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1) The Nobel Prize in Medicine 2018 Awarded for Discovery of CTLA-4 and PD-1

On 1 October 2018, the Nobel Assembly at Karolinska Institute has decided to award the 2018 Nobel Prize in Physiology or Medicine jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation". By stimulating the inherent ability of immune system to attack tumour cells this year's Nobel Laureates have established an entirely new principle for cancer therapy. For more than 100 years scientists attempted to engage the immune system in the fight against cancer. A number of therapeutic approaches are available for cancer treatment, including surgery, radiation, and other strategies, some of which have been awarded previous Nobel Prizes. These include methods for hormone treatment for prostate cancer (Huggins, 1966), chemotherapy (Elion and Hitchins, 1988), and bone marrow transplantation for leukaemia (Thomas 1990). However, advanced cancer remains immensely difficult to treat, and novel therapeutic strategies are desperately needed.

In the late 19th century and beginning of the 20th century the concept emerged that activation of the immune system might be a strategy for attacking tumour cells. Attempts were made to infect patients with bacteria to activate the defense. These efforts only had modest effects, but a variant of this strategy is used today in the treatment of bladder cancer. Despite remarkable scientific progress, attempts to develop generalizable new strategies against cancer proved difficult. The fundamental property of our immune system is the ability to discriminate "self" from "non-self" so that invading bacteria, viruses and other dangers can be attacked and eliminated. T cells are key players in this defense. T cells were shown to have receptors that bind to structures recognised as non-self and such interactions trigger the immune system to engage in defense. But additional proteins acting as T-cell accelerators are also required to trigger a full-blown immune response.

Many scientists contributed to this important basic research and identified other proteins that function as brakes on the T cells, inhibiting immune activation. This intricate balance between accelerators and brakes is essential for tight control. It ensures that the immune system is sufficiently engaged in attack against foreign microorganisms while avoiding the excessive activation that can lead to autoimmune destruction of healthy cells and tissues.

During the 1990s, in his laboratory at the University of California, Berkeley, James P. Allison studied the T-cell protein CTLA-4. He was one of several scientists who had made the observation that C TLA-4 functions as a brake on T cells. Other research teams exploited the mechanism as a target in the treatment of autoimmune disease. Allison, however, had an entirely different idea. He had already developed an antibody that could bind to CTLA-4 and block its function. He now set out to investigate if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. Allison and co-workers performed a first experiment at the end of 1994, and in their excitement it was immediately repeated over the Christmas break. The results were spectacular. Mice with cancer had been cured by treatment with the antibodies that inhibit the brake and unlock antitumor T-cell activity. Despite little interest from the pharmaceutical industry, Allison continued his intense efforts to develop the strategy into a therapy for humans. Promising results soon emerged from several groups, and in 2010 an important clinical study showed striking effects in patients with advanced melanoma. In several patients signs of remaining cancer disappeared. Such remarkable results had never been seen before in this patient group.

In 1992, a few years before Allison's discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. Determined to unravel its role, he meticulously explored its function in a series of elegant experiments performed over many years in his laboratory at Kyoto University. The results showed that PD-1, similar to CTLA-4, functions as a T-cell brake, but operates by a different mechanism. In animal experiments, PD-1 blockade was also shown to be a promising strategy in the fight against cancer, as demonstrated by Honjo and other groups. This paved the way for utilizing PD-1 as a target in the treatment of patients. Results were dramatic, leading to long-term remission and possible cure in several patients with metastatic cancer.

After the initial studies showing the effects of CTLA-4

and PD-1 blockade, the clinical development has been dramatic. We now know that the immune checkpoint therapy has fundamentally changed the outcome for certain groups of patients with advanced cancer. Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with the aim of improving therapies and reducing side effects.

Of the two treatment strategies, checkpoint therapy against PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer, renal cancer, lymphoma and melanoma. New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma. A large number of checkpoint therapy trials are currently underway against most types of cancer, and new checkpoint proteins are being tested as targets.

REFERENCE

1. The Nobel Prize in Physiology or Medicine 2018. NobelPrize.org. Nobel Media AB 2018. Tue. 2 Oct 2018

2) TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score

In hormone receptor (HR)-positive, HER2-negative, axillary node (AN)-negative breast cancer, the 21-gene expression assay (Oncotype DX Recurrence Score [RS]) is prognostic for distant recurrence, prognostic for low recurrence with endocrine therapy alone if low (0-10), and predictive of chemotherapy benefit if high (26 or higher).We performed a prospective, randomized trial of endocrine therapy (ET) versus chemoendocrine therapy (CET) in women with a mid-range RS of 11-25. Eligible patients (n=6711) were randomised to chemoendocrine therapy or endocrine therapy alone. The trial was designed to show the non-inferiority of endocrine therapy for the primary endpoint of 5-year invasive disease-free survival (iDFS; freedom from invasive disease recurrence, second primary cancer, or death) with a non-inferiority margin of HR. Of the 10,253 eligible women enrolled between 4/7/06-10/6/10, 6711 (65.5%) had a RS of 11-25 and adequate information. There were 836 iDFS events at final analysis with a median followup of 90 months. ET was non-inferior to CET for iDFS (HR 1.08, 95% confidence intervals [CI] 0.94, 1.24, p=0.26) in the intention-to-treat (ITT) population. ET was also non-inferior for distant recurrence-free interval (DRFI; HR 1.03, p=0.80), recurrence-free interval (RFI; HR 1.12, p=0.28), and overall survival (OS; HR 0.97, p=0.80). Nine year rates were similar for iDFS (83.3% vs. 84.3%), DRFI (94.5% vs. 95.0%), RFI (92.2% vs. 92.9%), and OS (93.9% vs. 93.8%). Recurrence accounted for 338 (41.6%) the first iDFS event, of which 199 (23.8%) were distant recurrences. Treatment interaction tests were significant for age (iDFS p=0.03; RFI p= 0.02), but not menopause, tumor size, grade, or RS (continuous or RS 11-15, 16-20, 21-25). In women with HR-positive, HER2-negative, AN-negative breast cancer and a RS of 11-25, adjuvant ET was not inferior to CET in the ITT analysis. The results of this trial mean that many women with early breast cancer do not need adjuvant chemotherapy, so avoiding the acute and chronic toxicities of the treatment.

The main barrier for the translation of the results to clinical practice in Australia is that Oncotype DX is not reimbursed and the private cost (~$4-5000) is prohibitive to most patients. This will hopefully change very soon.

3) CARMENA: Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma—Results of a phase III noninferiority trial

Cytoreductive nephrectomy (CN) has been the standard of care in mRCC in the past twenty years, supported by randomized and large retrospective studies. However the efficacy of targeted therapies has challenged this standard. CARMENA was designed to answer the question of whether upfront CN should continue to be performed before sunitinib. CARMENA was a randomized phase III trial. Patients (pts) with synchronous mRCC, amenable to CN, were enrolled after confirmation of clear cell histology on biopsy if PS 0-1, absence of symptomatic brain metastasis, acceptable organ function and eligible for sunitinib therapy. Pts were randomized 1:1 to either CN followed by sunitinib (arm A) or sunitinib alone (arm B), and stratified by MSKCC risk groups. Sunitinib was given at 50 mg/d, 4/6wk with dose adaptation to routine practice. In arm A, sunitinib had to start 4 to 6 wk after surgery. Primary endpoint was overall survival (OS). A total of 576 pts had to be enrolled to demonstrate non inferiority hypothesis Median age was 62, ECOG-PS was 0 in 56% and 1 in 44%. MSKCC risk groups were intermediate/poor in 55.6/44.4% (arm A) and in 58.5/41.5% (arm B). In arm A, 6.7% did not have CN and 22.5% never received sunitinib. In arm B, 4.9% never received sunitinib and 17% had secondary nephrectomy. At the time of the analysis, 326 deaths have been observed with a median follow-up of 50.9 mo. OS was not inferior in arm B, overall as well as by MSKCC risk groups (table). No difference in response rate and PFS was observed. Safety of sunitinib was as expected in both arms. Sunitinib alone is not inferior to CN followed by sunitinib in synchronous mRCC both in intermediate and poor MSKCC risk groups. CN should

not be anymore the standard of care when medical treatment is required.

4) Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.

The Unicancer GI PRODIGE 24/CCTG PA.6 trial investigated the role of adjuvant modified FOLFIRINOX (mFOLFIRINOX) versus gemcitabine in resected pancreatic cancer. mFOLFIRINOX has no 5-FU bolus; during the trial the starting irinotecan dose was also reduced from 180mg/m^2 to 150mg/m^2. The trial was designed to determine the superiority of mFOLFIRINOX over gemcitabine with a primary endpoint of disease free survival (DFS). 493 patients were enrolled from 77 French and Canadian centres. Patients in the mFOLFIRINOX arm compared with the gemcitabine arm had higher use of G-CSF (59.9% v 3.7%, p<0.001) but similar rates of neutropenia and febrile neutropenia, overall more toxicity especially diarrhoea (eg gr ¾ 18.6% v 3.7%), and lower overall dose intensity (66.4% v 79.0%, p=0.002). mFOLFIRINOX improved DFS (median DFS 21.6 v 12.8 months; HR 0.58; 95% CI 0.46-0.73, p<0.0001), OS (median OS 54.4 v 35 months; HR 0.64; 95% CI 0.48-0.86, p<0.003) and other secondary endpoints of metastasis free survival and specific survival. This trial was very well-received and was notable for the big improvements in survival with mFOLFIRINOX, the good performance of the control arm, and the benefits coming from good old chemotherapy. Despite the current standard of care being combination capecitabine and gemcitabine as per the ESPAC-4 trial, the results should have an immediate impact on clinical practice in Australia with mFOLFIRINOX the preferred adjuvant regimen for suitable patients. **Conclusion:** Adjuvant mFOLFIRINOX is safe and significantly improves DFS, MFS and OS compared to gem.

5) Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer.

We report the efficacy and safety of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) combination therapy in BRAF V600E-mutated anaplastic thyroid cancer, a rare, aggressive, and highly lethal malignancy with poor patient outcomes and no systemic therapies with clinical benefit. In this phase II, open-label trial, patients with predefined BRAF V600E-mutated malignancies received dabrafenib 150 mg twice daily and trametinib 2 mg once daily until unacceptable toxicity, disease progression, or death. Sixteen patients with BRAF V600E-mutated anaplastic thyroid cancer were evaluable (median follow-up, 47 weeks; range, 4 to 120 weeks). All patients had received prior radiation treatment and/or surgery, and six had received prior systemic therapy. The confirmed overall response rate was 69% (11 of 16; 95% CI, 41% to 89%), with seven ongoing responses. Median duration of response, progression-free survival, and overall survival were not reached as a result of a lack of events, with 12-month estimates of 90%, 79%, and 80%, respectively. The safety population was composed of 100 patients who were enrolled with seven rare tumor histologies. Common adverse events were fatigue (38%), pyrexia (37%), and nausea (35%). No new safety signals were detected.

These findings represent a meaningful therapeutic advance for this orphan disease. enrolling patients with rare cancers with the BRAF V600E mutation, including locally advanced, unresectable, or metastatic anaplastic thyroid cancer with no locoregional treatment options. The recommended doses for anaplastic thyroid cancer are 150 mg of dabrafenib orally twice daily and 2 mg of trametinib orally once daily. FDA granted on 4 May 2018 this application priority review. FDA also granted breakthrough designation and orphan drug designation for the combination of dabrafenib and trametinib in the anaplastic thyroid cancer with BRAF V600 mutation indication.