Immunotherapy and Esophageal Cancer

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Abstract

Cancer of the esophagus is characterized as an aggressive disease with a poor outcome. A few drugs have showed to significantly benefit the overall survival and disease free survival of esophageal cancer patients, and many are currently under clinical investigations in the therapy of esophageal cancer. The two most common types of esophageal cancer are squamous cell carcinoma and adenocarcinoma, according to the cell of origin and location. Little is known about the molecular pathogenesis of this tumor. Few genes, such as tumor suppressor genes, oncogene, and apoptotic genes, have been identified to have a function in its development. The existing modest results, with the conventional treatments in the management of esophageal carcinoma, generated a substantial interest in novel lines of attack, mainly immunotherapy. This chapter will highlight the different classes of immunotherapeutic agents explored in the therapy of esophageal carcinoma: Checkpoint Inhibitors, Vaccine based immunotherapy, Adoptive cell therapy, Monoclonal Antibodies, Adjuvant Immunotherapy, Cytokines, Kinase inhibitors, mammalian Target of Rapamycin inhibitors and proteasome inhibitors.

Keywords: Esophageal cancer; Squamous cell carcinoma; Adenocarcinoma; Monoclonal antibodies; Immunotherapy

Abbreviations: ATP : Adenosine triphosphate; ADC: Antibody-drug conjugate; ADCA: Adenocarcinoma; APC: Anaphase-promoting complex; APC: antigen-presenting cells; B7H1: B7 homolog 1; bcl-2: B-cell lymphoma -2; bcl-xl: B-cell lymphoma extra-large; BE: Barrett’s esophagus; bi-shRNA: bifunctional short hairpin RNA; DC: dendritic cell; BMI: body mass index; CAR: chimeric antigen receptor; CTSB: Cathepsin B; CDK4: Cyclin-dependent kinase 4; CTLA 4: cytotoxic T-lymphocyte-associated antigen-4; DP: Dipeptidyl peptidase; ECRG4: Esophageal cancer related gene 4; EZF-1: EZ Fatty acid desaturase-1; EGFR: epidermal growth factor receptor; ERK: extracellular signal-regulated kinase; FzE3: Frizzled gene in Human esophageal carcinoma cells 3; FRAT1: Frequently Rearranged In Advanced T-Cell Lymphomas 1; FEZ1: Fasciculation and Elongation protein Zeta 1; FBkp-12: immunophilin FK Binding Protein-12; FGFR: fibroblast growth factor receptor; FLT3: Fms-related tyrosine kinase 3; GERD: Gastro esophageal reflex disease; GASC1: Gene Amplified in Squamous Cell Carcinoma 1; HGFR :human hepatocyte growth factor receptor (or c-Met); HLA: human leukocyte antigen; HEGFR 2: human epidermal growth factor receptor 2; HPV: human papilloma virus; IgG1-interleukin-12; IL-2: interleukin-2; IgSF: immunoglobulin superfamily; IgG2: immunoglobulin G2; Int-2/hst-1: integrated – 2/heparin-binding secretory transforming-1; LAG-3: lymphocyte activation gene-3; LOH: loss of heterozygosity; MAGE-A3: melanoma antigen A3; MCC: Mutated In Colorectal Cancers; MHC: major histocompatibility complex; KIR: killer-cell immunoglobulin-like receptors; MDM-2: Mouse double minute 2; mTOR: mammalian Target of Rapamycin; MT: Metallothionein; NHS-IL-12: tumor necrosis-targeting human; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; PBMC: peripheral blood mononuclear cell; NY-ESO-1: New York-esophageal cancer-1; ODC: Ornithine decarboxylase; PI3K: phosphatidylinositol 3-kinase; PBL: peripheral blood lymphocyte; PCNA: Proliferating cell nuclear antigen; PD-1: programmed death-1 or programmed cell death-1; PDGFR-beta: platelet-derived growth factor receptor beta subunit; TIL: tumor-infiltrating lymphocytes; TAA: tumor-associated...
Esophageal cancer is the sixth most common cause of cancer death worldwide [1]. It arises from the mucosa and grows outward through the submucosa in the direction of the muscularis propria and adventitia [2]. Esophageal cancer can be classified according to the two types of mucosal cell lining. Squamous cell carcinoma (SCC) occur throughout the length of the esophagus, or the adenocarcinoma (ADCA) which is confined to the area just above the gastro-esophageal junction [2].

Esophageal cancer constitutes about 1% of all cancers diagnosed in the US; however, it is much more common in other parts of the world, such as northern China, Iran, southern Africa, and India where the main type is SCC [2]. Although not common in the United States (US), it is estimated that about 16,910 new esophageal cancer cases will be diagnosed in 2016, of which 13,460 are men and 3,450 are women. Cancer of the esophagus is expected to be the cause of approximately 15,690 deaths (e.g., 12,720 in men and 2,970 in women) in 2016 [2]. It is 3 to 4 times more common among men than women with a lifetime risk about 1 in every 125 men and about 1 in every 435 women. Adenocarcinoma (ADCA) is the most common type of esophageal cancer among whites, while SCC is more common in Blacks [1].

**Risk factors [2,3]**

Esophageal cancer may develop due to the deoxyribonucleic acid (DNA) damage caused by the chronic irritation of esophageal mucosal cells. Factors, commonly linked to the increased risk of esophageal cancer are as follows:

**Tobacco and Alcohol Use**

Tobacco use increases the risk of both SCC and ADCA types of esophageal cancer. Alcohol ingestion, although not a pertinent risk factor, may increase the risk of SCC subtype. The combination of both, smoking and alcohol use, amplifies the risk of esophageal cancer especially the SCC type [2].

**Obesity**

Overweight, is a body mass index (BMI) between 25.0-29.9, and obesity, BMI ≥30, have been shown to increase the risk of esophageal cancer by approximately 2- to 3-fold in 2 metaanalysis specifically the ADCA type. Those who are obese have a higher risk than overweight people to develop esophageal cancer [4,5].

**Diet**

The excessive consumption of red or processed meat may increase the risk of esophageal cancer. Moreover, the frequent consumption of very hot beverages, it may irritate or weaken the esophageal cells increasing the risk of esophageal cancer [3].

**Gastro esophageal reflux disease (GERD) and Barrett’s esophagus (BE)**

Barrett’s Esophagus (BE) are complications of a long standing gastroesophageal reflux disease (GERD) where patients suffer from recurrent acidic gastric reflux up the esophagus. GERD increases the risk of esophageal ADCA 5 times more in patients who have an acidic reflux every week or more compared to patients who have less or none. BE patients are 11 times more at risk to develop ADCA of esophageal cancer when compared to the general population [3].
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Achalasia

Patients with Achalasia, a neurogenic esophageal motility disorder, carries a high risk of esophageal cancer that lasting for approximately 15 years after its diagnosis [3].

Tylosis

Patients with Tylosis A, is a very rare genetic skin disorder with late onset of non-epidermolytic palmoplantar keratoderma (NEPPK) that affects those between the age of 5 and 15, placing them at a higher risk of developing SCC esophageal cancer. [3] On the other hand Tylosis B is a benign disorder, with an onset at the first year of life.

Plummer Vinson syndrome

Plummer-Vinson or Paterson-Kelly syndrome is a rare condition characterised by iron deficiency anemia and dysphagia. It is associated with increased risk of SCC of esophagus or pharynx [3].

Human Papilloma Virus (HPV)

Human papilloma virus (HPV) infection is a possible risk factor of SCC esophageal cancer. The HPV connection to esophageal cancer is only seen in parts of Asia and south Africa in about one-third of patients with the disease. This was not documented elsewhere in the western world [3].

Chemical exposure

Occupational hazards, such exposure to certain chemical fumes and solvents, have been implicated in the increased incidence of esophageal cancer among these workers [2].

Molecular Pathophysiology

Despite the advances in the molecular pathogenesis, it still unkown what are the precise genetic aberrations responsible for triggering and development of Esophageal Cancer. Some tumor related genes, such as tumor suppressor genes (TSG), oncogene, and apoptotic genes, are recognized for their role in the pathogenesis of Esophageal Carcinoma. These malfunctioning genes and their specific role in the cancer of the esophagus are discussed below (Figure 1):

Figure 1: Oncogenes found to be frequently up-regulated in esophageal malignancy are indicated in green; tumor-suppressor genes frequently inactivated are indicated in red.

Adopted from Cancer of the Upper Gastrointestinal Tract, By Mitchell C. Posner; Everett E. Vokes, Ralph R. Weichselbaum, American Cancer Societ 2002.


Tumor suppressor genes

Tumor suppressor genes (TSG) are normal genes that can be inactivated by genetic or epigenetic changes, such as point mutations, deletions, loss of heterozygosity (LOH), promoter methylation, abnormal splicing, deregulation of imprinting and haplo insufficiency. LOH, which causes inactivation of most candidate TSG, have been found in the critical regions of chromosomes 1p, 3p, 4, 5q, 9, 11q, 13q, 17q, and 18q in Esophageal Carcinoma. Chromosome region 17q25.2–25.3 carries the autosomal dominant premalignant dermatologic condition, tylosis [6,7]. In almost all cases of Esophageal Cancer, LOH, involving the Anaphase-promoting complex (APC) and Mutated In Colorectal Cancers (MCC) genetic loci, is implicated in the development and/or progression of the disease [8].

In specifically Esophageal SCC, WWOX (WW domain containing oxireductase) which is a TSG [9], and mutations in codons 175, 248, and 273 of p53 gene may give an added pathway for its occurrence [10].

Oncogenes

Oncogenes can into cancer if they become activated (Osborne, Wilson and Tripathy, 2006). Cyclin D1, EGFR, Her-2, FRAT1, c-myc, c-ras, and Int-2/hst-1 are the most commonly upregulated oncogenes in esophageal cancer. They are instigated through many different genetic aberrations, such as point mutations, amplification, rearrangement and over-expression. Amplification and overexpression are the most common existing types [10].

Apoptotic genes


Immunotherapy

The current available drugs, FDA/ Non FDA approved or still under clinical trials, are categorized according to their mechanism of action into the following groups: checkpoint inhibitors/immune modulators, therapeutic vaccines, adoptive T cell transfer, monoclonal antibodies, adjuvant immunotherapies, cytokines, kinase inhibitors and mTOR inhibitors [24].

Checkpoint Inhibitors / Immune Modulators

Several checkpoint inhibitors, targeting multiple different checkpoints, are currently in development. Additional details related to the non Food and Drug Administration (FDA) approved checkpoint inhibitors and immune modulators are presented in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDI4736</td>
<td>NCT01693562</td>
<td>Phase I, Phase II</td>
<td>Non-Randomized, Safety/Efficacy Study, open label</td>
<td>PD-L1</td>
</tr>
<tr>
<td>MK-3475 Pembrolizumab</td>
<td>NCT02054806</td>
<td>Phase I</td>
<td>Efficacy Study, open label</td>
<td>PD-1</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPDL3280A</td>
<td>NCT01375842</td>
<td>Phase I</td>
<td>Non-Randomized, open label</td>
<td>PD-L1</td>
</tr>
<tr>
<td>MPDL3280A</td>
<td>NCT01633970</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>PD-L1</td>
</tr>
<tr>
<td>BMS-663513 Urelumab</td>
<td>NCT01471210</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>4-1BB/CD137</td>
</tr>
<tr>
<td>PF-05082566</td>
<td>NCT01307267</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>4-1BB/CD137</td>
</tr>
<tr>
<td>Lirilumab + Nivolumab</td>
<td>NCT01714739</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>KIR PD-1</td>
</tr>
<tr>
<td>Ipilimumab + Imatinib Mesylate</td>
<td>NCT01738139</td>
<td>Phase I</td>
<td>Safety/Efficacy Study, open label</td>
<td>CTLA-4/CD-28</td>
</tr>
<tr>
<td>BMS-986016 Nivolumab</td>
<td>NCT01968109</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>LAG-3 PD-1</td>
</tr>
<tr>
<td>PDR001</td>
<td>NCT02404441</td>
<td>Phase I/II</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>PD-1</td>
</tr>
<tr>
<td>LAG525 +/- PDR001</td>
<td>NCT02460224</td>
<td>Phase I/II</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>LAG-3 and PD-1</td>
</tr>
</tbody>
</table>

**Table 1**: Non-FDA approved checkpoint inhibitors [25-35].

**Vaccine based immunotherapy**

In esophageal cancer, several trials of vaccines, given alone or with other therapies, are currently enrolling patients. The non FDA-approved vaccines are described in Table 2.

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1299 Lysate Vaccine</td>
<td>NCT02054104</td>
<td>Phase I, Phase II</td>
<td>Randomized, Efficacy Study, open label</td>
<td>Cytotoxic T Lymphocyte</td>
</tr>
<tr>
<td>DCVax-Direct</td>
<td>NCT01882946</td>
<td>Phase I, Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>To reduce tumor growth</td>
</tr>
<tr>
<td>FANG</td>
<td>NCT01061840</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>Furin protein production</td>
</tr>
<tr>
<td>DEC-205-NY-ESO-1</td>
<td>NCT01522820</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>NY-ESO-1</td>
</tr>
<tr>
<td>Tumor cell vaccines</td>
<td>NCT01341496</td>
<td>Phase I</td>
<td>Safety Study, open label</td>
<td>Immune response</td>
</tr>
<tr>
<td>Tumor cell vaccines</td>
<td>NCT01258868</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>Immune response</td>
</tr>
</tbody>
</table>

**Table 2**: Non-FDA approved Vaccines [36-41].

**Adoptive cell therapy**

Another major opportunity of immunotherapy for esophageal cancer is adoptive T cell transfer. Several trials of adoptive T cell transfer techniques are currently underway for patients with esophageal cancer. A list of non-FDA approved adoptive T cell therapies are included in Table 3.

---

Drug | Clinical trial identifier no. | Phase | Study Design | Target
---|-----------------------------|-------|--------------|-------
TIL | NCT01174121 | Phase II | Non-Randomized, Safety/Efficacy Study, open label | Cell growth
Anti-NY ESO-1 mTCR PBL | NCT01967823 | Phase II | Non-Randomized, Safety/Efficacy Study, open label | NY-ESO-1
Anti-MAGE-A3-DP4 TCR | NCT02111850 | Phase I, Phase II | Non-Randomized, Safety/Efficacy Study, open label | MAGE-A3-DP4
Anti-VEGFR2 CAR CD8 plus PBL | NCT01218867 | Phase I, Phase II | Non-Randomized, Safety/Efficacy Study, open label | VEGFR2

Table 3: Non-FDA approved adoptive T cell therapy [42-45].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>NCT00655876</td>
<td>Phase III</td>
<td>Randomized, double blind</td>
<td>EGFR</td>
</tr>
<tr>
<td>MM-111</td>
<td>NCT01774851</td>
<td>Phase II</td>
<td>Randomized, Efficacy Study, open label</td>
<td>HER2, HER3</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>NCT01212822</td>
<td>Phase II</td>
<td>Efficacy Study, open label</td>
<td>VEGF</td>
</tr>
<tr>
<td>IMMU-132</td>
<td>NCT01631552</td>
<td>Phase II, Phase I</td>
<td>Safety/Efficacy Study, open label</td>
<td>Trop-2</td>
</tr>
<tr>
<td>MORAb-004</td>
<td>NCT01748721</td>
<td>Phase I</td>
<td>Safety Study, open label</td>
<td>Endosialin/TEM1</td>
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<tr>
<td>OMP-52M51</td>
<td>NCT01778439</td>
<td>Phase I</td>
<td>Safety/Efficacy Study, open label</td>
<td>Tumor cells</td>
</tr>
<tr>
<td>ABT-700</td>
<td>NCT01472016</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>Tumor cells</td>
</tr>
<tr>
<td>MM-151</td>
<td>NCT01520389</td>
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<td>Non-Randomized, Safety Study, open label</td>
<td>EGFR</td>
</tr>
<tr>
<td>CEP-37250/KHK2804</td>
<td>NCT01447732</td>
<td>Phase I</td>
<td>Non-Randomized, Safety Study, open label</td>
<td>Glycolipids</td>
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<tr>
<td>Panitumumab</td>
<td>NCT01627379</td>
<td>Phase III</td>
<td>Randomized, Safety/Efficacy Study, open label</td>
<td>EGF</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>NCT02034968</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>EGFR</td>
</tr>
<tr>
<td>HuMax-TF-ADC</td>
<td>NCT02001623</td>
<td>Phase I/II</td>
<td>Safety/Efficacy Study, open label</td>
<td>Tissue Factor</td>
</tr>
</tbody>
</table>

Table 4: Non-FDA approved monoclonal antibodies [46-57].

FDA Approved Therapies

Trastuzumab: A recombinant humanized monoclonal antibody directed against human epidermal growth factor receptor 2 (HER2). After binding to HER2 on the tumor cell surface, trastuzumab induces an antibody-dependent cell-mediated cytotoxicity against tumor cells that overexpress HER2. HER2 is overexpressed by many adenocarcinomas, particularly breast adenocarcinoma [58].

Ramucirumab: A recombinant, fully human monoclonal antibody directed vascular endothelial growth factor receptor 2 (VEGFR-2) with antiangiogenesis activity. Ramucirumab specifically binds to and inhibits VEGFR-2, which may result in an inhibition of tumor an-

giogenesis and a decrease in tumor nutrient supply. VEGFR-2 is a pro-angiogenic growth factor receptor tyrosine kinase expressed by endothelial cells [59].

**Adjuvant Immunotherapy**

Adjuvants are substances that are either used alone or combined with other immunotherapy to boost the immune response. Some adjuvant immunotherapeutic modalities use ligands—molecules that bind to proteins such as receptors to help control the immune response. These ligands can be either stimulating (agonists) or blocking (antagonists).

**Non-FDA approved adjuvant therapy**

A treatment that is given in addition to the primary, main or initial treatment. The Non-FDA approved adjuvant therapy is described in Table 5.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBLB502</td>
<td>NCT01527136</td>
<td>Phase I</td>
<td>Safety study, open label</td>
<td>Stop tumor cells from growing</td>
</tr>
</tbody>
</table>

*Table 5: Non-FDA approved adjuvant immunotherapeutic drug [60].*

**Cytokines**

Cytokines are messenger molecules that help control the growth and activity of immune system cells. The Non-FDA approved cytokines are described in Table 6.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>rh IL-15</td>
<td>NCT01572493</td>
<td>Phase I</td>
<td>Safety study, open label</td>
<td>Stimulate the immune system</td>
</tr>
<tr>
<td>NHS-IL-12</td>
<td>NCT01417546</td>
<td>Phase I</td>
<td>Safety study, open label</td>
<td>Cancer cells</td>
</tr>
<tr>
<td>Aldesleukin</td>
<td>NCT01697527</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>NY-ESO-1</td>
</tr>
</tbody>
</table>

*Table 6: Non-FDA approved cytokines [61-63].*

**Kinase inhibitors**

A kinase inhibitor is described as a type of enzyme that blocks the action of one or more inhibitors (Broekman, Giovannetti and Peters, 2011). Table 7, below, describes the non FDA approved kinase inhibitors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Sunitinib</td>
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<td>Open label</td>
<td>VEGFR2, PDGFRb, c-kit</td>
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<td>Afatinib</td>
<td>NCT01522768</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>RTK, EGFR</td>
</tr>
<tr>
<td>PF-00299804</td>
<td>NCT01608022</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>EGFR</td>
</tr>
<tr>
<td>BKM120 Burparlisib</td>
<td>NCT01806649</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>Class I PIK3</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>NCT01913639</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>VEGFRs 2 and 3, and Ret, Kit, PDGFR and Raf kinases</td>
</tr>
<tr>
<td>Icotinib Hydrochloride</td>
<td>NCT01973725</td>
<td>Phase II</td>
<td>Safety/Efficacy Study, open label</td>
<td>EGFR</td>
</tr>
</tbody>
</table>

mTOR inhibitors

Mechanistic target of rapamycin (mTOR), a serine threonine protein kinase that controls cell growth, cell development, cell activity, cell progression, protein integration, autophagy, and imitation (Laplante and Sabatini, 2012). The Non FDA approved mTOR inhibitors are included in Table 8.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>NCT00985192</td>
<td>Phase II</td>
<td>Open label</td>
<td>FKBP-12</td>
</tr>
</tbody>
</table>

proteasome inhibitor

Proteasome inhibitors are anticancer therapies that work to regulate protein activities (Adams, 2003). The non FDA approved proteasome inhibitors are included in Table 9.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical trial identifier no.</th>
<th>Phase</th>
<th>Study Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib With Irinotecan</td>
<td>NCT01941316</td>
<td>Phase I</td>
<td>Open label</td>
<td>FKBP-12</td>
</tr>
</tbody>
</table>

Conclusion

Esophageal cancer has one of the highest mortality rates and carries an inferior prognosis. The ability to improve the overall survival as well as the disease free survival of esophageal cancer patients is increasing, as our knowledge and understanding of functioning of the immune system is expanding. Many promising advances has been attained in the oncology application of immunotherapy in the last decade. However, recent activities have enhanced our comprehension of the tumor microenvironment, various immunotherapeutic modalities or combination therapies, such as chemotherapy and immunotherapy. Moreover, the effects of the numerous strategies in combination with immunotherapy in different types cancer are still in the exploratory phase. Experimental preclinical and clinical trials are needed to uncover the vast potential of immunotherapy in treating cancer patients. Despite the large number of agents under investigations, the goal of therapy in cancer of the esophagus has not yet been realized.

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55. AIO-Studien-g GmbH. "Cisplatin and 5-FU +/- Panitumumab for Patients with Non resectable, Advanced or Metastatic Esophageal Squamous Cell Cancer (POWER)". In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 14 April 2016.


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