Assessment of quality and clinical significance of endpoints in cancer immunotherapy

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Abstract

This review describes available immunotherapeutic agents approved for the treatment of prostate cancer (sipuleucel-T), advanced melanoma (ipilimumab, pembrolizumab, nivolumab) and NSCLC (nivoluamb) and underline that their specific mechanism of action require to use appropriate endpoints for the efficacy evaluation.

The FDA and EMA guidelines on endpoints in clinical trials indicate the use of overall survival as a primary endpoints. However, there is a trend for using the time-to-event endpoints for drug approval since 1990. Oncological clinical trials utilize apart from OS also the endpoints based on tumor assessment – e.g. progression-free survival, disease-free survival or response rate.

This review presents the differences in mechanism of actions between standard chemotherapy and immunotherapy which imply the significant differences in the kinetic of response and long-term effects. The WHO and RECIST response criteria were developed to estimate the effect of cytotoxic drugs on cancer and the new patterns of response observed after treatment with immunotherapeutic agents indicate the need for adopting novel criteria in the evaluation of tumor responses.

The performed review of pivotal clinical trials assessing the efficacy of immunotherapy showed that the most commonly evaluated endpoints were: OS, PFS and RR. Prolonged survival with concomitant lack of benefit in PFS was explained by the need for applying irRC for evaluation of the efficacy of immunotherapeutic agents beyond the classical measurement.

It could be concluded that trial design which takes into account disease characteristics and immunotherapeutic agents' mechanism of action is the key to define appropriate endpoints and proper evaluation of the efficacy.

The first evidence that the immune system might respond to cancerous tissue appeared in the 18th century when it was noted that feverish infections in cancer patients were occasionally associated with the cancer remission. In the 1890s William Coley, performed intratumor injections of live or inactivated Streptococcus pyogenes or Serratia marcescens on cancer patients and observed tumor regression in some cases[1]. Nevertheless, during the next decades, the prevailing opinion among immunologists was that it is impossible for the immune system to recognize and respond to the malignant cells as they are indistinguishable from healthy cells.

In the 1950s, a series of animal experiments has shown that antigens (called "tumor-specific antigens" or "tumor-associated antigens") associated with tumor cells which can be recognized by the immune system have to exist. However, as successful results of immunotherapy seemed to be difficult to reproduce, oncologists relied on surgery and established effective methods, like radiotherapy and chemotherapy rather than on experimental therapies stimulating the immune system[2]. One significant exception was superficial bladder cancer – intravesical injection of live bacillus Calmette-Guerin following surgical resection prolonged survival significantly[2]. Nevertheless, for many years, using infectious and potentially pyrogenic agents was aborted as very burdensome for cancer patients.

Currently, it is generally accepted that the immune system recognizes and eliminates malignant cells[1]. However, tumor cells use a wide repertoire of mechanisms which protect them from the immune system or to an anergy.

An example of the effect of the immune system on cancer morbidity is Roithmaier et al 2007 study, which analysed recipients of transplanted hearts or lungs, or both, who received adequate immunosuppression to prevent graft rejection. Frequency of cancer among graft recipients was 7.2 times greater than in the general population. The most prevalent types of cancer were leukemias and lymphomas (26.2 times), head and neck cancer (21 times) and lung cancer (9.3 times)[3].

Immune response

The anticancer immune response develops in three steps: (1) maturation of antigen-presenting cells (e.g. dendritic cells) after sampling the antigen, (2) T-cell response, (3) action of cancer-specific T-cells in tumor bed[2,4].

In the first step, dendritic cells capture tumor-derived antigens from dead or dying tumor cells or delivered exogenously as a part of vaccine. The antigens reflect proteins which are typical for cancer – mutated proteins, non-mutated proteins which are exclusively expressed by cancer cells or antigens of differentiation associated with cancer tissue of origin but against which thymic or peripheral tolerance has not been completely established. Then the dendritic cells migrate to lymph nodes. On antigen encounter, the dendritic cells would also have to receive a suitable activation/maturation signal, allowing them to differentiate extensively to promote immunity as opposed to tolerance including enhanced processing and presentation of tumor-antigen-derived peptides. If dendritic cells do not receive a maturation signal, the antigen presentation promotes tolerance by producing regulatory T-cells[2].

In the second step, dendritic cells present the tumor antigen on major histocompatibility complex (MHC) molecule to generate T-cells responses in lymphoid organs[2]. Two signals are also required to activate T-cells – the first one is provided by the interaction of antigen presented in the MHC on the antigen-presenting cell (APC) with T-cell receptor on T-cell and the second one by interaction of modulators, e.g. co-stimulatory ligands (CD80/86) with CD28 on the T-cells[5]. If inhibitory signals appear in this step, e.g. interactions of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) with CD80/86 or programmed cell death-1 (PD-1) with PD-L2/PD-L2, they will promote immune tolerance instead of the T-cell response.

In third step effect or T-cell , B-cells and NK cells reach tumor bed and kill tumor cells.

Mechanisms which allow cancer to prevent immunization are being intensively studied. So far, several modes have been investigated, including: overexpressing of the inhibitory ligands and receptors – upregulation of PD-L1/L2 on the cancer cells surface, release of T-cell suppressors (PGE2, arginase or IDO) or release of VEGF which inhibits T-cell diapedesis from vasculature and thus infiltration into the tumor bed[2].

Immunotherapy

Therapy based on activation of the immune system is a result of an intensive search for a modern, effective therapy for cancer. The most prominent results of immunotherapy were obtained in melanoma and non-small cell lung carcinoma (NSCLC), but promising results were also observed in renal cell carcinoma (RCC).

By 2015, three antibodies – one anti-CTLA-4 antibody (ipilimumab), two anti-PD-1 antibodies (nivolumab, pembrolizumab) – and one cell based cancer vaccine (sipuleucel-T) have been approved by the Food and Drug Administration (FDA) and EMA[6-15].

All the antibodies were approved for treatment of advanced melanoma – ipilimumab in 2011, nivolumab and pembrolizumab in 2014 (EMA approval in 2015). Moreover, in 2015 nivolumab received FDA and EMA authorization in a second indication – NSCLC. Sipuleucel-T was approved for treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer in 2010 (EMA approval in 2013). Due to commercial reasons market authorization in Europe was withdrawn in 2015 at the request of the marketing authorization holder[16].

Immunotherapeutics could be classified into four main types[17]:

1. checkpoint inhibitors (e.g. anti-CTLA-4 and anti-PD-1 antibodies),
2. T-cell co-stimulators (e.g. anti-CD143 antibodies, anti-CD27 antibodies),
3. adoptive T-cell therapies (utilizing transgenic T-cell receptor or chimeric antigen receptor),
4. cancer vaccines (e.g. sipuleucel-T).

Immune checkpoints, which assure the balance between co-stimulatory and inhibitory signals, enable regulating response of T-cells after antigen recognition by T-cell receptors (TCR)[18]. The role of checkpoints is to maintain the self-tolerance (prevent autoimmunity) under normal, physiological conditions[18]. Antibodies which block immune checkpoints target tumor lymphocyte receptors or their ligands, and not the tumor directly, in order to enhance endogenous antitumor activity. Providing the agonist to co-stimulatory receptor or antagonist of inhibitory signal result in amplification of antigen-specific T-cell responses, which potentially has antitumor activity[18].

The best results were obtained with the use of antibodies involved in two inhibitory pathways – CTLA-4 and PD1.

Anti-CTLA-4-antibodies

CTLA-4 molecule is the key inhibitory receptor expressed exclusively on the surface of activated T-cells. It competes with the co-stimulatory receptor CD28 for binding with the CD80/86 expressed on the surface of APC (e.g. dendritic cells). While CD28 signalling strongly amplifies TCR signalling to activate T-cells, CTLA-4 signalling inhibit the TCR signalling and leads to diminish the T-cell function[4,18]. CTLA-4 regulates the amplitude of the early stages of T-cell activation.

Blocking CTLA-4 significantly enhances the immune responses and hypothetically allows for expansion of T-cells with antitumor activity[18,19].

Two fully human monoclonal anti-CTLA-4 antibodies were intensively investigated in clinical trials – ipilimumab and tremelimumab. However, only ipilimumab caused significant improvement in phase III trials and was the first therapy that showed a survival benefit for patients with metastatic melanoma[18]. The effect of ipilimumab on long-term survival is also impressive: 18% of ipilimumab-treated patients survived beyond two years (compared with 5% of patients in the control group)[18]. The percentage of patients who achieve clinical response (defined as a complete response (CR), partial response (PR) or stable disease (SD)) was relatively low (28.5%), but still significantly higher than in the control group (11%). Moreover, the achieved response was sustainable[4].

Adverse events (AEs) related to the ipilimumab treatment were mainly immune-related AEs, involving the skin and the gastrointestinal tract[4]. Long-term survival and response which persist after completion of therapy could indicate that immunotherapy re-educates the immune system to keep the tumor under control[18].

Anti-PD-1 antibodies

T-cell receptor PD-1 is expressed on activated and exhausted T (CD4, CD8 and regulatory cells) and B-cells, and on myeloid cells. PD-L1 and PD-L2 ligands are expressed by immune cells on a variety of tissues, especially after exposure to inflammatory cytokines (e.g. interferon gamma). PD-1 signalling leads to negative regulation of T-cells in peripheral tissues at the time of an inflammatory response to infection and limits autoimmunity[4]. Importantly, PD-L1 is expressed on a variety of human cancers, which could contribute to evading the antitumor immune response[20]. By blocking the PD-1 receptor, anti-PD-1 antibodies enhance the activity of effector T-cells in tissues and tumor microenvironment. Moreover, anti-PD1 antibodies probably enhance NK cells activity and enhance antibody production by affecting the population of B-cells which express the PD-1 protein[18].

The first important results obtained in phase I clinical trial with fully human anti-PD-1 antibody – nivolumab demonstrated a complete response (one patient with colorectal cancer) and a partial response (two patients – with RCC and melanoma). These results encourage the investigators to conduct further clinical trials on a population of patients with different types of cancer[20]. The safety profile of anti-PD-1 antibody is more favorable than that of anti-CTLA-4[4].

Summary results of clinical trials assessing immunotherapies in a population of cancer patients are presented in Table 5.

Melanoma

Melanoma, with incidence rapidly increasing in the United States and in Europe over the last two decades, and with overall survival of less than 1 year for patients with unresectable distant metastases, became one of the human malignancies with the worst prognosis[4].

For over 30 years, only three drugs were approved by FDA for treatment of melanoma: dacarbazine, hydroxyurea and interleukin-2. Dacarbazine, the most frequently used agent, showed no significant effect on survival and achieves a 10% response rate. Moreover, there were no effective treatment options for relapsed melanoma[26].

Melanoma is characterized by the highest frequencies of genetic and epigenetic abnormalities that should result in antigens that the immune system can use to distinguish melanoma cells from melanocytes[5]. It is also one of the most immunogenic malignancy as melanoma-antigen specific T-cells are present in the peripheral blood of many patients[4].

Endpoints

The National Institute of Health Biomarkers Definitions Working Group defined a clinical endpoint as "a characteristic or variable that reflects how a patient feels, functions, or survives" and a surrogate endpoint as a "biomarker intended to act as a clinical endpoint"[21].

Overall survival (OS) is defined as a time from randomization until death from any cause and is measured in the intent-to-treat population in clinical trials. Overall survival is a gold standard in the assessment in both cytostatic and immunotherapeutic drugs as the most reliable cancer endpoint[22-24]. There is no doubt that the drug is effective if it improved overall survival compared with the control group in an adequately designed and conducted randomized clinical trial[26]. OS is easy to assess, unambiguous, not subject to investigation bias and offers a clear assessment of risk and benefits[25].

Overall survival consists of two parts: progression-free survival and survival after progression. Different approaches to treatment after progression, namely: crossover to the other group in the trial, use of an alternative drug, continuation of treatment with the same drug or lack of further treatment, make it difficult to assess the effect of the analysed intervention on overall survival[24].

Moreover, the detection of differences in OS between analysed patients groups could be difficult, as many issues, e.g. trial duration, cost, sample size or treatment after progression confound the results.

Beyond the OS the most important are patient-reported outcomes, e.g. quality of life.

Surrogate endpoints

In comparison with overall survival, surrogate endpoints may offer some benefit, despite any potential risk and the increased need for validation[25]. The advantage of using surrogate endpoints is shorter trial duration, which implies drawing conclusions sooner than with the use of overall survival. This offers faster access to novel therapy, which is important, but only if there is true clinical benefit to the patient[26]. Surrogate endpoints are also less affected by sub-

sequent treatment, palliative care and comorbidities and allow for performing single arm trials with smaller a cohort of patients[24].

Validation of each surrogate for each intervention is very important. Different drugs could affect the same surrogate, however, if the mechanism of affecting cancer between those drugs differs, the benefit from the intervention could not be adequately captured.

Progression-free survival and time to progression (TTP) are the most commonly used surrogate endpoints[24]. TTP is defined as the time from randomization until objective tumor progression and does not include deaths and PFS is defined as the time from randomization until objective tumor progression or death[23]. TTP and PFS are the preferred endpoints for drug approval in case of conventional cytostatic therapies.

However, PFS as the primary outcome measure in trial design and analysis, carries a risk of drawing invalid conclusions about the long-term efficacy of a drug, particularly if it is not a true surrogate endpoint for that disease site. A strong correlation between PFS and OS has been demonstrated only for some types of cancer, e.g. advanced colorectal and extensive-stage small-cell lung cancer. Other disadvantage of PFS is the possibility of increased uncertainty from extrapolating how a surrogate endpoint would behave from historic trial data[24].

Although demonstration of a survival benefit is the preferred objective, regulatory bodies such as the FDA and EMA recognize that alternative endpoints which objectively measure patient benefit can be useful in specific disease settings. A review of drug approvals granted by the FDA revealed that time-to-event endpoints were being increasingly used for drug approvals – from 13% in 1990-1999 through 33% in 2000-2005 to 43% between 2006 and 2011[26].

Objective response rate defined as a sum of partial responses and the complete response is another important surrogate endpoint. ORR is assessed by bidimensional assessment provided by World Health Organisation (WHO) and/or unidimensional assessment of tumor burden formulated as Response Evaluation Criteria in Solid Tumors (RECIST) methodology. Using ORR allows to show clinical benefit for the patient in a single-arm trial, however the response rate could under- or overestimate the drugs' effect. High initial response rates with highly toxic biochemotherapy have not translated into overall survival benefit, whereas low response rates with immunotherapy have translated into a benefit in overall survival[27,50-52]. Recently, immune-related Response Criteria (ir-RC) were proposed for ORR assessment which is adequate for evaluation of immunotherapy[19].

The most important factors which need to be taken into account in the trial design when defining appropriate endpoints are: the disease characteristics (prognosis, aggressiveness, symptoms) and effect of available therapies on these characteristics. A review performed byWilson et al. mentions differences between metastatic gall bladder cancer and ovarian granulosa-cell tumor. In the first case, median overall survival is equal to less than a year and therefore even modest improvement in survival might be clinically relevant. A median overall survival in the second case is equal to over 15 years, so detection of a therapeutic benefit in terms of overall survival is not realistic and a short term, more clinically meaningful objective measure of benefit might instead be improvement in symptoms or quality of life[24].

International guidelines and consideration regarding endpoints in oncological clinical trials

Based on EMA and FDA guidelines[22,23], an efficacy and safety analysis of anticancer medicinal products should evaluate patient-oriented clinically significant endpoints, a change of which resulting from treatment would make the treatment preferred for the patients. It reflects the treatment effect, prolonging of life and improving the patients' quality of life.

The endpoints which should be evaluated in randomized clinical trials in oncology include: overall survival and endpoints based on tumor assessment such as: disease-free survival (DFS), ORR, PFS or TTP[22,23].

Challenges connected with clinical trial design

So far, classical molecules for cancer treatment were assessed primary in phase II clinical trials on the basis of tumor response (shrinkage) after a minimum number of doses. The decision on whether to move on to phase III trial was based on the proportion and duration of objective tumor responses and overall survival compared with historical controls[17]. Immunotherapy activates the immune system to fight cancer, which requires longer time to demonstrate the cytoreductive effects and to achieve remission in comparison to the traditionally used molecules[17] and requires a novel approach to clinical trial designing, statistical analysis and the drug development pipeline.

	Advantages	Disadvantages
Overall survival	• universally accepted measure of clinical benefit; • easily measured; • precisely measured;	• can include large patient numbers; • can be affected by crossover therapy and sequential therapy; • includes non-cancer deaths; • trials which assess OS frequently do not evaluate quality of life[26]; • require long observation period[26];
Symptom endpoints (patient-reported outcomes)	• patient perspective of clinical benefit;	• masking is often difficult; • data are often missing or incomplete; • clinical relevance of small changes is unknown; • multiple analyses; • lack of validated instruments; • often reported as mean or median group scores rather than individual results;
Disease-free survival (surrogate endpoint)*	• masked review recommended; • smaller sample size and shorter follow-up than overall survival;	• not statistically validated as a surrogate endpoint for survival in all settings; • not precisely measured; subject to bias, especially in open-label studies; • definitions vary between studies;
Progression-free survival (includes all deaths);time to progression (deaths before progression excluded);progression-free survival 2 (includes all deaths);time to second progression (deaths before progression excluded) (surrogate endpoint)*	• smaller sample size and shorter follow-up than overall survival; • includes measurement of stable disease; not affected by crossover or subsequent treatments (progression-free survival 2 less affected than overall survival); • generally based on objective and quantitative assessment;	• not statistically validated as a surrogate endpoint for survival in most settings; • not validated as measure of quality of life; • not precisely measured; • subject to assessment bias, especially in open-label studies; • definitions vary between studies; • frequent radiological or other assessments; • timing of assessments in treatment groups needs to be balanced; • affected by censoring of data;
Objective response rate (surrogate endpoint)*	• can be assessed in single-arm studies; • assessed earlier and in smaller studies than overall survival; • effect attributable to drug and not natural history of disease; • used in advanced setting;	• only a subset of patients benefit; • not a direct measure of clinical benefit; • not a comprehensive measure of drug activity; • does not measure duration of clinical benefit;
Complete response (surrogate endpoint)*	• can be assessed in single-arm studies; • durable complete responses can represent clinical benefit; • assessed earlier and in smaller studies than overall survival;	• not a direct measure of clinical benefit; • not a comprehensive measure of drug activity; • small subset of patients benefit;
Clinical benefit rate (surrogate endpoint)*	• can be assessed in single-arm studies; • assessed earlier and in smaller studies than overall survival; • includes complete response, partial response, and stable disease for a defined period	• not a direct measure of clinical benefit; • not a comprehensive measure of drug activity; • definition of duration of stable disease varies between studies; • stable disease can reflect inherent characteristics of tumor rather than disease activity

Table 1. The summary of advantages and disadvantages of endpoints used to assess efficacy of drugs in clinical trials. Table was adapted from FDA Guidelines for Industry – Clinical Trial endpoints for the Approval of cancer drugs and biologics and Wilson et al. 2015

**adequacy as a surrogate endpoint for accelerated approval or regular approval is very dependent on other factors such as effect size, effect duration, and benefits of other available treatment.*

The differences between mechanisms of action of classical cytotoxic drugs and immunotherapy could be translated into the following features:

- the optimal biologic dose is often not equal to the maximum tolerated dose;
- treatment effect is not proportionally linked to toxicity;
- conventional pharmacokinetics may not determine the dose and schedule;
- anti-tumor response is not the sole predictor of survival;
- clinical effects can be delayed in time and can occur after tumor volume increase (often categorized as progression)[29].

These prominent differences imply the need for the use of endpoints adjusted to the immunotherapy which will adequately assess the clinical effects.

Endpoints in immunotherapy trials

Overall survival

The effect of immunotherapy on survival of patients in randomized clinical trials is characterized by delayed separation in the Kaplan-Meier curves of the control versus experimental groups. The delayed separation, which could occur months after commencement of the treatment, reduces the statistical power of difference between the curves. An analysis of such a Kaplan-Meier plot requires different statistical assumptions, as conventional statistical methods assume a constant hazard ratio over time (proportional hazards), where the separation of curves occurs shortly after treatment initiation[17,29]. Therefore, alternative statistical methods which take into account delayed separation assumptions allow to avoid loss of statistical power and to compute the required number of events for final analysis should be implemented[17,31].

The effect of delayed separation of K-M curves and long-term survival after immunotherapy through reduction of statistical power of a trial might increase the chance of early termination of trial due to futility[17]. A delayed separation will increase the chances of a negative result at a time when curves have not yet parted, which could lead to unintended termination of trial[29]. Past failures in translations of immunotherapeutic clinical effects could be attributed to incomplete understanding of mechanism which determine the interaction of the immune system with the tumor, as well as methodological limitations and bias[29]. Thus, ensuring that the clinical trial is properly designed and methods of analysing the endpoints are chosen adequately is a very important issue.

The effect of ipilimumab on long-term survival was investigated in a pooled analysis based on 12 prospective (phase III, II, I/II) and retrospective studies. Data of 1,861 patients with unresectable or metastatic melanoma were analyzed[30]. Median OS was 11.4 months and OS curve reached plateau around year 3, when survival rates ranged from 20% to 26%, moreover some patients survived until the 10-year follow-up. These results suggest that the majority of patients who reached this milestone time point (3 years) had a low risk of death thereafter.

Response to immunotherapy

The kinetics of the response is the main feature which distinguishes immunotherapy from conventional chemotherapeutic agents or oncogene-targeted small molecule drugs.

Response to conventional cytotoxic therapies is triggered within weeks of initial administration and causes rapid tumor shrinkage due to direct killing of cancer cells. The immunotherapy causes a three-step response: 1. immune activation and T-cells proliferation which starts after first administration; 2. clinically measureable antitumor effects mediated by activated immune cells which occur weeks to months after administration; 3. potential effect on patient survival observed several months after first administration[31]. The effect of immunotherapy on cancer symptoms may take several months to occur. Tumors may increase in size on computed tomography or magnetic resonance imaging scans during this period[18]. This initial increase in total tumor burden in patients who subsequently develop objective response could be explained by either continued tumor growth until the sufficient immune response develops or transient immune-cell infiltration with or without edema. Both assumptions were confirmed by biopsies taken from patients with initial disease progression before response[19].

Patients treated with ipilimumab could initially experience a period of stable disease or even disease progression classified by WHO due to increase in tumor burden or the appearance of new lesions before any objective response to the treatment is observed. In clinical trials the response – tumor regression – was observed after 5-6 months[32]. The delay in response to treatment and initial progression are the most common reasons for treatment discontinuation. Studies which analyzed immune-activating cytokines, cancer vaccines or immune-modulating antibodies in treatment of cancer showed that response to treatment (complete response, partial response) or stabilization of the disease occurred after a primary increase in tumor burden characterized as progression in accordance with the WHO and RECIST criteria[19,46,47].

For decades, modified World Health Organization criteria and more recently, RECIST criteria, were applied to measure the clinical activity of anticancer agents. Response criteria for solid tumors were developed by the WHO in an attempt to standardize the characterization of chemotherapeutic efficacy and to facilitate comparisons between studies as well as comparisons with historical data[19]. However, traditional response criteria (WHO and RECIST) may not be sufficient for adequate characterization of new-era targeted therapies as were designed to assess the effect of cytotoxic drugs on the basis of tumor shrinkage. The response pattern observed in patients treated by immunotherapy differ from that observed after treatment with cytotoxic agents[31]. These findings demand a re-evaluation of response criteria for immunotherapeutics away from the conventional time-to-progression or RECIST objective response criteria, which were developed on the basis of experiences with chemotherapeutic agents[18]. New immune-related criteria which may aid clinical decision-making regarding continuation of therapy have been proposed for the evaluation of immune therapy[2,18].

A series of workshops and discussions conducted between oncologists, immunotherapists and other involved experts in 2004 and 2005 helped prepare a novel set of response criteria based on WHO criteria[19].

The conclusions which led to the preparation of the new criteria were as follows:

- the appearance of measurable antitumor activity may take longer for immune therapies than for cytotoxic therapies;
- responses to immune therapies may occur after conventional progressive disease (PD);
- discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed (as it is usually done in case of response);
- admissibility of "clinically insignificant" PD (e.g., small new lesions in the presence of other responsive lesions) is recommended;
- durable SD may represent antitumor activity.

Four types of obtained responses which could be attributed to other immunotherapeutic agents[17,19,20] were described for the ipilimumab therapy:

- Immediate response (shrinkage) in baseline/reference lesions and no new lesions emerging;
- Durable disease stabilization, with or without a subsequent slow decline in total tumor burden;
- Initial increase in total tumor burden, which may be followed by a gradual decline over time as the immune system is activated;
- Response in the presence of new lesion

The first two pathways are characteristic of chemotherapy response kinetics and can be identified using RECIST. In contrast, the latter 2 outcomes cannot be captured by RECIST and patients would be classified as having RECIST progressions and withdrawn from study. Using irRC, total disease burden is measured on a continuous scale and percent change between measurement times is used to quantify disease response as an immune-related complete response, immune-related partial response, immune-related stable disease, and immune-related progressive disease using the same categorical thresholds as defined under the standard WHO response criteria[17].

Taking into account the FDA guideline which underlines that conventional tumor assessment may not be appropriate for clinical trials of immunotherapies, the response should be based on both RECIST and irRC for treatment effect evaluations[17].

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor, burden), *%	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓	Absent/Stable	Any	irSD
↓	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

Table 2. adapted from Wolchok et al. 2009[19] Derivation of irRC overall response

**Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm); †Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 week apart.*

Immune-related response criteria

Immune-related response criteria were developed on the basis of bidimensional measurement of tumor lesions as done in the WHO criteria to adequately characterize particular response patterns observed after treatment with immunotherapy. Two major changes were implemented: (1) the size of individual lesions is added up to the total tumor burden and (2) transient increase in size of individual lesions beyond 25% or transient appearance of new lesions are not to be taken into account (both of which instances qualify as progressive disease following the standard WHO or RECIST criteria)[19].

Antitumor response is based on total measurable tumor burden.

WHO criteria do not require to measure the new lesions and do not include new lesion measurements in the characterization of evolving tumor burden. The new classification takes into account index and measureable new lesions. At baseline, tumor assessment consists of the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions). The total tumor burden which consist of the SPD of index lesions and of new, measurable lesions is evaluated at each subsequent assessment.

Antitumor response is based on the assessment of tumor burden; in the WHO criteria the appearance of new lesions always represents progressive disease, whereas according to the irRC, the appearance of new lesions does not automatically represent progression and could even lead to a response (but precludes complete response). Detailed differences between the irRC, RECIST and the WHO response criteria are described in the **Table 3.**

Percentage changes in tumor burden describe the size and growth kinetics of both index and new lesions as they appear. The response in lesions is defined at each assessment point based on the change in tumor burden relative to baseline measurements.

The definition of confirmation of progression represents an increase in tumor burden ≥ 25% compared with the nadir at two consecutive time points at least 4 weeks apart.

Confirmation of progression by repeated scans should be considered in patients with stable performance status, without significantly deteriorated laboratory results and with moderate tumor growth demonstrated during the physical exam or on radiographic imaging. Withdrawal of potentially beneficial immunotherapy should be avoided in those patients.

Even if new lesions are present, it could be considered patients will achieve irPR or irSD, as long as they met the described threshold of response. Moreover, irSD does not require confirmation in a second assessment. The confirmation of disease progression allows to capture all types of response according to the irRC as in many late-responding patients the response occurs within 4 weeks after the initial progression.

After the new criteria were formulated, they were evaluated in series of large, multinational studies of ipilimumab in the treatment of advanced (unresectable stage III or stage IV) melanoma[19].

IrCR, irPR, irSD include all patients who met the WHO criteria for CR, PR, SD as well as those who shift from WHO PD. Of 57 patients treated with ipilimumab and classified as PD with WHO criteria, 22 achieved objective response according to irRC: 5 had irPR and 17 had irSD[19].

Wolchok et al 2009[19] presents also an analysis of overall survival of three patient groups: (1) patients who achieve CR, PR and SD according the WHO criteria, (2) patients who achieve irRP or irSD and (3) patients with PD and patients with an unknown disease status. The analysis revealed comparable survival among patients from first two group, thus suggesting that by using irRC it is possible to identify the subpopulation of patients with favorable survival among patients classified as PD in accordance with WHO criteria. These findings emphasize the need to use the irRC evaluation criteria in order to identify the population of patients who benefit most from continuation of immunotherapy.

Review of clinical trials analysing immunotherapy for cancer patients

Detailed description of aim, the methodology of review and the summary of endpoints evaluated in the clinical trials assessing immunotherapeutic agents in comparison to standard chemotherapy/placebo and between two immunotherapeutic agents in the treatment of cancer patients are presented in **Table 4**.

Table 4 ▶

	WHO[33]	RECIST 1.1.[34]	irRC[19]
New measurable lesions (i.e. ≥5 × 5 mm)	Always represent PD	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e. < 5 × 5 mm)	Always represent PD	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR (best overall response) of CR, PR, SD and PD		Contribute to defining irCR (complete disappearance required)
CR (complete response)	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	(1) Disappearance of all target lesions(2) Normalization of tumor marker level for non-target lesions(3) Any pathological lymph nodes must have reduction in short axis to(4) Confirmation is required at least 4 weeks later	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
PR (partial response)	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 weeks apart, in the absence of new lesions or unequivocal progression of non-index lesions	(1) At least a 30% decrease in the sum of diameters of target lesions, taking the baseline sum diameters as reference(2) Confirmations is required at least 4 weeks later	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
SD (stable disease)	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	Neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for PD, taking the smallest sum of diameters on study as reference	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD (progressive disease)	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	(1) At least a 20% increase in the sum of diameters of target lesions, taking the smallest sum on study as references(2) In addition to the relative increase of 20% the sum must also demonstrate an absolute increase of at least 5 mm(3) Unequivocal progression of existing non-target lesion(4) The appearance of one or more new lesion is also considered progression	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

Table 3. Immune response criteria (irRC), RECIST version 1.1. and WHO response criteria which provide the definitions of the criteria used to determine objective tumor response (target and non-target lesions)

Aim	The aim of this targeted review was to present the results of pivotal clinical trials analysing the efficacy of immunotherapeutic agents for the treatment of cancer patients and to identify the endpoints evaluated in included clinical trials.
Methodology	The trials which assess the efficacy of immunotherapeutic agents – ipilimumab, nivolumab, pembrolizumab and sipuleucel-T – were searched.The population, according to the indications of the analysed agents were: melanoma, non-small cell lung cancer and prostate cancer.The pivotal, randomized clinical trials were identified. The comparison between the immunotherapeutic agents versus standard chemotherapy/placebo or comparison between two immunotherapeutic agents were considered.The studies which assessed the response with the different response criteria (RECIST v1.1. and irRC) were also included.The targeted, non-systematic search for pivotal randomized clinical trials was performed in November 2015 in PubMed.
Conclusions	The most commonly evaluated endpoints were: overall survival (median or 1,2,3-year survival), as well as response rate (assessed with mWHO, RECIST or irRC criteria); time to progression, time to response and duration of response. The immunotherapeutic agents significantly prolong the survival in comparison to standard chemotherapy and resulted in higher response rate. The response obtained with immunotherapy was durable and often exceeded the trials' follow-up period.Progression-free survival was comparable for immunotherapy and chemotherapy/placebo in majority of reviewed trials – according to the investigators the reason for lack of difference is using the mWHO or RECIST criteria which do not take into account possible response after initial increase in burden disease, which results in false-positive disease progression. There were proven disease regression/response achieved beyond the disease progression according the RECIST criteria. These results confirmed the need for applying immune related response criteria for evaluation of the efficacy of immunotherapeutic agents. For vaccine trials was also proven beneficial effect on survival while no effect on progression-free survival was reported.Disappointing is the lack of patients-oriented endpoints, e.g. assessing quality of life in analysed trials.

	Overall survival	Progression free survival /Time to progression	Response rate	Time to response	Duration of response	COMMENT ON EVALUATED ENDPOINTS
Indication: ADVANCED MELANOMA						
ipilimumab vs gp100 (Hodi 2010 [36])	+	+	+	+	+	The original primary endpoint was the best overall response rate (the proportion of patients with a partial or complete response), but on the basis of phase 2 data and in alignment with another ongoing phase 3 trial of ipilimumab involving patients with metastatic melanoma the primary end point was amended to overall survival in the ongoing blinded study.
ipilimumab vs DTIC (Robert 2011 [37])	+	+	+	+	+	Initial progression-free survival was to be the primary end point. Emerging data from other ipilimumab trials suggested that conventional definitions of disease progression and response incompletely reflect overall survival among patients who appear to have a long-term benefit the primary endpoint was changed from progression-free survival to overall survival before the treatment assignments were revealed.Secondary end points included: progression-free survival, the rate of best overall response (the proportion of patients who had a complete or partial response),the rate of disease control (defined as a complete response, a partial response, or stable disease), the time to a response,the duration of the response safety.
nivolumab vs dacarbazine (Robert 2015 [41])	+	+	+	+	+	The primary end point was overall survival.Secondary end points included: investigator-assessed progression-free survival, objective response rate, PD-L1 expression in the tumor.

	Overall survival	Progression free survival /Time to progression	Response rate	Time to response	Duration of response	COMMENT ON EVALUATED ENDPOINTS
nivolumab vs chemotherapy (Weber 2015 [42])	-^	+	+	+	+	Primary endpoints were an estimation of the proportion of patients who achieved an objective response and a comparison of overall survival between the two groups. Secondary endpoints were: progression-free survival PD-L1 expression overall survival health-related quality of life [^The investigators placed the information that assessment of overall survival will be performed when the minimum number of events is achieved for all randomly allocated patients, along with the final progression-free survival analysis]
pembrolizumab vs chemotherapy (Ribas 2015 [44])	-^	+	+	+	+	The primary endpoint was progression-free survival (the time from randomisation to first documented disease progression per RECIST v1.1 by independent central review or death from any cause, whichever occurred first). [^Overall survival, the time from randomisation to death from any cause, will be the primary endpoint at final analysis]
pemrolizumab vs ipilimumab (Robert 2015 [45])	+	+	+	+	+	Primary endpoints were progression-free survival (defined as the time from randomization to documented disease progression according to RECIST or death from any cause) and overall survival(defined as the time from randomization to death from any cause).Secondary end points included: objective response rate (defined as the percentage of patients with complete or partial response according to RECIST), the duration of response (defined as the time from the first documented response to radiologic progression according to RECIST), safety
nivolumab vs ipilimumab vs nivolumab+ipilimumab (Larkin 2015 [48])	+	+	+	+	-	Progression-free survival and overall survivalwere co-primary end points.Secondary endpoints included: objective response rate, tumor PD-L1 expression as a predictive biomarker for efficacy outcomes, safety
nivolumab+ipilimumab vs ipilimumab (Postow 2015 [49])	-	+	+	+	-	The primary endpoint was the rate of investigator-assessed, confirmed objective response.Secondary end points included: investigator-assessed progression-free survival the objective response rate progression-free survival safety.
pembrolizumab - two doses (Hamid 2013 [46])	-	-	+	-	-	Objective Response Rate assessed with irRC was the primary endpoint. The study compare response assessed with two criteria:RECISTv1.1 and irRC.

	Overall survival	Progression free survival /Time to progression	Response rate	Time to response	Duration of response	COMMENT ON EVALUATED ENDPOINTS
pembrolizumab - two doses (Robert 2014)	-	+	+	+	+	The primary study endpoint was the overall response rate (ORR) according to RECIST (version 1.1)as assessed by independent central review.ORR was also assessed according to immune-related response criteria by the investigator. The definition of ORR was the percentage of patients who achieved a best overall response of confirmed complete or partial response.Key secondary endpoints included: response duration (ie, time from best overall response of partial or complete response to time of first documented disease progression), PFS (ie, time from treatment initiation to time of first documented disease progression or death due to any cause), overall survival (ie, time from treatment initiation to death due to any cause).
Indication: NON-SMALL CELL LUNG CANCER						
nivolumab vs docetaxel (Brahmer 2015 [43])	+	+	+	+	+	The primary end point was overall survival. Initially, confirmed objective response rate was also a primary endpoint, but on the basis of mature data regarding the objective response rate in an expanded cohort of patients with NSCLC, the current trial was amended before the planned interim analysis to make overall survival the sole primary end point. The rate of investigator-assessed confirmed objective response was modified to be the first secondary end point.Additional end points included: progression-free survival, patient-reported outcomes, tumor PD-L1 expression, safety.
Indication: PROSTATE CANCER						
sipuleucel-T vs placebo (Kantoff 2010 [51])	+	+	+	-	-	Overall survival was the primary study endpoint. The time to objective disease progression and the time to disease-related painwere the original co-primary endpoints, but after a review of survival results from two previous phase 3 trials with a similar design and before the unblinding of group assignments in this study, overall survival was made the primary endpoint.Secondary endpoints were: the time to objective disease progression; the time to disease-related pain.
sipuleucel-T vs placebo (Small 2006 [52])	+	+	-	-	-	Time to progression was chosen as a primary endpoint.
sipuleucel-T vs placebo (Higano 2009 [50])	+	+	-	-	-	The primary objective was the time to disease progression.

Table 4. Methodology and the summary of endpoints evaluated in clinical trials analysing immunotherapy in comparison to conventional therapies for cancer patients included in review

Endpoints used to assess the immunotherapy included: overall survival, progression-free survival/time to progression, time to response, overall response and clinical benefit rate.

The approval of ipilimumab was based on its beneficial effect on survival of advanced melanoma cancer[36,37]. In both studies (in comparison to gp100 vaccine and to chemotherapy) despite the prolonged survival, time to progression was similar in compared groups. The response was assessed with mWHO criteria which do not take into account possible response after initial increase in disease burden – if the response would be assessed with ir-RC the rate of progression would differ significantly between compared groups. Achieved response after ipilimumab treatment was durable.

Two important RCTs[43,44] were performed to assessed the efficacy of nivolumab in comparison to standard chemotherapy in melanoma patients. Only one of them[43] assessed the median overall survival and 1-year survival rate – and showed improved survival in nivolumab group in comparison to chemotherapy as well as improvement in progression-free survival and response rate. In second study[42] the significant difference was showed for the objective response and duration of response but not in progression free survival. The absence of significant difference in progression-free survival could be attributed in part to the false-positive disease progression in the nivolumab group due to the use of RECIST version 1.1 as opposed to ir-RC for tumour assessment. The fact that some patients showed substantial tumour regression beyond RECIST 1.1-defined progression suggests that these response criteria might not fully take account of the potential benefit of nivolumab, and this result might account for the absence of a large difference observed in progression-free survival[42].

Notably, the proportion of patients with an objective response was the chosen primary endpoint for both nivolumab and pembrolizumab development programmes for treatment of patients with melanoma and both agents were approved by the FDA on the basis of responses of long duration[42].

The approval of nivolumab for the treatment of non-small-cell lung cancer was based on the result of RCT, which analyse the following endpoints: median overall survival, 1-year survival rate, progression free survival and 1-year PFS, time to response, duration of response and response rate assessed with RECIST v1.1. Nivolumab in comparison to chemotherapy showed clinically meaningful survival benefit as well as significant improvement in terms of: progression-free survival, duration of response and response rate[43].

The efficacy of pembrolizumab was proven in two RCTs - in comparison to chemotherapy[44] or ipilimumab[45]. In both trials primary endpoint was progression-free survival assessed with RECIST v1.1 criteria. Moreover, in Ribas 2015[44] PFS was also was assessed with modified RECIST v1.1. which require to confirm the progression after 4 weeks (similar to irRC criteria) and more meaningful differences between analysed groups were observed with these modified criteria. In another two trials[46,47] response rate was assessed with the use of two different criteria: RECIST v1.1 and ir-RC. Majority of patients analysed in Hamid 2013had a reduction in tumor burden and some of them achieve durable objective response with continued treatment after having stable disease. Similarly, in Robert 2014 was found that some patients who had a progressive disease according to RECISTv1.1 showed no progression after 24 weeks of treatment and had partial response using irRC. A high percentage of patients were progression free at 24 weeks. The finding that 19% of patients with progressive disease as per RECIST were progression free at 6 months as per irRC suggests that conventional use of RECIST might underestimate the therapeutic benefit of pembrolizumab. The finding of delayed response also suggests that additional objective responses will occur with longer follow-up. Overall, and as was previously suggested for ipilimumab, traditional response criteria might need to be revised for the overall therapeutic benefits of pembrolizumab to be fully appreciated[47].

The comparison between two immunotherapeutic agents (anti-CTLA-4 and anti-PD-1 antibody) was based on evaluation of progression-free survival, time to response and response rate (assessed with RECISTv1.1 criteria) in two RCTs showing the beneficial effect of anti-PD-1 antibody over anti-CTLA-4 antibody[48,49].

The results of three RCTs evaluating the sipuleucel-T were consistent: the vaccines significantly prolonged survival of prostate cancer patients whereas had no beneficial effect on progression-free survival. Moreover, the most beneficial effect occurred after at least 12 weeks of treatment due to delayed onset of antitumor responses after active immunotherapy. The conclusion from those trials is that the time to progression may not be an appropriate endpoint when testing the effect of immunotherapy as there is no a strong correlation between disease progression and overall survival[50-52].

The important aspect is that results of clinical trials assessing vaccines and anti-CTLA-4 or anti-PD-1 antibodies showed improvement in OS but no significant effect on PFS and TTP[17]. Due to lack of a simple correlation between the presence or absence of the response and improvement in overall survival for immunotherapies, it was proposed to use immune-related progression free

survival and overall survival as co-primary endpoints, with positive trials in case of a statistically significant benefit in either of them[17].

Based on the all analysed trials it could be concluded that immunotherapy (ipilimumab, nivolumab, pembrolizumab) is associated with long-term responses in contrast to targeted therapies, such as BRAF inhibitors (vemurafenib, dabrafenib), are associated with high response rates and a rapid effect, but the responses are often short-lived[41,46,47].

The results of the performed review are similar to the results of published systematic review, which aimed to identify the endpoints evaluated in clinical trials assessing therapies for malignant melanoma, non-small cell lung cancer and renal cell carcinoma[35]. The review covered a period between 2007 and 2012 and included systematic reviews and HTA reports. The most commonly used endpoints in the identified sources were: response rate or objective response rate, disease-free survival, progression-free survival, time to progression, median OS, recurrence rate and quality of life[35].

Median OS is calculated as a point in time when 50% of patients are still alive. The authors of the review underline that median OS could not serve as an adequate measure to evaluate the effect of therapies with potential long-term benefit in contrast to cytotoxic drugs or targeted therapies which causes rapid initial reduction in tumor volume but provides no or low prolonged benefit. This measurement do not provide information on duration of survival, especially the small proportion of patients who occupy the tail of the survival curve. To provide the most appropriate measure, the reviewed publications used, apart from median OS, also: robust HR (equal or less than 0.8), mean OS or cure fraction (the proportion of patients who survive and no longer experience excess mortality rate of the disease)[35].

The most commonly accepted progression-related endpoints were surrogates for the OS benefit, namely: PFS and DFS. When considering these endpoints, it should be kept in mind that a correlation between PFS and DFS and overall survival has been proven only for some cancer types. FDA allows for approval of agents on the basis of DFS, PFS or TTP and since 2012, EMA accepts PFS and DFS as primary endpoints in oncology trials. The important issue is to choose adequate endpoints for the analyzed intervention – DFS and PFS might underestimate the efficacy of immunotherapies which is associated with prolonged disease stabilization or unconventional responses, but subsequently could lead to a partial or even complete response and may translate into a prolonged survival benefit[35].

Conclusion

Overall survival remains the gold standard for efficacy assessment. However, to properly assess immunotherapy, clinical trial should implement the statistical methods which take into account delayed separation in the Kaplan-Meier curves of the control versus experimental groups (which is the consequence of specific mechanism of action of immunotherapeutic agents) and allow to avoid loss of statistical power and to compute the required number of events for final analysis. There is no simple correlation between PFS and OS for immunotherapy, especially if the progression is assessed with conventional criteria (WHO or RECIST) designed to assess the effect of cytotoxic drugs on the basis of tumor shrinkage. Immune related response criteria should be adopted in clinical trials to adequately cover the patterns of response (including the disease regression after initial increase in tumor burden) observed among cancer patients treated by immunotherapeutic agents. ■

Table 5 ▶

Comparison of anti-PD-1 antibodies (nivolumab) and chemotherapy based on RCTs						
Anti-CTLA-4 antibody (ipilimumab)						
Outcomes		Hodi 2010 [36] - REGISTRATION TRIAL			Robert 2011 [37]	
		IPI alone N=137	gp100 alone N=136	IPI+gp100 N=403	IPI+DTIC N=250	PL+DTIC N=252
Median overall survival, months (95% CI)		10.1 (8.0; 13.8)	6.4 (5.5; 8.7)	10.0 (8.5; 11.5)	11.2 (9.4; 13.6)	9.1 (7.8; 10.5)
HR (95%CI) for death, IPI vs control		0.66 (0.51-0.87) p=0.003	-	0.68 (0.55-0.85)p<0.001	0.72; p<0.001	-
1 year survival, % (95% CI)		45.6	25.3	43.6	47.3 (41.0-53.6)	36.3 (30.4-42.4)
2 years survival, % (95% CI)		23.5	13.7	21.6	28.5 (22.9-34.2)	17.9 (13.3-22.8)
3 years survival, % (95% CI)		-	-	-	20.8 (15.7-26.1)	12.2 (8.2-16.5)
Progression free survival, median (95% CI)		2.86 (2.76; 3.02)	2.76 (2.73; 2.83)	2.76 (2.73; 2.79)	NS	
Time to response, mean (95% CI)		3.18 (2.75-3.60)	2.74 (2.12-3.37)	3.32 (2.91-3.74)	-	
Duration of response, median (95% CI)		NR (28.1-NR)	NR (2.0-NR)	11.5 (5.4-NR)	19.3 (12.1-26.1)	8.1 (5.19-19.8)
Best overall response rate, % (95% CI)		10.9 (6.3-17.4)	1.5 (0.2-5.2)	5.7 (3.7-8.4)	15.2	10.3
Disease control rate*, % (95% CI)*the percentage of patients with PR, CR or SD according to the mWHO criteria		28.5 (21.1-6.8)	11.0 (6.3-17.5)	20.1 (21.1-36.8)	33.2	30.2
Any event, n (% of patients)	Grade 3	49 (37.4)	54 (40.9)	147 (38.7)	99 (40.1)	45 (17.9)
	Grade 4	11 (8.4)	8 (6.1)	26 (6.8)	40 (16.2)	24 (9.6)
Any immune-related event, n (% of patients)	Grade 3	16 (12.2)	4 (3.0)	37 (9.7)	78 (31.6)	8 (3.2)
	Grade 4	3 (2.3)	0 (0)	2 (0.5)	25 (10.1)	7 (2.8)

Outcomes	Robert 2015 [41] REGISTRATION TRIAL		Weber 2015 [42] REGISTRATION TRIAL	
	Nivolumab N=210	Dacarbazine N=208	Nivolumab N=120	Chemotherapy (dacarbazine or paclitaxel+carboplatin) N=47
Median OS, months (95% CI)	NR	10.8 (9.3; 12.1)	N/A	N/A
1 year survival, % (95% CI)	72.9 (65.5; 78.9)	42.1 (33.0; 50.9)	N/A	N/A
OS (HR=99.79% CI)	0.42 (0.25; 0.73),p<0.001		N/A	N/A
PFS in months, median (95% CI)	5.1 (3.5; 10.8)	2.2 (2.1; 2.4)	4.7 (2.3-6.5)	4.2 (2.1-6.3)
HR (95% CI/99% CI) of progression	0.43 (0.34; 0.56)p<0.001		0.82 (0.32-2.05)NS	
Objective response, n [% (95%CI)]	84 [40.0 (33.3; 47.0)]	29 [13.9 (9.5; 19.4)]	38 [31.7 (23.5; 40.8)]	5 [10.6 (3.5; 23.1)]
	Difference = 26.1 (18.0-34.1) OR (95% CI) = 4.06 (2.52-6.54), p<0.001		-	
Time to response in months, median (range)	2.1 (1.2-7.6)	2.1 (1.8-3.6)	2.1 (1.6; 7.4)	3.5 (2.1; 6.1)
Duration of response in months, median (95% CI) [range]	NR [0.0-12.5]	6.0 (3.0-NR) [1.1-10.0]	NR (1.4-10.0)	3.5 (1.3-3.5)

Comparison of anti-PD-1 antibodies (nivolumab) and chemotherapy based on RCTs				
6-month PFS, % (95% CI)	-	-	48 (38-56)	34 (18-51)
Treatment related AEs of 3 or 4 grade, n (%)	24 (11.7)	36 (17.6)	(9)	(31)
Treatment related SAEs of 3 or 4 grade, % of patients	-	-	(5)	(9)

Nivolumab in the treatment of non-small cell lung cancer		
Outcome	Brahmer 2015 [43]	
	Nivolumab - 3 mg/kg every 2 weeks N=135	Docetaxel - 75 mg/m2 every 3 weeks N=137
OS in months, median (95% CI)	9.2 (7.3-13.3)	6.0 (5.1-7.3)
HR for death (95% CI), p value	0.59 (0.44-0.79), p<0.001	-
1-year survival rate, % (95% CI)	42 (34-50)	24 (17-31)
Objective response, n [% (95% CI)]	27 [20 (14-28)] OR=2.6 (1.-5.5), p= 0.008	12 [9 (5-15)] -
PFS in months, median (95% CI)	3.5 (2.1-4.9)	2.8 (2.1-3.5)
HR (95% CI) for death or disease progression, p-value	0.62 (0.47-0.81), p<0.001	
1-year PFS rate, % (95% CI)	21 (14-28)	6 (3-12)
Time to response in months, median (range)	2.2 (1.6-11.8)	2.1 (1.8-9.5)
Duration of response in months, median (range)	NR (2.9-20.5)	8.4 (1.4-15.2)

Comparison of anti-PD-1 antibodies (pembrolizumb) and chemotherapy based on RCTs						
Outcomes	Ribas 2015 [44] REGISTRATIONAL TRIAL			Robert 2015 [45] REGISTRATION TRIAL		
	Pembrolizumab		Chemotherapy N=179	Pembrolizumab		ipilimumab 3 mg/kg N=278
	2 mg/kg N=180	10 mg/kg N=181		10 mg/kg every 2 wks N=279	10 mg/kg every 3 wks N=277	
1-year survival, %	-	-	-	74.1	68.4	58.2
HR (95% CI) for death, vs ipilimumab group	-	-	-	0.63 (0.47-0.83) p<0.0005	0.69 (0.52-0.90) p=0.0036	-
Median OS	-^	-^	-^	NR	NR	NR
PFS in months, median (95% CI)RECIST v1.1mRECIST v1.1	2.9 (2.8-3.8)4.2 (3.1-6.2)	2.9 (2.8-4.7)5.6 (4.2-7.7)	2.7 (2.5-2.8)2.6 (2.5-2.8)	5.5 (3.4-6.9)-	4.1 (2.9-6.9)-	2.8 (2.8-2.9)-
HR for death or disease progressionRECIST v1.1mRECIST v1.1	0.57 (0.45-0.73), p<0.00010.45 (0.35-0.57), p<0.0001	0.50 (0.9-0.64) p<0.00010.39 (0.30-0.51) p<0.0001	-	0.58 (0.46-0.72) p<0.001-	0.58 (0.47- 0.72) p<0.0001-	
PFS at 6 months, % (95% CI)RECIST v1.1mRECIST v1.1	34 (27-41)43 (35-50)	38 (31-45)48 (40-55)	16 (10-22)17 (12-23)	47.3-	46.4-	26.5-
PFS at 9 months, % (95% CI)RECIST v1.1mRECIST v1.1	24 (17-31)35 (27-43)	29 (23-37)38 (0-46)	8 (4-14)10 (6-16)	N/A	N/A	N/A
CR, n (%)	4 (2)	5 (3)	0	14 (5.0)	17 (6.1)	4 (1.4)
PR, n (%)	34 (19)	41 (23)	8 (4)	80 (28.7)	74 (26.7)	29 (10.4)
SD, n (%)	32 (18)	31 (17)	33 (8)	37 (13.3)	39 (14.1)	46 (16.5)
PD, n (%)	84 (47)	86 (48)	111 (62)	106 (38.0)	114 (41.2)	136 (48.9)

Comparison of anti-PD-1 antibodies (nivolumab) and chemotherapy based on RCTs						
Overall response, n [% (95% CI)]	38 (21 (15-28)]	46 [25 (19-23)]	8 [4 (2-9)]	94 [33.7 (28.2-39.6)]	91 [32.9 (27.4-38.7)]	33 [11.9 (8.3-16.3)]
Difference in overall response, vs chemotherapy, % (95% CI), p-value	13 (7-21), p<0.0001	18 (11-27), p<0.0001	-	16.1 (7.8-24.5) p<0.001	17.2 (9.5-25.6) p<0.001	-
TTR in weeks, median (IQE)/ in days, median (range)	13 (12-18)	15 (12-18)	13 (12-18)	86 (32-212)	85 (36-251)	87 (80-250)
Duration of response in days, median (range)	N/A	N/A	N/A	251 (42-251)	NR (42-246)	NR (33-239)
Treatment related AEs of grade 3 or 4, % of pts	20 (11)	25 (14)	45 (26)			

Anti-PD-1 antibody (pembrolizumab)						
Outcomes	Hamid 2013 [46] pembrolizumab at a dose of 10 mg/kg every 2 or 3 weeks or 2 mg/kg every 3 weeks					
	RECIST v1.1			ir-RC		
	10 mg/kg every 2 weeks	10 mg/kg every 3 weeks	2 mg/kg every 2 weeks	10 mg/kg every 2 weeks	10 mg/kg every 3 weeks	2 mg/kg every 2 weeks
Overall response (complete response + partial response), n/N (%)						
No prior ipilimumab	19/39 (49)	5/19 (26)	5/20 (25)	23/41 (56)	8/24 (33)	3/22 (14)
Prior ipilimumab	8/13 (62)	7/26 (27)	-	9/16 (56)	7/32 (22)	-
Total	44/117 (38)			50/135 (37)		
Duration of response in months, range						
No prior ipilimumab	1.9-10.8	2.6-5.6	2.1-5.5	-	-	-
Prior ipilimumab	2.8-8.3	2.8-8.3	-	-	-	-
Total	1.9-10.8			-		
PFS, median	>7 months (N=135)					
Outcomes	Robert 2014, pembrolizumab [47]					
	RECIST			ir-RC		
	2 mg/kg N=81		10 mg/kg N=76	2 mg/kg N=86		10 mg/kg N=84
CR, n (%)	1 (1)		1 (1)	3 (3)		0 (0)
PR, n (%)	20 (25)		19 (25)	21 (24)		27 (32)
SD, n (%)	20 (25)		18 (24)	31 (35)		27 (32)
PD, n (%)	27 (33)		31 (41)	24 (27)		19 (23)
ORR, % (95% CI)	26 (17; 37)		26 (17; 38)	27 (18; 37)		32 (22; 3)
Disease control rate, % (95% CI)	51 (39; 62)		50 (38; 62)	62 (51; 72)		64 (53; 74)
TTR in weeks, median (range)	12 (11; 3)		12 (7; 17)	12 (11; 24)		12 (7; 39)
Response duration in weeks, median (range)	NR (6-37)		NR (8-37)	NR (12-42)		NR (4-37)
Overall survival at 1 year, % (95%)	58% (47–68)		63% (51–72)	-		-
HR (95% CI) for death, pembrolizumab 2 mg/kg vs 10 mg/kg	1·09 (95% CI 0·68–1·75)					
PFS in weeks, median (95% CI)	22 (12; 36)		14 (12; 24)	14 (12; 24)		35 (24; NR)
PFS rate at 24 weeks, % (95% CI)	45 (34-55)		37 (27-48)	57 (46-67)		57 (45-67)

Anti –PD-1 antibody vs anti-CTLA-4 antibody						
Outcomes		Larkin 2015 [48]			Postow 2015 [49]	
		Nivolumab	Ipilimumab	Nivolumab+Ipilimumab	Nivolumab+Ipilimumab	Ipilimumab
Median OS (95% CI), months		-^^			not assessed	not assessed
OS (HR=95% CI)		-^^			not assessed	
1-year survival rate (% of patients)		-^^			not assessed	not assessed
Median PFS (95% CI), months		6.9 (4.3; 9.5)	2.9 (2.8; 3.4)	11.5 (8.9-16.7)	NR	4.4 (2.8-5.7)
					8.5 (2.8-not estimated)	2.7 (1.0-5.4)
PFS, (HR=99.5% CI) vs ipilimumab		0.57 (0.43-0.76) p<0.001	-	0.42 (0.31-0.57) p<0.001	0.40 (0.23; 0.68), p<0.001	
					0.38 (0.15; 1.00)	
OR (complete response or partial response, RECIST v1.1.), % (95% CI); n/N (% of patients)		43.7 (8.1-49.3) 138/316	19.0 (14.9-23.8) 60/315	57.6 (52.0-63.2) 181/314	44/72 [61(49-72)]	4/37 [11(3-25)]
					12/23 [52 (31-73)]	1/10 [10 (0-45)]
Odd ratio (95% CI) vs ipilimumab		3.40 (2.02-5.72) p<0.0001	-	6.11 (3.59-10.38) p<0.001	12.96 (3.91-45.49), P<0.001	
					-	
Time to objective response in months, median (range)		2.78 (2.3-12.5)	2.79 (2.5-12.4)	2.76 (1.1-11.6)	54	24
Treatment-related grade 3-5 adverse event, n/N (%)		51/313 (16.3)	85/311 (27.3)	172/313 (55.0)	51/94 (54)	11/46 (24)
Most common grade 3-5 adverse event of (% of patients)	diarrhoea	7/13 (2.2)	19/311 (6.1)	29/313 (9.3)	10/94 (11)	5/46 (11)
	colitis	2/313 (0.6)	27/311 (8.7)	24/313 (7.7)	16/94 (17)	3/46 (7)

Sipuleucel-T as immunotherapy for castration–resistant prostate cancer						
Outcome	Kantoff 2010 [51]		Small 2006 [52]		Higano 2009 [50]	
	Sipuleucel-T N=341	Placebo N=171	Sipuleucel-T N=82	Placebo N=45	Sipuleucel-T N=147	Placebo N=78
OS in months, median (95% CI)	25.8	21.7	25.9 (20.0-31.9)	21.4 (12.3-25.8)	23.2 (19.0-31.0)	18.9 (13.5-25.3)
OS (HR=95% CI), p	0.78 (0.61; 0.98), p=0.03		1.70 (1.13; 2.56), p=0.01		1.50 (1.10; 2.05), p=0.011	
3-year survival, % of patients	31.7	23.0	34	11	-	-
TTP in weeks, median (95% CI)	14.6	14.4	11.7 (9.1-16.6)	10.0 (8.7-13.1)	11.1 (10.0-16.3)	9.7 (8.7-13.3)
TTP (HR=95% CI)	0.95 (0.77; 1.17), p=0.63		1.45 (0.99; 2.11), p=0.052		1.26 (0.95; 1.68), p=0.111	
ImmuneResponse, % of patients	66.2	2.9	-		-	
Any AEs of grade 3-4, % of patients	31.7	35.1	24.4	24.4	33.3	27.6

Table 5. Results of clinical trials included in the targeted review

NR – not reached; N/A – not assessed; NS - not significant; ^Immature overall survival data, which were evaluated at a small α level at this interim analysis, did not meet the prespecified 0.25% superiority threshold for each pembrolizumab dose compared with chemotherapy (data not shown). Final overall survival will be assessed after 370 deaths; ^^ Data on overall survival are insufficiently mature to present; modified RECIST v1.1 (confirmation of disease progression on a scan ≥4 weeks after initial evidence of disease progression was required, which is similar to irRC).

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