Oncology Research Review™

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Issue 64 - 2021

In this issue:

Abbreviations used in this issue:

CI = confidence interval; **CRC** = colorectal cancer; **EGFR** = epidermal growth factor receptor; **GMH** = global mental health; **GPH** = global physical health; **HR** = hazard ratio; **ICI** = immune checkpoint inhibition; **iRECIST** = immune RECIST; **MSI/dMMR** = microsatellite instability–high/DNA mismatch repair; **NSCLC** = non-small-cell lung cancer; **OS** = overall survival; **PD(L)-1** = programmed cell death (ligand)-1; **PFS** = progression-free survival; **PSN** = peripheral sensory neuropathy; **PSPD** = pseudo-progression; **Q1W/Q2W** = once a week/ once every 2 weeks; **QoL** = quality of life; **RECIST** = Response Evaluation Criteria in Solid Tumours; **SCC** = squamous cell carcinomas; **TKI** = tyrosine kinase inhibitors.

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Welcome to the latest issue of Oncology Research Review.

In this edition we discuss the latest publications providing evidence for some promising new therapeutic options including an open-label phase 2 trial from China that finds antitumour activity of frontline camrelizumab plus gemcitabine and oxaliplatin (GEMOX) for advanced biliary tract cancer with a greater than 50% objective response rate. Preliminary phase 1 results from 20 patients with oesophageal cancer in PALACE show that neoadjuvant immuno-chemo-radiotherapy with pembrolizumab is safe, does not delay surgical intervention and elicits a pathological complete response in 65% of patients. We look forward to results from phase 2 testing. For patients with metastatic colorectal cancer (CRC) the evidence for the prevalence of immune checkpoint inhibitor (ICI) induced pseudo-progression manifesting as false signs of progression on imaging scans are conflicting with two studies in patients with microsatellite instability–high/DNA mismatch repair (MSI/dMMR) disease concluding opposing findings. Larger studies may help to elucidate the true figures. We review results from the CCOG-1302 study that indicates that in the adjuvant setting for patients with resected colon cancer, reducing the dose of oxaliplatin by introducing an intermittent dosing schedule significantly reduces long-lasting peripheral sensory neuropathy without compromising efficacy. An interesting Australian study highlights the increased risk of cancer with alcohol consumption and may aid in reducing the alcohol-associated health burden in our country by increasing population awareness. In the current climate of COVID-19 enforced social isolation and heightened anxiety which has led to increases in alcohol consumption in some groups this is especially relevant.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

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Association of radiotherapy for rectal cancer and second gynaecological malignant neoplasms

Authors: Guan X et al.

Summary: According to a cohort study published in *JAMA Network Open*, women who receive radiotherapy for rectal cancer may be at risk for secondary malignant gynaecological neoplasms such as uterine and ovarian cancer. The study examined the risk of second gynaecological malignant neoplasms (any gynaecological malignancy occurring > five years after the diagnosis of rectal cancer) in a total of 20,142 women (83.4% white; median age 65 years) diagnosed with localised or regional rectal cancer between 1973 and 2015 who were identified from nine cancer registries of the Surveillance, Epidemiology and End Results (SEER) database. The cumulative incidence of gynaecological malignancy during 30-year follow-up was 4.53% in the cohort of patients who were treated with surgery plus radiotherapy (n=5,310) compared to 1.53% in the cohort treated with surgery alone (n=14,832). Risk regression analysis revealed a greater than three-fold increased risk of subsequent uterine cancer and two-fold increased risk of ovarian cancer with radiotherapy treatment (adjusted hazard ratio [HR] 3.06; 95% confidence interval [CI], 2.14-4.37; $p<0.001$ and adjusted HR 2.08; 95% CI, 1.22-3.56; $p=0.007$, respectively). The radiotherapy-associated risk for uterine cancer decreased with increasing time since rectal cancer diagnosis but the risk for ovarian cancer increased (adjusted radiotherapy-related risk of uterine cancer at < 10 years, 10-20 years and 20-30 years 3.22, 2.72 and 1.95, respectively. Adjusted radiotherapy-related risk of ovarian cancer at the same time points, 0.70, 2.26 and 11.84, respectively). Ten-year overall survival (OS) rates were significantly worse in patients with radiotherapy-associated uterine cancer compared to patients with primary uterine cancer (21.5% vs 33.6%; $p=0.01$).

Comment: Neoadjuvant radiotherapy is an important component of treatment for locally advanced rectal carcinoma, with proven benefit in reducing local recurrence. This treatment does not, however, improve OS, a fact which must be taken into account in any risk/benefit analysis. Secondary malignancy after radiotherapy is an uncommon but recognised adverse effect. Available data regarding rates of gynaecologic malignancy after rectal cancer radiotherapy are conflicting. Guan et al have conducted a large retrospective cohort study using SEER database data from 20,142 women treated for rectal cancer. They describe an increased rate of secondary gynaecological malignant neoplasms in women receiving rectal radiotherapy, in particular cancers of the uterine corpus and the ovary. Interestingly, the patterns of risk for these two cancers differed, with the risk of uterine carcinoma higher in older women and greatest between five and 10 years of radiotherapy. Secondary uterine carcinoma was also associated with poorer survival to primary uterine carcinoma. Conversely, the risk of ovarian carcinoma was higher in younger women, and at an increased latency from radiotherapy (>20 years), whilst survival for those developing secondary ovarian carcinoma was equivalent to that seen with primary ovarian carcinoma. Some obvious limitations exist, including the lack of detailed radiotherapy treatment information. Radiotherapy techniques have progressed substantially since 1973 and it is conceivable that risks of radiotherapy in the current era would not be the same as those of over 40 years ago. This prevents definitive conclusions being drawn from this paper. None the less, this data does refocus clinicians on the need to consider longer term risks for patients, and the importance of survivorship care and follow-up. Regular gynaecological follow-up should be part of ongoing medical care for any woman who has received radiotherapy for rectal cancer.

Reference: JAMA Netw Open 2021;4(1):e2031661
Abstract

Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer

Authors: Chen X et al.

Summary: This single-arm, open-label, phase 2 trial (ClinicalTrials.gov Identifier: NCT03486678) assessed the antitumour activity of frontline camrelizumab plus gemcitabine and oxaliplatin (GEMOX) for advanced biliary tract cancer. A total of 38 patients with stage 4 disease were enrolled at Jiangsu Province Hospital, Nanjing, Jiangsu, China, and 37 commenced treatment with camrelizumab (3 mg/kg) in combination with GEMOX (800 mg/m^2 and 85 mg/m^2, respectively). At a median of 11.8 months follow-up an objective response was achieved by 54% of patients. The median progression-free survival (PFS) was 6.1 months and the median OS 11.8 months. Over 70% of patients experienced treatment-related adverse effects of fatigue and/or fever. No biomarkers of response were identified.

Comment: Biliary tract cancer is an uncommon malignancy with high associated mortality. Most patients present with unresectable disease and are dependent on systemic therapies for disease control. Combination chemotherapy with a platinum plus gemcitabine is considered standard of care for first-line treatment, providing median OS and five-year OS of nine to 12 months and <10% respectively. Recent studies have identified promising second-line treatment options including checkpoint inhibition, pemigatinib, ivosidenib, and dabrafenib/trametinib for biliary tract cancer with MSI/dMMR tumours, *FRGFR*, *IDH1* or *BRAFV600E* mutations, respectively. The combination of ICI with cytotoxic chemotherapy in other tumour types has resulted in higher response rates and improved survival outcomes. In this paper, Chen et al report a small non-randomised, open label, phase 2 study of camrelizumab (an anti-programmed cell death-1 [PD-1] antibody) combined with GEMOX chemotherapy in the front-line treatment of advanced biliary tract cancer. The treatment was tolerable and response rates were encouraging, especially in PD-L1 expressing tumours. Median PFS and median OS compared favourably with historical figures for GEMOX alone. Exploratory analyses were unable to identify an obvious biomarker for response, but should be included in future larger randomised studies of this combination in advanced biliary tract cancer.

Reference: J Immunother Cancer 2020;8(2): e001240
Abstract

Self-reported physical activity, sitting time, and mental and physical health among older cancer survivors compared with adults without a history of cancer

Authors: Rees-Punia E et al.

Summary: Older adults (77.8 ± 5.8 years) without a history of cancer are more active and have better mental health than adult cancer survivors according to this analysis of participants from the Cancer Prevention Study 2 published in *Cancer*. The study compared self-reported moderate-to-vigorous physical activity and duration of sedentary time on quality of life (QoL; assessed using global mental health [GMH] and global physical health [GPH] surveys) in cancer survivors one to five years after diagnosis (n=3,718) and six to ten years after diagnosis (n=4,248) with cancer-free participants (n=69,860). The difference in mean GMH and mean GPH between cancer survivors and cancer-free participants was significant but not clinically meaningful (mean difference in GMH 0.52; mean difference in GPH 0.88). Improved QoL was revealed in individuals with higher levels of physical activity and lower durations of sedentary activities (p for trend both <0.001) with the difference between the highest and lowest scores on each scale clinically meaningful (mean differences in most and least active ≥4.34 for GMH and ≥6.39 for GPH).

Comment: The importance of physical activity in health maintenance is widely recognised. Evidence suggests that a sedentary lifestyle may be more strongly predictive of future mortality than other risk factors such as smoking, hypertension, diabetes and obesity. The effect of exercise on cancer recurrence is also an area of interest, with data supporting a protective effect of regular exercise for patients receiving curative intent treatment for several cancer types. These authors have analysed self-reported data from a large cancer prevention study and report the association between activity level (metabolic equivalent levels of moderate to vigorous physical activity), sitting time and global mental and physical health. The data supports a positive association between higher levels of moderate to vigorous physical activity and/or shorter sitting time and improved GMH/GPH, with the benefits seen in both short and longer-term cancer survivors, as well as participants who had never had cancer. What cannot be determined from this paper is whether the increased moderate to vigorous physical activity and reduced sitting times were the primary cause of improved GMH/GPH, or whether they are simply representative of a group of patients with better overall health and physical functioning. Despite this uncertainty, there is little to lose in encouraging patients to increase levels of activity.

Reference: Cancer 2020;127(1):115-23
Abstract

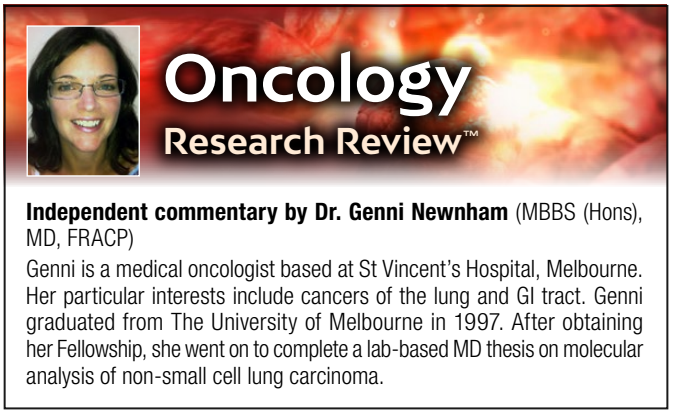
A phase 1 study of gefitinib combined with durvalumab in EGFR TKI-naive patients with *EGFR* mutation-positive locally advanced/metastatic non-small-cell lung cancer

Authors: Creelan B et al.

Summary: This Phase 1 open-label, multicentre trial (ClinicalTrials.gov Identifier: NCT02088112) published by Benjamin Creelan et al in *The British Journal of Cancer* found no increased PFS and increased toxicity with the combination of the PD-L1 inhibitor durvalumab and gefitinib in epidermal growth factor receptor (*EGFR)* mutated non-small-cell lung cancer (NSCLC). A total of 56 patients with locally advanced or metastatic *EGFR*-mutated (mostly activating L858R or Ex19del) NSCLC that either did not respond to, or who were unable to tolerate standard therapy and were EGFR tyrosine kinase inhibitor (TKI) naïve were enrolled from seven sites across the US, Japan and Korea and administered durvalumab 10 mg/kg every two weeks with concurrent gefitinib 250 mg/day. Over one-third of patients discontinued the study due to elevated liver enzymes. The objective response rate was 63.3%. A median response duration of 9.2 months was reported and a median PFS of 10.1 months. The authors commented that compared to historical controls there was no significant extension of PFS.

Comment: EGFR TKI remains the gold standard first-line treatment of metastatic NSCLC harbouring an activating mutation of EGFR. These agents are generally well tolerated, however, even with newer generation options acquired resistance is inevitable, usually developing within two years. ICI through blockade of either CTLA-4, PD-1 or PD-L1 has delivered impressive results in many tumour types, including non-*EGFR* mutated metastatic NSCLC. Results in the treatment of *EGFR* mutated metastatic NSCLC have been disappointing, however, with response rates under 10%. Some have postulated that this relates to the presence of a single driver mutation in these tumours, with resultant lower levels of immunogenic antigen production. The combination of chemotherapy with ICI, or the use of dual ICI is under investigation in a variety of cancer types in the hope of increasing response rates and durability. These authors report results of a small open label phase 1 study combining durvalumab (a PD-L1 inhibitor) with gefitninb (an EGFR TKI). Unfortunately, the results do not support further investigation of this combination, with unexpectedly high rates of dose-limiting hepatotoxicity, and response and survival rates no better than historical controls. As the authors discuss, other studies examining combinations of EGFR or anaplastic lymphoma kinase (ALK) targeted TKIs with ICI in the first-line treatment of metastatic NSCLC have also reported a lack of meaningful improvement in disease control with higher-than-expected rates of toxicity. Further study of such combinations in the first-line setting should not be undertaken.

Reference: Br J Cancer 2021;124(2):383-90
Abstract



Independent commentary by Dr. Genni Newnham (MBBS (Hons), MD, FRACP)

Genni is a medical oncologist based at St Vincent's Hospital, Melbourne. Her particular interests include cancers of the lung and GI tract. Genni graduated from The University of Melbourne in 1997. After obtaining her Fellowship, she went on to complete a lab-based MD thesis on molecular analysis of non-small cell lung carcinoma.

Alcohol consumption, drinking patterns and cancer incidence in an Australian cohort of 226,162 participants aged 45 years and over

Authors: Sarich P et al.

Summary: Sarich et al provide an analysis of drinking patterns and cancer risk from 226,162 participants (≥ 45 years) in the prospective, Australian 45 and Up Study. Linkage to the New South Wales Cancer Registry enabled identification of 17,332 incident primary cancer cases in this population, diagnosed over a median of 5.4 years. A significantly increased risk of cancer was associated with higher levels of alcohol intake with a 22% increased risk of cancer of the oesophagus and liver (HR 1.22; 95% CI, 1.04-1.43 for both), 19% and 18% increased risk of cancer of the upper aerodigestive tract and mouth and pharynx (HR 1.19; 95% CI, 1.10-1.29 and HR 1.18; 95% CI, 1.08-1.29, respectively), 13% increased risk of colon cancer (HR 1.13; 95% CI, 1.06-1.20), 11% increase risk of breast cancer (HR 1.11; 95% CI, 1.02-1.21) and a 9% increased risk of colorectal cancer (HR 1.09; 95% CI, 1.04-1.15). A pattern of increased risk of breast cancer was seen with concentrated drinking (i.e., intake concentrated on one to three days per week versus spread out over the week; $p_{interaction}$=0.049).

Comment: Alcohol use has been associated with cancer risk in numerous observational studies, with greater use linked to higher risk. The International Agency for Research on Cancer has classified alcohol as a class 1 carcinogen for cancers of the mouth, pharynx, larynx, oesophagus and liver, and attributed a causal relationship between alcohol and colorectal as well as female breast cancers. In this paper, Sarich et al provide data regarding alcohol intake and cancer risk in an Australian population. Using self-reported alcohol consumption data from the NSW based "45 and Up" prospective cohort study and cancer data from the NSW cancer registry, they confirm increased cancer risk with increasing alcohol intake for cancers of the breast, colon, mouth and pharynx, upper aerodigestive tract, oesophagus and liver. Attempts to assess the impact of different consumption patterns were limited by the need to use a quantity/frequency construct, and they were unable to identify any consistent link between consumption pattern and risk. As with all similar studies, the validity of these results is limited by the self-reported nature of alcohol consumption patterns, however, it is likely that consumption was uniformly under-reported rather than over-reported. There is clearly a link between alcohol intake and cancer risk. The challenge of altering widespread behaviour in our community remains.

Reference: Br J Cancer 2021;124(2):513-23
Abstract

Pseudoprogression in patients treated with immune checkpoint inhibitors for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer

Authors: Colle R et al.

Summary: This retrospective study from Saint-Antoine Hospital, France investigated the prevalence of pseudo-progression (PSPD) in patients with MSI/dMMR metastatic CRC treated with ICIs. Analysis of 123 patients treated between February 2015 to December 2019 with a median follow-up of 22.3 months revealed radiological progressive disease in 36 patients, 12 of which were PSPD (unconfirmed disease progression according to immune Response Evaluation Criteria in Solid Tumours, version 1.1 [iRECIST 1.1]; 10% of entire cohort and 52% of primary radiological progression group). All cases of PSPD occurred within three months with a median time to PSPD of 5.7 weeks. Higher rates of PSPD were observed in patients administered anti-PD-1 monotherapy compared to those receiving combination anti-PD1/anti-CTL4-A therapy (14.8% vs 4.8%).

Reference: Eur J Cancer 2021; 144:9-16
Abstract

RECIST and iRECIST criteria for the evaluation of nivolumab plus ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer

Authors: Cohen R et al.

Summary: The GERCOR NIPICOL phase 2 study compared clinical response rates as defined by RECIST 1.1 and immune RECIST (iRECIST) criteria in patients with MSI/dMMR metastatic CRC treated with a combined immunotherapy regimen of nivolumab plus ipilimumab. A total of 57 patients (all previously treated with fluoropyrimidines, oxaliplatin and irinotecan) were enrolled and administered a 12-week combined immunotherapy induction regimen followed by nivolumab monotherapy for up to 12 months. Adverse events led to treatment discontinuation in seven patients. There was one on-treatment death deemed treatment-related. Response rates as per RECIST 1.1 and iRECIST criteria were as follows: 12-week disease control rate, 86% vs 87.7%; 12-month PFS, 72.9% and 76.5%; overall response rate, 59.7% by both criteria. At a median of 18.4 months follow-up the median PFS and OS were not reached. The 12-month OS rate was 84%. Two cases of PSPD were observed.

Reference: J Immunother Cancer 2020;8(2): e001499
Abstract

Comment: ICI is an effective treatment option for MSI or dMMR metastatic CRC, with a recent phase 3 study confirming superiority of pembrolizumab over front-line combination chemotherapy ± bevacizumab or cetuximab. Historically, response to treatment has been assessed using radiological imaging and measured according to RECIST criteria. The phenomenon of PSPD during ICI therapy has been recognised, and can confuse treatment decision-making. It is theorised that infiltration of activated immune cells into malignant deposits during treatment with ICI is responsible for PSPD seen on imaging. Clearly it is important to be able to distinguish PSPD from true progression in order to avoid ceasing potentially effective treatment, or continuing futile treatment. Altered assessment criteria have been developed for use with immunotherapy, iRECIST, acknowledging the possibility for PSPD determined by unconfirmed RECIST progression. Colle et al have conducted a retrospective review of 123 patients treated with ICI for MSI/dMMR metastatic CRC at a single centre. This was a pre-treated group of patients who received either ICI monotherapy or dual checkpoint inhibition on clinical trial or via an access program. Notable findings include the high proportion of PSPD (52% of patients with RECIST progressive disease) and high rates of clinical benefit after PSPD (70% two-year PFS and 75% two-year OS), as well as the observation that PSPD did not occur after three months of ICI therapy. In their single arm open label study of 57 patients Bennounna et al also explored rates of PSPD in pre-treated patients receiving dual ICI for MSI/dMMR metastatic CRC. They report RECIST progressive disease in 11/57 patients, with unconfirmed progressive disease (PSPD) in two of those patients (18%). Similar to the report from Colle et al, disease control rates were high (disease control rate at 12 weeks, 86% – 87.7%). Unfortunately, the conclusions reached by these two studies were contradictory, with Colle et al suggesting PSPD is common and should be considered in the first three months of treatment, and Bennounna et al concluding PSPD is rare and RECIST 1.1 criteria for progressive disease are sufficient. Neither of these studies is large or robust enough to provide definitive conclusions, so clinicians will need to continue to consider PSPD as well as true progressive disease in these patients.

Randomised phase II trial of capecitabine plus oxaliplatin with continuous versus intermittent use of oxaliplatin as adjuvant chemotherapy for stage II/III colon cancer

Authors: Nakayama G et al.

Summary: Results from the phase 2 CCOG-1302 study published in *European Journal of Cancer* indicate that in the adjuvant setting for patients with colon cancer an intermittent dosing schedule of oxaliplatin in a capecitabine plus oxaliplatin (CAPOX) regimen provides non-inferior efficacy to a continuous dosing schedule and significantly improves long-lasting peripheral sensory neuropathy (PSN). The trial enrolled a total of 200 patients who had undergone curative resection for stage 2,3 disease and assessed the CAPOX regimen with oxaliplatin doses continuously (eight cycles of CAPOX) or intermittently (two cycles of CAPOX, four cycles of capecitabine and two cycles of CAPOX). The intermittent dosing elicited similar three-year disease-free survival rates compared to continuous dosing (84% vs 81%; HR 0.87; 95% CI, 0.47-1.63) in the overall population but higher rates in high-risk patients (T4 or N2-3; 74% vs 57%; HR 0.66). Intermittent dosing conferred significantly lower rates of PSN (one-year PSN; 16% vs 60%; $p<0.001$) and significant improved treatment completion compared to the continuous dosing schedule (89% vs 65%; $p<0.001$).

Comment: Until results of the IDEA collaboration were available, standard adjuvant treatment for resected stage 3 colon carcinoma consisted of six months of oxaliplatin-based chemotherapy. Whilst effective, this treatment is associated with high rates of troublesome PSN. Most gastrointestinal oncologists have interpreted results of the IDEA analysis to mean that three months of CAPOX is sufficient for most patients with stage 3 colon carcinoma, providing equivalent survival with greatly reduced rates of PSN. For patients at higher risk (T4 &/or N2 disease), six months of treatment is preferred. Uncertainty remains regarding the equivalence of FOLFOX to CAPOX in those receiving three months of treatment, and about the ideal adjuvant approach for patients with stage 2 colon carcinoma. These authors designed their open-label randomised phase 2 study before results of the IDEA collaboration were available. They have provided further good evidence that reducing the amount of oxaliplatin administered over the course of chemotherapy significantly reduces rates of PSN. It is difficult to know how these results will be incorporated into clinical practice, however. Is there additional benefit in three months of capecitabine alone interspersed with three months of CAPOX for patients with low-intermediate risk stage 3 colon carcinoma? And for those with high-risk stage 3 disease, is the alternating regimen as effective as six months of CAPOX as is currently used? And how do we identify which patients with stage 2 colon carcinoma require adjuvant treatment? A phase 3 study in a larger group is required to make sense of these results, and clarification of the clinical question being asked necessary.

Reference: Eur J Cancer 2021;144:61-71
Abstract

Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma

Authors: Li C et al.

Summary: The phase 1 PALACE-1 trial assessed neoadjuvant immuno-chemo-radiotherapy with the anti-PD-1 antibody pembrolizumab for oesophageal cancer. A total of 20 patients with resectable disease received carboplatin, paclitaxel, radiotherapy and pembrolizumab treatment followed by surgical resection within six weeks. This immuno-chemo-radiotherapy was deemed safe with grade ≥ 3 adverse events - most commonly lymphopenia - observed in 65% of patients and only a single case of a grade 5 adverse event. A pathologic complete response was achieved in 55.6% of patients and 18 proceeded to surgery within nine weeks of adjuvant treatment. This neoadjuvant immuno-chemo-radiotherapy regimen is now being assessed in a phase 2 trial (NCT04435197).

Comment: Oesophageal carcinoma is associated with significant morbidity and mortality worldwide. Even for localised disease, outcomes from surgical resection alone are uniformly disappointing and guidelines now recommend multi-modality neoadjuvant or adjuvant therapy. Comparative data regarding potential multi-modality approaches is lacking. Although historically adeno- and squamous cell carcinomas (SCC) of the oesophagus have been treated as a single disease, it is likely that they represent distinct entities, with clear differences in aetiology, pathophysiology and disease behaviour. Earlier studies of SCC of the oesophagus have demonstrated relatively high tumour mutation burden and PD-L1 expression rates, both factors associated with greater likelihood of benefit from ICI. With this in mind, as well as encouraging early results of pembrolizumab in studies of advanced oesophageal SCC, these authors designed a study assessing the safety, feasibility and utility of adding pembrolizumab to the CROSS combined chemoradiotherapy neoadjuvant protocol in patients with localised oesophageal SCC. In a small unselected group of patients, they demonstrated the combination to be safe and feasible, with pathologic complete response rates exceeding 50%. The study also provided some interesting information regarding the role of T cell subtypes in response to ICI immunotherapy. It is now recognised that adequate numbers of transcription factor 1 positive CD8 T cells are required for ICI to be effective, and Li et al report an increased proportion of such cells in tumours achieving pathologic complete response in this study. This approach is worthy of further study in larger randomised populations.

Reference: Eur J Cancer 2021;144:232-241
Abstract

Noninferiority of cetuximab every-2-weeks versus standard once-weekly administration schedule for the first-line treatment of *RAS* wild-type metastatic colorectal cancer

Authors: Kasper S et al.

Summary: In this pooled analysis of post-authorisation studies cetuximab dosed once every two weeks (Q2W) was found to be non-inferior to standard once-weekly dosing (Q1W) for survival in adult patients with *RAS* wild-type metastatic CRC. Analysis was based on patients administered front-line cetuximab (500 mg/m^2 Q2W or 250 mg/m^2 Q1W) in combination with chemotherapy. The propensity score adjusted Cox proportional hazards regression model for Q2W versus Q1W met the prespecified non-inferiority margin of 1.25 to a establish non-inferior survival benefit with dosing every two weeks (median OS, 27.9 vs 24.7 months; HR 0.87; 95% CI, 0.715-0.956). No statistical difference was found between dose schedules in PFS (HR 0.915; 95% CI, 0.804-1.042) or serious adverse events rate. Overall response rates and rates of lung/liver metastases resection favoured the Q2W dosing schedule (odds ratio 1.292; 95% Ci, 1.031-1.617 and odds ratio 1.419; 95% CI, 1.043-1.932, respectively).

Comment: EGFR antibodies such as cetuximab or panitumumab are a key component of treatment for *RAS* wild-type metastatic CRC. Initial studies saw cetuximab being delivered at a dose of 250mg/m^2 weekly (after a 400mg/m^2 loading dose). The ability to administer cetuximab less frequently has been a point of interest for those treating metastatic CRC, mostly with respect to patient convenience. In fact, based on available data, administration of 500mg/m^2 Q2W has become common-place in many countries. Previous studies have confirmed equivalent pharmacokinetics for Q1W and Q2W administration, as well equivalent health care costs in the US system. These authors report an analysis of pooled individual patient data from countries in the European Union and Asia-Pacific, confirming non-inferior OS and unaltered serious adverse event rates from the Q2W regimen when compared to the Q1W regimen. This is a reassuring confirmation that what many oncologists are practising is appropriate, however, it is not entirely new information. Although the authors introduction cites an absence of previous similar studies, the data provided on the Cancer Institute of NSW EviQ site references a previous study of Q2W cetuximab in front-line metastatic CRC with the same conclusion (Brodowicz, T et al. 2013. FOLFOX4 plus cetuximab administered weekly or every second week in the first-line treatment of patients with *KRAS* wild-type metastatic colorectal cancer: a randomized phase II CECOG study. Ann Oncol 24[7]:1769-77).

Reference: Eur J Cancer 2021;144:291-301
Abstract

