors provide a series of considerations for healthcare providers looking after families with cancer predisposition syndromes such as utilising surveillance visits as opportunity to assess psychological needs and exploring difficulties in communication with adolescents

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