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Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. This report is an overview of key scientific presentations made during the Congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2016 scientific programme, as well as advances in oncology.

ESMO 2016 record breaking Congress
IMMUNOTHERAPY IN CANCER

Sequencing analysis reveals baseline tumour T cell receptor and neo antigen load associates with sequential nivolumab followed by ipilimumab benefit in melanoma patients

Jeffery S. Weber, the Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, USA presented the results of an analysis of tumour samples obtained pre- and post-treatment in a phase II trial that determined the optimal sequence of immunotherapy with nivolumab and ipilimumab in melanoma. The investigators randomised 140 patients with metastatic unresectable melanoma to be treated with nivolumab followed by ipilimumab with a planned switch at week 12 (arm A), or the reciprocal combination of ipilimumab followed by nivolumab (arm B); both arms received maintenance. In the trial, arm A demonstrated superior best overall response rates and overall survival compared to arm B, while similar safety profiles were observed with each sequence (Weber, J et al. Lancet Oncology, 2016).

At ESMO 2016, Dr. Weber presented the results of the analysis done on 94 pre- and post-treatment tumour samples and peripheral blood samples obtained in the trial, which were assessed by DNA sequencing for T cell receptor clonality and the tumours were also analysed for the degree of T cell infiltration. Whole exome sequencing was also performed to assess mutational and neo-epitope load in pre-treatment tumours.

The response to treatment observed in arm A was found to associate with a combination of high T cell fraction and T cell clonality (p = 0.019 using Fishers exact test, odds ratio = 6.7), and with survival (p = 0.05). However, this association was not seen in arm B. In 22 paired samples, responding patients showed an increase in the tumour T cell fraction and clonality post treatment at week 13 (p = 0.015 – signed ranked Wilcox test), whereas tumours from progressing patients showed a decrease in T cell fraction compared to responders’ tumours (p = 0.004, U-test of pooled arms A and B).

In both arms, changes in tumour T cell clonality and T cell fraction were assessed together at week 13, which showed a strong association with response to treatment (p = 0.0023; odds ratio 30). Tumour mutational load was also associated with response in the nivolumab then ipilimumab sequence administered in arm A (p = 0.03), but not with response in the ipilimumab followed by nivolumab sequence in arm B. Analysis of the peripheral blood revealed no differences in T cell receptor clonality, or the abundance of the top T cell receptor clone post-treatment compared to baseline, peripheral blood pre-treatment T cell receptor parameters did not associate with response to treatment in either arm. NCT01783938. Weber et al. Abstract 1047O

Practice point and future research opportunities
Superior response was observed with the sequential administration of nivolumab followed by ipilimumab over the converse sequence. The response from this sequence significantly associated with the tumour micro-environment, degree of T cell infiltration, T cell receptor and clonality at baseline and all were demonstrated to be crucial determinants of the response to this treatment sequence with the PD-1 blocking antibody nivolumab. Altering both parameters may impact on resistance to immunotherapy in melanoma.

ZUMA-1 data demonstrate safety, and feasibility of KTE-C19 anti-CD19 CAR T cells in patients with refractory aggressive B cell NHL

Durable complete responses (CRs) were reported following a single dose of KTE_C19 in patients with non-Hodgkin lymphoma (NHL), according to Frederick L. Locke, Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, USA. Dr. Locke discussed updated findings from the ZUMA-1 phase I-II study of KTE-C19, anti-CD19 chimeric antigen receptor (CAR) T cells. KTE-C19 is an investigational therapy wherein a patient's T cells are genetically modified to express a CAR that is designed to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukaemias. ZUMA-1 administered KTE-C19 at a target dose of $2 \times 10^6$ anti-CD19 CAR T cells/kg after cyclophosphamide at 500 mg/m$^2$/day and fludarabine at 30 mg/m$^2$/day conditioning chemotherapy to 7 patients with refractory aggressive B cell NHL. The patients had ECOG performance status 0-1 and had chemotherapy-refractory disease, which was defined as progressive disease (PD) or stable disease as best response to the last line of therapy, or PD ≤ 12 months after autologous stem cell transplant (ASCT).

The primary objective of the study was the safety of KTE-C19. Secondary objectives included overall response rate (ORR), duration of response, and levels of blood CAR T cells and serum cytokines.

As of April 16, 2016, all 7 patients had received KTE-C19. One patient experienced a dose-limiting toxicity (DLT) of grade 4 encephalopathy and cytokine release syndrome (CRS), and grade 5 intracranial haemorrhage that was determined to be unrelated to KTE-C19. Aside from this patient, all other toxicity related to KTE-C19 of grade ≥3 was resolved.

The ORR was 71%; CR was achieved by 57% of patients and 3 patients experiencing PD within 6 months of ASCT have ongoing CR at 6 to 9 plus months following KTE-C19 therapy. Complete remission was reported for 43% of patients that continued through month 12. The concentration of CAR T cells peaked within two weeks and were detectable from one to 6 months post infusion. This study is ongoing. NCT02348216. Locke et al. Abstract 1048O

Practice point and future research opportunities

KTE-C19 utilizes the same CAR construct as the CD28/CD3ζ anti-CD19 CAR T cells that have led to durable remissions in patients with relapsed/refractory B cell malignancies. In this study, a single dose of therapy with the KTE-C19 CAR T cell construct resulted in several CRs that
were durable at 12 months and ongoing in patients with refractory aggressive NHL. Cytochrome release syndrome and neurotoxicity were self-limiting and generally reversible. This study demonstrated that the central manufacturing process and KTE-C19 regimen were safe and feasible for further study. These data support the potential for KTE-C19 to be a breakthrough therapy for chemorefractory, aggressive NHL.

**Preventive dendritic cell vaccination is feasible in healthy Lynch syndrome mutation carriers**

Colorectal cancer, especially in young individuals, has a link to the Lynch syndrome (LS), an inherited syndrome that is caused by monoallelic germline aberrations affecting one of the DNA mismatch repair (MMR) genes; these defects in the DNA MMR pathway provide the basis for the development of microsatellite instability that is the hallmark of cancer associated with Lynch syndrome, according to Harm Westdorp, Tumour Immunology and Medical Oncology, Radboud University Medical Centre Nijmegen, in Nijmegen, Netherlands. The cumulative risk of colorectal cancer varies between 10 to 80% and is strongly associated with the causative germline defect. MMR deficiency in tumour DNA causes shifts in the translational reading frame resulting in the production of altered peptides, or neopeptides that are recognised as foreign by the immune system, leading Dr. Westdorp and colleagues to investigate a preventive neoantigen-based vaccination using dendritic cells (DCs), which present antigen that results in T cell priming and activation. The investigators recruited 20 patients that were HLA-A*02.01 positive and carriers of germline MMR-gene mutation but did not have signs of Lynch syndrome-associated disease or were more than 5-years beyond detection of a non-metastasized Lynch syndrome-associated cancer. The primary endpoint was to investigate the safety and feasibility of DC vaccinations. Secondary objectives were to evaluate whether monocyte-derived peptide-loaded DC can induce an immune response to the selected neoantigens (caspase-5 and TGF-βRII) and the tumour-associated antigen carcinoembryonic antigen (CEA).

The investigators found that preventive DC vaccination was feasible and safe. Generally, DC vaccinations were well tolerated and no hospitalisations were required during study treatment. All vaccinated individuals experienced flu-like symptoms and 17 of 20 patients developed an injection site reaction following intradermal DC administration. One patient had grade 4 fever of more than 40°C for more than 24 hours, which lead to treatment discontinuation.

All immunised and tested patients demonstrated a cellular immune response against the control antigen. The investigators determined that 15 of the 20 immunised patients displayed functional neoantigen- or CEA-specific T cells in the challenged skin upon DC vaccination. NCT01885702. Westdorp et al. Abstract 1056PD

**Practice point and future research opportunities**

This study demonstrated that Lynch syndrome mutation positive carriers could be immunised with dendritic cells. The vaccination was feasible and safe and resulted in the majority of individuals having functional neoantigen- and CEA-specific immune responses. This study
opens the door for future investigation and immunotherapy trials of preventative immunisation with the intention of cancer prevention.
RELATED INFORMATION

Click here to access the Congress abstracts.

Click here to access the meeting webcast page.

Save the date

ESMO 2017 Congress, Madrid, Spain, 8-12 September 2017.

Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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