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Immune checkpoint inhibitors plus chemotherapy versus chemotherapy or immune checkpoint inhibitors for first- or second-line treatment of advanced gastric and gastro-esophageal junction cancer (Protocol)

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Immune checkpoint inhibitors plus chemotherapy versus chemotherapy or immune checkpoint inhibitors for first- or second-line treatment of advanced gastric and gastro-esophageal junction cancer.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD013369.
DOI: 10.1002/14651858.CD013369.

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[Intervention Protocol]

Immune checkpoint inhibitors plus chemotherapy versus chemotherapy or immune checkpoint inhibitors for first- or second-line treatment of advanced gastric and gastro-esophageal junction cancer

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Editorial group: Cochrane Upper GI and Pancreatic Diseases Group.
Publication status and date: New, published in Issue 7, 2019.

Citation: Özdemir BC, Moehler M, Syn NLX, Tai BC, Wagner AD. Immune checkpoint inhibitors plus chemotherapy versus chemotherapy or immune checkpoint inhibitors for first- or second-line treatment of advanced gastric and gastro-esophageal junction cancer. *Cochrane Database of Systematic Reviews* 2019, Issue 7. Art. No.: CD013369. DOI: 10.1002/14651858.CD013369.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and safety of immune checkpoint inhibitors, alone or in combination with chemotherapy, in people with advanced gastric and gastroesophageal junction adenocarcinoma in first and subsequent treatment lines.

BACKGROUND

Description of the condition

Gastric cancer is a major health problem worldwide. Every year about 1 million people are diagnosed with gastric cancer (WHO 2018). It ranks as the 4th most common cancer and 3rd leading cause of cancer-related death in both sexes, with two-fold higher age-standardized incidence rates in men. Gastric cancer incidence shows significant variation internationally, with about half of the cases occurring in East Asia (Ferlay 2015; WHO 2018).

Gastric cancers can be classified according to:

1. localization: cardia (proximal) or non-cardia (distal), as well as gastro-esophageal junction adenocarcinomas;
2. histology: intestinal (well-differentiated) or diffuse (undifferentiated);
3. molecular subtype (CGARN 2014):
   a. Epstein-Barr virus positive (EBV)
   b. microsatellite instable (MSI)
   c. genomically stable (GS)
   d. chromosomally instable (CNI).

Furthermore, from a therapeutic perspective, HER-2-positive and HER-2-negative cancers need to be distinguished. Other biomarkers, such as Claudion or FGFR, might be of relevance in the future.

Risk factors for gastric cancer development include infections with *Helicobacter pylori*, atrophic gastritis and intestinal metaplasia or dysplasia resulting from gastro-esophageal reflux (Karimi 2014).

During the last three decades, incidence rates for non-cardia cancers have been declining worldwide, which is attributed mainly to eradication of *Helicobacter pylori*. In contrast, cardia cancer incidence rates are stable or increasing, especially in Western countries, possibly as a result of an increasing prevalence of obesity and gastro-esophageal reflux, and pointing to differences in the pathogenesis of cardia and non-cardia cancers (Karimi 2014). About 10% of gastric cancer cases occur as part of inherited cancer predisposition syndromes due to germline mismatch repair deficiency or p53 mutations (Heong 2018), but only 1% to 3% of the cases are caused by germline E-cadherin (CDH1) mutations inherited in an autosomal dominant pattern, giving rise to early onset diffuse hereditary gastric cancer (Oliveira 2004).

Despite a worldwide trend towards a decreasing mortality (Ferro 2014), in developing countries significantly higher mortality rates are observed for both sexes (Ferlay 2015).

In the Western world, most people with gastric cancer are diagnosed with locally advanced or metastatic disease, when surgical treatment is no longer an option. In contrast, in Asia (China, Japan and South Korea), due to the presence of endoscopic screening programs, most cases are diagnosed at an early stage where resection can be performed (Rahman 2014). Systemic chemotherapy remains the standard of care for advanced disease and improves survival and quality of life significantly when compared to best supportive care. However, median survival for people with good performance status treated with chemotherapy alone usually does not exceed nine to 11 months (Wagner 2017).

In HER2-negative advanced gastric cancer, first-line chemotherapy often consists of a doublet including a fluoropyrimidine and a platinum, with or without a taxane (Wagner 2017). An alternative for 5-Fluorouracil (5-FU) is capecitabine, which has the advantage of oral administration. In Asia, 5-FU is often replaced by S1, comprising an oral prodrug of 5-FU combined with gimestat and oteracil, leading to prolonged 5-FU tumor concentrations and decreased toxicity. Its combination with cis- or oxaliplatin is a standard treatment option (Kubota 2008). For HER2-positive patients, the addition of trastuzumab to 5-FU/cisplatin improves median survival significantly, especially in those with strong HER-2 overexpression (IHC 2+ and FISH-positive or IHC 3+) (Bang 2010).

In patients with good performance status, second-line chemotherapy, such as irinotecan, docetaxel or paclitaxel, is associated with a further significant survival benefit over best supportive care alone, in general providing approximately a six-week gain in median overall survival (OS) (Ford 2014; Kang 2012). Overall, and despite all benefits, chemotherapy is not only limited in efficacy, but is also associated with significant toxicities, such as neuropathy and hematological toxicity, which are often dose-limiting and negatively affect the person's quality of life. Apart from trastuzumab, the only other approved targeted treatment of gastric cancer is ramucirumab, a fully human IgG antibody targeting vascular endothelial growth factor receptor-2 (VEGFR-2), which has comparable efficacy to systemic chemotherapy as a single agent (Fuchs 2014), and increases the efficacy of paclitaxel (Wilke 2014) in second-line treatment. Interestingly, important geographical differences in treatment efficacy have been reported in several clinical trials testing targeted therapies such as bevacizumab (AVAGAST) (Ohtsu 2011), cetuximab (EXPAND) (Lordick 2013), trastuzumab (ToGA) (Bang 2010; Hecht 2016), lapatinib (LOGIC) (Hecht 2016), onartuzumab (METGastric) (Shah 2017), ramucirumab (RAINBOW (Wilke 2014), REGARD (Fuchs 2014) and everolimus (GRANITE) (Ohtsu 2013) alone or in combination with chemotherapy in advanced disease. Although these disparities might in part be due to differences in the geographic distribution of gastric cancer subtypes, biological factors, such as differences in T-cell signatures (Lin 2015) and composition of gastric microbiota, also need consideration in this context (Escobar 2014).

However, despite the integration of targeted therapies and all other recent progress, the prognosis of metastatic gastric cancer remains dismal, and more effective and better tolerable treatments are urgently required.

Immunotherapy is currently revolutionizing all fields of oncology, and the recent development of immune checkpoint inhibitors has changed the treatment landscape of many cancer types. Despite the absence of established predictive biomarkers, high PD-L1 expression and mutational load have been correlated with response (Gibney 2016; Rizvi 2015; Snyder 2014). Gastric cancer develops often in the context of chronic inflammation, providing a rationale for the use of immunotherapy. It has been shown that EBV-associated tumors present with elevated PD-L1/2 expression. In addition, microsatellite instable tumors have a hypermutated phenotype and have shown high response rates (around 40%) in clinical trials with various tumor types (Le 2017), leading to the approval of the anti-PD-1 antibody pembrolizumab for tumors with mismatch repair deficiency. Indeed, in a recent comprehensive analysis of 61 Asian people with metastastic gastric cancer treated with anti-PD1 therapy, the overall response rate was 100% in those

with EBV-positive tumors and 85% in those with MSI-high tumors. Moreover, PD-L1 expression is positively associated with response (Kim 2018).

Description of the intervention

The aim of treatment with checkpoint inhibitors is to re-establish and/or increase the host immune responses by overcoming the mechanisms that allow cancer cells to escape the immune system (Syn 2017). The generation of an effective anticancer immune response leading to cancer-cell killing is a tightly regulated multi-step process, also referred to as the 'cancer-immunity cycle' (Chen 2013). In order to induce effective killing of cancer cells, cancer cell antigens released from dying cancer cells must be presented to T-cells by antigen-presenting cells (APCs) which leads to priming and activation of dendritic cells (DCs) and T-cells. These primed cells (cytotoxic T–cells, CTLs) must home to tumors and infiltrate the tumor tissue. Cancer cells that are recognized as foreign by CTLs are killed. This leads to additional cancer antigen release and reinforces the cancer-immunity cycle (Chen 2013). Each step relies on the balance between inhibitory and stimulatory molecules, also called immune checkpoints. While stimulatory factors promote immunity, inhibitors decrease immune activity or prevent autoimmunity, or both. Immune cells residing in tumor tissue, such as T regulatory cells (Tregs), macrophages, and myeloid-derived suppressor cells (MDSCs) are key sources of many of these inhibitory factors (Chen 2013).

Immune checkpoints currently targeted by drugs are CTLA4, PD-1/PD-L1, LAG-3 and TIM-3.

How the intervention might work

Different immune checkpoint inhibitors act on different cell populations to restore anti-cancer immunity: anti-PD-1 antibodies induce the expansion of tumor-infiltrating exhausted-like CD8-T cells, while anti-CTLA-4 antibodies lead to the expansion of inducible T-cell co-stimulator (CD278, ICOS) positive Th1-like CD4 effector cells, as well as specific subsets of exhausted-like CD8-T cells (Wei 2017).

According to preclinical studies, cytotoxic drugs and targeted therapies may synergize with immune checkpoint inhibitors by increasing the immunogenicity of cancer cells and repressing immunosuppressive signaling pathways (Galluzzi 2015). This applies particularly to cisplatin and 5-FU, one of the most commonly used chemotherapy regimens for gastric cancer. Mechanisms for how chemotherapies may enhance the activity of immune checkpoint inhibitors include:

1. Causing new mutations and thereby increasing the mutational load in cancer cells (Szikriszt 2016). Both mutational load and the presence of neoantigen were positively correlated with response to checkpoint inhibitors (Rizvi 2015; Snyder 2014; Syn 2017);
2. Inducing immunogenic cell death through exposure of calreticulin with increased neoepitope presentation by APCs (Galluzzi 2015; Pfirschke 2016);
3. Altering the tumor micro-environment by depleting immunsuppressive Tregs, MDSCs and reactivating exhausted antigen-specific CD8 T-cells (Galluzzi 2015);
4. Normalizing tumor vessels by anti-angiogenic effects (Schwartz 2009), resulting in increased CD8-T cell influx into tumors. The tumor endothelium has the capacity to selectively kill effector T cells but not Tregs through high FasL expression (Motz 2014);
5. Promoting MHC class I expression and components of the antigen presentation machinery in cancer cells (De Biasi 2014);
6. Enhancing the sensitivity of cancer cells to the T-cell effector cytokine interferon y (INFy) by modulating STAT signaling, resulting in diminished cancer cell proliferation and increased cancer cell apoptosis (Hato 2014).

Immune checkpoint inhibition leads to complete and durable tumor responses in about 20% of people treated with melanoma, as a result of an effective endogenous antitumor immunity (Harris 2016). This rate increases to up to 40% upon dual immune checkpoint inhibition (Harris 2016). As with other therapies, tumors might be resistant to immunotherapies right from the start (primary resistance) or acquire resistance after an initial response (Sharma 2017).The mechanisms contributing to resistance are alteration of signaling pathways such as MAPK, PI3K, WNT and INF, absence of neoantigens recognized by the immune system due to a low mutation burden, dedifferentiation of cancer cells with loss of tumor antigen expression, alterations in antigen processing, constitutive PD-L1 expression or lacking HLA expression (Sharma 2017).

Anti-CTLA4 antibodies

CTLA4 is a homolog of CD28. It is expressed at low levels on the surface of T effector cells and abundantly on Tregs. When the T-cell receptor engages in an immune response through recognition of an antigen by the MHC, CTLA4 localizes to the plasma membrane and outcompetes the co-stimulatory molecule CD28 for binding the ligands CD80 (B7-1) and CD86 (B7-2) on APCs by its higher avidity, resulting in inhibition of the T effector cell activation and stimulation of Treg function, resulting in immune tolerance (Peggs 2009).

Anti-CTLA4 antibodies lead to Treg depletion by suppressing CTLA-4-mediated inhibitory signaling and induce an increased anti-tumor immune response through T effector cell proliferation (Chen 2013).

Ipilimumab is a fully humanized IgG1 kappa recombinant monoclonal antibody (mAb) targeting CTLA-4. It modulates the TCR signal and induces Treg depletion in a specific, Fc gamma receptor-dependent manner (Lipson 2011). It is approved for treatment of metastatic melanoma (Hodi 2010). The recommended dose is 3 mg/kg every three weeks for metastatic disease, or 10 mg/kg every three weeks as adjuvant treatment.

Tremelimumab is a fully human IgG2 mAb against CTLA-4. In clinical trials with metastatic melanoma it showed similar response rates to ipilimumab. Notably, a recent analysis of phase I and II tremelimumab trials has revealed long-term responses with 20% five-year survival and 16% 12-year survival (Eroglu 2015; Ribas 2013).

Anti-PD-1 antibodies

Programmed death-1 (PD-1, also known as CD279) is part of the CD28 immunoglobulin superfamily. It suppresses anti-cancer T-cell responses by binding to its ligands PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273). PD-L1 is expressed on tumor cells and PD-L2 is expressed on DCs, macrophages and some B cells. After binding of PD-1 to its ligands, T-cell activation is attenuated (peripheral

tolerance). In contrast to CTLA4, PD-L1 modulates active immune responses in the tumor bed rather than affecting the proliferation or development of T-cells (Chen 2013).

Examples of currently investigated PD-1 inhibitors include:

1. **Nivolumab:** a fully human IgG4 mAb against PD-1. It is approved for treatment of metastatic melanoma, NSCLC, renal cell carcinoma, urothelial carcinoma, head and neck carcinoma and Hodgkin lymphoma. The recommended dose is 240 mg every two weeks;
2. **Pembrolizumab** (formerly known as lambrolizumab): a humanized IgG4 mAb against PD-1. It is approved for treatment of metastatic melanoma, NSCLC, urothelial carcinoma, head and neck carcinoma, Hodgkin lymphoma and MSI-high colorectal cancer. The recommended dose is 200 mg every three weeks;
3. **Pidilizumab:** a humanized IgG1 kappa recombinant mAb targeting PD-1 and Delta like 1, resulting in inhibition of apoptosis of effector and memory T-cells.

Anti-PDL1 antibodies

Atezolizumab (MPDL3280A) is a human IgG1 mAb containing an engineered Fc portion targeting PD-L1. It is approved for treatment of metastatic urothelial carcinoma and NSCLC (Rosenberg 2016). The recommended dose is 1200 mg every three weeks.

Durvalumab (MEDI4736) is a human mAb of the IgG1 k subclass against PD-L1. It is approved for the treatment of metastatic urothelial carcinoma (Massard 2016). The recommended dose is 10 mg/kg every two weeks.

Avelumab is a fully human IgG1 mAb that binds PD-L1. It is approved for treatment of metastatic urothelial carcinoma and Merkel-cell carcinoma (Kaufman 2016). The recommended dose is 10mg/kg every two weeks.

BMS-936559 is a high-affinity fully human IgG4 mAb against PD-1-L1.

Of note, different checkpoint inhibitors (e.g. anti-PD-1 and CTLA4-antibodies) can be rationally combined. In addition, checkpoint inhibitors can be combined with targeted drugs and other molecules, opening a wealth of opportunities for future development.

Why it is important to do this review

Given, on the one hand, the dismal prognosis of advanced gastric cancer treated with chemotherapy and targeted treatments, and on the other hand the great success of checkpoint inhibitors in different types of cancers, as well as favorable preliminary results of treatment with immune checkpoint inhibitors in chemorefractory gastric cancer (Muro 2016), immunotherapy is currently considered as one of the most promising approaches to improve the prognosis of advanced gastric cancer.

However, as for any new treatment, bias in the perception of outcomes of new treatment strategies may be introduced, for example by more rapid and selective publication of positive results, as well as many other mechanisms. Correspondingly, consideration of the potential side effects and significant costs of these newly-developed treatments and a critical assessment of the evidence for the use of immune checkpoint inhibitors in advanced gastric cancer, which is the aim of this review, are of major importance for rational decision-making in clinical practice.

OBJECTIVES

To evaluate the efficacy and safety of immune checkpoint inhibitors, alone or in combination with chemotherapy, in people with advanced gastric and gastroesophageal junction adenocarcinoma in first and subsequent treatment lines.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials with or without blinding. To limit publication bias, we will also include meeting abstracts and unpublished online data if they provide sufficient results for analysis and if full information and final results are confirmed by the first author.

Types of participants

We will include adults (aged 18 years and older) with histologically-confirmed, locally-advanced (T3-T4NxM0 if technically inoperable; all TxNxM1), recurrent or metastatic adenocarcinoma of the stomach or gastro-esophageal junction. We will also consider individuals to be eligible with esophageal adenocarcinoma, if they have been enrolled in the trial together with those with gastric and gastro-esophageal junction cancer. We will include participants regardless of their subtype of adenocarcinoma and molecular pathology (PD-L1 expression, HER-2 expression and microsatellite instability status). Studies of mixed solid tumors (basket trials) are eligible only if the results for people with gastric cancer are provided separately in stratified analyses.

Types of interventions

Immune checkpoint inhibition is defined as treatment with antibodies that target CTLA-4 (ipilimumab, tremelimumab), PD-1 (nivolumab, pembrolizumab, pidilizumab) or PD-L1 (atezolizumab, durvalumab and avelumab), applied as single agents or in combination. Chemotherapy is defined as the administration of cytotoxic drugs and can include, but is not limited to: 5-FU, cisplatin, carboplatin, oxaliplatin, paclitaxel, irinotecan, docetaxel, given as single agents or in combination. We will conduct subgroup analyses according to the chemotherapy backbone used in the included trials, and for trials using best supportive care versus an active comparator in comparison B.

Comparisons will be as follows:

Comparison A: Experimental treatment: Immune checkpoint inhibitor plus chemotherapy.
Comparison A: Control: Chemotherapy alone.
Comparison B: Experimental treatment: Immune checkpoint inhibitor alone.
Comparison B: Control: best supportive care or physicians' choice of treatment.

Chemotherapy plus immune checkpoint inhibitor versus chemotherapy alone as first-line treatment

Chemotherapy plus immune checkpoint inhibitor, versus chemotherapy alone as first-line treatment. We will conduct an overall analysis, with further subgroup analyses to be conducted based on the type of immune checkpoint inhibitor, namely antibodies targeting CTLA-4 versus PD-1/PD-L1.

Immune checkpoint inhibitors (without chemotherapy) versus best supportive care or physicians' choice of treatment for people with chemorefractory gastric and gastro-esophageal junction cancer

Again, we will first conduct an overall analysis, with further subgroup analyses to be performed based on the type of immune checkpoint inhibitor, namely antibodies targeting CTLA-4 versus PD-1/PD-L1. We will further subdivide people with chemorefractory cancer into those failing one or two and more lines of chemotherapy. We will analyze people who either respond to chemotherapy or have stable disease and are treated with immunotherapy as maintenance, in a separate comparison.

We will update these comparisons as we find further studies in the future.

Types of outcome measures

Primary outcomes

Due to their clinical relevance, we have selected two co-primary endpoints for this review:

1. Progression-free survival (PFS): time from randomization until disease progression or death from any cause. If progression-free survival is not provided, we will extract the time to progression, time to treatment failure or relapse-free survival, as well as duration of disease control.
2. Overall survival (OS): time from randomization until death.

Secondary outcomes

1. Objective response rate (according to RECIST or immune-related RECIST (Wolchok 2009)).
2. Treatment-related adverse events (grade 3 or above, graded with the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (NCI-CTCAE 2010) including the percentage of treatment-related deaths), as well as (if separate data are available) immune-related adverse events (irAEs).
3. Quality of life, measured by a validated scale.
4. Duration of response.

Search methods for identification of studies

Electronic searches

The Information Specialist of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group will search for randomized controlled trials in the in the following databases from 2010:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1)
2. MEDLINE (via OvidSP) (Appendix 2)
3. Embase (via OvidSP) (Appendix 3)

The review authors will conduct searches for unpublished and ongoing trials in the following databases:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov),
2. European Organization for Research and Treatment (www.eortc.be)
3. www.CenterWatch.com

We will model the search strategies for the databases on the search strategies designed for CENTRAL and Ovid MEDLINE. Where needed, we will combine these with the search strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled trials (Lefebvre 2011).

Searching other resources

We will handsearch the reference lists of all primary publications and review articles identified by electronic searching for additional references. We will also search published abstracts from the following conference proceedings from 2010 onwards:

1. American Society of Clinical Oncology (ASCO), published in the *Journal of Clinical Oncology.*
2. European Society for Medical Oncology (ESMO), published in the *Annals of Oncology.*
3. European Council of Clinical Oncology (ECCO), published in the *European Journal of Cancer*.
4. American Association of Cancer Research (AACR), published in the *Clinical Cancer Research* or *Cancer Research* or *Cancer Immunology Research*.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management system. Two review authors (BÖ, NS) will independently screen the title, abstracts and keywords of all the studies identified, for potential inclusion. We will then retrieve the full-text publications for further assessment.

Two review authors (BÖ, NS) will independently evaluate the identified studies for inclusion, and record the reasons for exclusion of the ineligible studies. We will resolve disagreements through discussion or, if needed, by consulting a third review author (AW or MM). We will identify and exclude duplicated reports of the same study, and will document the selection process in a PRISMA flow diagram and in 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Data extraction and management

Two review authors will independently extract detailed study characteristics from the included studies, resolving differences in data extraction by discussion with a third review author, and referring back to the original article. If data are missing from a published report, we will contact the first author of the study.

The data extraction form will include the following items:

1. Author, year of publication and journal citation
2. Methods:
   a. Random sequence generation
   b. Allocation concealment
   c. Type of analysis, e.g. intention-to-treat (ITT), modified ITT or per protocol, including potential sources of attrition bias, i.e.

incomplete efficacy or safety data. If adjusted analyses were performed, we will record the adjustment variables used
   d. Primary, secondary and exploratory endpoints
   e. Whether radiological images were reviewed by investigators or by an independent radiologist, and whether the latter was blinded
   f. Duration of follow-up for each outcome
3. Participants
   a. Total number enrolled in each group
   b. Country
   c. Inclusion and exclusion criteria and key baseline characteristics, e.g. percentage of HER-2+ gastric cancer, stage, age, proportion of men and women, proportion of white, Asian and African American participants, percentage of EBV-positive and MSI-H participants, and if separate results for these subgroups have been reported
4. Interventions
   a. Detail of intervention, e.g. choice and dosing schedule of immune checkpoint inhibitors and chemotherapies

We will extract results as follows:

1. For time-to event data (survival and disease progression), we will extract the log of the hazard ratio (log(HR)) and its standard error from the trial reports. If these are missing, we will attempt to estimate the log (HR) and its standard error using the methods of Parmar 1998 and Tierney 2007.
2. For dichotomous outcomes (e.g. adverse events or deaths) if it is not possible to use a hazard ratio we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at the endpoint, in order to estimate a risk ratio or an odds ratio.
3. For continuous outcomes (e.g. quality-of-life measures) we will extract the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at the endpoint in each comparison arm at the end of the follow-up, in order to estimate the mean difference between treatment arms, and its standard error. If the median or range are provided instead of the mean and SD, we will estimate the mean and SD using the method proposed by Hozo 2005.
4. For ordinal outcomes (e.g. quality-of-life measures) as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* Section 7.7.4 (Higgins 2011b) we will either dichotomize the scale for analysis or treat the ordinal scale as a continuous outcome. We will extract data in all forms in which they are reported, since it will not be clear which is the dominant method used for analyzing data until we have reviewed all the studies.

If reported, we will extract both unadjusted and adjusted statistics, as well as data relevant to an intention-to-treat and per protocol analysis. For meta-analysis we will apply the estimates from adjusted or per protocol analyses, or both, if provided.

Assessment of risk of bias in included studies

Two unblinded review authors (BÖ, NS) will independently assess the quality of the eligible studies using the 'Risk of bias' tool as outlined in the *Cochrane Handbook for Systematic Reviews of Intervention*.

We will resolve disagreements by discussion or by involving a third review author . We will consider the following criteria:

1. Selection bias: random sequence generation and allocation concealment.
2. Performance bias: blinding of participants and caregivers.
3. Detection bias: blinding of outcome assessment.
4. Attrition bias: incomplete outcome data regarding efficacy and toxicity.
5. Reporting bias: selective reporting of outcomes.
6. Other potential sources of bias:
   a. Was the sample size predefined and was the target accrual number reached?
   b. Was there unplanned interim analysis?
   c. Was radiological tumor response assessed by trial investigators or by independent/blinded radiologists?
   d. Were baseline characteristics balanced?

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol, and will report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We will use the following measures of the effect of treatment:

1. For time-to-event data, we will use methods of survival analysis and express the intervention effects as a hazard ratio (HR), if possible.
2. For dichotomous outcomes, we will use the relative risk (RR), if possible.
3. For continuous outcomes, we will use the mean difference, if possible.

If the continuous outcome is skewed, we may apply natural logarithmic transformation, to improve the normality of data before the pooled analysis. We will perform meta-analysis only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

Unit of analysis issues

For studies with more than one intervention arm, if clinically meaningful, we will combine groups to create a single pairwise comparison. For example for a clinical trial with three arms (Arm A: Immune checkpoint inhibition plus chemotherapy; Arm B: chemotherapy X alone, Arm C: chemotherapy Y alone), we will combine the results of Arms B + C and compare Arm A against the combined results of Arm B + C.

Dealing with missing data

We will contact the first author of the study to verify key study characteristics and outcomes in case of studies published either as abstract only or to obtain missing numerical outcome data. Where necessary, we will estimate unreported hazard ratios and their variances from log-rank Chi^2 or P values, ratios of median time-to-events, observed-to-expected event ratios, and survival rates at given time points, using the methods of Parmar 1998 and Tierney 2007. Also, unreported median time-to-event outcomes

and survival rates can be read from the Kaplan-Meier survival curves. If there is insufficient information to impute the treatment effect estimates using the methods proposed above, we may reconstruct survival time data from the published Kaplan-Meier (KM) survival curves, using the methodology of Guyot 2012, if the number at risk and the number of events at each time point are available. We can therefore estimate the HR and its 95% confidence interval from the reconstructed KM data.

Assessment of heterogeneity

Where studies are similar enough in terms of participants, intervention and outcome measures to allow pooling of data to perform meta-analysis, we will estimate the degree of heterogeneity by visual inspection of forest plots and by performing tests for heterogeneity using the Chi^2 test, with significance set at $P < 0.10$. We will inspect the I^2 statistic to estimate the total variation across studies due to heterogeneity; we will consider heterogeneity as significant if the I^2 is greater than 30% or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias if we include more than 10 studies. We will explore funnel plot asymmetry visually, and if asymmetry is suggested by this assessment we will perform exploratory analyses to investigate it (Higgins 2011a).

Data synthesis

We will use a random-effects model for the meta-analysis. We will further investigate sources of heterogeneity where necessary. We will use Review Manager 5 to record and analyze data (Review Manager 2014).

For time-to event data, we will pool hazard ratios using the generic inverse variance. If a substantial number of studies exhibit non-proportionality of hazards in the treatment comparisons, we will implement the Cox time-dependent covariate model to estimate treatment effects at three or five years. To do this, we would have to construct the individual patient data from information extracted from the Kaplan-Meier curve, using the method of Guyot 2012. This method has been shown to have a high degree of reproducibility, with reasonable accuracy for estimating the HR if at least the numbers at risk or the total number of events are reported. The Schoenfeld test (Grambsch 1994) for non-proportionality may then be implemented on the reconstructed KM data. When the assumption of proportionality is violated for the treatment variable, a Cox model with treatment as the time-dependent covariate may be generated, to estimate the HR at three and five years (Tai 2014).

For dichotomous outcomes, we will calculate the odds ratio (OR) or risk ratio (RR) as appropriate for each study and will obtain a pooled estimate from these studies. We will analyze data based on the number of events and the number of participants assessed in the intervention and comparison groups, and will use these to calculate the RR and 95% confidence interval (CI).

For continuous outcomes, we will pool the mean differences (MD) between the treatment arms at the end of follow-up, if all studies measure the outcome on the same scale. If more than one study measures the same outcome using different tools, we will calculate the standardized mean difference (SMD) and 95% CI using the inverse variance method. We will summarize the continuous outcomes based on the mean, standard deviation (SD) and the number of participants for the intervention and comparison groups to calculate mean differences between treatment arms and their associated 95% CIs. If the MD is reported without individual group data, we will use this to report the study results.

If any study has multiple treatment groups, we will combine the respective treatment groups as appropriate, to avoid the issue of multiplicity.

If we are unable to pool the data statistically to conduct meta-analysis, we will perform a narrative synthesis of the results. We will describe the major outcomes and results, organized by intervention categories according to the major types or aims of the identified interventions, or both. Depending on the assembled data, we may also explore the possibility of presenting the data by population. Within the data categories we will explore the main comparisons of the review.

Subgroup analysis and investigation of heterogeneity

We will consider the following factors as possible sources of heterogeneity and will attempt to investigate them through subgroups analysis:

1. HER-2-positive versus HER-2-negative gastric cancer
2. PD-L1 expression and MSI- or EBV-positive tumors (if data are available)
3. Choice of chemotherapy regimen in the control or experimental arms, or both arms (in case of studies using combinations of chemo- and immunotherapy)
4. Choice of immune checkpoint inhibitor in the experimental arm
5. Studies with a heterogeneous population including Asian and African American participants versus studies with a homogeneous population
6. The type of study population according to the geographical region
7. Men versus women

Sensitivity analysis

We will perform sensitivity analyses by excluding studies with unclear or high risks of bias for allocation concealment. For the endpoint of overall survival, we will assess if the pooled hazard ratio and statistical heterogeneity change considerably with the exclusion of studies with a large proportion (> 20%) of participants who cross over from the chemotherapy arm to the immunotherapy or chemo-immunotherapy arms.

'Summary of findings' tables

We will generate a 'Summary of findings' table using the GRADEprofiler software. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of evidence from the studies that we include in the meta-analysis for the predetermined outcomes.

'Summary of findings' tables present the review's main findings and provide key information about the best estimate of the magnitude of the effect, in relative terms, and the absolute differences for each

relevant comparison of alternative therapy strategies, the number of participants and studies addressing each important outcome and the rating of our overall confidence in the effect estimates for the comparisons in an outcome-specific manner. The outcomes that we will include in the 'Summary of findings' table are:

1. Overall survival;
2. Progression-free survival or time to progression, or both; time-to treatment failure or relapse-free survival, or both;
3. Objective response rates;
4. Duraton of response;
5. Adverse events;
6. Quality of life.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will give the reader a clear sense of where the focus of any future research in the area should be, and what the remaining uncertainties are.

ACKNOWLEDGEMENTS

We acknowledge the following authors for kindly providing additional data on their trials: [Insert name(s)].

We acknowledge the help and support of the Cochrane Upper Gastrointestinal Diseases Review Group. The authors would also like to thank the following editors and peer referees who provided comments to improve the protocol: Sarah Rhodes (Editor), Anonymous clinical reviewer, Alfretta Vanderheyden, and Reviewer 3 (Editor) and to Kate Cahill for copy editing the protocol.

The Methods section of this protocol is based on a standard template used by Cochrane Gastrointestinal and Pancreatic Diseases Review Group.

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APPENDICES

Appendix 1. CENTRAL search strategy

1. exp Stomach Neoplasms/
2. ((gastric or gastro* or stomach) adj3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma*)).tw,kw.
3. 1 or 2
4. ((checkpoint* or PD-1 or PD1 or PD-L1 or PDL1 or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
5. (anti adj3 (PD-1 or PD1 or PD-L1 or PDL1 or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3)).tw,kw.
6. (Ipilimumab or Yervoy or strentarga or bms 734016 or bms734016 or "mdx 010" or mdx010 or mdx 101 or mdx101 or mdx ctla 4).tw,kw.
7. (Tremelimumab or ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206).tw,kw.
8. (Nivolumab or Opdivo or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538).tw,kw.
9. (Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475).tw,kw.
10. (Pidilizumab or "ck 011" or ct011).tw,kw.
11. (Atezolizumab or Tecentriq or tecntriq or MPDL3280A or mpdl 3280a or rg 7446 or rg7446).tw,kw.
12. (Durvalumab or Imfinzi or MEDI4736 or medi4736).tw,kw.
13. (Avelumab or Bavencio or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c).tw,kw.
14. (BMS-936559 or mdx1105 or mdx1105).tw,kw.
15. or/4-14
16. 3 and 15

Appendix 2. MEDLINE search strategy

1. exp Stomach Neoplasms/
2. ((gastric or gastro* or stomach) adj3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma*)).tw,kw.
3. 1 or 2
4. ((checkpoint* or PD-1 or PD1 or PD-L1 or PDL1 or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
5. (anti adj3 (PD-1 or PD1 or PD-L1 or PDL1 or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3)).tw,kw.
6. exp Ipilimumab/
7. (Ipilimumab or Yervoy or strentarga or bms 734016 or bms734016 or "mdx 010" or mdx010 or mdx 101 or mdx101 or mdx ctla 4).tw,kw.
8. (Tremelimumab or ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206).tw,kw.
9. (Nivolumab or Opdivo or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538).tw,kw.
10. (Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475).tw,kw.
11. (Pidilizumab or "ck 011" or ct011).tw,kw.
12. (Atezolizumab or Tecentriq or tecntriq or MPDL3280A or mpdl 3280a or rg 7446 or rg7446).tw,kw.
13. (Durvalumab or Imfinzi or MEDI4736 or medi4736).tw,kw.
14. (Avelumab or Bavencio or msb 0010682 or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c).tw,kw.
15. (BMS-936559 or mdx1105 or mdx1105).tw,kw.
16. or/4-15
17. 3 and 16

Appendix 3. Embase search strategy

1. exp stomach tumor/
2. ((gastric or gastro* or stomach) adj3 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas* or adenocarcinoma*)).tw,kw.
3. 1 or 2

4. exp ipilimumab/
5. exp ticilimumab/
6. exp nivolumab/
7. exp pembrolizumab/
8. exp pidilizumab/
9. exp atezolizumab/
10. exp durvalumab/
11. exp avelumab/
12. ((checkpoint* or PD-1 or PD1 or PD-L1 or PDL1 or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3) adj5 (inhibitor* or block* or antagon* or antibod*)).tw,kw.
13. (anti adj3 (PD-1 or PD1 or PD-L1 or PDL1 or CTLA-4 or CTLA4 or LAG-3 or LAG3 or TIM-3 or TIM3)).tw,kw.
14. (Ipilimumab or Yervoy or strentarga or bms 734016 or bms734016 or "mdx 010" or mdx010 or mdx 101 or mdx101 or mdx ctla 4).tw,kw.
15. (Tremelimumab or ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206).tw,kw.
16. (Nivolumab or Opdivo or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538).tw,kw.
17. (Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475).tw,kw.
18. (Pidilizumab or "ck 011" or ct011).tw,kw.
19. (Atezolizumab or Tecentriq or tecntriq or MPDL3280A or mpdl 3280a or rg 7446 or rg7446).tw,kw.
20. (Durvalumab or Imfinzi or MEDI4736 or medi4736).tw,kw.
21. (Avelumab or Bavencio or "msb 0010682" or msb 0010718c or msb 10682 or msb 10718c or msb0010682 or msb0010718c or msb10682 or msb10718c).tw,kw.
22. (BMS-936559 or mdx1105 or mdx1105).tw,kw.
23. exp bms 936559/
24. or/4-23
25. 3 and 24
26. random*.mp.
27. (placebo: or double-blind:).mp.
28. clinical trial:.mp.
29. blind:.tw.
30. exp health care quality/
31. or/26-30
32. exp animal/ not exp human/
33. 31 not 32
34. 25 and 33

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: AW
Designing the protocol: BÖ, AW, MM, NS, BCT
Designing search strategies: NS, BCT
Writing the protocol: BÖ, NS

DECLARATIONS OF INTEREST

BCÖ: None known.
MM: Markus Moehler has received consulting fees from Falk Nordic, Amgen, AstraZeneca. MCZ, Lilly, MSD, Merck Serono, BMS, Pfizer, Roche, research funds from Amgeb, BMS, MSD, Merck Serono and travel expenses from Merck Serono, BMS, Roche, MSD, Amgen.
NLXS: None known.
B-CT:Bee-Choo Tai has received funds from Boehringer Ingelheim Singapore for providing lectures and royalties from Wiley-Blackwell publishers.
ADW: Dorothea Wagner has received consulting fees from BMS, Pfizer, Merck, Servier, Lilly, Shire, Celgene, MSD