REVIEW ARTICLE

Immunotherapy in Tumors

Activated T Cells as a New Treatment Modality

Sebastian Kobold, Peter Duewell, Max Schnurr, Marion Subklewe, Simon Rothenfusser, Stefan Endres

SUMMARY

Background: A number of new drugs for tumor immunotherapy have been approved in the past few years. They work by activating T cells to combat tumors.

Method: This review is based on publications on recently approved T-cell-activating drugs that were retrieved by a selective search in PubMed.

Results: Randomized, controlled trials of "checkpoint" inhibitors, i.e., inhibitory antibodies for use against tumors, have shown that the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab can prolong the survival of patients with advanced melanoma by 2 to 4 months. No data on median overall survival are yet available for the two programmed-death-1 (PD-1) inhibitors pembrolizumab und nivolumab; the endpoint "tumor response" was achieved in 24% and 32% of patients receiving these drugs, respectively. Grade 3 or 4 adverse effects occurred in 50% of patients receiving ipilimumab and in 12 to 13% of those taking either of the two PD-1-inhibitors. Nivolumab prolonged the median survival of patients with metastatic non-small-cell lung cancer from 6 to 9 months. In refractory or recurrent Philadelphia-chromosome-negative pre-B acute lymphoblastic leukemia (pre-B-ALL), treatment with the bispecific antibody construct blinatumomab led to complete remission in 43% of the patients, while grade 3, 4 or 5 toxicities occurred in 83%.

Conclusion: T-cell-directed strategies have been established as a new pillar of treatment in medical oncology. As these drugs have frequent and severe adverse effects, therapeutic decision-making will have to take account not only of the predicted prolongation of survival, but also of the potential for an impaired quality of life while the patient is under treatment.

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Center of Integrated Protein Science Munich (CIPS-M) and Division of Clinical Pharmacology, Department of Internal Medicine IV, Klinikum der Universität München: PD Dr. med. Kobold, Dr. hum. biol. Duewell, Prof. Dr. med. Schnurr, Prof. Dr. med. Rothenfusser, Prof. Dr. med. Endres

Department of Internal Medicine III, Klinikum der Universität München, München: Prof. Dr. med. Subklewe

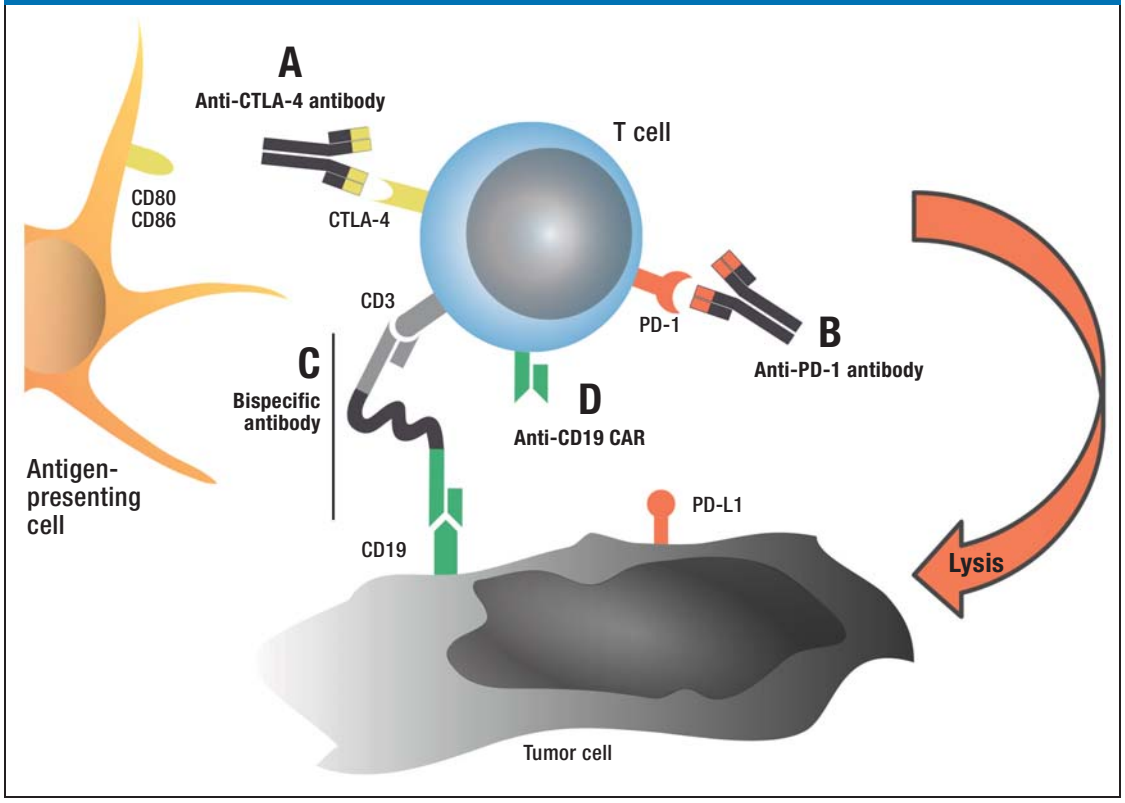
Cancer continues to pose an enormous challenge to both medicine and society. According to data reported by the Robert Koch Institute, the lifetime risk of developing cancer is 43% for women and 51% for men (e1). Since 1998, the probability of dying of cancer has been stable at 20% and 26%, respectively (e1). Cancer is frequently diagnosed at an early stage where it can be cured with local treatment, especially surgical resection, improving the prognosis of these patients.

Local and systemic treatment of cancer patients has been dominated by a tumor cell-centered approach for many years (e2). At the heart of this dogma is the idea that in the long term a patient will only benefit from a treatment directly targeted at the tumor cell (e2). Against this background, the idea of cancer immunotherapy (immuno-oncology), which involves the activation of components of the immune system, was considered not promising for many years (1). This view was fueled by the disappointing results of several vaccination studies (2). In contrast, passive immunotherapies, such as using tumor-specific antibodies, have become an established treatment modality following the approval of the monoclonal antibody rituximab for the treatment of B cell lymphomas in 1997 (3). Most monoclonal antibodies developed to treat tumors bind to the surface of the tumor cell and subsequently unfold their mode of action. Since the introduction of rituximab, 13 further tumor-directed antibodies have been approved. These have become an integral part of the therapeutic armamentarium in hemato-oncology (4). In 2011, ipilimumab became the first approved antibody to target T cells instead of tumor cells. This compound improved the survival of patients with metastatic melanoma by 2 to 4 months (5, 6). This showed that the unspecific activation of T cells can induce tumor regression, making immune cells attractive targets for tumor therapy. Over the last years, there have been further developments and approvals in rapid succession. The aim of this review is to provide insights into the new therapeutic principles, to summarize the data available on clinical benefits, and to offer an outlook on future approaches.

Methods

The efficacy data reported in this review are mainly from published phase III studies on the described compounds which are available via the National Library's

FIGURE



Overview of newly approved T-cell activating strategies in tumor immunotherapy.
A) Antibody-based blockade of CTLA-4/CD80 and CD86 interaction
B) Antibody-based blockade of PD-1/PD-L1 interaction
C) T-cell activation by anti-CD3 × anti-CD19 bispecific antibody
D) Treatment based on adoptive transfer of CAR-transduced T cells (not yet approved)
CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD, programmed death; PD-L, programmed death ligand; CAR, chimeric antigen receptor

database or the German National Library. The following search terms were used in the "clinical trial" category:

- "ipilimumab" + "melanoma"
- "nivolumab" + "melanoma"
- "pembrolizumab" + "melanoma"
- "nivolumab" + "lung cancer"
- "pembrolizumab" + "lung cancer"
- "blinatumomab" + "leukemia".

The search identified 83 articles altogether, which had been published between December 2005 and February 2015. The search was last updated on August 10, 2015.

Results

Immune checkpoint inhibitors

A T cell is activated when it recognizes its specific antigen and is then capable of destroying or damaging the antigen-expressing cell. To prevent an activated T cell from inflicting uncontrolled damage, it is equipped with mechanisms to inhibit its activation. These mechanisms, referred to as immune checkpoints, are mediated by a family of T cell surface molecules and their corresponding ligands on other cells. Whenever a T cell re-encounters its antigen, its activation is inhibited by the interaction of immune checkpoint ligand and receptor. This mechanism is vital to the body as it protects against autoimmunity. However, it is also hijacked by tumors to avoid being attacked by the immune system (7).

The approach to treat patients by targeting and blocking the immune checkpoint axis was based on evidence of tumor regression derived from preclinical models (e3, e4). The targets currently used to treat patients include cytotoxic T-lymphocyte antigen 4 (CTLA-4, ligands CD80 and CD86) and programmed death 1 (PD-1, ligands PD-L1 and PD-L2). Specific antibodies are used to reduce the immune checkpoint-mediated deactivation of tumor-reactive T cells, thereby restoring the ability of T cells to attack tumor cells *(Figure)*.

Based on data from two phase III studies in which, for the first time, improvements in overall survival were demonstrated for the anti-CTLA-4 antibody ipilimumab in patients with metastatic melanoma, the European Medicines Agency (EMA) approved the drug

TABLE 1

Studies on immune checkpoint inhibitors in approved indications in patients with advanced melanoma and non-small-cell lung cancer

Drug	Phase	Publication year	Indication	Endpoint	Sample size	Median overall survival		Reference
						Treatment group	Control group	
Ipilimumab	III	2010	Second-line, metastatic or advanced melanoma	Overall survival	676	10 months (ipilimumab + vaccine)	6 months (vaccine)	(5)
	III	2011	First-line, metastatic or advanced melanoma	Overall survival	502	11 months	9 months (DTIC)	(6)
Nivolumab	III	2015	Metastatic melanoma without BRAF mutation	Overall survival	418	NR	14 months (DTIC)	(10)
	III	2015	Second-line, advanced squamous non-small cell lung cancer	Overall survival	272	9 months	6 months (docetaxel)	(20)
Nivolumab + Ipilimumab	III	2015	Metastatic or locally advanced melanoma	Overall survival and PFS	945	NR PFS 12 months	NR PFS 3 and 7 months, resp. (ipilimumab, nivolumab)	(16)
	III	2015	Metastatic or locally advanced melanoma	Overall response	142	NR	NR PFS 4 months (ipilimumab)	(17)
Pembrolizumab	I	2014	Ipilimumab-refractory melanoma	Safety and efficacy	173	NREP	none	(9)
	I	2014	Metastatic or locally advanced melanoma	Safety and efficacy	411	NR	none	*
	I	2015	Second-line, advanced non-small-cell lung cancer	Safety and efficacy	495	12 months	none	(20)
	III	2015	Metastatic or locally advanced melanoma	Overall survival and PFS	834	NR	NR (ipilimumab)	(18)

NREP, not reported; NR, not reached, i.e. at the time of analysis of the study more than half of the patients in the treatment group survived; PFS, progression-free survival; DTIC, Dacarbazin; BRAF, B-rapidly accelerated fibrosarcoma gene

* Ribas A. et al.: Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL). J Clin Oncol 2014; 32: Abstract LBA9000.

for the treatment of unresectable or metastatic melanoma in August 2011 *(Table 1)*. Both studies demonstrated a significant overall survival advantage for ipilimumab (10 versus 6 months and 11 versus 9 months, respectively) (5, 6). Complete remission was experienced by 2 to 17% of patients (8). However, more than 50% of patients developed grade 3 to 4 adverse effects:

- Grade 3: severe adverse effects requiring hospitalization of the patient
- Grade 4: life-threatening adverse effects
- Grade 5: death related to adverse effect (e5).

These include ipilimumab-related dermatitis, colitis, hypophysitis, and uveitis.

The first anti-PD-1 antibody, pembrolizumab, was approved by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma after prior ipilimumab and BRAF-inhibitor treatment. The decision was based on two studies, demonstrating a response to the drug in 24 to 40% of the 584 patients even before the survival benefit was revealed (9) (Ribas A, et al.: Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients [pts] with melanoma [MEL]. J Clin Oncol 2014; 32: Abstract LBA9000). In Germany, the drug was approved for the treatment of advanced (unresectable or metastatic) melanoma on 17 July, 2015. Nivolumab, another anti-PD-1 antibody, was approved by the FDA in December 2014 for the treatment of advanced melanoma with inadequate response to other medicines. This decision was based on a response rate of 32% in two studies and survival advantages over chemotherapy with dacarbazine (1-year overall survival of 73% versus 42% [10, 11]). At the time of publication, the median overall survival had not yet been reached in the group treated with nivolumab. The European Medicines Agency (EMA) recommended granting a marketing authorization for nivolumab. Thus, it is likely that it will be approved for the treatment of melanoma in the near future (press releases from 22 May, 2015). The adverse-effect profile of PD-1 blockade appears to be more favorable compared with that of CTLA-4 blockade using ipilimumab: 12% grade 3 and 4 toxicities for nivolumab and 13% for pembrolizumab. However, it has to be noted that adverse effects of a higher grade occurred with a comparable frequency in patients receiving conventional chemotherapy with dacarbazine (18%) (12, 13).

It appears that PD-1 blockade is effective even in patients who failed to respond or developed resistance to CTLA-4 blockade (9, 14, 15). In one study, patients

TABLE 2

Studies on blinatumomab in B cell precursor acute lymphoblastic leukemia

Drug	Phase	Year of publication	Endpoint	Sample size	Response rate (%)	Median overall survival (months)	References
Blinatumomab	II	2011	Efficacy	21	80	NREP	(25)
	II	2014	Efficacy	189	43	6	(26)
	II	2014	Efficacy	36	69	10	(27)
	II	2014	Efficacy	39	31	4	*1
	II	2014	Efficacy	116	80	NREP	*2

NREP, not reported

*1 Gore L. et al.: Initial results from a phase 2 study of blinatumomab in pediatric patients with relapsed/refractory B cell precursor acute lymphoblastic leukemia. Blood 2014; 124: Abstract 3703.

*2 Goekbuget N. et al.: A confirmatory,. single-arm, phase 2 study of Blinatumomab, a bispecific T-cell engager (BiTE) antibody construct, in patients with minimal residual disease B-precursor acute lymphoblastic leukemia (ALL). Blood 2014; 124: Abstract 379.

who did not respond to ipilimumab had a subsequent response to nivolumab: 28% overall response rate to nivolumab after non-response to ipilimumab versus 40% without prior treatment with ipilimumab (e3). The authors of a recently published phase III study comparing the combination of nivolumab and ipilimumab with the respective drug alone showed an advantage in progression-free survival among patients who received the combination therapy: 11.5 months for the combination therapy versus 2.9 and 6.9 months, respectively, for the monotherapies. A post-hoc subgroup analysis indicated that these results only apply to patients with PD-L1-negative tumors. To patients with PD-L1-positive tumors, the combination therapy does not offer an advantage over treatment with nivolumab alone (16). So far, only data on progression-free survival have been published from this study. The combination of the drugs appears to also amplify the toxicities, since 55% of patients experienced grade 3 and 4 toxicities. In contrast, this type of adverse effects only occurred in 16 to 27% of patients receiving either nivolumab or ipilimumab alone. These data were supported by another randomized trial comparing combination therapy with ipilimumab monotherapy: Here, again, the median progression-free survival achieved with combination therapy was superior (not reached versus 4.4 months). The adverse effect rates (grade 3 and 4 toxicities: 54% and 24%, respectively) were comparable with those found in the first-mentioned study (17). It remains to be seen whether the superior response—at the price of significantly increased toxicities—will also have an impact on overall survival.

The question arises whether differences in efficacy exist between CTLA-4 and PD-1 blockade in patients with melanoma. The above mentioned study indicates that nivolumab is superior to ipilimumab, at least with regard to progression-free survival (6.9 versus 2.9 months [16]). Another phase III study comparing pembrolizumab with ipilimumab showed 1-year survival rates of 74% versus 58%. Consequently, this study also points to a potential advantage of pembrolizumab (18). Whether PD-1 blockade will be preferred over CTLA-4 blockade with ipilimumab as a first-line treatment still needs to be supported by evidence, demonstrating improvements in median overall survival.

In March 2015, the US Food and Drug Administration (FDA) approved the anti-PD-1 antibody nivolumab for the treatment of patients with refractory metastatic squamous non-small cell lung cancer. The approval was based on a phase III study with 272 patients, randomized 1:1 to receive either nivolumab or docetaxel. This study was terminated early due to the results of an interim analysis, showing that the primary endpoint with an overall survival advantage of 3 months had been reached: Median survival was 9.2 months in patients treated with nivolumab versus 6.0 months in patients receiving docetaxel (19). The approval for this indication was granted in Germany on 20 July, 2015. Similarly, the anti-PD-1 antibody pembrolizumab had antitumor activity in patients with non-small cell lung cancer (NSCLC): 495 patients were treated with pembrolizumab. The response rate (partial or complete) was 19% and the median overall survival was 12 months (20). In this single-arm phase I study, i.e. no control group data were taken into account, patients with high PD-L1 expression showed a superior response to the anti-PD-1 antibody. It remains to be seen whether or not a comparable advantage over chemotherapy can be confirmed in a future randomized trial.

At present, studies are underway to determine whether other tumor entities, including refractory Hodgkin's lymphoma (e6), renal cell carcinoma (Hammers HJ, et al.: A phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2015; suppl; Abstract TPS4578) and metastatic bladder cancer (e7), respond to treatment with immune checkpoint inhibitors (e6).

Bispecific T-cell-activing antibodies

The activation of T cells is mediated by CD3, a surface protein which forms part of the T cell receptor. When an activating anti-CD3 antibody binds to a T cell,

TABLE 3

Studies on CD19-directed CAR T cell therapy in CD19-expressing B cell precursor acute lymphoblastic leukemia

Cell preparation	Phase	Publication year	Indication	Endpoint	Sample size	Response rate (%)	Median overall survival (months)	References
CTL019	I/IIA	2014	CD19-expressing ALL	Safety and feasibility	30	90 (CR)	NR	(22)
	I	2011	CLL	Safety and feasibility	3	66 (CR)	NR	(e11)
	II	2014	CLL	Dose escalation	26	35	NR	*1
FMC63	II	2013	CD19-expressing B cell malignancies	Feasibility	10	30	NR	(e12)
	I	2015	CD19-expressing ALL	Safety and dose escalation	21	60 (CR)	NR	(e13)
	II	2015	CD19-expressing B cell malignancies	Feasibility and efficacy	15	80	NR	(23)
MSK-CD19	I	2014	CD19-expressing ALL	Safety and feasibility	16	88 (CR)	NR	(e14)
MSK-CD19	I	2014	Relapsed ALL	Safety and feasibility	4	50 (CR)	NR	*2
NA	I	2013	CD19-expressing B cell malignancies	Safety and feasibility	8	33	NR	(e15)

*1 Porter DL. et al.: Randomized. phase II dose optimization study of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL. Blood 2014; 124: Abstract 1982.
*2 Curran KJ. et al.: Chimeric antigen receptor (CAR) T cells targeting the CD19 antigen for the treatment of pediatric relapsed B cell ALL. Blood 2014; 124: Abstract 3716.
CAR, chimeric antigen receptor; ALL, acute lymphoblastic leukemia; CLL, chronic lymphoblastic leukemia; CD, cluster of differentiation;
CR, complete response; NA, not applicable; NR, not reached

specific antigen recognition can be mimicked. To make therapeutic use of this mechanism, bispecific antibodies capable of recognizing a second antigen on the surface of a tumor cell in addition to CD3 on the T cell have been developed. By these means, any T cell can be brought into contact with the tumor cell and activated, resulting in T cell degranulation and tumor cell lysis (e8).

By choosing a small antibody format with shorter half-life and superior tissue penetration, bispecific antibody derivatives can be administered systemically with high efficacy. These modified antibodies are referred to as bispecific T cell engagers. In December 2014, the FDA granted approval for blinatumomab, the first representative of its class with specificity against CD3 on T cells and against CD19 on lymphoblastic leukemia cells, for the treatment of Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia (pre-B ALL). The decision was based on a rate of 43% complete remissions observed in a phase II study with 189 patients *(Table 2)* (Goekbuget N, Dombret H, Bonifacio M, et al.: A confirmatory, single-arm, phase 2 study of Blinatumomab, a bispecific T cell engager [BiTE] antibody construct, in patients with minimal residual disease B-pre-cursor acute lymphoblastic leukemia [ALL]. Blood 2014; 124: Abstract 379). The FDA accepted this endpoint as pivotal, because the prognosis for patients with refractory B-precursor acute lymphoblastic leukemia is extremely poor and the condition is classified as a rare disease (e9). At the same time, the FDA called for the conduction of further studies to assess whether the high response rate will ultimately translate into improved overall survival. The EMA approval process has been initiated. However, this effect has to be weighed up with grade 3 to 5 toxicities, occurring at a rate of 83%. These include primarily hematological (neutropenia and thrombocytopenia as well as anemia) and neurological adverse effects, most of which appear to be immune-mediated. Data from a phase I study and results from an ongoing phase II study in patients with CD19-positive B cell non-Hodgkin's lymphoma indicate response rates of 43% for this indication as well (21) (Viardot A, et al.: Treatment of relapsed/refractory diffuse large B cell lymphoma with the bispecific T cell engager [BiTE] antibody construct blinatumomab: primary analysis results from an open-label, phase 2 study. Blood 2014; 124: Abstract 4460).

Adoptive cell therapies with chimeric antigen receptor (CAR)-transduced T cells

Another approach to use T cells therapeutically involves the ex-vivo manipulation of T cells by means of genetic engineering based on viral gene transfer. Any T cell from the peripheral blood can be modified to become tumor-specific by introducing the gene for a chimeric antigen receptor. A chimeric receptor is created by fusing the antigen-binding part of an antibody with signaling components of the T cell receptor complex (e10). When the receptor encounters the

antigen it recognizes, the T cell is activated and induces the lysis of the cell expressing the antigen (e10).

The most advanced clinical studies use CD19, a B cell antigen expressed by most B cell malignancies, as a target. In 2014, the FDA granted the breakthrough therapy designation to several CD19-targeting CAR T cell therapies for the treatment of relapsed or refractory pre-B ALL, thereby enabling an accelerated approval process. These T cell therapies achieved high rates of complete remissions (30 to 90%) *(Table 3)* in patients with in some cases multiple prior treatments (22, 23). Whether these results from phase I and II studies will be confirmed in larger studies and ultimately translate into survival benefits remains to be demonstrated.

Opportunities and risks

Three immune checkpoint inhibitors and one bispecific antibody derivative recently approved for the treatment of specific types of cancer have expanded the oncologist's therapeutic armamentarium. T cells have been established as a new therapeutic target. Offering proven survival benefits to patients treated with those drugs, ipilimumab and nivolumab have received market approval. Both pembrolizumab and blinatumomab were granted approval because of their response rates. However, their impact on overall survival still needs to be confirmed.

The immunotherapies mentioned above are associated with at times severe adverse effects, the majority of which can be explained by an activation of the immune system that is not directed at the tumor. The new spectrum of adverse effect requires special attention by the physician and proper treatment (24). For this reason, it is likely that these therapies with their intense adverse effects shall only be applied in specialized in- or out-patient centers.

Furthermore, the benefits of these new immunotherapies for the patient needs to be weighed against treatment costs. The cost of a standard treatment with ipilimumab (four doses) is EUR 83 576 for a patient with a body weight of 70 kg (as of January 2015). The prices of newer drugs have not yet been determined, but will presumably be in the same range. Thus, the annual treatment costs are comparable with those of newer tyrosine kinase inhibitors. For example, the annual costs of treating a patient with chronic myelogenous leukemia with the tyrosine kinase inhibitor ponatinib amount to EUR 77 830. In view of growing healthcare spending in general and increasing costs of medicines in particular, the benefits and costs of new pharmacotherapies will need to be weighed thoroughly. Given the frequent and severe adverse effects, the question arises as to how survival benefits are evaluated in the context of the patients' quality of life. The quantifiable prolongation of life needs to be appraised with regard to potential negative impact of the treatment (quality-adjusted life years, QALY). This is an integral part of the medicines evaluation process in Germany. For ipilimumab, a process pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG, *Arzneimittelmarktneuordnungsgesetz*) according to section 35a of the Fifth Book of the Social Code (SGB V) was conducted. The Institute for Quality and Efficiency in Healthcare (IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*) classified ipilimumab as a drug with significant additional benefit. The AMNOG process for nivolumab was started on 15 July 2015; for pembrolizumab and blinatumomab it is still pending.

Conclusion and outlook

Groundbreaking advances in tumor immunology achieved in the 20th are now bearing fruit in the form of new immunotherapies. The final common path of three successful new strategies—immune checkpoint inhibitors, bispecific antibody derivatives and adoptive CAR T cell therapy— is the activated T cell with tumor cell recognition. Both patients and the treating physicians must be aware of the new spectrum of adverse effects associated with immunotherapies and need to carefully weigh the benefits and risks of these new treatment modalities.

Dedication

The authors dedicate this review to Prof. Dr. Dr. h. c. Peter C. Scriba for his 80th birthday.

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KEY MESSAGES

- The anti-CTLA-4 antibody ipilimumab and the anti-PD-1 antibody nivolumab extend the median survival of patients with advanced melanoma by 2 to 4 months.
- Nivolumab extends the median survival of patients with unresectable squamous non-small cell lung cancer by 3 months.
- The anti-PD-1 antibody pembrolizumab is effective in patients with advanced melanoma und non-small cell lung cancer.
- The bispecific T-cell-recruiting antibody derivative blinatumomab is effective in patients with refractory B cell precursor acute lymphoblastic leukemia (pre-B-ALL).
- The described T-cell-activating strategies are associated with characteristic, at times severe adverse effects which are different from those of conventional chemotherapies

Conflict of interest statement
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Corresponding author:
PD Dr. med. Sebastian Kobold
Abteilung für Klinische Pharmakologie
Medizinische Klinik und Poliklinik IV
Klinikum der Universität München
Lindwurmstr. 2a, 80337 München, Germany
Sebastian.kobold@med.uni-muenchen.de

Supplementary material
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Immunotherapy in Tumors

Activated T Cells as a New Treatment Modality

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