Seminars in Cancer Biology 86 (2022) 834–850

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Neoadjuvant immunotherapy in gastrointestinal cancers – The new standard of care?

Branka Petricevic [a,1], Julijan Kabiljo [a,d,1], Rebecca Zirnbauer [a], Henning Walczak [b,c], Johannes Laengle [a,d,*], Michael Bergmann [a,d]

[a] Division of Visceral Surgery, Department of General Surgery, Comprehensive Cancer Center Vienna, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria
[b] Institute for Biochemistry I, Medical Faculty, University of Cologne, Cologne, Germany
[c] Centre for Cell Death, Cancer, and Inflammation (CCCI), UCL Cancer Institute, University College, London WC1E 6BT UK
[d] Ludwig Boltzmann Institute Applied Diagnostics, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

ARTICLE INFO

Keywords:
Neoadjuvant
Immunotherapy
Immune checkpoint inhibitors
ICI
Gastrointestinal
GI cancer

ABSTRACT

The development of immune checkpoint inhibitors (ICI) offers novel treatment possibilities for solid cancers, with the crucial benefit of providing higher cure rates. These agents have become part of standard treatments in the metastatic and adjuvant setting for select cancers, such as melanoma, non-small cell lung cancer (NSCLC) or urological malignancies. Currently, there is ample clinical interest in employing ICI in a neoadjuvant setting with a curative intent. This approach is especially supported by the scientific rationale that ICI primarily stimulate the host immune system to eradicate tumor cells, rather than being inherently cytotoxic. Aside from tumor

Abbreviations: AVC, ampulla of Vater cancer; AC, anal cancer; ALK, anaplastic lymphoma kinase; APC, antigen presenting cell; BATF3, basic leucine zipper transcription factor ATF-like 3; BTC, biliary tract cancer; CALR, calreticulin; CAPOX, capecitabine, oxaliplatin; CB, carboplatin; CRT, chemoradiotherapy; ChT, chemotherapy; CD, cluster of differentiation; CC, colon cancer; CRC, colorectal cancer; CLM, colorectal liver metastases; CPS, combined positive score; COX-2, cyclooxygenase-2; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; DFS, disease-free survival; dCCA, distal cholangiocarcinoma; DOC, docetaxel, oxaliplatin, capecitabine; AC, doxorubicin, cyclophosphamide; EGFR, epidermal growth factor receptor; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous-cell carcinoma; EFS, event-free survival; eCCA, extrahepatic cholangiocarcinoma; 5-FU, fluorouracil; FLOT, fluorouracil, docetaxel, oxaliplatin, leucovorin; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; FOLFOX4, folinic acid, fluorouracil, oxaliplatin 4; GBM, Glioblastoma; FDA, food and drug administration; GEJ, gastroesophageal junction; GI, gastrointestinal; GI NET, gastrointestinal neuroendocrine tumor; GIST, gastrointestinal stromal tumors; GEMOX, gemcitabine, oxaliplatin; cGAS, GMP-AMP synthase; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gy, gray; HNSCC, head and neck squamous cell carcinoma; HSP, heat shock proteins; HCC, hepatocellular carcinoma; HSV, herpes simplex viruses; HMGB1, high-mobility-group-protein b1; HPV, human papillomavirus; ICI, immune checkpoint inhibitors; irAEs, immune-related adverse events; ICD, immunogenic cell death; IDO, indoleamine-pyrrole 2,3-dioxygenase; IAV, influenza A virus; IMRT, intensity modulated radiotherapy; ITT, intention-to-treat; IFN, interferon; IL, interleukin; INMC, international neoadjuvant melanoma consortium; iCCA, intrahepatic cholangiocarcinoma; i.p., intraperitoneal; i.v., intravenously; LARC, locally advanced rectal cancer; LN, lymph node; LAG-3, lymphocyte-activation gene 3, MPR: major pathological response; MV, measles virus; MSI, microsatellite instable; MSS, microsatellite stable; MIS, minimally invasive surgery; MoA, mode of action; mFOLFOX6, modified folinic acid, fluorouracil, oxaliplatin 6; MSI-L, MSI-Low; MKI, multikinase-inhibitor; MIBC, muscle invasive bladder cancer; MG, myasthenia gravis; NK, natural killer cell; NDV, newcastle-disease-virus; NMIBC, non-muscle-invasive bladder cancer; NSCLC, non-small cell lung cancer; OV, oncolytic viruses; OS, overall survival; PTX, paclitaxel; PDAC, pancreatic ductal adenocarcinoma; pCR, pathological complete response; pCCA/Klatskin, perihilar cholangiocarcinoma; POT, perioperative treatment; PD-L1, programmed cell death 1 ligand 1; PD-1, programmed cell death protein 1; PFS, progression-free survival; RT, radiotherapy; RWD, real world data; RC, rectal cancer; RFS, relapse-free survival; SASP, senescence-associated secretory phenotype; SCPRT, short-course pre-operative radiotherapy; SIRPα, signal regulatory protein α; S1P, sphingosine-1-phosphate receptor modulator; SOC, standard of care; SBRT, stereotactic body radiation therapy; STING, stimulator of interferon genes; s.c., subcutaneous; TIM-3, T cell immunoglobulin and mucin-domain containing-3; Th17, T helper 17 cell; Treg, T regulatory cell; TREX1, three prime repair exonuclease 1; TLR4, toll-like receptor 4; TNT, total neoadjuvant therapy; TACE, transcatheter arterial chemoembolization; TNBC, triple negative breast cancer; TIME, tumor immune microenvironment; TMB, tumor mutational burden; TAAs, tumor-associated antigens; TAM, tumor-associated macrophage; VV, vaccina virus; VEGF-A, vascular endothelial growth factor A; vs, versus; VSV, vesicular stomatitis virus; W&W, watch and wait.

* Correspondence to: Division of Visceral Surgery. Department of General Surgery, Comprehensive Cancer Center Vienna, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
E-mail address: johannes.laengle@meduniwien.ac.at (J. Laengle).

[1] Contributed equally.

https://doi.org/10.1016/j.semcancer.2022.05.015
Received 1 September 2021; Received in revised form 31 May 2022; Accepted 31 May 2022
Available online 4 June 2022

downstaging, neoadjuvant immunotherapy offers the potential of an *in situ* cancer vaccination, leading to a systemic adjuvant immunological effect after tumor resection. Moreover, preclinical data clearly demonstrate a synergistic effect of ICI with radiotherapy (RT), chemoradiotherapy (CRT) or chemotherapy (ChT). This review harmonizes preclinical concepts with real world data (RWD) in the field of neoadjuvant ICI in gastrointestinal (GI) cancers and discusses their limitations. We believe this is a crucial approach, since up to now, neoadjuvant strategies have been primarily developed by clinicians, whereas the advances in immunotherapy primarily originate from preclinical research. Currently there is limited published data on neoadjuvant ICI in GI cancers, even though neoadjuvant treatments including RT, CRT or ChT are frequently employed in locally advanced/oligometastatic GI cancers (*i.e.* rectal, pancreatic, esophagus, stomach, *etc.*). Utilizing established therapies in combination with ICI provides an abundance of opportunities for innovative treatment regimens to further improve survival rates.

1. Introduction

Neoadjuvant treatment concepts, including chemotherapy (ChT), radiotherapy (RT) or chemoradiotherapy (CRT) have been primarily developed by clinicians. In light of novel developments in the field of immunotherapy [1], neoadjuvant application of immune checkpoint inhibitors (ICI) has become an attractive approach, increasingly being implemented in routine clinical practice. To develop new clinically applicable neoadjuvant ICI concepts, it is necessary to reflect the principles and limitations of current clinical neoadjuvant standards in regard to timing of ChT, CRT and/or RT, ICI and surgery (induction/consolidation, sequential/concomitant). Similarly, with respect to preclinical testing, we need to consider novel approaches in animal models or *in vitro* cell cultures and reconsider interpretations of current models to the extent that experimental models better reflect the canon of clinical therapy applied with the intention to cure.

2. The neoadjuvant treatment concept as part of a multi-modal cure approach

Surgical tumor resection is usually the most relevant part of any treatment concept aiming for cure in solid cancer, which applies to all non-metastatic/oligometastatic stages. In locally advanced/oligometastatic stages, ChT, CRT, RT and/or immunotherapy including ICI are clinically implemented to purge micro-metastases, which are not detected at initial diagnosis but cause local or distant tumor recurrence, the latter being associated with incurable disease in most cases. Unfortunately, response rates of solid tumors to cytotoxic therapy are rather low. For example, in stage III colon cancer (CC) only 20% of the patients receiving adjuvant ChT have an actual benefit in terms of improved overall survival (OS). The remaining 50% would have been cured by surgery alone, and around 30% still develop tumor recurrence despite receiving adjuvant ChT [2,3]. In other words, 80% of the patients are at unnecessary risk for side effects, such as neuropathy, without an improved survival benefit. Moreover, despite the progress in molecular medicine, we still lack reasonable predictive parameters for patient selection. There is a clear need for improvements. ICI-based immunotherapy administered in the adjuvant setting represents an alternative therapeutic approach [4]. This is based on its ability to re-stimulate exhausted immune cells and reduce potential immunosuppressive effects of surgery to purge micro-metastases. Thus, ICI-based immunotherapy appears to be limited to malignancies with an inherent pre-stimulated immune system. The current task is to identify these specific patients, which will have a substantial benefit from adjuvant ICI. With respect to gastro intestinal (GI) cancers, only a small group of microsatellite instable (MSI) tumors appear to fulfill those intrinsic requirements for the use of ICI [5]. The alternative is to identify combination therapies rendering weakly immunogenic tumors responsive to ICI. The neoadjuvant setting appears to be a valuable option for implementing such concepts.

The concept of neoadjuvant therapy/perioperative treatment (POT) in addition to surgery has been developed to improve the treatment of locally advanced/oligometastatic solid tumors, located in regions where surgical resection margins might harm essential adjacent organs or anatomic structures. This preoperative downsizing allows organ preservation and complete resection without residual tumor (R0), which is necessary for cancer cure. As neoadjuvant therapy can even lead to pathological complete remission (pCR), surgery might even become dispensable for selected patients, as observed in rectal cancer (RC) [6]. Another advantage of a POT approach is the improved patient compliance and fitness compared to an adjuvant setting, which might in part be explained by potential surgical complications with a prolonged hospital stay. Furthermore, POT gives the unique benefit to study individual tumor biology/response in humans *in vivo,* which has a big translational impact and can be further utilized for a personalized adjuvant treatment approach. Neoadjuvant therapy usually consists of RT, CRT and/or ChT. However, neoadjuvant treatment, which is usually given to patients with a curative intent, should have limited side effects in order to avoid harm to patients or prevent a potentially curative resection. Neoadjuvant treatment options might be specifically attractive for immunotherapeutic concepts, as the mode of action (MoA) of ICI-based immunotherapy can be seen as an *in situ* cancer vaccine model, leading to systemic tumor control. Efficient *in situ* cancer vaccination requires the presence of a sufficient load of tumor-associated antigens (TAAs) in an immunogenic context. Maximum TAAs load is certainly achieved prior to surgical resection. In this line, it is relevant to point out, that the primary cancer lesion usually harbors the largest amount of subclones with the potential to form metastasis [7]. A therapeutic *in situ* cancer vaccination appears to be less likely when the primary tumor mass is gone after surgical resection, as this is the case in an adjuvant treatment setting (Fig. 1).

As mentioned earlier, GI cancers usually insufficiently respond to ICI-based immunotherapy, due to the lack of an endogenous immune stimulation and due to a rather low baseline of TAAs. Implementing a preceding immunogenic stimulus by the induction of an immunogenic cell death (ICD) can potentially induce responsiveness to ICI. This can probably be best achieved by oncolytic viruses (OV) [8,9] but also by RT [10] and selected clinically-applied ChT [11]. The latter options provide an exciting rationale to combine ICIs with established RT, CRT or ChT concepts, currently given in the neoadjuvant setting, to enhance its therapeutic local effects, as well as induce systemic tumor control (Fig. 2). Importantly, initial preclinical and clinical data suggest there is potential to ultimately enhance cure rates. Neoadjuvant immunotherapy gives the opportunity to monitor the ICI-induced changes in the tumor immune microenvironment (TIME) via analysis of sequential tissue and liquid biopsies, as well as of the surgical specimen. Consequently, we will gain a better understanding of how immunotherapy induces tumor control and will be able to define predictive markers. This review

provides current pre-clinical and clinical evidence supporting the rationale of neoadjuvant immunotherapy in GI cancers as a new standard of care (SOC).

3. Preclinical evidence

3.1. The benefit of immunotherapy applied in a neoadjuvant setting

Despite the overwhelming theoretical concepts and clinical interest to investigate immunotherapy in a neoadjuvant setting, currently only a handful of preclinical studies exist. Usually, researchers investigated tumor outgrowth in a re-challenge model of genetically identical tumor cells following resection of the original treated tumor. While these models do not exactly reflect the nature of the clinical setting, they still provide evidence for the potential of neoadjuvant immunotherapy. For example, intratumoral gene therapy coding for interleukin-12 (IL-12) in combination with dendritic cells (DCs) applied in a neoadjuvant setting completely prevented tumor outgrowth of intravenously (i.v.) injected hepatocellular carcinoma (HCC) [12]. A similar re-challenge model of colorectal cancer (CRC), as well as in non-small cell lung cancer (NSCLC) has recently been utilized to show synergism of programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade with CRT in a neoadjuvant setting [13]. Another study demonstrated that neoadjuvant therapy of a subcutaneous (s.c.) cell line injection model of oral cavity carcinoma revealed a benefit of PD-1 axis blockade compared to its adjuvant administration [14]. A neoadjuvant preclinical model assessing local remissions of a s.c. applied bladder cancer cell line injection model after neoadjuvant treatment and surgery found a benefit for the combination of PD-1 inhibition, granulocyte-macrophage colony-stimulating factor (GM-CSF), gemcitabine and cisplatin administration [15]. Nevertheless, the study designs in the stated experiments are limited in respect to their extrapolation potential for humans. The s.c. grafted tumors cell line of different tissue origins rarely disseminate and mostly remain a solitary mass, necessitating re-challenge with a clonally identical tumor in a different location as a model for the metastatic setting. This tremendous reduction of biological complexity exhibits detrimental limitations in comparison to the real-world clinical setting. This limitation is especially relevant in light of differences regarding clonal complexity between primary tumors and metastases [16–19].

A model which more closely reflects clinical reality was used by Edris *et al.* [20]. Subcutaneous grafting of the LMS04 cell line led to lung metastasis formation, which was exploited for testing neoadjuvant therapeutic effects. They demonstrated that neoadjuvant inhibition of the immune checkpoint CD47/signal regulatory protein α (SIRPα) axis facilitated tumor phagocytosis. This blockade applied before tumor resection prevented metastatic outgrowth in lung and lymph nodes. Furthermore, anti-CD47-induced phagocytosis facilitates antigen presentation and subsequent antigen-specific immune stimulation [21].

To date the most important study for preclinical neoadjuvant immunotherapy was performed by Liu *et al.* [22]. Orthotopic injection of a murine breast cancer cell line allowed for a metastatic growth pattern of the tumor and therefore a more realistic demonstration of neoadjuvant treatment response. The authors compared systemic ICI based immunotherapy given in a neoadjuvant versus (vs.) adjuvant setting. The neoadjuvant application of the of anti-programmed cell death 1 ligand 1 (PD-L1) and agonistic CD137 antibody was exceedingly superior in preventing lung metastases as compared to the adjuvant application. Purging of regulatory T (Treg) cells using an anti-CD25 antibody was highly relevant in preventing metastatic disease progression. In this line it is important to note that some anti-CTLA-4 antibody clones are shown to be as efficient as an anti-CD25 antibody to purge Treg cells in preclinical models [23,24]. This effect however is not reproduced to the same scale in humans [25]. The improved effect of neoadjuvant compared to adjuvant immunotherapy was further validated in a clinical human melanoma setting [26].

Overall mechanistical hallmarks for successful immunotherapy (immunogenicity, immunosuppression and susceptibility of cancer cells; composition, localization and functionality of immune cells), as well as resistance mechanisms (primary, adaptive and/or acquired) [27–29] do not differ in a neoadjuvant or adjuvant setting. However, the starting situation (having the full tumor mass at the initiation of immunotherapy) is fundamentally different. In particular neoadjuvant immunotherapy leads to the expansion of more tumor-resident T cell clones in the peripheral blood compared to the adjuvant application [26]. Furthermore, it seems to enable epitope spreading by the prevention of subdominant T cell clone death [22]. Classical resistance mechanisms, such as immune suppression (*i.e.* low tumor T cell infiltration), mutational escape (*i.e.* lower MHC expression) or tumor evolution (low PD-L1 expression) are associated with early relapse after neoadjuvant ICI [30].

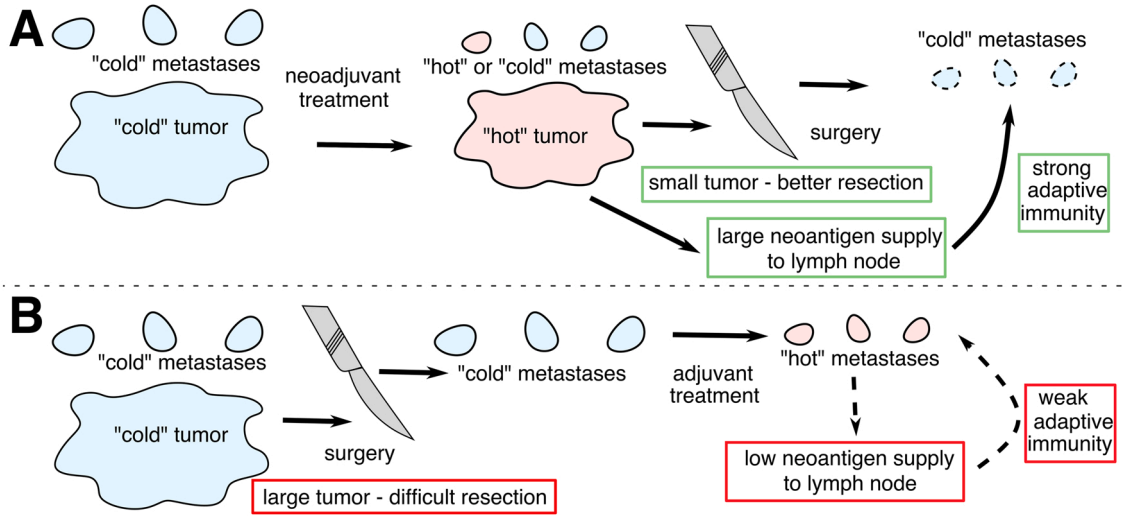

Fig. 1. Neoadjuvant therapy induces an anti-tumor immune response compared to adjuvant treatment. (A) Schematic representation of neoadjuvant treatment. Immediate treatment turns the "cold" primary tumor into a "hot" tumor containing multiple activated immune cells. The down-sizing of the tumor eases surgical resection and the adaptive anti-immune response within the tumor and its draining LN. (B) Schematic representation of an adjuvant treatment. The "cold" primary tumor is immediately resected. Adjuvant treatment stimulates low anti-tumor immune responses due to little antigen presence in micrometastases, leading to almost exclusively local effects of adjuvant therapy and lack of adaptive immunity induction.

A subsequent work provided data, that 2 cycles of neoadjuvant therapy was sufficient to induce a protective immune response [31]. Adding further adjuvant immunotherapy increased toxicity but did not contribute to therapeutic efficacy. As would have been predicted, neoadjuvant therapy was associated with higher induction of tumor-specific CD8+ T cells, as compared to adjuvant therapy. This finding strongly supported the notion that this *in situ* vaccination effect can be better achieved by ICI when sufficient amount of TAAs is present. In the respective setting type I interferon (IFN) receptor blockade abrogated T cell stimulation, which further correlates with the findings in the field of OV, that an functional type I IFN pathway is highly relevant for an efficient stimulation of tumor ablative T cells [32]. Moreover, the immune response was also abrogated in mice lacking basic leucine zipper transcription factor ATF-like 3 positive (BATF3+) DCs [33]. Correspondingly, blockade of lymphocytes migration by fingolimod (a sphingosine-1-phosphate receptor modulator; S1P) strongly attenuated the induction of cancer-specific T cells. This correlates with the finding that early surgical resection of tumor-draining lymph nodes abrogates ICI-induced tumor regression and decreases tumor immune-infiltration [34]. This migration of immune cells including DCs between the primary tumor site and draining lymph nodes has been confirmed in humans [35]. It is important to note that to convert immunological "cold" tumors into "hot" tumors targeting the TIME has shown promising results in preclinical studies. In particular in a neoadjuvant setting where emphasis is made on the presentation of TAAs, combining standard of care therapies with CD47-SIRPα blockade [36,37] or CD40 agonism [38] can enhance efficiency of tumor specific cytotoxic T cell priming. Most recently Etxeberria *et al.* generated an CD137 agonist with reduced liver toxicity [39]. This probody (a recombinant and proteolytically activated antibody prodrug) is activated by a protease of the TIME. Neoadjuvant application of this CD137 probody combined with anti-PD-1 prevented outgrowth of lung metastasis in a breast cancer model, similarly to the strategy proposed by Liu *et al.* [22]. Together this data suggest not to perform surgical resection within the first week after neoadjuvant immunotherapy.

In a recent study Brooks *et al.* generated the murine model of neoadjuvant therapy [40] mimicking the clinical development of a malignancy most closely. Pancreatic cancer was genetically induced by surgical electroporation of plasmids bearing oncogenes into the pancreatic tail. After neoadjuvant or mock treatment and subsequent surgical resection local recurrence and distant metastases were observed. Standard ChT (gemcitabine) was relatively effective in reducing local recurrence and enhancing survival in an adjuvant setting, while anti-PD-1 was significantly more effective when administered before surgery and in combination with ChT. This effect depended on natural killer (NK) cells and CD8+ T cells, but not CD4+ T cells, which could be even further enhanced by the addition of the NK cell ICI anti-CD96 after resection. In fact, only the combination with the CD96 inhibitor significantly reduced distant metastases. The study suggests that rationally timed combinations of neoadjuvant and adjuvant immunotherapeutic treatments targeting various cell types at distinct times are highly advantageous for the treatment of aggressive cancer types.

Overall, these data not only support the concept of neoadjuvant application of ICI-based immunotherapy but also favor this concept over adjuvant application (Fig. 3). However, in the majority of previously described neoadjuvant preclinical models, immunotherapy alone was sufficient to induce a therapeutic effect. This is in contrast with clinical trials done in metastatic disease, which indicate little therapeutic value in the majority of solid malignancies. Most likely the cause the lack of

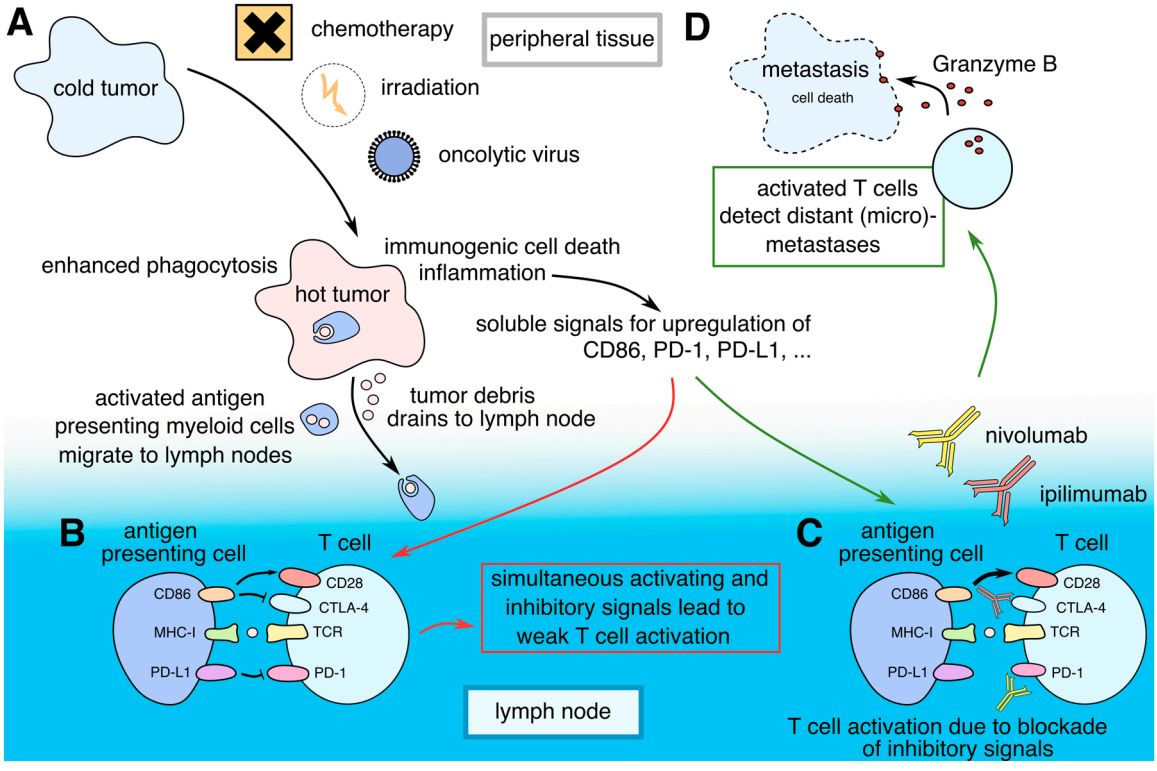

Fig. 2. Combinatorial neoadjuvant immunotherapy with induces an in situ cancer vaccination. (A) Certain types of ChT, RT, CRT or OV can induce ICD in the TIME. This leads to inflammation and drainage of tumor neoantigens into the LN. (B) The immunological synapse of APCs and T cells. Acute inflammation simultaneously induces activating and inhibitory co-stimulatory signals. Long term immunosuppressive conditioning by signals from the tumor enhances inhibitory signals, resulting in weak T cell activation. (C) Inhibition of the major T cell inhibitory pathways with clinically approved ICI enables optimized T cell activation. (D) The adaptive immune response generated by combined immunotherapy and standard treatment detects and eradicates distant micrometastases. ChT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy; OV: oncolytic viruses; ICD: immunogenic cell death; TIME: tumor immune microenvironment; APCs: antigen presenting cells, ICI: immune checkpoint inhibitors, LN: lymph node.

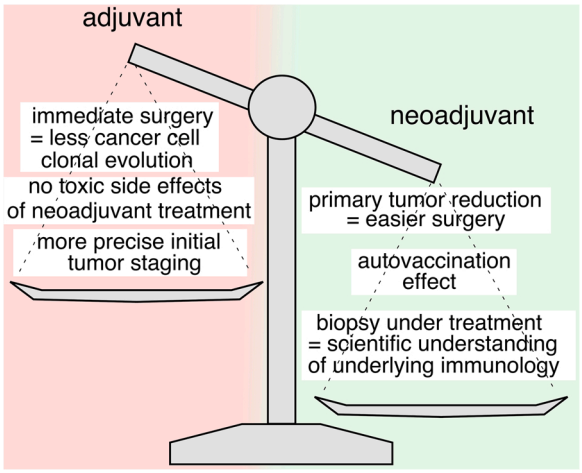

Fig. 3. Advantages of neoadjuvant immunotherapy application outweigh adjuvant dispensation. Advantages of neoadjuvant treatment are listed on the right side. Advantages of adjuvant treatment/immediate surgery are listed on the left side.

response is that efficient ICI therapy requires an initial induction of an anti-tumor immune response by an ICD. Most solid cancers obviously lack strong endogenous ICD and are characterized by low CD8+ T cell infiltrates and/or low levels of TAAs. However, there are ample preclinical data, indicating that ICD is initiated by a number of different clinically applicable approaches such as i) ChT [11], ii) RT/CRT iii) [41], targeted therapies [42,43] and iv) OV [44]. As CRT and RT are frequently part of standard neoadjuvant treatment options, this real-life clinically applied setting serves as a perfect *in vivo* model to study combinatorial ICI in a human translational setting.

3.2. Combing immunotherapy with chemotherapy

Neoadjuvant ChT targets the primary tumor as well as distant undiagnosed micrometastases. Thus, the addition of immunotherapy may enhance effective tumor elimination. In the clinical setting ChT is known for its immunosuppressive effect mediated by leucopenia. However, selected drugs such as anthracycline, oxaliplatin, cisplatin, cyclophosphamide and taxanes induce an ICD and a proinflammatory response [45].

As early as 2005 the groups of Kroemer and Zitvogel described that caspase 3-dependent cell death induced by anthracycline stimulated a DC-mediated tumor-specific CD8+ T cell response, which is tumor ablative [46]. Similarly, apoptotic bodies of oxaliplatin-treated tumor cells induced IL-2 secretion in DCs via the toll-like receptor 4 (TLR4). TLR4 stimulation was mediated by the damage-associated molecular patterns (DAMPs), specifically by the high-mobility-group-protein b1 (HMGB1) secreted by dying tumor cells [47]. Importantly, the lack of TLR4 in host cells prevented effective treatment with oxaliplatin, indicating that the immune system is at least in part essential for the therapeutic effect of oxaliplatin. Other immunogenic mediators of the ChT-induced stress response are heat shock proteins (HSP), such as the chaperon calreticulin (CALR). The humoral response seems to be less crucial for the immune-mediated tumor ablative effect of ChT drugs, such as anthracyclines [48]. This supports the clinical observation, that tumor ablative effects mainly correlate with an efficient T cell stimulation. Moreover, cyclophosphamide has been shown to reduce immunosuppressive Treg cell density in the TIME, which further provides a proinflammatory stimulus [49]. The group of Zitvogel *et al.* was also the first to describe the impact of the intestinal microbiome on the tumor ablative effect of ChT. This observed effect is depended on a fraction of pathogenic T helper 17 (Th17) cells [50]. Specifically, the induction of a CD8+ T cell mediated response by selected ChT drugs correlates with the finding, that ChT-induced the expression of ICI targets such as PD-1, PD-L1 or CTLA-4 [51–53]. Furthermore, CTLA-4 expression inversely correlated with pathological response to neoadjuvant ChT including bevacizumab (anti-vascular endothelial growth factor A; VEGF-A) in patients with resectable colorectal liver metastases (CLM) [54].

All together these observations provided a rational concept to combine immunogenic ChT with ICI. Thus, ChT, such as oxaliplatin or cyclophosphamide, which induces tumor-infiltrating CD8+ T cells, can be efficiently combined with ICI to prevent outgrowth of genetic models of lung adenocarcinoma [55]. A number of other reports confirmed this concept in murine models including lung cancer [56], CC [57] head and neck squamous cell carcinoma (HNSCC) [53], urothelial carcinoma [58] and ovarian cancer. Other studies combined RT with ChT in addition to immunotherapy. In this line, the combination of a single fraction of 10 gray (Gy) and low-dose cisplatin was more effective in combination with an anti-PD-1/CD137-based immunotherapy than RT alone [59]. These results suggest that multi-modal therapy might be more effective than a single or dual agent approach. The understanding of the complementary activities of all those drugs will be critical for rational combinations. Similarly, Hao *et al.* found that the senescence-associated secretory phenotype (SASP) overcomes resistance to ICI therapy [60]. The SASP is known to induced the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway. Intraperitoneal (i.p.) injection of cisplatin and irinotecan treated senescent cells in combination with anti-PD-1 antibody prevented outgrowth of ovarian cancer cells.

It should be noted that drugs were frequently given only for a short time in most animal models, which indicates an immunogenic effect of ChT. Short-courses of ChT might also be associated with less immunosuppression than long term application, supporting beneficial effects in a neoadjuvant setting.

3.3. Combining immunotherapy with radiotherapy

RT represents a common therapeutic tool utilized in multiple malignancies which has shown promise in combination with ICI. It is known that RT can induce ICD, leading to the stimulation of antigen presenting cells (APCs) and the release of TAAs in the TIME. This results in the activation of anti-tumor T cell clones in the draining lymph nodes upon migration of the activated APCs [10]. Furthermore, this immunogenic stimulus can induce T cell migration into the tumor [61–64], which is favorable in the light of T cell abundance, which is a positive predictive factor for anti-PD-1 response [65]. Correspondingly, there is a growing body of preclinical and clinical evidence supporting the effectiveness of this combination [10].

One question of major importance when combining ICI with RT is timing. Since the mechanism of action of ICD inducers, such as RT in an immunological context is believed to be the generation of a classical immunogenic DAMP signals it seems likely, that concomitant ICI administration would be preferable to consolidation approach. Experimental evidence has shown, that for the 2 checkpoint pathways blocked in current clinical practice (anti-PD-1 and anti-CTLA-4), the optimal timing in combination with RT slightly varies. CTLA-4 blockade, mostly acting early in the process of central T cell priming, is most enhanced in effectiveness when delivered 1 week before hypo-fractionated RT [66]. A comparison of 2 prospective clinical trials in melanoma applying this combination similarly shows, that only administration immanently prior to the start of RT seemed to induce tumor remission [67,68]. PD-1 blockade, which acts on peripheral T cells directly in the TIME, seems most effective when delivered concomitantly to RT [69]. Multiple retrospective studies and meta analyses have confirmed the benefit of concomitant RT in combination with either CTLA-4 or PD-1 blockade [66,70–74]. Similar preclinical models also demonstrated beneficial effect of RT with inhibition of indoleamine-pyrrole 2,3-dioxygenase (IDO) [75] and T cell immunoglobulin and mucin-domain containing-3 (TIM-3) [76].

Another consideration besides timing is RT dosage. A comprehensive

and extensive review about RT dose and fraction with immunotherapy, providing a framework for tumor-specific considerations on the immunomodulatory effect of RT, has been published recently [77]. While there is evidence that optimal immunostimulatory effects of RT in combination with anti-PD-1 treatment are achieved with lower fractionation and with higher dosage up to 8 Gy per fraction [78], long term low dose RT with a high cumulative dose (2×5 Gy) can potently enhance immunotherapy in mice as well [69]. Some studies have found an upregulation of the 3 prime repair exonuclease 1 (TREX1), a cytosolic DNA cleavage enzyme, at around 10 Gy and higher, which abolishes the major immunogenic cGAS-STING pathway [79,80]. This mechanism reduced the immunogenic effect of RT in mouse models and results from clinical practice support this assertion [81]. However, some studies have found sufficient effects even at very high single radiation doses (3×9 Gy) [81].

A third consideration when designing protocols combining RT and ICI is opting for maximum precision in the irradiation field of the tumor. Not only could irradiation of surrounding tissue possibly cause unwanted local side effects and unexpected immunological effects, but irradiation of the tumor-draining lymph nodes has shown to reduce the effectiveness of such combinations. This is of little surprise considering the importance of secondary lymphatic organs in arming adaptive T cell responses [82].

Clinically some cancers such as RC can either be treated in a neoadjuvant setting by short-course pre-operative radiotherapy (SCPRT) or by a CRT. This prompted some researchers to investigate combined RT and ChT in combination with immunotherapy. In this line it was shown that the combination of a single fraction of 10 Gy and low-dose cisplatin was more effective in combination with an anti-PD-1/CD137 based immunotherapy than RT alone [59]. Similarly, Josef *et al.* analyzed the immunogenic effect of RT (8 Gy) vs. CRT with cisplatin and fluorouracil (5-FU) in a CT-26 mouse model. The addition of ChT to RT not only strongly enhanced mRNA expression of activation markers in NK cells and T cells but also of exhaustion markers and IFNγ production. Correspondingly, depletion of CD4+ or CD8+ T cells or inhibition of IFNγ abrogated the RT-induced tumor ablative effect. Furthermore, adding anti-CTLA-4 and PD-1 antibodies to CRT was more effective than any other combination. Thus, the understanding of the complementary activities of those drugs/treatments is critical for further rational combinations.

Overall, there is abundant preclinical evidence, that RT is a promising combination partner with ICIs. Thus, adding ICI in the context of neoadjuvant treatment for cancer types where RT is part of the SOC, serves as an attractive model for novel practice changing clinical developments in the field of immunotherapy.

3.4. Combining immunotherapy with oncolytic viruses

One of the most potent mechanisms to induce ICD in a malignant cell is the infection with an OV. This fact is based on the evolutionary developed immune system, which is established to be activated by and to eradicate microbial infections. Correspondingly, OV have been found to be ideal for the synergistic enhancement of ICI therapy, frequently leading to a complete ablation of established tumors. This has been shown for a number of RNA viruses including reovirus [83], vesicular stomatitis virus (VSV) [9], newcastle-disease-virus (NDV), measles virus (MV) [84] and influenza A virus (IAV) [85] and even more effectively for DNA viruses including adenovirus [86], vaccina virus (VV) [87], herpes simplex viruses (HSV) [88] and others [89]. Tumor re-challenge experiments usually indicated an immunological memory induced by the *in situ* anti-cancer vaccination effect. This tumor ablative immune response dependent on cytotoxic T cells and a functional induced by type I and type II IFN system. With respect to the TIME, viruses repolarized tumor-associated macrophages (TAMs) from an M2-like phenotype towards a more proinflammatory M1-like phenotype. Armed viruses expressing T cell stimulating cytokines such as IL-12, IL-15 or GM-CSF could further enhance tumor ablative immune stimulation [90,91]. Despite the huge potential of OV, development and licensing are rather cumbersome, preventing its rapid implementation in clinical studies, particularly in a neoadjuvant setting in which patients are treated with a curative intent.

4. Neoadjuvant/adjuvant immunotherapy in solid non-GI cancers

With respect to solid non-GI cancers there is already a large body of evidence including clinical phase III trials, suggesting neoadjuvant immunotherapy as a reasonable treatment option.

4.1. Breast cancer

Combined ChT with immunotherapy in the neoadjuvant setting of triple negative breast cancer (TNBC) targets several steps in the cancer-immunity cycle. ChT induces the release of DAMPs reducing Treg cell activity, while increasing CD8+ T cell activity, as well as the expression of PD-L1, synergistically promoting the killing of cancer cells [92,93].

The first phase III trial exploring this combination in stage II/III TNBC was the KEYNOTE-522 trial, comparing the combination of intensive neoadjuvant ChT (12 weeks of paclitaxel and carboplatin followed by 12 weeks of doxorubicin/cyclophosphamide) with concomitant pembrolizumab (anti-PD-1) vs. placebo, followed by surgery [94]. Postoperatively patients remained on immunotherapy up to 1 year vs. placebo. The 2 main end points were pCR and event-free survival (EFS). A second smaller IMpassion031 study randomized patients into neoadjuvant platinum-free ChT (nab-paclitaxel) followed by accelerated doxorubicin/cyclophosphamide (AC) with or without atezolizumab (anti-PD-L1). After surgery patients were unblinded receiving immunotherapy or solely a follow-up with the primary end point pCR in the intention-to-treat (ITT) population [95].

Both trials showed a substantial increase in pCR rates for the addition of immunotherapy to ChT from 51.2% to 64.8% in KEYNOTE-522 and from 41.1% to 57.6% in the IMpassion031 trial. Very interesting results were revealed after subgroup analysis in the KEYNOTE-522 trial. Patients with lymph node (LN) involvement treated only with ChT usually have lower pCR rates as compared to the LN negative subgroup (44.1% vs. 58.6%). Adding pembrolizumab was associated with a similar pCR in both subgroups (64.8% vs. 64.9%) [94]. The same was observed in the IMpassion03 study, where the addition of atezolizumab increased pCR from 30.6% to 57.1% in LN positive and from 49% to 57.8% in LN negative patients [95].

In contrast to data from the metastatic TNBC setting, patients had a significant benefit in the neoadjuvant setting independent of their PD-L1 status. The added benefit observed was the same across different PD-L1 expression groups. As expected, overall higher responses were achieved in higher PD-L1 expressing tumors, but the benefit observed by the addition of immunotherapy was the same as compared with PD-L1 negative tumors. The percentages of patients with a pCR were 68.9% among those who received combination treatment and 54.9% among those who were treated with ChT alone in the PD-L1 positive patient groups. While in the PD-L1 negative population the pCR rate was 45.3% in the pembrolizumab/ChT group, the pCR rate was 30.3% among those who received placebo/ChT [94]. IMpassion031 provides similar results with a pCR of 68.8% vs. 49.3% in PD-L1 positive patients and 47.7% vs. 34.4% in PD-L1 negative patients [95]. Strikingly, conversion rates from negative to positive PD-L1 status reached 63% just 2–3 weeks after the application of immunotherapy.

Results of the KEYNOTE-522 trial show 91.3% of EFS in the combination group compared to 85.3% in the ChT only cohort after 18 months follow up with an HR of 0.63 (not statistically significant). Notably, patients who did not achieve pCR treated with immunotherapy/ChT still had a benefit in regard to EFS in comparison to ChT only group (69.59% vs. 61.7%) [96].

4.2. Lung cancer

Pilot studies of immunotherapy in a neoadjuvant setting of NSCLC show similarly encouraging results as they do for breast cancer. Nivolumab (anti-PD-1) administered twice preoperatively in surgically resectable early stage (I, II, IIIA), independent of PD-L1 status, is associated with few side effects, does not delay surgery and induces major pathological response (MPR) in 45% of the treated patients [97]. Similarly, the larger LCMC3 study applying 2 cycles of single agent atezolizumab preoperatively in NSCLC stage IB to IIIB patients resulted in a MPR rate of 21% and a pCR rate of 7% [98]. Surgery was accomplished within a narrow protocol-defined window in 88% of the patients. These results provide additional clinical evidence and are in support of the ongoing placebo-controlled phase III IMpower030 study, combining atezolizumab with platinum-based ChT [99].

A potentially new neoadjuvant ChT/immunotherapy regimen for patients with resectable NSCLC was shown in the phase III CheckMate 816 trial where adding nivolumab to ChT significantly increased pCR rates in comparison to ChT alone (24% vs. 2%), without an increase in overall toxicity or delays to surgery [100,101]. This study randomized adults with NSCLC stage IB to IIIA with no known activating alterations in epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genes to 3 times nivolumab and platinum-doublet ChT vs. ChT for 3 cycles, followed by definitive surgery within 6 weeks after the end of treatment. The pCR was improved across all study subgroups independent of disease stage, NSCLC subtype, PD-L1 status and tumor mutational burden (TMB). Furthermore, surgical outcomes showed that combination treatment was associated with a higher rate of minimally invasive surgery (MIS) 30% vs. 22% and had a lower conversion rate with 11% vs. 16% in the nivolumab combination arm. Neoadjuvant immunochemotherapy treatment also displayed a reduced pneumectomy rate 17% vs. 25%, as well as a reduced lobectomy rate (61% vs. 77%). In regards to the pathological response the addition of nivolumab resulted in median residual viable tumor cells in the primary tumor of just 10% compared to 74% in the ChT only arm. These results were achieved without increasing the duration of hospitalization or increasing the overall toxicity. Overall, the surgical outcomes and improved pCR rates from CheckMate 816 support the treatment combination of immunotherapy and ChT as a neoadjuvant option for resectable NSCLC.

4.3. Melanoma

Melanoma trials provide the most advanced and rigorous data of neoadjuvant treatment regimes. Recently a pooled analysis of 6 clinical studies from the International Neoadjuvant Melanoma Consortium (INMC) was published [102]. It summarizes neoadjuvant trials of resectable stage IIIB or IIIC melanoma receiving either ICI or targeted therapy. Although pCR rates were higher in the target therapy group (47%) compared to the immunotherapy group (33%), together they reached 43%. Overall survival (OS) rates at 2 years reached 99% for patients achieving a pCR with ICI, and 91% with targeted therapies. Interestingly, patients with any pathological response (pCR, near pCR or pathologic partial response; pPR), had a 2-year relapse-free survival (RFS) rate of 96% in the immunotherapy treatment groups. The OS for the immunotherapy combination group was 96% at 2 years compared to 76% for the monotherapy treatment group, independent of pathological response, supporting the application of ICI combination in the neoadjuvant setting.

A second smaller study, the OpACIN-neo trial, analyzed the neoadjuvant ICI as well [103]. It recruited 3 treatment arms: 2 cycles of ipilimumab 3 mg/nivolumab 1 mg; 2 cycles of ipilimumab 1 mg/nivolumab 3 mg or sequential nivolumab and ipilimumab for a total of 4 applications followed by surgery. The 2-year follow-up showed a RFS of 84% whereas the OS reached 95%. There was no significant difference between the treatment arms, however toxicity was much lower in the ipilimumab 1 mg/nivolumab 3 mg arm with about 27% grade 3, 4, or 5 immune-related adverse events (irAEs). These results support the conduction of further randomized controlled clinical trials of neoadjuvant or neoadjuvant/adjuvant treatment vs. adjuvant treatment alone.

4.4. Urothelial cancer

Cisplatin-based neoadjuvant ChT in bladder carcinoma is associated with relatively high toxicity in a patient group, which is often frail and has multiple comorbidities. Ongoing trials applying ICI in a neoadjuvant setting are well-tolerated by the majority of patients and are therefore of great interest. One of the first trials investigating such a regimen was the phase 2 PURE-01 study [104]. Preoperatively pembrolizumab (3 cycles) applied prior to radical cystectomy in muscle invasive bladder cancer (MIBC) resulted in 42% of pCR, and 54% of tumor downstaging. 54.3% of cPR was achieved in patients exhibiting a PD-L1 combined positive score (CPS) of $\geq$10%. Authors conclude neoadjuvant pembrolizumab could be safely administered in patients with MIBC.

Another phase II study investigating atezolizumab as a monotherapy (2 cycles preoperatively) in MIBC was the ABACUS trial [105], resulting in 29% of pCR rates and 39% of tumor tumors being downstaged to non-muscle-invasive bladder cancer (NMIBC).

As the combination of ICI appears to increase pathological response rates, multiple trials are investigating the combination of immunotherapeutic agents. The phase IB NABUCCO trial [106] was performed to mitigate the risk of irAEs. Patients received ipilimumab 3 mg/kg (day 1), ipilimumab 3 mg/kg + nivolumab 1 mg/kg (day 22), and nivolumab 3 mg/kg (day 43), followed by resection. Overall, a downstaging rate of 59% and a pCR of 45% was achieved. Interestingly, response was associated with massive tumor bed infiltration of cytotoxic CD8+ T cells. Furthermore, cisplatin ineligible patients had an encouraging pCR rate of 46%.

More ongoing trails are investigating the role of ICI in bladder preservation when combined with concurrent CRT, such as the phase III trial INTACT using atezolizumab [107] and the KEYNOTE-992 using pembrolizumab [108].

To increase effectivity in platinum-fit patients, a combination of immunochemotherapy is being tested in the neoadjuvant setting of MIBC. In a recently presented phase II study, patients received 1 cycle of atezolizumab prior to 4 cycles of ChT (cisplatin-gemcitabin) concomitantly with atezolizumab [109]. A high rate of 70% of tumor downstaging was achieved as well as 44% of pCR rate, outperforming previous ChT results. Very importantly authors report non-significant changes or increase in the toxicity profiles.

4.5. Head and neck cancer

Further promising data of immunotherapy in a neoadjuvant setting comes from a trial investigating locally advanced human papillomavirus (HPV) negative HNSCC [110]. The 2 preoperatively applied cycles of pembrolizumab improved response rates in comparison to the previously investigated single cycle. 43% of the patients experienced a pTR-2 (tumor response >50%) and 16% had a MPR (>90% of tumor response). It was a well-tolerated treatment and has the potential of having a favorable impact on the clinical outcome.

4.6. Glioblastoma (GBM)

Neoadjuvant immunotherapy yields also promising effects in immune-privileged sites, such as the brain. The phase II Neo-nivo trial demonstrated higher tumor immune cell infiltration, increased T cell receptor (TCR) clonal diversity and an upregulated expression of chemokine transcripts after neoadjuvant nivolumab, following surgery and adjuvant nivolumab [111]. These results were further confirmed in recurrent GBM, where patients received neoadjuvant pembrolizumab,

Table 1
Published and ongoing clinical trials with neoadjuvant immunotherapy in resectable GI cancers.

Tumor Entity	NCT Number	ICI agent	Setting	Combination	Phase	Ref.
Esophageal cancer (EC)						
ESCC	NCT04804696	PD-1 (Toripalimab)	Neoadjuvant	Concomitant ChT (paclitaxel, cisplatin)	II	
EAC, ESCC	NCT02735239	PD-L1 (Durvalumab)	Neoadjuvant	Concomitant ChT / CRT (FLOT, CAPOX / CROSS)	I/II	
EAC	NCT03399071 ICONIC	PD-L1 (Avelumab)	Neoadjuvant	Concomitant ChT (FLOT)	II	[134]
EAC	NCT03087864 PERFECT	PD-L1 (Atezolizumab)	Neoadjuvant	Concomitant CRT (CROSS)	II	[135]
EAC + GEJ	NCT02639065	PD-L1 (Durvalumab)	Adjuvant	Neoadjuvant CRT	II	[136]
EAC + GEJ	NCT03604991 EA2174	PD-1 (Nivolumab) CTLA-4 (Ipilimumab)	Neoadjuvant/Adjuvant	Neoadjuvant CRT (CAR, PAC, 50.4 Gy)	II/III	[137]
EAC + GEJ	NCT03490292	PD-L1 (Avelumab)	Neoadjuvant	Induction CRT (CROSS)	I/II	[138]
EAC, ESCC, GEJ	NCT02743494 CheckMate-577	PD-1 (Nivolumab)	Adjuvant	Neoadjuvant CRT	III	[113]
EAC, GEJ, GC	NCT03064490 PROCEED	PD-1 (Pembrolizumab)	Neoadjuvant/Adjuvant	Neoadjuvant CRT (CROSS)	II	
EAC + GEJ	NCT03784326	PD-L1 (Atezolizumab)	Neoadjuvant/Adjuvant	Concomitant ChT (mFOLFOX6)	I	
EAC + GEJ	NCT02962063	PD-L1 (Durvalumab) CTLA-4 (Tremelimumab)	Neoadjuvant/Adjuvant	Induction ChT (mFOLFOX6) Concomitant CRT (50.4 Gy + FOLFOX/CAPOX/CB+PTX)	I/II	
ESCC	NCT02520453	PD-L1 (Durvalumab)	Adjuvant	Neoadjuvant CRT (N.A.)	II	
EAC + ESCC + GEJ	NCT03544736 INEC	PD-1 (Nivolumab)	Neoadjuvant/Adjuvant	Concomitant CRT (CROSS)	I/II	
EAC + ESCC + GEJ	NCT03044613	PD-1 (Nivolumab) + /- LAG-3 (Relaltimab)	Neoadjuvant	Consolidation/ Concomitant CRT (CROSS)	I	[139]
Gastric cancer (GC)						
GC + GEJ	NCT03878472	PD-1 (Camrelizumab)	Neoadjuvant	+ /- concomitant ChT (apatinib/S1/oxaliplatin)	II	[140]
GC + GEJ	NCT03221426 KEYNOTE-585	PD-1 (Pembrolizumab)	Neoadjuvant	Concomitant ChT (FLOT/FP/XP)	III	[141]
GC + GEJ	NCT03448835 PANDA	PD-L1 (Atezolizumab)	Neoadjuvant	Concomitant ChT (DOC)	II	
GC + GEJ	NCT02918162	PD-1 (Pembrolizumab)	Neoadjuvant/Adjuvant	Concomitant ChT (CAPOX +/- epirubicin)	II	[142]
GC + GEJ	NCT04367025	PD-1 (Camrelizumab)	Neoadjuvant/Adjuvant	Concomitant ChT (oxaliplatin, S1)	II	
GC + GEJ	NCT03421288 DANTE	PD-L1 (Atezolizumab)	Adjuvant	Neoadjuvant ChT (FLOT)	II	[143]
Pancreatic ductal adenocarcinoma (PDAC)						
	NCT03970252	PD-1 (Nivolumab)	Neoadjuvant	Concomitant ChT (mFOLFIRINOX)	I	
	NCT03161379	PD-1 (Nivolumab)	Neoadjuvant	Concomitant ChT/SBRT (Cyclophosphamide, GVAX, 6.6 Gy)	II	
	NCT03767582	PD-1 (Nivolumab) CCR2/5 (BMS-813160)	Neoadjuvant/Adjuvant	Concomitant ChT/SBRT (GVAX, 6.6 Gy)	I/II	
	NCT02451982	PD-1 (Nivolumab) CD137 (Urelumab)	Neoadjuvant/Adjuvant	Concomitant ChT, CRT (Cyclophosphamide, GVAX)	I/II	
	NCT02305186	PD-1 (Pembrolizumab)	Neoadjuvant	Concomitant CRT (capecitabine, 50.4 Gy)	Ib/II	[144]
	NCT03727880	PD-1 (Pembrolizumab)	Neoadjuvant/Adjuvant	Induction ChT, adjuvant ChT (gemcitabine +/- Defactinib)	II	[145]
	NCT04940286	PD-L1 (Durvalumab) CD73 (Oleclumab)	Neoadjuvant/Adjuvant	Concomitant ChT (gemcitabine, nab-paclitaxel)	II	
	NCT03572400	PD-L1 (Durvalumab)	Neoadjuvant/Adjuvant	Concomitant CRT (gemcitabine)	II	
	NCT04627246	PD-1 (Nivolumab)	Adjuvant	ChT (gemcitabine), PEP-DC vaccine	I	
Hepatocellular carcinoma (HCC)						
	NCT03510871	PD-1 (Nivolumab) CTLA-4 (Ipilimumab)	Neoadjuvant	None	II	[146]
	NCT04658147	PD-1 (Nivolumab) LAG-3 (Relatlimab)	Neoadjuvant	None	I	
	NCT04123379	PD-1 (Nivolumab) CCR2/5 (BMS-81316) IL-8 (BMS-986253)	Neoadjuvant	None	II	
	NCT04857684	PD-L1 (Atezolizumab)	Neoadjuvant	Concomitant SBRT + VEGF-A (Bevacizumab)	I	
	NCT04850040	PD-1 (Camrelizumab)	Neoadjuvant	Concomitant ChT (apatinib and oxaliplatin)		
	NCT04850157	PD-1 (Tislelizumab)	Neoadjuvant	Concomitant IMRT	II	
+ GC, ESCC	NCT04196465 NeoChance	PD-L1 (IMC-001)	Neoadjuvant	None	II	[147]
	NCT04954339	PD-L1 (Atezolizumab)	Neoadjuvant/Adjuvant	Concomitant VEGF-A (Bevacizumab)	II	
	NCT03867370	PD-1 (Toripalimab)	Neoadjuvant/Adjuvant	Concomitant Lenvatinib	I/II	
	NCT04521153	PD-1 (Camrelizumab)	Neoadjuvant/Adjuvant	Concomitant apatinib, adjuvant TACE	II	
Biliary tract cancer (BTC)						
	NCT04989218	PD-L1 (Durvalumab) CTLA-4 (Tremelimumab)	Neoadjuvant	Concomitant ChT (gemcitabine and cisplatin)	I/II	
	NCT04669496	PD-1 (Toripalimab)	Neoadjuvant	Concomitant ChT (GEMOX, lenvatinib)	II	
	NCT04308174 DEBATE	PD-L1 (Durvalumab)	Neoadjuvant/Adjuvant	Concomitant ChT (gemcitabine, cisplatin)	II	
Colon cancer (CC)						
	NCT03026140 NICHE	CTLA-4 (Ipilimumab) PD-1 (Nivolumab)	Neoadjuvant	None	II	[120]
	NCT04123925 NICOLE	PD-1 (Nivolumab)	Neoadjuvant	None	II	

(*continued on next page*)

Table 1 (*continued*)

Tumor Entity	NCT Number	ICI agent	Setting	Combination	Phase	Ref.
CC + RC	NCT03926338 PICC	PD-1 (Toripalimab)	Neoadjuvant	Concomitant COX-2 (Celecoxib)	I/II	
resectable CLM	NCT04940546	PD-1 (Sintilimab)	Neoadjuvant	Concomitant ChT (XELOX + Bevacizumab)	I/II	
resectable CLM	NCT02754856	PD-L1 (Durvalumab) CTLA-4 (Tremelimumab)	Neoadjuvant/Adjuvant	None	I	
	NCT02912559 ATOMIC	PD-L1 (Atezolizumab)	Adjuvant	Concomitant ChT (mFOLFOX6)	III	[148]
	NCT03827044 POLEM	PD-L1 (Durvalumab)	Adjuvant	ChT (Capecitabine or CAPOX)	III	[149]
Rectal cancer (RC)						
	NCT04124601 CHINOREC	CTLA-4 (Ipilimumab) PD-1 (Nivolumab)	Neoadjuvant	Concomitant CRT (50 Gy + Capecitabine)	II	[150]
	NCT04109755 PEMREC	PD-1 (Pembrolizumab)	Neoadjuvant	Concomitant SCPRT (25 Gy)	II	[151]
	NCT02948348 VOLTAGE-A	PD-1 (Nivolumab)	Neoadjuvant	Induction CRT (50.4 Gy + Capecitabine)	Ib/II	[130]
	NCT02948348 VOLTAGE-B	PD-1 (Nivolumab)	Neoadjuvant	Induction CRT (50.4 Gy + Capecitabine)	Ib/II	[131]
	NCT04017455 TARZAN	PD-L1 (Atezolizumab)	Neoadjuvant	Induction RT (N.A.) Concomitant VEGF-A (Bevacizumab)	II	
	NCT04293419 DUREC	PD-L1 (Durvalumab)	Neoadjuvant	Concomitant TNT (mFOLFOX6, 50.4 Gy + Capecitabine)	II	
	NCT03102047 NSABP FR-2	PD-L1 (Durvalumab)	Neoadjuvant	Induction CRT (50.4 Gy + Capecitabine)	II	[152]
	NCT03299660 Ave-Rec	PD-L1 (Avelumab)	Neoadjuvant	Induction CRT (50.4 Gy + Capecitabine)	II	[153]
	NCT04083365 PANDORA	PD-L1 (Durvalumab)	Neoadjuvant	Induction CRT (50.4 Gy + Capecitabine)	II	[154]
	NCT04643041 BASKET	PD-1 (N.A.)	Neoadjuvant / W&W	N.A.	N.A.	
	NCT04304209	PD-1 (Sintilimab)	Neoadjuvant/Adjuvant	Consolidation CRT (50.4 Gy + Capecitabine)	II/III	[155]
	NCT03854799 AVANA	PD-L1 (Avelumab)	Neoadjuvant	Concomitant CRT (50.4 Gy + Capecitabine)	II	[156]
	NCT04357587	PD-1 (Pembrolizumab)	Neoadjuvant	Concomitant CRT (50 Gy + Capecitabine)	I	
	NCT03921684	PD-1 (Nivolumab)	Neoadjuvant	Induction CRT (50.4 Gy + Capecitabine), Concomitant ChT (mFOLFOX6)	II	
	NCT02921256 NRG-GI002	PD-1 (Pembrolizumab)	Neoadjuvant	Induction ChT (mFOLFOX6) Concomitant CRT (50.4 Gy + Capecitabine)	II	[157]
	NCT03127007 R-IMMUNE	PD-L1 (Atezolizumab)	Neoadjuvant	Concomitant CRT (50.4 Gy + 5-FU)	Ib/II	
	NCT04443543	PD-1 (Tislelizumab)	Neoadjuvant / W&W	Induction CRT (50 Gy + Capecitabine)	II	
	NCT04411524	PD-1 (N.A.)	Neoadjuvant	Consolidation CRT (50 Gy + Capecitabine + Irinotecan)	II	
	NCT04411537	PD-1 (N.A.)	Neoadjuvant	Consolidation CRT (50 Gy + Capecitabine + Irinotecan)	II	
	NCT04636008	PD-1 (Sintilimab)	Neoadjuvant	Concomitant SCPRT (25 Gy)	Ib	
	NCT04503694 REGINA	PD-1 (Nivolumab)	Neoadjuvant	Concomitant MKI (Regorafenib) Consolidation SCPRT (25 Gy)	II	
	NCT03503630	PD-L1 (Avelumab)	Neoadjuvant	Induction SCPRT (25 Gy) Concomitant ChT (mFOLFOX6)	II	[158]
	NCT04231552	PD-1 (Camrelizumab)	Neoadjuvant	Induction SCPRT (25 Gy) Concomitant ChT (CAPOX)	II	[159]
	NCT04621370 PRIME-RT	PD-L1 (Durvalumab)	Neoadjuvant	Concomitant SCPRT / CRT (25 Gy / 50 Gy + Capecitabine) Consolidation ChT (mFOLFOX6)	II	
	NCT04558684	PD-1 (Camrelizumab)	Neoadjuvant	Induction SCPRT (25 Gy) Concomitant ChT (CAPOX)	I/II	
	NCT04518280	PD-1 (Toripalimab)	Neoadjuvant	Induction SCPRT (25 Gy) Concomitant ChT (CAPOX)	II	
	NCT04906044	PD-1 Tilelimumab	Neoadjuvant	Induction SCPRT + ChT	I	
	NCT04663763	PD-1 (Sintilimab)	Neoadjuvant	Induction SCPRT (25 Gy) Concomitant ChT (CAPOX)	II	

Biliary tract cancer (BTC) includes intrahepatic, extrahepatic, perihilar and distal cholangiocarcinoma (iCCA, eCCA, pCCA/Klatskin tumor, dCCA), gallbladder cancer (GBC) and ampulla of Vater cancer (AVC). At the time of the present review there are no published nor ongoing clinical trials for neoadjuvant immunotherapy in anal cancer (AC), gastrointestinal neuroendocrine tumor (GI NET), gastrointestinal stromal tumors (GIST) or small bowel cancer. XP: capecitabine, cisplatin; FP: 5-Fluorouracil, cisplatin; FLOT: 5-Fluorouracil, docetaxel, oxaliplatin, leucovorin; DOC: docetaxel, oxaliplatin, capecitabine; SCPRT: short-course pre-operative radiotherapy; CRT: Chemoradiotherapy; ChT: Chemotherapy; CAPOX: capecitabine, oxaliplatin; MKI: Multikinase-Inhibitor; VEGF-A: Vascular endothelial growth factor A; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; W&W: watch and wait; PTX: paclitaxel; CB: carboplatin; CLM: colorectal liver metastases. mFOLFOX6: modified folinic acid, fluorouracil, oxaliplatin, ESCC: esophageal squamous cell carcinoma, EAC: esophageal adenocarcinoma; GEJ: gastroesophageal junction; LAG-3: lymphocyte-activation gene 3; TNT: total neoadjuvant therapy; IMRT: intensity modulated radiotherapy; TACE: transcatheter arterial chemoembolization; SBRT: stereotactic body radiation therapy; GEMOX: gemcitabine, oxaliplatin; COX-2: cyclooxygenase-2.

which was continued after surgery [112]. Translational analyses revealed an upregulation of T cell and IFNγ-related gene expression and a downregulation of cell-cycle-related gene expression in the tumor. The OS was also significantly prolonged in the neoadjuvant compared to the adjuvant only group (median OS 228 days vs. 417 days, HR 0.39, p=0.04). Such a clinical effect however, could not be seen in the Neo-nivo trial. Overall neoadjuvant immunotherapy was well tolerated in resectable/recurrent GBM and did not bring up any new safety considerations. Further long-term clinical results of phase III clinical trials are awaited.

5. Neoadjuvant/adjuvant immunotherapy in GI cancers

In contrast to non-GI solid cancers, there are currently no phase III trials investigating neoadjuvant ICI-based therapy in GI cancers (Table 1). One reason might be that apart from MSI-high cancers, there is sparse data supporting the use of ICI in microsatellite stable (MSS) / MSI-low (MSI-L) GI cancers. However, considering the synergistic effect of RT or CRT with ICI, as well as the scientific rational behind this combinatorial effect, it is pertinent to re-evaluate the application of these agents in a neoadjuvant setting.

So far the only phase III clinical trial implementing immunotherapy in GI cancer is the CheckMate 577 study [113]. Patients with esophageal adenocarcinoma (EAC), esophageal squamous-cell carcinoma (ESCC) or gastroesophageal junction (GEJ) cancer received neoadjuvant CRT, following adjuvant nivolumab for up to 1 year in the case of residual pathologic disease (≥ypT1 or ≥ypN1). Adjuvant nivolumab provided superior disease-free survival (DFS) with a 31% reduction in the risk of recurrence or death and a doubling in median DFS.

The differences between MSI and MSS tumors must be taken into account, when discussing ICI therapy in the context of GI cancers. For metastatic MSI solid cancers Lee *et al.* demonstrated that pembrolizumab (anti-PD-1) was associated with a highly significant prolonged progression-free survival (PFS) compared to standard ChT [114]. The rationale to treat MSI cancers with ICI is based on the fact that the MSI phenotype is associated with a high number of neoantigens [115]. The high number of neoantigens in MSI tumors are partially generated by the dysfunction of proteins in the DNA damage repair machinery, leading to a high TMB [116]. A subsequent phase III study performed in metastatic MSI CRC, supported the benefit of ICI therapy over ChT. Consequently ICI have become the first line treatment option in metastatic MSI CRC [117]. It should be noted, that surgically resectable oligometastatic CRC (liver/lung limited) still has an option for a therapeutic approach in a curative intent (*i.e.* long time cure rate for CLM is about 30%). The high response rates of MSI cancers promoted a retrospective study of neoadjuvant PD-1 blockade with or without ChT in 7 patients with locally advanced/metastatic MSI positive CRC [118]. 5 of 7 resected patients revealed a pCR, supporting this concept. A larger prospective study cohort is needed for validation but might be difficult to recruit due to the slim number of patients. Another small trial with 24 patients including 2 MSI patients of resectable CLM was conducted to evaluate the neoadjuvant application of CTLA-4 and PD-1 inhibitors. Both MSI and 2 MSS experienced pCRs [119].

The recently published NICHE study demonstrated exciting results of 2 neoadjuvant administered cycles of nivolumab and ipilimumab in 20 MSI and 20 MSS primary resectable CC patients [120]. The SOC would have been resection with a curative intent, followed by potential adjuvant ChT [121]. The decision whether resectable CC requires adjuvant ChT is determined after pathological tumor staging. This explains and reveals the novelty of the study, in which patients who would otherwise be curatively treated by surgery alone, received neoadjuvant ICI. Neoadjuvant ICI therapy led to a MPR or pCR in 19 out of 20 MSI, as well as in 4 out of 15 MSS patients. Furthermore, tumors of patients, which tended to respond to ICI, had an increased CD8+ immune infiltrate. Fortunately, the clinical investigators did not encounter any irAEs higher than grade 2. Despite the small number of patients, these results are of major interest for a practice changing treatment approach. Supporting the data provided by Liu *et al.* [22], the NICHE study provides real world clinical data that 2 cycles of ICI therapy are sufficient to induce a therapeutic response. Moreover, these results confirm preclinical data, that ICI therapy leads to the inflitration of IFNγ positive T cells into the tumor. Additionally, the data suggests that a small part of MSS tumors (around 1/4) also do respond to ICI, which is currently only believed to be true for MSI tumors. It seems that intrinsically ICI-responsive tumors most likely stimulate the immune system by an endogenous ICD. This is in line with the data from a retrospective clinical study, showing that patients with CLM exhibiting low DNA damage, high ICD and high T cell tumor infiltrates have an improved OS [122]. The future task will be to identify those patients eligible for a personalized treatment approach.

As nicely summarized by Galon and Bruni, these patients harbor an immunogenic tumor which is characterized by an exhausted T cell immune infiltrate [123]. It should be noted, that exhausted CD8+ T cells (Tex) comprise of 4 different dynamic subsets (Tex^{prog1}, Tex^{prog2}, Tex^{int}, Tex^{term}) with different effector rearrangement potential to ICI. In particular, only the Tex^{prog2} and Tex^{int} subsets are being reinvigorated after PD-1 blockade [124]. These findings suggest that MSS tumor can respond to ICI if the immune system is stimulated by other means. This certainly raises the urgent need for combinatorial treatments to induce an ICD in intrinsically non immunogenic tumors. Preclinical data clearly demonstrate that RT or ChT, such as cisplatin or oxaliplatin can induce an ICD and synergize with PD1/PD-L1as well as CTLA-4 inhibition, supporting the idea of combining ICI with standard therapy (CRT, RT, ChT) in a neoadjuvant setting. However, the clinical development of mentioned novel neoadjuvant ICI regimens might not be implemented as commemorated, due to the fact of the existing standard neoadjuvant treatment modalities. It is not considered ethical to exclude them in a curative established setting.

Fortunately, CRT is the backbone of locally advanced rectal cancer (LARC) [125] and is a SOC treatment option for ESCC, EAC or GEJ cancer [126]. Oxaliplatin is part of standard regimens used for CRC and pancreatic ductal adenocarcinoma (PDAC) [127]. With respect to RT, several translational data support the hypothesis, that the mode and dose of RT applied clinically in a standard setting has proinflammatory components, despite of its known immunosuppressive aspect, such as lymphopenia. In this line, we have found that SCPRT (5×5 Gy over 5 days) in RC patients leads to in repolarization of M2-like macrophages towards a M1-like phenotype with reduced expression of the T cell suppressing cytokine IL-10. [128]. Despite the positive proinflammatory stimulus of RT on macrophages, the absolute number of T cells and macrophages decreased, supporting the idea of an activation-induced cell death. The observation of the RT-induced phenotypical changes in macrophages was further simulated by cultivating surgically resected CRC tumor fragments. Irradiation of the small tumor fragments provided evidence that macrophages not only reveal a proinflammatory phenotype but improve their phagocytosis activity, which supports antigen presentation and induction of an adaptive anti-tumor immune response. Similarly, Josef *et al.* found that neoadjuvant CRT-treated tumors were associated with a more potent expression of a proinflammatory mRNA profile as compared to untreated tumors [129].

Together this data highlights the preclinical finding that RT has an immunogenic component which might be synergistic with ICI, especially in GI cancers. Preliminary clinical data derived from the VOLTAGE A and B trials support these results [130,131]. In this trial CRT was combined with nivolumab given sequentially after the course of CRT. This phase II trial of 37 patient was associated with a pCR rate of 30%, compared to current 10% pCR achieved by CRT alone. Importantly, immunotherapy did not interfere with surgery and irAEs were limited to 2 patients experiencing grade 3 irAEs, myasthenia and nephritis. The high pCR rate of around 30% has otherwise only been achieved by applying highly toxic ChT (FOLFIRINOX) prior to CRT [132] or SCPRT following ChT (CAPOX or FOLFOX4) [133]. This

concept might not be acceptable for a fraction of patients due to a rather high toxicity and a low performance status.

Nevertheless, a general overall benefit of a neoadjuvant treatment approach is clearly indicated, whether it will be immunotherapy or any other therapy must be critically evaluated by weighing benefit of clinical outcome against potential adverse events (AE).

6. Safety considerations of neoadjuvant immunotherapy

Reactivation of the immune system by ICI includes the risk for patients to develop a plethora of irAEs, some of which can be lethal. Over the years a vast number of toxicities have evolved, revealing that any organ can be affected. Most frequently affected organs are the colon/rectum, endocrine organs, lung, skin and liver. Some AEs, for instance neurological disorders and myocarditis are rare, however they can be extremely serious and even fatal [160].

Initial data on irAEs came from ipilimumab (dosage 3 mg/kg). Grade 1 and 2 AE have been reported in a very high percentage of metastatic melanoma patients (60%−85%), whereas 10%−27% developed grade 3 and 4 toxicities and lethal events reached 2.1% (in the first phase III trial) [161].

Anti-PD-1 inhibitors, on the other hand, are associated with fewer high-grade toxic events. Taking nivolumab as an example, 74%−85% of metastatic melanoma patients develop any irAE and 12%−20% develop grade 3 or 4 irAEs respectively [162–164]. 58% of Patients with advanced squamous NSCLC develop any and 7% are confronted with grade 3–4 irAEs. [165] In metastatic non-squamous NSCLC 69% and 10%, are affected with any or grade 3–4 irAEs respectively [166].

A substantial challenge considering irAEs is the combination of different ICI concomitantly. Combining nivolumab and ipilimumab in metastatic melanoma triggered substantially more irAEs than PD-1 monotherapy (55%−60% vs. 10%−20% grade 3–5) [167]. Therefore, despite their considerable benefits and association with superior outcomes, ICI treatment combinations can be limited by potentially life threatening irAEs.

Another important concern is the timeframe of irAE onset. Generally, toxicities occur quite early and appear between a couple of weeks and 3 months after treatment initiation. However, first onsets have been reported as early as the first week of application and as late as 1 year after discontinuation of ICIs [168]. Moreover, RWD has shown, that even a single application of any of the current Food and Drug Administration (FDA) approved ICI has the potential to induce a life threatening and rare irAE, such as myocarditis, myositis, pneumonitis or myasthenia gravis (MG). Thus, potential irAEs have to be taken very seriously when licensed and non-licensed ICIs are given in a neoadjuvant setting, as the latter is done in patients treated with a curative intent.

Meticulous clinical examination and patient history is mandatory in preparation of every ICI application. A set of laboratory tests is highly recommendable, this includes a complete blood count, complete metabolic panel (*i.e.* electrolytes, glucose, HbA1c, liver, pancreas, kidney), hormones (*i.e.* TSH, fT3, fT4; occasionally ACTH, FSH, LH and/or cortisol) and cardio/musculoskeletal diagnostics (*i.e.* CPK, CPK-MB, myoglobin, troponin T and/or I, proBNP) [169]. A prepared algorithm of interventions and medications to prevent or treat these adverse events should be considered beforehand [160].

Future directions

As outlined in this review, there are no major safety concerns of neoadjuvant immunotherapy application, alone or in combination (RT, CRT or ChT), in solid GI cancers. Consequently, there is an urgent need to push these promising results to the next level.

Longitudinal translational analysis (*i.e.* sequential tissue and liquid biopsies, stool samples, fecal swabs *etc.*) of innovative neoadjuvant immunotherapy trials (*i.e.* CHINOREC) will grant novel insights into the therapeutic mechanism of action in the TIME in terms of immunoediting and tumor evolution in space and time. Such RWD will not only answer the million-dollar question of treatment timing (concomitant/sequential, induction/consolidation), but will streamline novel and innovative therapeutic combinations. Overall, the harmonization of physician scientists and tumor immunologists is the foundation for the future of practice changing cancer therapy.

Funding

This review was in part supported by research funds of the Division of Visceral Surgery, Department of General Surgery, Comprehensive Cancer Center Vienna, Medical University of Vienna; the Ludwig Boltzmann Institute Applied Diagnostics (lbi:ad); an investigator-sponsored research (ISR) from Bristol-Myers Squibb (BMS); as well as by a research scholarship of the Fellinger Cancer Research (granted to J. L.) and by the Georg Stumpf Scholarship of the Austrian Society of Surgical Oncology (granted to J.L.).

Authors' contributions

All authors participated in writing and editing of the manuscript, as well as approved the final version of the review.

Competing interests

All authors declare no competing interest in the context of the present review.

Acknowledgements

We would like to thank all group and lab members for their fruitful curiosity and discussions in the context of the present review.

References

[1] D.R. Leach, M.F. Krummel, J.P. Allison, Enhancement of antitumor immunity by CTLA-4 blockade, Science 271 (1996) 1734–1736, https://doi.org/10.1126/science.271.5256.1734.

[2] T. André, C. Boni, L. Mounedji-Boudiaf, M. Navarro, J. Tabernero, T. Hickish, C. Topham, M. Zaninelli, P. Clingan, J. Bridgewater, I. Tabah-Fisch, A. de Gramont, Multicenter International Study of Oxaliplatin/5-Fluorouracil/leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) investigators, oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer, N. Engl. J. Med. 350 (2004) 2343–2351, https://doi.org/10.1056/NEJMoa032709.

[3] T. André, C. Boni, M. Navarro, J. Tabernero, T. Hickish, C. Topham, A. Bonetti, P. Clingan, J. Bridgewater, F. Rivera, A. de Gramont, Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial, J. Clin. Oncol. 27 (2009) 3109–3116, https://doi.org/10.1200/JCO.2008.20.6771.

[4] A.M.M. Eggermont, C.U. Blank, M. Mandala, G.V. Long, V. Atkinson, S. Dalle, A. Haydon, M. Lichinitser, A. Khattak, M.S. Carlino, S. Sandhu, J. Larkin, S. Puig, P.A. Ascierto, P. Rutkowski, D. Schadendorf, R. Koornstra, L. Hernandez-Aya, M. Maio, A.J.M. van den Eertwegh, J.-J. Grob, R. Gutzmer, R. Jamal, P. Lorigan, N. Ibrahim, S. Marreaud, A.C.J. van Akkooi, S. Suciu, C. Robert, Adjuvant pembrolizumab versus placebo in resected stage III melanoma, New Engl. J. Med. 378 (2018) 1789–1801, https://doi.org/10.1056/NEJMoa1802357.

[5] M.J. Overman, R. McDermott, J.L. Leach, S. Lonardi, H.-J. Lenz, M.A. Morse, J. Desai, A. Hill, M. Axelson, R.A. Moss, M.V. Goldberg, Z.A. Cao, J.-M. Ledeine, G.A. Maglinte, S. Kopetz, T. André, Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study, Lancet Oncol. 18 (2017) 1182–1191, https://doi.org/10.1016/S1470-2045(17)30422-9.

[6] A. Habr-Gama, R.O. Perez, W. Nadalin, J. Sabbaga, U. Ribeiro, A.H. Silva e Sousa, F.G. Campos, D.R. Kiss, J. Gama-Rodrigues, Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results, Ann. Surg. 240 (2004) 711–717, https://doi.org/10.1097/01.sla.0000141194.27992.32.

[7] L. Losi, B. Baisse, H. Bouzourene, J. Benhattar, Evolution of intratumoral genetic heterogeneity during colorectal cancer progression, Carcinogenesis 26 (2005) 916–922, https://doi.org/10.1093/carcin/bgi044.

[8] J. Ma, M. Ramachandran, C. Jin, C. Quijano-Rubio, M. Martikainen, D. Yu, M. Essand, Characterization of virus-mediated immunogenic cancer cell death and the consequences for oncolytic virus-based immunotherapy of cancer, Cell Death Dis. 11 (2020) 48, https://doi.org/10.1038/s41419-020-2236-3.

[9] J. Kabiljo, J. Laengle, M. Bergmann, From threat to cure: understanding of virus-induced cell death leads to highly immunogenic oncolytic influenza viruses, Cell Death Discov. 6 (2020) 48, https://doi.org/10.1038/s41420-020-0284-1.
[10] J. Kabiljo, F. Harpain, S. Carotta, M. Bergmann, Radiotherapy as a Backbone for Novel Concepts in Cancer Immunotherapy, Cancers (2019) 79, https://doi.org/10.3390/cancers12010079.
[11] L. Galluzzi, J. Humeau, A. Buqué, L. Zitvogel, G. Kroemer, Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors, Nat. Rev. Clin. Oncol. 17 (2020) 725–741, https://doi.org/10.1038/s41571-020-0413-z.
[12] C. Wang, J. Sandhu, C. Ouyang, J. Ye, P.P. Lee, M. Fakih, Clinical response to immunotherapy targeting programmed cell death receptor 1/programmed cell death ligand 1 in patients with treatment-resistant microsatellite stable colorectal cancer with and without liver metastases, JAMA Netw. Open. 4 (2021), e2118416, https://doi.org/10.1001/jamanetworkopen.2021.18416.
[13] E. Lauret Marie Joseph, A. Kirilovsky, B. Lecoester, C. El Sissy, L. Boullerot, L. Rangan, A. Marguier, F. Tochet, M. Dosset, J. Boustani, P. Ravel, R. Boidot, L. Spehner, N. Haicheur-Adjouri, F. Marliot, J.-R. Pallandre, F. Bonnefoy, V. Scripcariu, M. Van den Eynde, E. Cornillot, C. Mirjolet, F. Pages, O. Adotevi, Chemoradiation triggers antitumor Th1 and tissue resident memory-polarized immune responses to improve immune checkpoint inhibitors therapy, J. Immunother. Cancer 9 (2021), e002256, https://doi.org/10.1136/jitc-2020-002256.
[14] J. Friedman, E.C. Moore, P. Zolkind, Y. Robbins, P.E. Clavijo, L. Sun, S. Greene, M.V. Morisada, W.K. Mydlarz, N. Schmitt, J.W. Hodge, H. Schreiber, C. Van Waes, R. Uppaluri, C. Allen, Neoadjuvant PD-1 immune checkpoint blockade reverses functional immunodominance among tumor antigen–specific T cells, Clin. Cancer Res. 26 (2020) 679–689, https://doi.org/10.1158/1078-0432.CCR-19-2209.
[15] M. Miyake, S. Hori, S. Ohnishi, M. Toritsuka, T. Fujii, T. Shimizu, T. Owari, Y. Morizawa, D. Gotoh, Y. Itami, Y. Nakai, S. Anai, K. Torimoto, N. Tanaka, K. Fujimoto, Supplementary granulocyte macrophage colony-stimulating factor to chemotherapy and programmed death-ligand 1 blockade decreases local recurrence after surgery in bladder cancer, Cancer Sci. 110 (2019) 3315–3327, https://doi.org/10.1111/cas.14158.
[16] M. Jamal-Hanjani, A. Hackshaw, Y. Ngai, J. Shaw, C. Dive, S. Quezada, G. Middleton, E. de Bruin, J. Le Quesne, S. Shafi, M. Falzon, S. Horswell, F. Blackhall, I. Khan, S. Janes, M. Nicolson, D. Lawrence, M. Forster, D. Fennell, S.-M. Lee, J. Lester, K. Kerr, S. Muller, N. Iles, S. Smith, N. Murugaesu, R. Mitter, M. Salm, A. Stuart, N. Matthews, H. Adams, T. Ahmad, R. Attanoos, J. Bennett, N. J. Birkbak, R. Booton, G. Brady, K. Buchan, A. Capitano, M. Chetty, M. Cobbold, P. Crosbie, H. Davies, A. Denison, M. Djearman, J. Goldman, T. Haswell, L. Joseph, M. Kornaszewska, M. Krebs, G. Langman, M. MacKenzie, J. Millar, B. Morgan, B. Naidu, D. Nonaka, K. Peggs, C. Pritchard, H. Remmen, A. Rowan, R. Shah, E. Smith, Y. Summers, M. Taylor, S. Veeriah, D. Waller, B. Wilcox, M. Wilcox, I. Woolhouse, N. McGranahan, C. Swanton, Tracking genomic cancer evolution for precision medicine: the lung TRACERx study, PLoS Biol. 12 (2014), e1001906, https://doi.org/10.1371/journal.pbio.1001906.
[17] T.-M. Kim, S.-H. Jung, C.H. An, S.H. Lee, I.-P. Baek, M.S. Kim, S.-W. Park, J.-K. Rhee, S.-H. Lee, Y.-J. Chung, Subclonal genomic architectures of primary and metastatic colorectal cancer based on intratumoral genetic heterogeneity, Clin. Cancer Res. 21 (2015) 4461–4472, https://doi.org/10.1158/1078-0432.CCR-14-2413.
[18] H.-N. Chen, Y. Shu, F. Liao, X. Liao, H. Zhang, Y. Qin, Z. Wang, M. Luo, Q. Liu, Z. Xue, M. Cao, S. Zhang, W.-H. Zhang, Q. Hou, X. Xia, H. Luo, Y. Zhang, L. Yang, J.-K. Hu, X. Fu, B. Liu, H. Hu, C. Huang, Y. Peng, W. Cheng, L. Dai, L. Yang, W. Zhang, B. Dong, Y. Li, Y. Wei, H. Xu, Z.-G. Zhou, Genomic evolution and diverse models of systemic metastases in colorectal cancer, gutjnl-2020-323703, Gut (2021), https://doi.org/10.1136/gutjnl-2020-323703.
[19] H. Allgayer, J.H. Leupold, N. Patil, Defining the "Metastasome": perspectives from the genome and molecular landscape in colorectal cancer for metastasis evolution and clinical consequences, Semin. Cancer Biol. 60 (2020) 1–13, https://doi.org/10.1016/j.semcancer.2019.07.018.
[20] B. Edris, K. Weiskopf, A.K. Volkmer, J.-P. Volkmer, S.B. Willingham, H. Contreras-Trujillo, J. Liu, R. Majeti, R.B. West, J.A. Fletcher, A.H. Beck, I. L. Weissman, M. van de Rijn, Antibody therapy targeting the CD47 protein is effective in a model of aggressive metastatic leiomyosarcoma, Proc. Natl. Acad. Sci. 109 (2012) 6656–6661, https://doi.org/10.1073/pnas.1121629109.
[21] C.A. von Roemeling, Y. Wang, Y. Qie, H. Yuan, H. Zhao, X. Liu, Z. Yang, M. Yang, W. Deng, K.A. Bruno, C.K. Chan, A.S. Lee, S.S. Rosenfeld, K. Yun, A.J. Johnson, D. A. Mitchell, W. Jiang, B.Y.S. Kim, Therapeutic modulation of phagocytosis in glioblastoma can activate both innate and adaptive antitumour immunity, Nat. Commun. 11 (2020) 1508, https://doi.org/10.1038/s41467-020-15129-8.
[22] J. Liu, S.J. Blake, M.C.R.R. Yong, H. Harjunpa a, S.F. Ngiow, K. Takeda, A. Young, J.S. O'Donnell, S. Allen, M.J. Smyth, M.W.L.L. Teng, H. Harjunpää, S.F. Ngiow, K. Takeda, A. Young, J.S. O'Donnell, S. Allen, M.J. Smyth, M.W.L.L. Teng, H. Harjunpa a, S.F. Ngiow, K. Takeda, A. Young, J.S. O'Donnell, S. Allen, M. J. Smyth, M.W.L.L. Teng, Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease, Cancer Disco 6 (2016) 1382–1399, https://doi.org/10.1158/2159-8290.CD-16-0577.
[23] F. Arce Vargas, A.J.S. Furness, I. Solomon, K. Joshi, L. Mekkaoui, M.H. Lesko, E. Miranda Rota, R. Dahan, A. Georgiou, A. Sledzinska, A. Ben Aissa, D. Franz, M. Werner Sunderland, Y.N.S. Wong, J.Y. Henry, T. O'Brien, D. Nicol, B. Challacombe, S.A. Beers, S. Turajlic, M. Gore, J. Larkin, C. Swanton, K. A. Chester, M. Pule, J.V. Ravetch, T. Marafioti, K.S. Peggs, S.A. Quezada, L. Spain, A. Wotherspoon, N. Francis, M. Smith, D. Strauss, A. Hayes, A. Soultati, M. Stares, L. Spain, J. Lynch, N. Fotiadis, A. Fernando, S. Hazell, A. Chandra, L. Pickering, S. Rudman, S. Chowdhury, C. Swanton, M. Jamal-Hanjani, S. Veeriah, S. Shafi, J. Czyzewska-Khan, D. Johnson, J. Laycock, L. Bosshard-Carter, G. Goh, R. Rosenthal, P. Gorman, N. Murugaesu, R.E. Hynds, G. Wilson, N.J. Birkbak, T.B. K. Watkins, N. McGranahan, S. Horswell, R. Mitter, M. Escudero, A. Stewart, P. Van Loo, A. Rowan, H. Xu, S. Turajlic, C. Hiley, C. Abbosh, J. Goldman, R. K. Stone, T. Denner, N. Matthews, G. Elgar, S. Ward, J. Biggs, M. Costa, S. Begum, B. Phillimore, T. Chambers, E. Nye, S. Graca, M. Al Bakir, J.A. Hartley, H.L. Lowe, J. Herrero, D. Lawrence, M. Hayward, N. Panagiotopoulos, S. Kolvekar, M. Falzon, E. Borg, C. Simeon, G. Hector, A. Smith, M. Aranda, M. Novelli, D. Oukrif, S.M. Janes, R. Thakrar, M. Forster, T. Ahmad, S.M. Lee, D. Papadatos-Pastos, D. Carnell, R. Mendes, J. George, N. Navani, A. Ahmed, M. Taylor, J. Choudhary, Y. Summers, R. Califano, P. Taylor, R. Shah, P. Krysiak, K. Rammohan, E. Fontaine, R. Booton, M. Evison, P. Crosbie, S. Moss, F. Idries, L. Joseph, P. Bishop, A. Chaturved, A.M. Quinn, H. Doran, A. Leek, P. Harrison, K. Moore, R. Waddington, J. Novasio, F. Blackhall, J. Rogan, E. Smith, C. Dive, J. Tugwood, G. Brady, D.G. Rothwell, F. Chemi, J. Pierce, S. Gulati, B. Naidu, G. Langman, S. Trotter, M. Bellamy, H. Bancroft, A. Kerr, S. Kadiri, J. Webb, G. Middleton, M. Djearaman, D. Fennell, J.A. Shaw, J. Le Quesne, D. Moore, A. Nakas, S. Rathinam, W. Monteiro, H. Marshall, L. Nelson, J. Bennett, J. Riley, L. Primrose, L. Martinson, G. Anand, S. Khan, A. Amadi, M. Nicolson, K. Kerr, S. Palmer, H. Remmen, J. Miller, K. Buchan, M. Chetty, L. Gomersall, J. Lester, A. Edwards, F. Morgan, H. Adams, H. Davies, M. Kornaszewska, R. Attanoos, S. Lock, A. Verjee, M. MacKenzie, M. Wilcox, H. Bell, N. Iles, A. Hackshaw, Y. Ngai, S. Smith, N. Gower, C. Ottensmeier, S. Chee, B. Johnson, A. Alzetani, E. Shaw, E. Lim, P. De Sousa, M.T. Barbosa, A. Bowman, S. Jorda, A. Rice, H. Raubenheimer, C. Proli, M.E. Cufari, J.C. Ronquillo, A. Kwayie, H. Bhayani, M. Hamilton, Y. Bakar, N. Mensah, L. Ambrose, A. Devaraj, S. Buderi, J. Finch, L. Azcarate, H. Chavan, S. Green, H. Mashinga, A.G. Nicholson, K. Lau, M. Sheaff, P. Schmid, J. Conibear, V. Ezhil, B. Ismail, M. Irvin-sellers, V. Prakash, P. Russell, T. Light, T. Horey, S. Danson, J. Bury, J. Edwards, J. Hill, S. Matthews, Y. Kitsanta, K. Suvarna, P. Fisher, A.D. Keerio, M. Shackcloth, J. Gosney, P. Postmus, S. Feeney, J. Asante-Siaw, Fc-optimized anti-CD25 depletes tumor-infiltrating regulatory T cells and synergizes with PD-1 blockade to eradicate established tumors, Immunity 46 (2017) 577–586, https://doi.org/10.1016/j.immuni.2017.03.013.
[24] T.R. Simpson, F. Li, W. Montalvo-Ortiz, M. a Sepulveda, K. Bergerhoff, F. Arce, C. Roddie, J.Y. Henry, H. Yagita, J.D. Wolchok, K.S. Peggs, J.V. Ravetch, J. P. Allison, S. a Quezada, Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma, J. Exp. Med. 210 (2013) 1695–1710, https://doi.org/10.1084/jem.20130579.
[25] A. Sharma, S.K. Subudhi, J. Blando, J. Scutti, L. Vence, J. Wargo, J.P. Allison, A. Ribas, P. Sharma, Anti-CTLA-4 immunotherapy does not deplete Foxp3 þ regulatory T cells (Tregs) in human cancers, Clin. Cancer Res. 25 (2019) 1233–1238, https://doi.org/10.1158/1078-0432.CCR-18-0762.
[26] C.U. Blank, E.A. Rozeman, L.F. Fanchi, K. Sikorska, B. van de Wiel, P. Kvistborg, O. Krijgsman, M. van den Braber, D. Philips, A. Broeks, J.V. van Thienen, H. A. Mallo, S. Adriaansz, S. ter Meulen, L.M. Pronk, L.G. Grijpink-Ongering, A. Bruining, R.M. Gittelman, S. Warren, H. van Tinteren, D.S. Peeper, J.B.A. G. Haanen, A.C.J. van Akkooi, T.N. Schumacher, Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma, Nat. Med. 24 (2018) 1655–1661, https://doi.org/10.1038/s41591-018-0198-0.
[27] L. Galluzzi, T.A. Chan, G. Kroemer, J.D. Wolchok, A. López-Soto, The hallmarks of successful anticancer immunotherapy, Sci. Transl. Med 10 (2018) eaat7807, https://doi.org/10.1126/scitranslmed.aat7807.
[28] I. Vitale, E. Shema, S. Loi, L. Galluzzi, Intratumoral heterogeneity in cancer progression and response to immunotherapy, Nat. Med. 27 (2021) 212–224, https://doi.org/10.1038/s41591-021-01233-9.
[29] P. Sharma, S. Hu-Lieskovan, J.A. Wargo, A. Ribas, Primary, adaptive, and acquired resistance to cancer immunotherapy, Cell 168 (2017) 707–723, https://doi.org/10.1016/j.cell.2017.01.017.
[30] A.C. Huang, R.J. Orlowski, X. Xu, R. Mick, S.M. George, P.K. Yan, S. Manne, A. A. Kraya, B. Wubbenhorst, L. Dorfman, K. D'Andrea, B.M. Wenz, S. Liu, L. Chilukuri, A. Kozlov, M. Carberry, L. Giles, M.W. Kier, F. Quagliarello, S. McGettigan, K. Kreider, L. Annamalai, Q. Zhao, R. Mogg, W. Xu, W. M. Blumenschein, J.H. Yearley, G.P. Linette, R.K. Amaravadi, L.M. Schuchter, R. S. Herati, B. Bengsch, K.L. Nathanson, M.D. Farwell, G.C. Karakousis, E.J. Wherry, T.C. Mitchell, A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma, Nat. Med. 25 (2019), https://doi.org/10.1038/s41591-019-0357-y.
[31] J. Liu, J.S. O'Donnell, J. Yan, J. Madore, S. Allen, M.J. Smyth, M.W.L. Teng, Timing of neoadjuvant immunotherapy in relation to surgery is crucial for outcome, Oncoimmunology 8 (2019), e1581530, https://doi.org/10.1080/2162402X.2019.1581530.
[32] D. Zamarin, R.B. Holmgaard, S.K. Subudhi, J.S. Park, M. Mansour, P. Palese, T. Merghoub, J.D. Wolchok, J.P. Allison, Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy, Sci. Transl. Med. 6 (2014) 226ra32, https://doi.org/10.1126/scitranslmed.3008095.
[33] J. Liu, E.A. Rozeman, J.S. O'Donnell, S. Allen, L. Fanchi, M.J. Smyth, C.U. Blank, M.W.L. Teng, Batf3 + DCs and type I IFN are critical for the efficacy of neoadjuvant cancer immunotherapy, Oncoimmunology 8 (2019), e1546068, https://doi.org/10.1080/2162402X.2018.1546068.
[34] M.F. Fransen, M. Schoonderwoerd, P. Knopf, M.G.M. Camps, L.J.A.C. Hawinkels, M. Kneilling, T. van Hall, F. Ossendorp, Tumor-draining lymph nodes are pivotal in PD-1/PD-L1 checkpoint therapy, JCI Insight 3 (2018), https://doi.org/10.1172/jci.insight.124507.

[35] Q. Zhang, Y. He, N. Luo, S.J. Patel, Y. Han, R. Gao, M. Modak, S. Carotta, C. Haslinger, D. Kind, G.W. Peet, G. Zhong, S. Lu, W. Zhu, Y. Mao, M. Xiao, M. Bergmann, X. Hu, S.P. Kerkar, A.B. Vogt, S. Pflanz, K. Liu, J. Peng, X. Ren, Z. Zhang, Landscape and dynamics of single immune cells in hepatocellular carcinoma, Cell 179 (2019) 829–845, https://doi.org/10.1016/j.cell.2019.10.003.

[36] A. Zhang, Z. Ren, K.-F. Tseng, X. Liu, H. Li, C. Lu, Y. Cai, J.D. Minna, Y.-X. Fu, Dual targeting of CTLA-4 and CD47 on T reg cells promotes immunity against solid tumors, Sci. Transl. Med. 13 (2021) eabg8693, https://doi.org/10.1126/scitranslmed.abg8693.

[37] M.E.W. Logtenberg, F.A. Scheeren, T.N. Schumacher, The CD47-SIRPα Immune Checkpoint, Immunity 52 (2020) 742–752, https://doi.org/10.1016/j.immuni.2020.04.011.

[38] E.C. Patin, M.T. Dillon, P. Nenclares, L. Grove, H. Soliman, I. Leslie, D. Northcote, G. Bozhanova, E. Crespo-Rodriguez, H. Baldock, H. Whittock, G. Baker, J. Kyula, J. Guevara, A.A. Melcher, J. Harper, H. Ghadially, S. Smith, M. Pedersen, M. McLaughlin, K.J. Harrington, Harnessing radiotherapy-induced NK-cell activity by combining DNA damage–response inhibition and immune checkpoint blockade, J. Immunother. Cancer 10 (2022), e004306, https://doi.org/10.1136/jitc-2021-004306.

[39] I. Etxeberria, E. Bolaños, A. Teijeira, S. Garasa, A. Yanguas, A. Azpilikueta, W. M. Kavanaugh, O. Vasiljeva, M. Belvin, B. Howng, B. Irving, K. Tipton, J. West, L. Mei, A.J. Korman, E. Sega, I. Olivera, A. Cirella, M.C. Ochoa, M.E. Rodriguez, A. Melero, M.F. Sanmamed, J.J. Engelhardt, I. Melero, Antitumor efficacy and reduced toxicity using an anti-CD137 Probody therapeutic, Proc. Natl. Acad. Sci. 118 (2021), e2025930118, https://doi.org/10.1073/pnas.2025930118.

[40] J. Brooks, B. Fleischmann-Mundt, N. Woller, J. Niemann, S. Ribback, K. Peters, I. E. Demir, N. Armbrecht, G.O. Ceyhan, M.P. Manns, T.C. Wirth, S. Kubicka, G. Bernhardt, M.J. Smyth, D.F. Calvisi, E. Gürlevik, F. Kühnel, Perioperative, spatiotemporally coordinated activation of T and NK cells prevents recurrence of pancreatic cancer, Cancer Res 78 (2018) 475–488, https://doi.org/10.1158/0008-5472.CAN-17-2415.

[41] M.E. Rodriguez-Ruiz, I. Vitale, K.J. Harrington, I. Melero, L. Galluzzi, Immunological impact of cell death signaling driven by radiation on the tumor microenvironment, Nat. Immunol. 21 (2020) 120–134, https://doi.org/10.1038/s41590-019-0561-4.

[42] G. Petroni, A. Buqué, L. Zitvogel, G. Kroemer, L. Galluzzi, Immunomodulation by targeted anticancer agents, Cancer Cell 39 (2021) 310–345, https://doi.org/10.1016/j.ccell.2020.11.009.

[43] J. Laengle, J. Kabiljo, L. Hunter, J. Homola, S. Prodinger, G. Egger, M. Bergmann, Histone deacetylase inhibitors valproic acid and vorinostat enhance trastuzumab-mediated antibody-dependent cell-mediated phagocytosis, J. Immunother. Cancer 8 (2020), e000195, https://doi.org/10.1136/jitc-2019-000195.

[44] O. Kepp, A. Marabelle, L. Zitvogel, G. Kroemer, Oncolysis without viruses — inducing systemic anticancer immune responses with local therapies, Nat. Rev. Clin. Oncol. 17 (2020) 49–64, https://doi.org/10.1038/s41571-019-0272-7.

[45] L. Galluzzi, A. Buqué, O. Kepp, L. Zitvogel, G. Kroemer, Immunological effects of conventional chemotherapy and targeted anticancer agents, Cancer Cell 28 (2015) 690–714, https://doi.org/10.1016/j.ccell.2015.10.012.

[46] N. Casares, M.O. Pequignot, A. Tesniere, F. Ghiringhelli, S. Roux, N. Chaput, E. Schmitt, A. Hamai, S. Hervas-Stubbs, M. Obeid, F. Coutant, D. Métivier, E. Pichard, P. Aucouturier, G. Pierron, C. Garrido, L. Zitvogel, G. Kroemer, Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death, J. Exp. Med. 202 (2005) 1691–1701, https://doi.org/10.1084/jem.20050915.

[47] L. Apetoh, F. Ghiringhelli, A. Tesniere, M. Obeid, C. Ortiz, A. Criollo, G. Mignot, M.C. Maiuri, E. Ullrich, P. Saulnier, H. Yang, S. Amigorena, B. Ryffel, F.J. Barrat, P. Saftig, F. Levi, R. Lidereau, C. Nogues, J.-P. Mira, A. Chompret, V. Joulin, F. Clavel-Chapelon, J. Bourhis, F. André, S. Delaloge, T. Tursz, G. Kroemer, L. Zitvogel, Toll-like receptor 4–dependent contribution of the immune system to anticancer chemotherapy and radiotherapy, Nat. Med. 13 (2007) 1050–1059, https://doi.org/10.1038/nm1622.

[48] D. Hannani, C. Locher, T. Yamazaki, V. Colin-Minard, M. Vetizou, L. Aymeric, S. Viaud, D. Sanchez, M.J. Smyth, P. Bruhns, G. Kroemer, L. Zitvogel, Contribution of humoral immune responses to the antitumor effects mediated by anthracyclines, Cell Death Differ. 21 (2014) 50–58, https://doi.org/10.1038/cdd.2013.60.

[49] F. Ghiringhelli, C. Menard, P.E. Puig, S. Ladoire, S. Roux, F. Martin, E. Solary, A. Le Cesne, L. Zitvogel, B. Chauffert, Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients, Cancer Immunol. Immunother. 56 (2007) 641–648, https://doi.org/10.1007/s00262-006-0225-8.

[50] S. Viaud, F. Saccheri, G. Mignot, T. Yamazaki, R. Daillere, D. Hannani, D.P. Enot, C. Pfirschke, C. Engblom, M.J. Pittet, A. Schlitzer, F. Ginhoux, L. Apetoh, E. Chachaty, P.-L. Woerther, G. Eberl, M. Berard, C. Ecobichon, D. Clermont, C. Bizet, V. Gaboriau-Routhiau, N. Cerf-Bensussan, P. Opolon, N. Yessaad, E. Vivier, B. Ryffel, C.O. Elson, J. Dore, G. Kroemer, P. Lepage, I.G. Boneca, F. Ghiringhelli, L. Zitvogel, The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide, Science 342 (2013) 971–976, https://doi.org/10.1126/science.1240537.

[51] L. Fournel, Z. Wu, N. Stadler, D. Damotte, F. Lococo, G. Boulle, E. Ségal-Bendirdjian, A. Bobbio, P. Icard, J. Trédaniel, M. Alifano, P. Forgez, Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer, Cancer Lett. 464 (2019) 5–14, https://doi.org/10.1016/j.canlet.2019.08.005.

[52] W. Peng, L.J. Williams, C. Xu, B. Melendez, J.A. McKenzie, Y. Chen, H.L. Jackson, K.S. Voo, R.M. Mbofung, S.E. Leahey, J. Wang, G. Lizee, H.A. Tawbi, M.A. Davies, A. Hoos, J. Smothers, R. Srinivasan, E.M. Paul, N. Yanamandra, P. Hwu, Anti-OX40 antibody directly enhances the function of tumor-reactive CD8 + T cells and synergizes with PI3Kβ inhibition in PTEN loss melanoma, Clin. Cancer Res. 25 (2019) 6406–6416, https://doi.org/10.1158/1078-0432.CCR-19-1259.

[53] L. Tran, C.T. Allen, R. Xiao, E. Moore, R. Davis, S.-J. Park, K. Spielbauer, C. Van Waes, N.C. Schmitt, Cisplatin alters antitumor immunity and synergizes with PD-1/PD-L1 inhibition in head and neck squamous cell carcinoma, cancer, Immunol. Res 5 (2017) 1141–1151, https://doi.org/10.1158/2326-6066.CIR-17-0235.

[54] J. Stift, A. Graf, B. Neudert, M. Herac, K. Woeran, D. Tamandl, J. Laengle, C. Schwarz, F. Wrba, K. Kaczirek, S. Stremitzer, Immune checkpoints and liver resection after neoadjuvant chemotherapy including bevacizumab in patients with microsatellite-stable colorectal liver metastases, HPB (2021), https://doi.org/10.1016/j.hpb.2021.05.015.

[55] C. Pfirschke, C. Engblom, S. Rickelt, V. Cortez-Retamozo, C. Garris, F. Pucci, T. Yamazaki, V. Poirier-Colame, A. Newton, Y. Redouane, Y.-J. Lin, G. Wojtkiewicz, Y. Iwamoto, M. Mino-Kenudson, T.G. Huynh, R.O. Hynes, G. J. Freeman, G. Kroemer, L. Zitvogel, R. Weissleder, M.J. Pittet, Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy, Immunity 44 (2016) 343–354, https://doi.org/10.1016/j.immuni.2015.11.024.

[56] K. Otsuka, A. Mitsuhashi, H. Goto, M. Hanibuchi, K. Koyama, H. Ogawa, H. Ogino, A. Saijo, H. Kozai, H. Yoneda, M. Tobiume, M. Kishuku, K. Ishizawa, Y. Nishioka, Anti-PD-1 antibody combined with chemotherapy suppresses the growth of mesothelioma by reducing myeloid-derived suppressor cells, Lung Cancer 146 (2020) 86–96, https://doi.org/10.1016/j.lungcan.2020.05.023.

[57] R. Stewart, M. Morrow, S.A. Hammond, K. Mulgrew, D. Marcus, E. Poon, A. Watkins, S. Mullins, M. Chodorge, J. Andrews, D. Bannister, E. Dick, N. Crawford, J. Parmentier, M. Alimzhanov, J.S. Babcook, I.N. Foltz, A. Buchanan, V. Bedian, R.W. Wilkinson, M. McCourt, Identification and characterization of MEDI4736, an antagonistic anti–PD-L1 monoclonal antibody, Cancer Immunol. Res 3 (2015) 1052–1062, https://doi.org/10.1158/2326-6066.CIR-14-0191.

[58] H. Fukushima, S. Yoshida, T. Kijima, Y. Nakamura, S. Fukuda, S. Uehara, Y. Yasuda, H. Tanaka, M. Yokoyama, Y. Matsuoka, Y. Fujii, Combination of cisplatin and irradiation induces immunogenic cell death and potentiates postirradiation Anti–PD-1 treatment efficacy in urothelial carcinoma, Int. J. Mol. Sci. 22 (2021) 535, https://doi.org/10.3390/ijms22020535.

[59] P. Kroon, E. Frijlink, V. Iglesias-Guimarais, A. Volkov, M.M. van Buuren, T. N. Schumacher, M. Verheij, J. Borst, I. Verbrugge, Radiotherapy and cisplatin increase immunotherapy efficacy by enabling local and systemic intratumoral T-cell activity, Cancer Immunol. Res 7 (2019) 670–682, https://doi.org/10.1158/2326-6066.CIR-18-0654.

[60] X. Hao, B. Zhao, W. Zhou, H. Liu, T. Fukumoto, D. Gabrilovich, R. Zhang, Sensitization of ovarian tumor to immune checkpoint blockade by boosting senescence-associated secretory phenotype, IScience 24 (2021), 102016, https://doi.org/10.1016/j.isci.2020.102016.

[61] Y. Lee, S.L. Auh, Y. Wang, B. Burnette, Y. Wang, Y. Meng, M. Beckett, R. Sharma, R. Chin, T. Tu, R.R. Weichselbaum, Y.-X. Fu, Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment, Blood 114 (2009) 589–595, https://doi.org/10.1182/blood-2009-02-206870.

[62] S. Matsumura, B. Wang, N. Kawashima, S. Braunstein, M. Badura, T.O. Cameron, J.S. Babb, R.J. Schneider, S.C. Formenti, M.L. Dustin, S. Demaria, Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells, J. Immunol. 181 (2008) 3099–3107, https://doi.org/10.4049/jimmunol.181.5.3099.

[63] H. Chen, L. Xu, L. Li, X. Liu, J. Gao, Y. Bai, Inhibiting the CD8+ T cell infiltration in the tumor microenvironment after radiotherapy is an important mechanism of radioresistance, Sci. Rep. 8 (2018) 11934, https://doi.org/10.1038/s41598-018-30417-6.

[64] R. Ganss, E. Ryschich, E. Klar, B. Arnold, G.J. Hämmerling, Workshop R: tumor immunology, abstract R1 bis R30, Immunobiology 204 (2001) 289–309, https://doi.org/10.1078/0171-2985-00078.

[65] A. Uryvaev, M. Passhak, D. Hershkovits, E. Sabo, G. Bar-Sela, The role of tumor-infiltrating lymphocytes (TILs) as a predictive biomarker of response to anti-PD1 therapy in patients with metastatic non-small cell lung cancer or metastatic melanoma, Med. Oncol. 35 (2018) 25, https://doi.org/10.1007/s12032-018-1080-0.

[66] K.H. Young, J.R. Baird, T. Savage, B. Cottam, D. Friedman, S. Bambina, D. J. Messenheimer, B. Fox, P. Newell, K.S. Bahjat, M.J. Gough, M.R. Crittenden, Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy, PLoS One 11 (2016), e0157164, https://doi.org/10.1371/journal.pone.0157164.

[67] C. Twyman-Saint Victor, A.J. Rech, A. Maity, R. Rengan, K.E. Pauken, E. Stelekati, J.L. Benci, B. Xu, H. Dada, P.M. Odorizzi, R.S. Herati, K.D. Mansfield, D. Patsch, R.K. Amaravadi, L.M. Schuchter, H. Ishwaran, R. Mick, D.A. Pryma, X. Xu, M.D. Feldman, T.C. Gangadhar, S.M. Hahn, E.J. Wherry, R.H. Vonderheide, A.J. Minn, Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer, Nature 520 (2015) 373–377, https://doi.org/10.1038/nature14292.

[68] S.M. Hiniker, S.A. Reddy, H.T. Maecker, P.B. Subrahmanyam, Y. Rosenberg-Hasson, S.M. Swetter, S. Saha, L. Shura, S.J. Knox, A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma, Int. J. Radiat. Oncol. 96 (2016) 578–588, https://doi.org/10.1016/j.ijrobp.2016.07.005.

[69] S.J. Dovedi, A.L. Adlard, G. Lipowska-Bhalla, C. McKenna, S. Jones, E.J. Cheadle, I.J. Stratford, E. Poon, M. Morrow, R. Stewart, H. Jones, R.W. Wilkinson,

J. Honeychurch, T.M. Illidge, Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade, Cancer Res 74 (2014) 5458–5468, https://doi.org/10.1158/0008-5472.CAN-14-1258.
[70] K.R. Patel, S. Shoukat, D.E. Oliver, M. Chowdhary, M. Rizzo, D.H. Lawson, F. Khosa, Y. Liu, M.K. Khan, Ipilimumab and stereotactic radiosurgery versus stereotactic radiosurgery alone for newly diagnosed melanoma brain metastases, Am. J. Clin. Oncol. 40 (2017) 444–450, https://doi.org/10.1097/COC.0000000000000199.
[71] O. Cohen-Inbar, H.-H. Shih, Z. Xu, D. Schlesinger, J.P. Sheehan, The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab, J. Neurosurg. 127 (2017) 1007–1014, https://doi.org/10.3171/2016.9.JNS161585.
[72] H. Schmidberger, M. Rapp, A. Ebersberger, S. Hey-Koch, C. Loquai, S. Grabbe, A. Mayer, Long-term survival of patients after ipilimumab and hypofractionated brain radiotherapy for brain metastases of malignant melanoma: sequence matters, Strahlenther. Und Onkol. 194 (2018) 1144–1151, https://doi.org/10.1007/s00066-018-1356-5.
[73] J.M. Qian, J.B. Yu, H.M. Kluger, V.L.S. Chiang, Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery, Cancer 122 (2016) 3051–3058, https://doi.org/10.1002/cncr.30138.
[74] R. Kotecha, J.M. Kim, J.A. Miller, A. Juloori, S.T. Chao, E.S. Murphy, D. M. Peereboom, A.M. Mohammadi, G.H. Barnett, M.A. Vogelbaum, L. Angelov, J. H. Suh, M.S. Ahluwalia, The impact of sequencing PD-1/PD-L1 inhibitors and stereotactic radiosurgery for patients with brain metastasis, Neuro Oncol. 21 (2019) 1060–1068, https://doi.org/10.1093/neuonc/noz046.
[75] E. Ladomersky, L. Zhai, A. Lenzen, K.L. Lauing, J. Qian, D.M. Scholtens, G. Gritsina, X. Sun, Y.Y. Liu, F. Yu, W. Gong, Y.Y. Liu, B. Jiang, T. Tang, R. Patel, L.C. Platanias, C.D. James, R. Stupp, R.V. Lukas, D.C. Binder, D.A. Wainwright, IDO1 inhibition synergizes with radiation and PD-1 blockade to durably increase survival against advanced glioblastoma, Clin. Cancer Res. 24 (2018) 2559–2573, https://doi.org/10.1158/1078-0432.CCR-17-3573.
[76] A. Oweida, M.K. Hararah, A. Phan, D. Binder, S. Bhatia, S. Lennon, S. Bukkapatnam, B. Van Court, N. Uyanga, L. Darragh, H.M. Kim, D. Raben, A. C. Tan, L. Heasley, E. Clambey, R. Nemenoff, S.D. Karam, Resistance to radiotherapy and PD-L1 blockade is mediated by TIM-3 upregulation and regulatory T-cell infiltration, Clin. Cancer Res. 24 (2018) 5368–5380, https://doi.org/10.1158/1078-0432.CCR-18-1038.
[77] S. Demaria, C. Guha, J. Schoenfeld, Z. Morris, A. Monjazeb, A. Sikora, M. Crittenden, S. Shiao, S. Khleif, S. Gupta, S.C. Formenti, B. Vikram, C. N. Coleman, M.M. Ahmed, Radiation dose and fraction in immunotherapy: one-size regimen does not fit all settings, so how does one choose? J. Immunother. Cancer 9 (2021), e002038 https://doi.org/10.1136/jitc-2020-002038.
[78] M. Morisada, P.E. Clavijo, E. Moore, L. Sun, M. Chamberlin, C. Van Waes, J. W. Hodge, J.B. Mitchell, J. Friedman, C.T. Allen, PD-1 blockade reverses adaptive immune resistance induced by high-dose hypofractionated but not low-dose daily fractionated radiation, Oncoimmunology 7 (2018), e1395996, https://doi.org/10.1080/2162402X.2017.1395996.
[79] C. Vanpouille-Box, A. Alard, M.J. Aryankalayil, Y. Sarfraz, J.M. Diamond, R. J. Schneider, G. Inghirami, C.N. Coleman, S.C. Formenti, S. Demaria, DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity, Nat. Commun. 8 (2017) 15618, https://doi.org/10.1038/ncomms15618.
[80] J.M. Diamond, C. Vanpouille-Box, S. Spada, N.-P. Rudqvist, J.R. Chapman, B. M. Ueberheide, K.A. Pilones, Y. Sarfraz, S.C. Formenti, S. Demaria, Exosomes shuttle TREX1-Sensitive IFN-Stimulatory dsDNA from Irradiated Cancer Cells to DCs, Cancer Immunol. Res 6 (2018) 910–920, https://doi.org/10.1158/2326-6066.CIR-17-0581.
[81] G. Minniti, D. Anzellini, C. Reverberi, G.C.A. Cappellini, L. Marchetti, F. Bianciardi, A. Bozzao, M. Osti, P.C. Gentile, V. Esposito, Stereotactic radiosurgery combined with nivolumab or Ipilimumab for patients with melanoma brain metastases: evaluation of brain control and toxicity, J. Immunother. Cancer 7 (2019) 102, https://doi.org/10.1186/s40425-019-0588-y.
[82] A.E. Marciscano, A. Ghasemzadeh, T.R. Nirschl, D. Theodros, C.M. Kochel, B. J. Francica, Y. Muroyama, R.A. Anders, A.B. Sharabi, E. Velarde, W. Mao, K. R. Chaudhary, M.G. Chaimowitz, J. Wong, M.J. Selby, K.B. Thudium, A. J. Korman, D. Ulmert, D.L.J. Thorek, T.L. DeWeese, C.G. Drake, Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy, Clin. Cancer Res. 24 (2018) 5058–5071, https://doi.org/10.1158/1078-0432.CCR-17-3427.
[83] A. Samson, K.J. Scott, D. Taggart, E.J. West, E. Wilson, G.J. Nuovo, S. Thomson, R. Corns, R.K. Mathew, M.J. Fuller, T.J. Kottke, J.M. Thompson, E.J. Ilett, J. V. Cockle, P. Van Hille, S. Gnanamurthy, E.S. Polson, S.J. Turnbull, E.S. Appleton, G. Migneco, A. Rose, M.C. Coffey, D.A. Beirne, F.J. Collinson, R. Christy, D. A. Anthoney, C.J. Twelves, A.J. Furness, S.A. Quezada, H. Wurdak, F. Errington-Mais, H. Pandha, K.J. Harrington, P.J. Selby, R.G. Vile, S.D. Griffin, L.F. Stead, S. C. Short, A.A. Melcher, Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade, Sci. Transl. Med. 10 (2018) eaam7577, https://doi.org/10.1126/scitranslmed.aam7577.
[84] P. Msaouel, M. Opyrchal, A. Dispenzieri, K.W. Peng, M.J. Federspiel, S.J. Russell, E. Galanis, Clinical trials with oncolytic measles virus: current status and future prospects, Curr. Cancer Drug Targets 18 (2018) 177–187, https://doi.org/10.2174/1568009617666170222125035.
[85] M. Bergmann, I. Romirer, M. Sachet, R. Fleischhacker, A. García-Sastre, P. Palese, K. Wolff, H. Pehamberger, R. Jakesz, T. Muster, I. Romirer, K. Wolff, H. Pehamberger, T. Muster, A. Garc, A Sastre, P. Palese, A genetically engineered influenza A virus with ras-dependent oncolytic properties, Cancer Res 61 (2001) 8188–8193. ⟨http://cancerres.aacrjournals.org/content/61/22/8188.short⟩.
[86] F.F. Lang, C. Conrad, C. Gomez-Manzano, W.K.A. Yung, R. Sawaya, J. S. Weinberg, S.S. Prabhu, G. Rao, G.N. Fuller, K.D. Aldape, J. Gumin, L.M. Vence, I. Wistuba, J. Rodriguez-Canales, P.A. Villalobos, C.M.F. Dirven, S. Tejada, R. D. Valle, M.M. Alonso, B. Ewald, J.J. Peterkin, F. Tufaro, J. Fueyo, Phase I Study of DNX-2401 (Delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma, J. Clin. Oncol. 36 (2018) 1419–1427, https://doi.org/10.1200/JCO.2017.75.8219.
[87] J. Heo, T. Reid, L. Ruo, C.J. Breitbach, S. Rose, M. Bloomston, M. Cho, H.Y. Lim, H.C. Chung, C.W. Kim, J. Burke, R. Lencioni, T. Hickman, A. Moon, Y.S. Lee, M. K. Kim, M. Daneshmand, K. Dubois, L. Longpre, M. Ngo, C. Rooney, J.C. Bell, B.-G. Rhee, R. Patt, T.-H. Hwang, D.H. Kirn, Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer, Nat. Med. 19 (2013) 329–336, https://doi.org/10.1038/nm.3089.
[88] R.H.I.I. Andtbacka, H.L. Kaufman, F. Collichio, T. Amatruda, N. Senzer, J. Chesney, K. a Delman, L.E. Spitler, I. Puzanov, S.S. Agarwala, M. Milhem, L. Cranmer, B. Curti, K. Lewis, M. Ross, T. Guthrie, G.P. Linette, G. a Daniels, K. Harrington, M.R. Middleton, W.H. Miller, J.S. Zager, Y. Ye, B. Yao, A. Li, S. Doleman, A. Van Der Walde, J. Gansert, R.S. Coffin, a VanderWalde, J. Gansert, R.S. Coffin, Talimogene laherparepvec improves durable response rate in patients with advanced melanoma, J. Clin. Oncol. 33 (2015) 2780–2788, https://doi.org/10.1200/JCO.2014.58.3377.
[89] H.L. Kaufman, F.J. Kohlhapp, A. Zloza, Oncolytic viruses: a new class of immunotherapy drugs, Nat. Rev. Drug Discov. 14 (2015) 642–662, https://doi.org/10.1038/nrd4663.
[90] K. Hock, J. Laengle, I. Kuznetsova, A. Egorov, B. Hegedus, B. Dome, T. Wekerle, M. Sachet, M. Bergmann, Oncolytic influenza A virus expressing interleukin-15 decreases tumor growth in vivo, Surgery 161 (2017) 735–746, https://doi.org/10.1016/j.surg.2016.08.045.
[91] S.-N. Zhang, I.-K. Choi, J.-H. Huang, J.-Y. Yoo, K.-J. Choi, C.-O. Yun, Optimizing DC vaccination by combination with oncolytic adenovirus coexpressing IL-12 and GM-CSF, Mol. Ther. 19 (2011) 1558–1568, https://doi.org/10.1038/mt.2011.29.
[92] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (2013) 1–10, https://doi.org/10.1016/j.immuni.2013.07.012.
[93] C.I. Liakou, A. Kamat, D.N. Tang, H. Chen, J. Sun, P. Troncoso, C. Logothetis, P. Sharma, CTLA-4 blockade increases IFN -producing CD4+ICOShi cells to shift the ratio of effector to regulatory T cells in cancer patients, Proc. Natl. Acad. Sci. 105 (2008) 14987–14992, https://doi.org/10.1073/pnas.0806075105.
[94] P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y. H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, J. O'Shaughnessy, Pembrolizumab for early triple-negative breast cancer, N. Engl. J. Med. 382 (2020) 810–821, https://doi.org/10.1056/NEJMoa1910549.
[95] E.A. Mittendorf, H. Zhang, C.H. Barrios, S. Saji, K.H. Jung, R. Hegg, A. Koehler, J. Sohn, H. Iwata, M.L. Telli, C. Ferrario, K. Punie, F. Penault-Llorca, S. Patel, A. N. Duc, M. Liste-Hermoso, V. Maiya, L. Molinero, S.Y. Chui, N. Harbeck, Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 tria, Lancet 396 (2020) 1090–1100, https://doi.org/10.1016/S0140-6736(20)31953-X.
[96] P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, J. O'Shaughnessy, VP7-2021: KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC, Ann. Oncol. 32 (2021) 1198–1200, https://doi.org/10.1016/j.annonc.2021.06.014.
[97] P.M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann, M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez, N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang, J. X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson, H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube, V. E. Velculescu, S.L. Topalian, J.R. Brahmer, D.M. Pardoll, Neoadjuvant PD-1 blockade in resectable lung cancer, New Engl. J. Med. 378 (2018) 1976–1986, https://doi.org/10.1056/NEJMoa1716078.
[98] D.J. Kwiatkowski, V.W. Rusch, J.E. Chaft, B.E. Johnson, A. Nicholas, I.I. Wistuba, R. Merritt, J.M. Lee, P.A. Bunn, Y. Tang, S.-C. Phan, S.N. Waqar, A. Patterson, E. B. Haura, E.M. Toloza, K.L. Reckamp, D. Raz, K. Schulze, A. Johnson, D. P. Carbone, Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3), J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.8503.
[99] S. Peters, A.W. Kim, B. Solomon, D.R. Gandara, R. Dziadziuszko, A. Brunelli, M. C. Garassino, M. Reck, L. Wang, I. To, S.W. Sun, B.J. Gitlitz, A. Sandler, N. Rizvi, IMpower030: Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy, Ann. Oncol. 30 (2019) ii30, https://doi.org/10.1093/annonc/mdz064.014.
[100] P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S. Broderick, J. Brahmer, S.J. Swanson, K. Kerr, C. Wang, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, C. Dorange, J. Cai, J. Fiore, N. Girard, Abstract CT003: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial, Cancer Res 81 (2021), https://doi.org/10.1158/1538-7445.AM2021-CT003.

[101] J. Spicer, C. Wang, F. Tanaka, G.B. Saylors, K.-N. Chen, M. Liberman, E.E. Vokes, N. Girard, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, P.M. Forde, S. Swanson, J.R. Brahmer, K. Kerr, C. Dorange, J. Cai, S. Broderick, Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC), J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.8503.

[102] A.M. Menzies, R.N. Amaria, E.A. Rozeman, A.C. Huang, M.T. Tetzlaff, B.A. van de Wiel, S. Lo, A.A. Tarhini, E.M. Burton, T.E. Pennington, R.P.M. Saw, X. Xu, G. C. Karakousis, P.A. Ascierto, A.J. Spillane, A.C.J. van Akkooi, M.A. Davies, T. C. Mitchell, H.A. Tawbi, R.A. Scolyer, J.A. Wargo, C.U. Blank, G.V. Long, Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC), Nat. Med. 27 (2021) 301–309, https://doi.org/10.1038/s41591-020-01188-3.

[103] E.A. Rozeman, E.P. Hoefsmit, I.L.M. Reijers, R.P.M. Saw, J.M. Versluis, O. Krijgsman, P. Dimitriadis, K. Sikorska, B.A. van de Wiel, H. Eriksson, M. Gonzalez, A. Torres Acosta, L.G. Grijpink-Ongering, K. Shannon, J.B.A. G. Haanen, J. Stretch, S. Ch'ng, O.E. Nieweg, H.A. Mallo, S. Adriaansz, R. M. Kerkhoven, S. Cornelissen, A. Broeks, W.M.C. Klop, C.L. Zuur, W.J. van Houdt, D.S. Peeper, A.J. Spillane, A.C.J. van Akkooi, R.A. Scolyer, T.N.M. Schumacher, A. M. Menzies, G.V. Long, C.U. Blank, Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma, Nat. Med. 27 (2021) 256–263, https://doi.org/10.1038/s41591-020-01211-7.

[104] A. Necchi, A. Anichini, D. Raggi, A. Briganti, S. Massa, R. Lucianò, M. Colecchia, P. Giannatempo, R. Mortarini, M. Bianchi, E. Farè, F. Monopoli, R. Colombo, A. Gallina, A. Salonia, A. Messina, S.M. Ali, R. Madison, J.S. Ross, J.H. Chung, R. Salvioni, L. Mariani, F. Montorsi, Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study, J. Clin. Oncol. 36 (2018) 3353–3360, https://doi.org/10.1200/JCO.18.01148.

[105] T. Powles, A. Rodriguez-Vida, I. Duran, S.J. Crabb, M.S. Van Der Heijden, A. Font Pous, G. Gravis, U. Anido Herranz, A. Protheroe, A. Ravaud, D. Maillet, M. J. Mendez-Vidal, C. Suarez, A. Lorch, C.N. Sternberg, M.D. Linch, S.-J. Sarker, A. Prendergast, K. Mousa, D.E. Castellano, A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS), J. Clin. Oncol. 36 (2018), https://doi.org/10.1200/JCO.2018.36.15_suppl.4506.

[106] N. Van Dijk, A. Gil Jimenez, K. Silina, K. Hendricksen, L. Smit, J. De Feijter, M. L. van Montfoort, A. Broeks, Y. Lubeck, K. Sikorska, T.N. Boellaard, P. Kvistborg, D.J. Vis, E. Hooijberg, T. Schumacher, M. van den Broek, L.F. Wessels, C.U. Blank, B.W.G. van Rhijn, M.S. Van Der Heijden, Biomarker analysis and updated clinical follow-up of preoperative ipilimumab (ipi) plus nivolumab (nivo) in stage III urothelial cancer (NABUCCO), J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.15_suppl.5020.

[107] P. Singh, C. Tangen, J.A. Efstathiou, S.P. Lerner, S.G. Jhavar, N.M. Hahn, B. A. Costello, S.S. Sridhar, W. Du, J.J. Meeks, B.M. Faltas, P. Grivas, F.Y. Feng, R. C. Chen, A.K. Morgans, A. Gupta, R.C. Bangs, K.A. Winter, N.J. Vogelzang, I. M. Thompson, INTACT: phase III randomized trial of concurrent chemoradiotherapy with or without atezolizumab in localized muscle invasive bladder cancer—SWOG/NRG1806, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.6_suppl.TPS586.

[108] A.V. Balar, N.D. James, S.F. Shariat, N.D. Shore, M.S. Van Der Heijden, A. J. Weickhardt, X. Fang, J.L. Godwin, E. Kapadia, J.M. Michalski, Phase III study of pembrolizumab (pembro) plus chemoradiotherapy (CRT) versus CRT alone for patients (pts) with muscle-invasive bladder cancer (MIBC): KEYNOTE-992. J. Clin. Oncol. 38 (2020) https://doi.org/10.1200/JCO.2020.38.15_suppl.TPS5093.

[109] S.A. Funt, M. Lattanzi, K. Whiting, H.A. Al-Ahmadie, C. Quinlan, M.Y. Teo, J. Kamradt, M.F. Khalil, I. Ostrovnaya, A.S. McCoy, G. Hettich, M. Jihad, E. Folefac, W.C. Huang, D.F. Bajorin, G. Iyer, B.H. Bochner, A.V. Balar, A. Mortazavi, J.E. Rosenberg, Neoadjuvant atezolizumab (A) with gemcitabine and cisplatin (GC) in patients (pts) with muscle-invasive bladder cancer (MIBC): a multicenter, single-arm, phase 2 trial, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.4517.

[110] R. Uppaluri, R. Chernock, M. Mansour, R. Jackson, J. Rich, P. Pipkorn, R. C. Paniello, S. Puram, J.P. Zevallos, D.J. Annino, L.A. Goguen, L. Morris, R. I. Haddad, G.J. Hanna, P.J. Oppelt, L. Dunn, J.C. Ley, D. Kallogjeri, A.M. Egloff, D. Adkins, Enhanced pathologic tumor response with two cycles of neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV-negative head and neck squamous cell carcinoma (HNSCC), J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.6008.

[111] K.A. Schalper, M.E. Rodriguez-Ruiz, R. Diez-Valle, A. López-Janeiro, A. Porciuncula, M.A. Idoate, S. Inogés, C. de Andrea, A. López-Diaz de Cerio, S. Tejada, P. Berraondo, F. Villarroel-Espindola, J. Choi, A. Gúrpide, M. Giraldez, I. Goicoechea, J. Gallego Perez-Larraya, M.F. Sanmamed, J.L. Perez-Gracia, I. Melero, Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma, Nat. Med. 25 (2019) 470–476, https://doi.org/10.1038/s41591-018-0339-5.

[112] T.F. Cloughesy, A.Y. Mochizuki, J.R. Orpilla, W. Hugo, A.H. Lee, T.B. Davidson, A.C. Wang, B.M. Ellingson, J.A. Rytlewski, C.M. Sanders, E.S. Kawaguchi, L. Du, G. Li, W.H. Yong, S.C. Gaffey, A.L. Cohen, I.K. Mellinghoff, E.Q. Lee, D. A. Reardon, B.J. O'Brien, N.A. Butowski, P.L. Nghiemphu, J.L. Clarke, I. C. Arrillaga-Romany, H. Colman, T.J. Kaley, J.F. de Groot, L.M. Liau, P.Y. Wen, R. M. Prins, Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma, Nat. Med. 25 (2019) 477–486, https://doi.org/10.1038/s41591-018-0337-7.

[113] R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, M. Moehler, Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer, New Engl. J. Med. 384 (2021) 1191–1203, https://doi.org/10.1056/NEJMoa2032125.

[114] D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A. D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D. M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R. A. Anders, J.R. Eshleman, B. Vogelstein, L.A. Diaz, PD-1 Blockade in Tumors with Mismatch-Repair Deficiency, N. Engl. J. Med. 372 (2015) 2509–2520, https://doi.org/10.1056/NEJMoa1500596.

[115] M. Kloor, M. von Knebel Doeberitz, The immune biology of microsatellite-unstable cancer, Trends Cancer 2 (2016) 121–133, https://doi.org/10.1016/j.trecan.2016.02.004.

[116] G. Germano, S. Lamba, G. Rospo, L. Barault, A. Magrì, F. Maione, M. Russo, G. Crisafulli, A. Bartolini, G. Lerda, G. Siravegna, B. Mussolin, R. Frapolli, M. Montone, F. Morano, F. de Braud, N. Amirouchene-Angelozzi, S. Marsoni, M. D'Incalci, A. Orlandi, E. Giraudo, A. Sartore-Bianchi, S. Siena, F. Pietrantonio, F. Di Nicolantonio, A. Bardelli, Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth, Nature 552 (2017) 116–120, https://doi.org/10.1038/nature24673.

[117] T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, L.A. Diaz, Pembrolizumab in microsatellite-instability–high advanced colorectal cancer, N. Engl. J. Med. 383 (2020) 2207–2218, https://doi.org/10.1056/NEJMoa2017699.

[118] D.-X. Liu, D.-D. Li, W. He, C.-F. Ke, W. Jiang, J.-H. Tang, L.-H. Kong, Y. Li, Q.-Q. Sui, B.-Y. Xiao, W.-R. Li, Z.-G. Hong, R.-H. Xu, Z.-Z. Pan, X.-S. Zhang, P.-R. Ding, PD-1 blockade in neoadjuvant setting of DNA mismatch repair-deficient/microsatellite instability-high colorectal cancer, Oncoimmunology 9 (2020), 1711650, https://doi.org/10.1080/2162402X.2020.1711650.

[119] P. Kanikarla Marie, C. Haymaker, E.R. Parra, Y.U. Kim, R. Lazcano, S. Gite, D. Lorenzini, I.I. Wistuba, R.S.S. Tidwell, X. Song, W.C. Foo, D.M. Maru, Y. S. Chun, A. Futreal, B. Kee, D. Menter, L. Solis, C.-W. Tzeng, C. Parseghian, K. Raghav, V. Morris, C.-C. Chang, R. Jenq, A. Tam, C. Bernatchez, S. Kopetz, J.-N. Vauthey, M.J. Overman, Pilot clinical trial of perioperative durvalumab and tremelimumab in the treatment of resectable colorectal cancer liver metastases, Clin. Cancer Res 27 (2021) 3039–3049, https://doi.org/10.1158/1078-0432.CCR-21-0163.

[120] M. Chalabi, L.F. Fanchi, K.K. Dijkstra, J.G. Van den Berg, A.G. Aalbers, K. Sikorska, M. Lopez-Yurda, C. Grootscholten, G.L. Beets, P. Snaebjornsson, M. Maas, M. Mertz, V. Veninga, G. Bounova, A. Broeks, R.G. Beets-Tan, T.R. de Wijkerslooth, A.U. van Lent, H.A. Marsman, E. Nuijten, N.F. Kok, M. Kuiper, W. H. Verbeek, M. Kok, M.E. Van Leerdam, T.N. Schumacher, E.E. Voest, J. B. Haanen, Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers, Nat. Med. 26 (2020) 566–576, https://doi.org/10.1038/s41591-020-0805-8.

[121] G. Argilés, J. Tabernero, R. Labianca, D. Hochhauser, R. Salazar, T. Iveson, P. Laurent-Puig, P. Quirke, T. Yoshino, J. Taieb, E. Martinelli, D. Arnold, Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 31 (2020) 1291–1305, https://doi.org/10.1016/j.annonc.2020.06.022.

[122] J. Laengle, J. Stift, A. Bilecz, B. Wolf, A. Beer, B. Hegedus, S. Stremitzer, P. Starlinger, D. Tamandl, D. Pils, M. Bergmann, DNA damage predicts prognosis and treatment response in colorectal liver metastases superior to immunogenic cell death and T cells, Theranostics 8 (2018) 3198–3213, https://doi.org/10.7150/thno.24699.

[123] J. Galon, D. Bruni, Approaches to treat immune hot, altered and cold tumours with combination immunotherapies, Nat. Rev. Drug Discov. 18 (2019) 10–13, https://doi.org/10.1038/s41573-018-0007-y.

[124] J.-C. Beltra, S. Manne, M.S. Abdel-Hakeem, M. Kurachi, J.R. Giles, Z. Chen, V. Casella, S.F. Ngiow, O. Khan, Y.J. Huang, P. Yan, K. Nzingha, W. Xu, R. K. Amaravadi, X. Xu, G.C. Karakousis, T.C. Mitchell, L.M. Schuchter, A.C. Huang, E.J. Wherry, Developmental relationships of four exhausted CD8+ T cell subsets reveals underlying transcriptional and epigenetic landscape control mechanisms, Immunity 52 (2020) 825–841, https://doi.org/10.1016/j.immuni.2020.04.014.

[125] R. Glynne-Jones, L. Wyrwicz, E. Tiret, G. Brown, C. Rödel, A. Cervantes, D. Arnold, Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 28 (2017) iv22–iv40, https://doi.org/10.1093/annonc/mdx224.

[126] F. Lordick, C. Mariette, K. Haustermans, R. Obermannová, D. Arnold, Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 27 (2016) v50–v57, https://doi.org/10.1093/annonc/mdw329.

[127] M. Ducreux, A.S. Cuhna, C. Caramella, A. Hollebecque, P. Burtin, D. Goéré, T. Seufferlein, K. Haustermans, J.L. Van Laethem, T. Conroy, D. Arnold, Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 26 (2015) v56–v68, https://doi.org/10.1093/annonc/mdv295.

[128] V. Stary, B. Wolf, D. Unterleuthner, J. List, M. Talic, J. Längle, A. Beer, J. Strobl, G. Stary, H. Dolznig, M. Bergmann, Short-course radiotherapy promotes pro-inflammatory macrophages via extracellular vesicles in human rectal cancer, J. Immunother. Cancer 8 (2020), e000667, https://doi.org/10.1136/jitc-2020-000667.

[129] I. Seo, H.W. Lee, S.J. Byun, J.Y. Park, H. Min, S.H. Lee, J.-S. Lee, S. Kim, S.U. Bae, Neoadjuvant chemoradiation alters biomarkers of anticancer immunotherapy responses in locally advanced rectal cancer, J. Immunother. Cancer 9 (2021), e001610, https://doi.org/10.1136/jitc-2020-001610.

[130] S. Yuki, H. Bando, Y. Tsukada, K. Inamori, Y. Komatsu, S. Homma, M. Uemura, T. Kato, D. Kotani, S. Fukuoka, N. Nakamura, M. Fukui, M. Wakabayashi, M. Kojima, Y. Togashi, A. Sato, H. Nishikawa, M. Ito, T. Yoshino, Short-term results of VOLTAGE-A: Nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with microsatellite stable and microsatellite instability-high locally advanced rectal cancer, 4100–4100, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.15_suppl.4100.

[131] T. Kato, H. Bando, Y. Tsukada, K. Inamori, M. Uemura, S. Yuki, Y. Komatsu, S. Homma, D. Kotani, S. Fukuoka, T. Sasaki, Y. Nishizawa, N. Nakamura, M. Wakabayashi, M. Kojima, Y. Togashi, A. Sato, H. Nishikawa, T. Yoshino, M. Ito, VOLTAGE-B study: nivolumab monotherapy and subsequent curative surgery following preoperative chemoradiotherapy in patients with locally recurrent rectal cancer (LRRC) without previous radiotherapy, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.100.

[132] T. Conroy, J.-F. Bosset, P.-L. Etienne, E. Rio, É. François, N. Mesgouez-Nebout, V. Vendrely, X. Artignan, O. Bouché, D. Gargot, V. Boige, N. Bonichon-Lamichhane, C. Louvet, C. Morand, C. de la Fouchardière, N. Lamfichekh, B. Juzyna, C. Jouffroy-Zeller, E. Rullier, F. Marchal, S. Gourgou, F. Castan, C. Borg, C. Borg, P.-L. Etienne, E. Rio, N. Mesgouez-Nebout, É. François, V. Vendrely, T. Conroy, X. Artignan, O. Bouché, D. Gargot, V. Boige, N. Bonichon-Lamichhane, C. Louvet, C. Morand, C. de la Fouchardière, P. Ronchin, J.-F. Seitz, S. Corbinais, E. Maillard, M. Noirclerc, F. El Hajbi, P. Ronchin, A.-L. Villing, Y. Bécouarn, L. Foong Fat Lam Kam Sang, P. Artru, J.-B. Bachet, F. Hocine, C. Ligeza-Poisson, C. Vautravers, M. Ben Abdelghani, T. Aparicio, E. Desot, I. Marquis, Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial, Lancet Oncol. 22 (2021) 702–715, https://doi.org/10.1016/S1470-2045(21)00079-6.

[133] R.R. Bahadoer, E.A. Dijkstra, B. van Etten, C.A.M. Marijnen, H. Putter, E.M. K. Kranenbarg, A.G.H. Roodvoets, I.D. Nagtegaal, R.G.H. Beets-Tan, L. K. Blomqvist, T. Fokstuen, A.J. ten Tije, J. Capdevila, M.P. Hendriks, I. Edhemovic, A. Cervantes, P.J. Nilsson, B. Glimelius, C.J.H. van de Velde, G.A. P. Hospers, L. Østergaard, F. Svendsen Jensen, P. Pfeiffer, K.E.J. Jensen, M. P. Hendriks, W.H. Schreurs, H.P. Knol, J.J. van der Vliet, J.B. Tuynman, A.M. E. Bruynzeel, E.D. Kerver, S. Festen, M.E. van Leerdam, G.L. Beets, L.G.H. Dewit, C.J.A. Punt, P.J. Tanis, E.D. Geijsen, P. Nieboer, W.A. Bleeker, A.J. Ten Tije, R.M. P.H. Crolla, A.C.M. van de Luijtgaarden, J.W.T. Dekker, J.M. Immink, F.J. F. Jeurissen, A.W.K.S. Marinelli, H.M. Ceha, T.C. Stam, P. Quarles an Ufford, W. H. Steup, A.L.T. Imholz, R.J.I. Bosker, J.H.M. Bekker, G.J. Creemers, G.A. P. Nieuwenhuijzen, H. van den Berg, W.M. van der Deure, R.F. Schmitz, J.M. van Rooijen, A.F.T. Olieman, A.C.M. van den Bergh, D.J.A. de Groot, K. Havenga, J. C. Beukema, J. de Boer, P.H.J.M. Veldman, E.J.M. Siemerink, J.W.P. Vanstiphout, B. de Valk, Q.A.J. Eijsbouts, M.B. Polée, C. Hoff, A. Slot, H.W. Kapiteijn, K.C.M. J. Peeters, F.P. Peters, P.A. Nijenhuis, S.A. Radema, H. de Wilt, P. Braam, G. J. Veldhuis, D. Hess, T. Rozema, O. Reerink, D. Ten Bokkel Huinink, A. Pronk, J. Vos, M. Tascilar, G.A. Patijn, C. Kersten, O. Mjåland, M. Grønlie Guren, A. N. Nesbakken, J. Benedik, I. Edhemovic, V. Velenik, J. Capdevila, E. Espin, R. Salazar, S. Biondo, V. Pachón, J. die Trill, J. Aparicio, E. Garcia Granero, M. J. Safont, J.C. Bernal, A. Cervantes, A. Espí Macías, L. Malmberg, G. Svaninger, H. Hörberg, G. Dafnis, A. Berglund, L. Österlund, K. Kovacs, J. Hol, S. Ottosson, G. Carlsson, C. Bratthäll, J. Assarsson, B.L. Lödén, P. Hede, I. Verbiené, O. Hallböök, A. Johnsson, M.L. Lydrup, K. Villmann, P. Matthiessen, J. H. Svensson, J. Haux, S. Skullman, T. Fokstuen, T. Holm, P. Flygare, M. Walldén, B. Lindh, O. Lundberg, C. Radu, L. Påhlman, A. Piwowar, K. Smedh, U. Palenius, S. Jangmalm, P. Parinkh, H. Kim, M.L. Silviera, Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial, Lancet Oncol. 22 (2021) 29–42, https://doi.org/10.1016/S1470-2045(20)30555-6.

[134] A. Athauda, N. Starling, I. Chau, D. Cunningham, D.J. Watkins, S. Rao, E. Kalaitzaki, E. Bourmpaki, M. Davidson, A. Gillbanks, R. Lazaro-Alcausi, M. Moneypenny, R. Begum, K. von Loga, I. Rana, P. Patel, S. Doran, S. Kumar, A. Chaudry, M. Gerlinger, Perioperative FLOT plus anti-PD-L1 avelumab (FLOT-A) in resectable oesophagogastric adenocarcinoma (OGA): Interim safety analysis results from the ICONIC trial, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.3_suppl.201.

[135] T. van den Ende, N.C. de Clercq, M.I. van Berge Henegouwen, S.S. Gisbertz, S. L. Meijer, S. Schokker, J.J.G.H.M. Bergman, N. Haj Mohammad, J.P. Ruurda, R. van Hillegersberg, S. Mook, M. Nieuwdorp, T.T.D. Soeratram, B. Ylstra, N.C. T. van Grieken, T.D. de Gruijl, M.F. Bijlsma, M.C.C.M. Hulshof, H.W.M. Van Laarhoven, A phase II feasibility trial of neoadjuvant chemoradiotherapy combined with atezolizumab for resectable esophageal adenocarcinoma: The PERFECT trial, 4045–4045, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.4045.

[136] H. Mamdani, B.J. Schneider, L.I. Abushahin, T.J. Birdas, K. Kesler, A. Lee, H. Burney, S. Perkins, S.I. Jalal, Safety and efficacy of durvalumab following trimodality therapy for locally advanced esophageal and GEJ adenocarcinoma: early efficacy results from Big Ten Cancer Research Consortium study, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.4_suppl.5.

[137] J.R. Eads, M. Weitz, P.J. Catalano, M.K. Gibson, L. Rajdev, O. Khullar, S.H. Lin, C. Gatsonis, I.I. Wistuba, A. Sanjeevaiah, A.B. Benson, N. Bahary, K.R. Spencer, N. F. Saba, S.R. Hamilton, C.A. Staley, B. Chakravarthy, G.A. Fisher, T.Z. Wong, P. J. O'Dwyer, A phase II/III study of perioperative nivolumab and ipilimumab in patients (pts) with locoregional esophageal (E) and gastroesophageal junction (GEJ) adenocarcinoma: Results of a safety run-in—A trial of the ECOG-ACRIN Cancer Research Group (EA2174), J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.4064.

[138] N.V. Uboha, J.D. Maloney, D. McCarthy, D.A. Deming, N.K. LoConte, K. Matkowskyj, J.C. Eickhoff, P. Emmerich, M.M. DeCamp, S.J. Lubner, A. A. Turk, M.F. Bassetti, Safety of neoadjuvant chemoradiation (CRT) in combination with avelumab (A) in the treatment of resectable esophageal and gastroesophageal junction (E/GEJ) cancer, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.4041.

[139] R.J. Kelly, K.N. Smith, V. Anagnostou, E. Thompson, R.K. Hales, R.J. J. Battafarano, K.R. Voong, S.C. Yang, J.L. Feliciano, E.J. Shin, C. Hu, M. El Asmar, H.Y. Chan, V.E. Velculescu, C. Sears, D.M. Pardoll, A.I. Amjad, P. Guerrieri, B.A. Jobe, A.H. Zaidi, Neoadjuvant nivolumab plus concurrent chemoradiation in stage II/III esophageal/gastroesophageal junction cancer, 142–142, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.4_suppl.142.

[140] S. Li, W. Yu, F. Xie, Z. Liu, W. Lv, D. Shi, D. Yu, M. Wei, J. Wang, Y. Zhao, C. Chen, Z. Zhao, J. Gao, L. Sheng, L. Liu, A prospective, phase II, single-arm study of neoadjuvant/conversion therapy with camrelizumab, apatinib, S-1 ± oxaliplatin for locally advanced cT4a/bN+ gastric cancer, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.4061.

[141] Y.-J. Bang, E. Van Cutsem, C.S. Fuchs, A. Ohtsu, J. Tabernero, D.H. Ilson, W. J. Hyung, V.E. Strong, T.O. Goetze, T. Yoshikawa, L.H. Tang, P.M.T. Hwang, K. Shitara, KEYNOTE-585: phase 3 study of chemotherapy (chemo) + pembrolizumab (pembro) vs chemo + placebo as neoadjuvant/adjuvant treatment for patients (pts) with gastric or gastroesophageal junction (G/GEJ) cancer, TPS4136–TPS4136, J. Clin. Oncol. 36 (2018), https://doi.org/10.1200/JCO.2018.36.15_suppl.TPS4136.

[142] P.E. Oberstein, B. Schrope, T. Gonda, A. Sethi, A. Han, G.K. Schwartz, M.A. Shah, A phase II study of chemotherapy and immune checkpoint blockade with pembrolizumab in the perioperative and maintenance treatment of locoregional gastric or GE junction adenocarcinoma, TPS197–TPS197, J. Clin. Oncol. 36 (2018), https://doi.org/10.1200/JCO.2018.36.4_suppl.TPS197.

[143] S.-E. Al-Batran, S. Lorenzen, M. Schenk, P.C. Thuss-Patience, E. Goekkurt, R. Hofheinz, A. Kretzschmar, C. Bolling, S. Angermeier, A. Wicki, A. R. Siebenhuener, E. Eigendorff, C. Pink, T.J. Ettrich, H. Schmalenberg, L. Waberer, J. Talbot, C. Pauligk, T.O. Goetze, N. Homann, Safety of perioperative atezolizumab in combination with FLOT versus FLOT alone in patients with resectable esophagogastric adenocarcinoma: an interim safety analysis of the DANTE, a randomized, open-label phase II trial of the German Gastric Group at the, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.398.

[144] O.E. Rahma, M.H.G. Katz, B.M. Wolpin, A. Dias-Costa, J. Nowak, S.J. Rodig, S. Dougan, T.S. Bekaii-Saab, C.-C.H. Stucky, R. Elias, G.R. Petroni, T.W. Bauer, C. L. Slingluff, Randomized multicenter phase Ib/II study of neoadjuvant chemoradiation therapy (CRT) alone or in combination with pembrolizumab in patients with resectable or borderline resectable pancreatic cancer, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.4128.

[145] A. Wang-Gillam, A.C. Lockhart, B.R. Tan, R. Suresh, K.-H. Lim, L. Ratner, A. Morton, J. Huffman, S. Marquez, N. Boice, D.G. DeNardo, Phase I study of defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer, 380–380, J. Clin. Oncol. 36 (2018), https://doi.org/10.1200/JCO.2018.36.4_suppl.380.

[146] A.O. Kaseb, D.G. Duda, H.S. Tran Cao, Y.I. Abugabal, L.M. Vence, A. Rashid, R. Pestana, J.M. Blando, S. Singh, J.-N. Vauthey, M. Hassan, H.M. Amin, A. Qayyum, Y.S. Chun, C.-W.D. Tzeng, D. Sakamuri, R.A. Wolff, J.C. Yao, J. P. Allison, P. Sharma, Randomized, open-label, perioperative phase II study evaluating nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.486.

[147] H.-S. Im, J.S. Song, W.R. Jo, M.-W. Yoo, Y.-H. Kim, H.R. Kim, H.J. Song, D.H. Kim, K.D. Choi, J.H. Lee, J.Y. Ahn, H.K. Na, K. Song, S.R. Park, Preliminary results of a phase II study of neoadjuvant immune checkpoint inhibitor IMC-001 (anti-PD-L1 monoclonal antibody) in patients with resectable gastrointestinal cancers (NeoChance Study), J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.15_suppl.e16542.

[148] F.A. Sinicrope, F.-S. Ou, T. Zemla, A.B. Nixon, K. Mody, A. Levasseur, A.C. Dueck, A.R. Dhanarajan, C.H. Lieu, D.J. Cohen, F. Innocenti, R.J. Behrens, W. Peters, N. Sommer, E.M. O'Reilly, J.A. Meyerhardt, Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient mismatch repair (ATOMIC, Alliance A021502), J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.e15169.

[149] D. Lau, D. Cunningham, A. Gillbanks, R. Crux, R. Powell, E. Kalaitzaki, N. E. Annels, F. Sclafani, M. Gerlinger, I. Chau, I. Tomlinson, N. Starling, H. S. Pandha, D.N. Church, T. Dhillon, POLEM: avelumab plus fluoropyrimidine-

based chemotherapy as adjuvant treatment for stage III dMMR or POLE exonuclease domain mutant colon cancer—a phase III randomized study, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS3615.
[150] J. Laengle, I. Kuehrer, D. Pils, J. Kabiljo, J. Stift, F. Herbst, B. Dauser, M. Monschein, P. Razek, S. Haegele, W. Huller, R. Fuegger, H. Geinitz, A. L. Petzer, C. Bitterman, F. Laengle, D. Tamandl, J. Widder, R. Schmid, M. Bergmann, Neoadjuvant chemoradiotherapy with sequential ipilimumab and nivolumab in rectal cancer (CHINOREC): a prospective randomized, open-label, multicenter, phase II clinical trial, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS3623.
[151] T. Kossler, B. Nicolas, V. Dutoit, G. Puppa, P. Tsantoulis, J.-L. Frossard, P. Bichard, X. Montet, T. McKee, M. Di Marco, P.-Y. Dietrich, A. Roth, T. Zilli, F. Ris, A phase II study to evaluate safety and efficacy of neoadjuvant pembrolizumab and radiotherapy in localized MSS rectal cancer, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.TPS272.
[152] T.J. George, G. Yothers, S.A. Jacobs, G.G. Finley, H.D. Parekh, T.D. Moore, B. N. Maalouf, J.C. Krauss, M. Deutsch, J.J. Lee, C.J. Allegra, N. Wolmark, NSABP FR-2: Phase II study of durvalumab following neoadjuvant chemoRT in stage II-IV rectal cancer, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.TPS264.
[153] M. Michael, R. Wong, S.S. Gill, D. Goldstein, S. Ngan, A.G. Heriot, E. Link, M. Farrell, P.J. Neeson, R.G. Ramsay, K. Wilson, C. Mitchell, J. Tie, N. Pavlakis, J. R. Zalcberg, E. Segelov, Phase II trial PD-L1/PD-1 blockade avelumab with chemoradiotherapy for locally advanced resectable T3B-4/N1-2 rectal cancer: the ave-Rec trial, J. Clin. Oncol. 37 (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS3622.
[154] S. Tamberi, E. Grassi, M. aurelia Barbera, J. Corbelli, G. Papiani, I. Montroni, M. Di Bartolomeo, S. Cascinu, M. Marzola, A. Bonetti, G. Frassineti, C. Pinto, C. Zingaretti, O. Nanni, C. Carli Moretti, I. Panzini, G. Rossi, G. Ugolini, A phase II study of capecitabine plus concomitant radiation therapy followed by durvalumab (MEDI4736) as preoperative treatment in rectal cancer (PANDORA), J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.TPS259.
[155] G. Chen, F. Wang, W. Xiao, Y. Jin, R.-X. Zhang, P. Cai, M. Liu, L. He, S. Xi, X. Chen, H. Zhang, Z.-Z. Pan, R. Xu, Pd1 antibody sintilimab for dMMR/MSI-H locally advanced rectal cancer: an open-label, phase 2, single-arm study (cohort A), J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.e15602.
[156] L. Salvatore, M. Bensi, S. Corallo, F. Bergamo, I. Pellegrini, C. Rasola, B. Borelli, E. Tamburini, G. Randon, S. Galuppo, A. Boccaccino, M.G. Viola, A. Auriemma, E. Fea, C. Barbara, S. Bustreo, V. Smiroldo, B. Barbaro, M.A. Gambacorta, G. Tortora, Phase II study of preoperative (PREOP) chemoradiotherapy (CTRT) plus avelumab (AVE) in patients (PTS) with locally advanced rectal cancer (LARC): The AVANA study, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.15_suppl.3511.
[157] O.E. Rahma, G. Yothers, T.S. Hong, M.M. Russell, Y.N. You, W. Parker, S. A. Jacobs, L.H. Colangelo, P.C. Lucas, M.J. Gollub, W.A. Hall, L.A. Kachnic, N. Vijayvergia, N. Wolmark, T.J. George, NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally advanced rectal cancer (LARC)—Pembrolizumab experimental arm (EA) primary results, 8–8, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.3_suppl.8.
[158] A. Shamseddine, Y. Zeidan, I.M. Khalifeh, J.G. Kattan, R. Turfa, D. Mukherji, S. N. Temraz, F. Jamali, Y.H. Shaib, A. Soweid, S. Deeba, M. Kreidieh, Z. zuheir El Husseini, M. Charafeddine, M. Al Darazi, F.B. Geara, Short-course radiation followed by mFOLFOX-6 plus avelumab for locally advanced rectal adenocarcinoma, J. Clin. Oncol. 38 (2020), https://doi.org/10.1200/JCO.2020.38.4_suppl.139.
[159] Z. Lin, M. Cai, P. Zhang, X. Li, K. Cai, X. Nie, K. Tao, T. Zhang, Short-course radiotherapy and subsequent CAPOX plus camrelizumab followed by delayed surgery for locally advanced rectal cancer:Short-term results of a phase II trial, J. Clin. Oncol. 39 (2021), https://doi.org/10.1200/JCO.2021.39.3_suppl.63.
[160] J.R. Brahmer, H. Abu-Sbeih, P.A. Ascierto, J. Brufsky, L.C. Cappelli, F.B. Cortazar, D.E. Gerber, L. Hamad, E. Hansen, D.B. Johnson, M.E. Lacouture, G.A. Masters, J. Naidoo, M. Nanni, M.-A. Perales, I. Puzanov, B.D. Santomasso, S.P. Shanbhag, R. Sharma, D. Skondra, J.A. Sosman, M. Turner, M.S. Ernstoff, Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events, J. Immunother. Cancer 9 (2021), e002435, https://doi.org/10.1136/jitc-2021-002435.
[161] F.S. Hodi, S.J. O'Day, D.F. McDermott, R.W. Weber, J.A. Sosman, J.B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J.C. Hassel, W. Akerley, A.J.M. van den Eertwegh, J. Lutzky, P. Lorigan, J.M. Vaubel, G.P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J.I. Clark, J.D. Wolchok, J.S. Weber, J. Tian, M.J. Yellin, G.M. Nichol, A. Hoos, W.J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma, New Engl. J. Med. 363 (2010) 711–723, https://doi.org/10.1056/NEJMoa1003466.
[162] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G. a McArthur, P. a Ascierto, G.V. Long, M.K. Callahan, M. a Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, J. D. Wolchok, Combined nivolumab and ipilimumab or monotherapy in untreated melanoma, N. Engl. J. Med. 373 (2015) 23–34, https://doi.org/10.1056/NEJMoa1504030.
[163] C. Robert, G.V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, J.C. Hassel, P. Rutkowski, C. McNeil, E. Kalinka-Warzocha, K.J. Savage, M.M. Hernberg, C. Lebbé, J. Charles, C. Mihalcioiu, V. Chiarion-Sileni, C. Mauch, F. Cognetti, A. Arance, H. Schmidt, D. Schadendorf, H. Gogas, L. Lundgren-Eriksson, C. Horak, B. Sharkey, I.M. Waxman, V. Atkinson, P.A. Ascierto, Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med 372 (2015) 320–330, https://doi.org/10.1056/NEJMoa1412082.
[164] J.S. Weber, F.S. Hodi, J.D. Wolchok, S.L. Topalian, D. Schadendorf, J. Larkin, M. Sznol, G.V. Long, H. Li, I.M. Waxman, J. Jiang, C. Robert, Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma, J. Clin. Oncol. 35 (2017) 785–792, https://doi.org/10.1200/JCO.2015.66.1389.
[165] J. Brahmer, K.L. Reckamp, P. Baas, L. Crinò, W.E.E. Eberhardt, E. Poddubskaya, S. Antonia, A. Pluzanski, E.E. Vokes, E. Holgado, D. Waterhouse, N. Ready, J. Gainor, O. Arén Frontera, L. Havel, M. Steins, M.C. Garassino, J.G. Aerts, M. Domine, L. Paz-Ares, M. Reck, C. Baudelet, C.T. Harbison, B. Lestini, D. R. Spigel, Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer, New Engl. J. Med. 373 (2015) 123–135, https://doi.org/10.1056/NEJMoa1504627.
[166] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, J.R. Brahmer, Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer, New Engl. J. Med. 373 (2015) 1627–1639, https://doi.org/10.1056/NEJMoa1507643.
[167] A.N. Shoushtari, C.F. Friedman, P. Navid-Azarbaijani, M.A. Postow, M. K. Callahan, P. Momtaz, K.S. Panageas, J.D. Wolchok, P.B. Chapman, Measuring toxic effects and time to treatment failure for nivolumab plus ipilimumab in melanoma, JAMA Oncol. 4 (2018) 98, https://doi.org/10.1001/jamaoncol.2017.2391.
[168] F. Martins, L. Sofiya, G.P. Sykiotis, F. Lamine, M. Maillard, M. Fraga, K. Shabafrouz, C. Ribi, A. Cairoli, Y. Guex-Crosier, T. Kuntzer, O. Michielin, S. Peters, G. Coukos, F. Spertini, J.A. Thompson, M. Obeid, Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance, Nat. Rev. Clin. Oncol. 16 (2019) 563–580, https://doi.org/10.1038/s41571-019-0218-0.
[169] I. Puzanov, A. Diab, K. Abdallah, C.O. Bingham, C. Brogdon, R. Dadu, L. Hamad, S. Kim, M.E. Lacouture, N.R. LeBoeuf, D. Lenihan, C. Onofrei, V. Shannon, R. Sharma, A.W. Silk, D. Skondra, M.E. Suarez-Almazor, Y. Wang, K. Wiley, H. L. Kaufman, M.S. Ernstoff, Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group, J. Immunother. Cancer 5 (2017) 95, https://doi.org/10.1186/s40425-017-0300-z.