IMMUNOTHERAPY: THE NEW FACE OF CANCER TREATMENTS

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• No disclosures
NEW CANCER DRUG INDICATIONS APPROVED BY THE FDA 2012

• 2010 only one new drug was approved

• 2011 Ipilumimab, Vandetanib, Zytiga, Crizotinib, Vemurafenib

• 2012 record year with 8 new drugs approved

1. Axitinib
2. Vismodegib
3. Pertuzumab
4. Carlfizomib
5. Aflibercept
6. Enzalutamide
7. Regorafenib
8. Bosutinib
9. Cabozatinib
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>Adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma</td>
<td>Supplement</td>
<td>PR, AA</td>
</tr>
<tr>
<td>Olaparib</td>
<td>First-line maintenance treatment of patients with newly diagnosed BRCA-mutated advanced-stage ovarian cancer</td>
<td>Supplement</td>
<td>PR, AAid</td>
</tr>
<tr>
<td>Calaspargase pegol-mknl</td>
<td>As a component of a multi-agent chemotherapeutic regimen for patients with ALL</td>
<td>New</td>
<td>—</td>
</tr>
<tr>
<td>Tagraxofusp-erzs</td>
<td>Adult and paediatric patients aged ≥2 years with blastic plasmacytoid dendritic cell neoplasms</td>
<td>New</td>
<td>PR, BTD, OD</td>
</tr>
<tr>
<td>Trastuzumab-pkrb</td>
<td>Trastuzumab biosimilar for use in patients with HER2-overexpressing breast cancer</td>
<td>Biosimilar</td>
<td>—</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>In combination with bevacizumab, paclitaxel, and carboplatin for first-line metastatic non-squamous NSCLC</td>
<td>Supplement</td>
<td>PR</td>
</tr>
<tr>
<td>Gilteritinib</td>
<td>Relapsed and/or refractory FLT3-mutant AML</td>
<td>New</td>
<td>FTD, PR, OD, CoDx</td>
</tr>
<tr>
<td>Rituximab-abbs</td>
<td>Rituximab biosimilar for patients with CD20-positive, B cell NHL to be used as a single agent or in combination with chemotherapy</td>
<td>Biosimilar</td>
<td>—</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Adult and paediatric patients with advanced-stage or metastatic solid tumours that have a NTRK gene fusion who have no satisfactory alternative treatments</td>
<td>New</td>
<td>BTD, PR, AA, OD</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>In combination with azacytidine or decitabine or LDAC for newly diagnosed AML in patients ≥75 years of age or in those with comorbidities precluding intensive induction chemotherapy</td>
<td>Supplement</td>
<td>BTD, PR, AA, OD</td>
</tr>
<tr>
<td>Clasdegib</td>
<td>In combination with LDAC for newly diagnosed AML in patients ≥75 years of agent or in those with comorbidities precluding intensive induction chemotherapy</td>
<td>New</td>
<td>PR, OD</td>
</tr>
<tr>
<td>Emapalumab</td>
<td>Adult and paediatric (newborn and older) patients with primary HLH with refractory, recurrent or progressive disease or who are intolerant of conventional HLH therapy</td>
<td>New</td>
<td>BTD, PR, OD</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>In combination with chemotherapy for adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T cell lymphoma</td>
<td>Supplement</td>
<td>BTD, RTOR, PR, AAid</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>HCC previously treated with sorafenib</td>
<td>Supplement</td>
<td>PR, AA</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>Metastatic ALK-positive NSCLC after disease progression on another ALK inhibitor</td>
<td>New</td>
<td>BTD, PR, AA, CoDx, OD</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>In combination with carboplatin and paclitaxel ornab-paclitaxel for the first-line treatment of metastatic squamous NSCLC</td>
<td>Supplement</td>
<td>PR</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>Deleterious or suspected deleterious germline BRCA- mutated, HER2-negative, locally advanced or metastatic breast cancer</td>
<td>New</td>
<td>PR, CoDx</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>Metastatic or locally advanced cutaneous squamous cell carcinoma</td>
<td>New</td>
<td>BTD, PR</td>
</tr>
<tr>
<td>Dacominib</td>
<td>First-line treatment of metastatic NSCLC with an EGFR exon 19 deletion or exon 21 L858R substitution</td>
<td>New</td>
<td>PR, OD, CoDx</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>Relapsed and/or refractory CLL, SLL or FL after at least two prior therapies</td>
<td>New</td>
<td>PR, OD</td>
</tr>
<tr>
<td>Medicine</td>
<td>Description</td>
<td>Reference</td>
<td>Change</td>
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<tr>
<td>Moxetumomab pasudotox-tdfk</td>
<td>Relapsed and/or refractory hairy cell leukaemia after at least two prior systemic therapies, including a purine nucleoside analogue</td>
<td>New</td>
<td>PR, FTD, OD</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>In combination with platinum and pemetrexed for the first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK aberrations</td>
<td>Supplement</td>
<td>RTOR, PR</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Label update: restricted use to patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (CPS ≥10), or those who are not eligible for any platinum-containing chemotherapy</td>
<td>Supplement</td>
<td>CoDx</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Updated Label: restricted use to patients with locally advanced-stage or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (stained tumour-infiltrating immune cells covering ≥5% of the tumour area), or those who are not eligible for any platinum-containing chemotherapy</td>
<td>Supplement</td>
<td>CoDx</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy</td>
<td>Supplement</td>
<td>PR, AA</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>First-line treatment of patients with unresectable HCC</td>
<td>Supplement</td>
<td>—</td>
</tr>
<tr>
<td>Mogamulizumab-kpkc</td>
<td>Relapsed and/or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy</td>
<td>New</td>
<td>BTD, PR, OD</td>
</tr>
<tr>
<td>Iobenguane I-131</td>
<td>Adult and paediatric patients (aged ≥12 years) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy</td>
<td>New</td>
<td>BTD, PR, FTD, OD</td>
</tr>
<tr>
<td>Ivosidenib</td>
<td>Relapsed and/or refractory AML with a sensitizing IDH1 mutation</td>
<td>New</td>
<td>PR, FTD, OD, CoDx</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>In combination with an aromatase inhibitor as initial endocrine-based therapy for premenopausal or perimenopausal women with HR-negative, HER2-negative advanced-stage or metastatic breast cancer</td>
<td>Supplement</td>
<td>PR, FTD, RTOR, AAid</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Non-metastatic CRPC</td>
<td>Supplement</td>
<td>—</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>In combination with nivolumab for patients aged ≥12 years with MSI-H or dMMR mCRC that has progressed following fluoropyrimidine, oxaliplatin and irinotecan therapy</td>
<td>Supplement</td>
<td>BTD, PR, AA</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>In combination with ipilimumab for patients aged ≥12 years with MSI-H or dMMR mCRC that has progressed following fluoropyrimidine, oxaliplatin and irinotecan therapy</td>
<td>Supplement</td>
<td>BTD, PR, AA</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>In combination with binimetinib for patients with unresectable or metastatic BRAFV600E/K-mutant melanoma</td>
<td>New</td>
<td>CoDx, OD</td>
</tr>
<tr>
<td>Binimetinib</td>
<td>In combination with encorafenib for patients with unresectable or metastatic BRAFV600E/K-mutant melanoma</td>
<td>New</td>
<td>CoDx, OD</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Adult and paediatric patients with refractory primary mediastinal B cell lymphoma</td>
<td>Supplement</td>
<td>PR, OD, AA</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>In combination with carboplatin and paclitaxel after initial surgical resection of stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer</td>
<td>Supplement</td>
<td>OD</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Recurrent or metastatic cervical cancer that has progression on or after chemotherapy and has expression of PD-L1 (CPS ≥1)</td>
<td>Supplement</td>
<td>PR, AA, CoDx</td>
</tr>
<tr>
<td>Drug</td>
<td>Indication</td>
<td>Status</td>
<td>Codes</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
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</tr>
<tr>
<td>Venetoclax</td>
<td>CLL or SLL with or without 17p deletion after at least one prior therapy</td>
<td>Supplement</td>
<td>BTD, PR</td>
</tr>
<tr>
<td>Pegfilgrastim-jmdb</td>
<td>Pegfilgrastim (Neulasta) biosimilar</td>
<td>Biosimilar</td>
<td>—</td>
</tr>
<tr>
<td>Epoetin alfa-epbx</td>
<td>Epoetin alfa (Epogen/Procrit) biosimilar</td>
<td>Biosimilar</td>
<td>—</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>In combination with trametinib for anaplastic thyroid cancer with BRAFV600E mutation</td>
<td>Supplement</td>
<td>BTD, PR, OD</td>
</tr>
<tr>
<td>Trametinib</td>
<td>In combination with dabrafenib for anaplastic thyroid cancer with BRAFV600E mutation</td>
<td>Supplement</td>
<td>BTD, PR, OD</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>Adult patients with relapsed and/or refractory large B cell lymphoma after two or more lines of systemic therapy</td>
<td>Supplement</td>
<td>BTD, PR, OD</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>In combination with trametinib for adjuvant treatment of BRAFV600E/K-mutant melanoma with lymph node involvement</td>
<td>Supplement</td>
<td>BTD, PR, CoDx</td>
</tr>
<tr>
<td>Trametinib</td>
<td>In combination with dabrafenib for adjuvant treatment of BRAFV600E/K-mutant melanoma with lymph node involvement</td>
<td>Supplement</td>
<td>BTD, PR, CoDx</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>First-line treatment of metastatic NSCLC with an EGFR exon 19 deletion or exon 21 L858R substitution</td>
<td>Supplement</td>
<td>BTD, PR, CoDx</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>In combination with nivolumab for intermediate or poor risk, previously untreated advanced-stage RCC</td>
<td>Supplement</td>
<td>BTD, PR</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>In combination with ipilimumab for intermediate or poor risk, previously untreated advanced-stage RCC</td>
<td>Supplement</td>
<td>BTD, PR</td>
</tr>
<tr>
<td>Everolimus tablets for oral suspension</td>
<td>Adjunctive treatment of adult and paediatric patients aged ≥2 years with TSC-associated partial-onset seizures</td>
<td>Supplement</td>
<td>—</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>Maintenance treatment of recurrent ovarian, fallopian tube or primary peritoneal cancer after a complete or partial response to platinum-based chemotherapy</td>
<td>Supplement</td>
<td>PR</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Adult and paediatric patients with B cell-precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%</td>
<td>Supplement</td>
<td>PR, OD, AA</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Paediatric patients aged ≥1 year with newly diagnosed Ph+ CML-CP or those with Ph+ CML-CP that is resistant to, or who are intolerant of, prior TKI therapy</td>
<td>Supplement</td>
<td>PR, OD</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>Previously untreated stage III or IV cHL, in combination with chemotherapy</td>
<td>Supplement</td>
<td>BTD, PR</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with HR-negative, HER2-negative advanced-stage or metastatic breast cancer</td>
<td>Supplement</td>
<td>PR</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Unresectable stage III NSCLC that has not progressed following concurrent platinum-based chemotherapy and radiation therapy</td>
<td>Supplement</td>
<td>BTD, PR</td>
</tr>
<tr>
<td>Apalutamide</td>
<td>Non-metastatic CRPC</td>
<td>New</td>
<td>PR</td>
</tr>
<tr>
<td>Abiraterone acetate</td>
<td>Non-metastatic CSPC</td>
<td>Supplement</td>
<td>PR</td>
</tr>
<tr>
<td>Lutetium Lu-177 dotatate</td>
<td>Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours, including foregut, midgut and hindgut neuroendocrine tumours</td>
<td>New</td>
<td>PR, OD</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Broadened indication in the first-line treatment of metastatic NSCLC 'non-resistant' EGFR mutations other than exon 19 deletions or exon 21 L858R substitution</td>
<td>Supplement</td>
<td>PR, OD, CoDx</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Deleterious or suspected deleterious germline BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer</td>
<td>Supplement</td>
<td>PR, CoDx</td>
</tr>
</tbody>
</table>
The Hallmarks of Cancer
HALLMARKS OF CANCER
IMMUNOTHERAPY IN CANCER

• The immune system protects the body from foreign agents by recognizing “non-self” proteins (antigens) displayed on their surface
  • Initiates a protective response to neutralize them

• Cancer cells often display unusual or inappropriate antigens
  • Cancer cells have evolved mechanisms to evade the immune response and render it ineffective
  • Immune tolerance (immune-editing)
Cancer immunotherapy also known as immuno-oncology is a form of cancer treatment that uses the power of the immune system to prevent, target, control, and eliminate cancer.

- Re-Educate the immune system to recognize and attack specific cancer cells
- Boost immune cells to help eliminate cancer
- Provide the body with additional components to enhance the immune response
IMMUNOTHERAPY IN CANCER

• Immunotherapy refers to a very diverse range of therapeutic approaches

• It aims to harness the immune system to reestablish a targeted antitumor immune response

• The goal is to enable the patient’s immune system to specifically recognize and kill cancer cells
SO... HOW DOES THE IMMUNE SYSTEM FIGHT OFF CANCER

THE CANCER IMMUNITY CYCLE

• Refers to a series of stepwise events that must be initiated and allowed to proceed and expand for an anticancer immune response to lead to effective killing
IMMUNOTHERAPY IN CANCER

TYPES OF IMMUNOTHERAPY

• **Immune checkpoint therapy**
  - Helps T cells mount a longer lasting response against cancer (blocks interaction of PD-1/PDL-1 which normally inhibits cancer cell death), CTLA-4
  - Pembrolizumab, Nivolumab, Atezolizumab, Cemiplimab, Durvalumab, Avelumab
  - Agonism of costimulatory molecules and others
  - Combinations

• **Adoptive cell therapy (manipulating T cells)**
  - Chimeric Antigen Receptor (CAR) T-cell therapy
    - Gives patients large amounts of T cells that are genetically engineered to find and fight cancer (from pts own cells)
    - Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel: Approved in DLBCL
  - Tumor infiltrating lymphocyte (TIL) therapy
  - Endogenous T cell therapy
  - Bispecific T-cell engager antibodies (BiTe) CD3-Specific target Ags

• **Cancer vaccines**: help the body recognize cancer cells and stimulate the immune system to destroy them (provenge)

• **Monoclonal antibodies**: attach to specific proteins on cancer cells and immune cells

• **Cytokine therapy**: Interferons, Interleukins (IL-2), (BCG), Lenalidomide, pomalidomide

• **Oncolytic viruses**: Infrcf preferentially tumor cells, Tamilogene laheparevec (T-VEC)

• Other immune targets: NK cells, Anti-KIR Abs,, Macrophages, IDO
Generation and regulation of antitumour immunity.

Mellman et al. Nature 480, 480-489 (2011) doi:10.1038/nature10673
THE CANCER IMMUNITY CYCLE

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)
STIMULATORY AND INHIBITORY FACTORS IN THE CANCER-IMMUNITY CYCLE

1. Release of cancer cell antigens
   - Immunogenic cell death
   - Tolerogenic cell death

2. Cancer antigen presentation
   - TNF-α
   - IL-1
   - IFN-α
   - CD40L/CD40
   - CDN
   - ATP
   - HMGB1
   - TLR
   - IL-10
   - IL-4
   - IL-13

3. Priming and activation
   - CD28/B7.1
   - CD137/Cd137L
   - OX40/OX40L
   - CD27/CD70
   - HVEM
   - GITR
   - IL-2
   - IL-12
   - CTLA4/B7.1
   - PD-L1/PD-1
   - PD-L1/B7.1
   - prostaglandins

4. Trafficking of T cells to tumors
   - CX3CL1
   - CXCL9
   - CXCL10
   - CCL5

5. Infiltration of T cells into tumors
   - LFA1/ICAM1
   - Selectins
   - VEGF
   - Endothelin B receptor

6. Recognition of cancer cells by T cells
   - T cell receptor
   - Reduced pMHC on cancer cells

7. Killing of cancer cells
   - IFN-γ
   - T cell granule content
   - PD-L1/PD-1
   - PD-L1/B7.1
   - LAG-3
   - Arginase
   - IDO
   - MICA/MICB
   - TGF-β
   - B7-H4
   - BTLA
   - TIM-3/phospholipids
   - VISTA

- Green: Stimulatory factors
- Red: Inhibitors
T cell targets for immunoregulatory antibody therapy.

I Mellman et al. Nature 480, 480-489 (2011) doi:10.1038/nature10673
Simplified immune synapse in a naïve (CD4 or) CD8 T cell and for an activated CD8+ T cell

Initially, CD8α/β chains recognize the MHC class 1 of a peptide presented by an antigen-presented cell, and CD28 binds to CD80/86 to lead to downstream activation (bottom), which releases IL-12, IFN-γ, and meanwhile leads to feedback production of CTLA-4 in cytoplasm, which is rapidly brought to the surface (red). Additional costimulatory receptors (not pictured) on activated T cell/APC synapses include OX40/OX40-ligand, CD40-L/CD40, glucocorticoid-induced tumor necrosis factor (GITR)/GITR-L.

CTLA-4 acting as physiologic "brake" on costimulation of CD8+ T cell

CTLA4 outcompetes CD28 for CD80 and CD86, and the costimulatory signal ceases as the target is eliminated, reducing the release of pro-effector cytokines such as IL-12 and cytotoxic enzymes such as perforin and granzyme B. Homeostasis is restored.

PD-1-PD-L1 binding leads to peripheral CD8+ T cell "exhaustion" phenotype.

In a state of chronic antigen presentation, such as malignancy, the chronic presence of antigen or pro-inflammatory cytokines (IL-12, IFN gamma, etc) can upregulate PD-1 expression on the T cell; tumor clones can also select for PD-L1 expression. With PD-1-PD-L1 binding, even in the presence of the costimulatory molecule, "peripheral exhaustion" can occur.

PD-L1: programmed death-ligand 1; CD: cluster of differentiation; PD-1: programmed cell death-1; APC: antigen-presenting cells; MHC: major histocompatibility complex; IL: interleukin; IFN gamma: interferon gamma.
Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.

A simplified view of co-stimulatory and co-inhibitory ligand-receptor pairs that regulate T cell activity

T cell activating interactions

- 4-1BBL
- OX40L
- GITRL
- ICOSL
- B7.1, B7.2

T cell inhibitory interactions

- CTLA-4
- PD-1
- BTLA
- VISTA
- TIM-3
- LAG-3

T cell

Note that some binding partners involving some molecules, such as VISTA, are still being explored. Many additional co-stimulatory and co-inhibitory molecules (not shown) are involved in T cell activity and in the tumor microenvironment.

Original figure modified for this publication. Callahan MK, Postow MA, Wolchok JD. Immunomodulatory therapy for melanoma: ipilimumab and beyond. Clin Dermatol 2013; 31:191. Illustration used with the permission of Elsevier Inc. All rights reserved.
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IMMUNE CHECKPOINT INHIBITORS
EXAMPLES:

• Pembrolizumab in lung cancer: A New Standard
  • Keynote 189 trial (616 non squam NSCLC)
  • 12 month Overall Survival improvements over standard chemotherapy depending on PDL-1 expression:
    • <1 percent PDL1 expression– 62 versus 52 percent (HR 0.59, 95% CI 0.38-0.92)
    • 1 to 49 percent – 72 versus 51 percent (HR 0.55, 95% CI 0.34-0.90)
    • ≥50 percent – 73 versus 48 percent (HR 0.42, 95% CI 0.26-0.68) instead of chemotherapy
A Overall Survival

No. at Risk
Pembrolizumab combination 410 377 347 278 163 71 18 0
Placebo combination 206 183 149 104 59 25 8 0

Hazard ratio for death, 0.49 (95% CI, 0.38–0.64)
P<0.001

Months

B Subgroup Analysis of Overall Survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>235/616</td>
<td>0.49 (0.38–0.64)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>133/312</td>
<td>0.43 (0.31–0.61)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>102/304</td>
<td>0.64 (0.43–0.95)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143/363</td>
<td>0.70 (0.50–0.99)</td>
</tr>
<tr>
<td>Female</td>
<td>92/253</td>
<td>0.29 (0.19–0.44)</td>
</tr>
<tr>
<td>ECOG performance-status score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>74/266</td>
<td>0.44 (0.28–0.71)</td>
</tr>
<tr>
<td>1</td>
<td>159/346</td>
<td>0.53 (0.39–0.73)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former</td>
<td>211/543</td>
<td>0.54 (0.41–0.71)</td>
</tr>
<tr>
<td>Never</td>
<td>24/73</td>
<td>0.23 (0.10–0.54)</td>
</tr>
<tr>
<td>Brain metastases at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51/108</td>
<td>0.36 (0.20–0.62)</td>
</tr>
<tr>
<td>No</td>
<td>184/508</td>
<td>0.53 (0.39–0.71)</td>
</tr>
<tr>
<td>PD-L1 tumor proportion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>84/190</td>
<td>0.59 (0.38–0.92)</td>
</tr>
<tr>
<td>≥1%</td>
<td>135/388</td>
<td>0.47 (0.34–0.66)</td>
</tr>
<tr>
<td>1–49%</td>
<td>65/186</td>
<td>0.55 (0.34–0.90)</td>
</tr>
<tr>
<td>≥50%</td>
<td>70/202</td>
<td>0.42 (0.26–0.68)</td>
</tr>
<tr>
<td>Platinum-based drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>176/445</td>
<td>0.52 (0.39–0.71)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>59/171</td>
<td>0.41 (0.24–0.69)</td>
</tr>
</tbody>
</table>
FDA APPROVAL TIMELINE OF IMMUNE-CHECKPOINT INHIBITORS FOR THE TREATMENT OF MALIGNANCIES

Oct 1, 2015 Nivolumab + Ipilimumab for Melanoma (BRAF V600 wild-type)

Mar 4, 2015 Nivolumab for second line squamous NSCLC

Oct 2, 2015 Pembrolizumab for NSCLC

Oct 9, 2015 Nivolumab for second line adeno NSCLC

Nov 10, 2016 Nivolumab For SCCHN

Oct 24, 2016 Pembrolizumab for first line NSCLC

Nov 21, 2016 Daratumumab for Multiple Myeloma

Nov 21, 2016 Nivolumab for metastatic Melanoma with complete resection

Oct 22, 2015 Pembrolizumab for unresectable Melanoma

Mar 25, 2011 Ipilimumab for unresectable or metastatic Melanoma

Sept 4, 2014 Pembrolizumab for unresectable or metastatic Melanoma

Dec 22, 2014 Nivolumab for unresectable or metastatic Melanoma

Sept 22, 2017, Nivolumab for HCC

Sept 22, 2017 Pembrolizumab for gastric cancer

Aug 1, 2017 Nivolumab for colorectal cancer

May 23, 2017 Pembrolizumab for colorectal cancer and other solid tumor

May 18, 2017 Pembrolizumab for Urothelial Carcinoma

May 10, 2017 Pembrolizumab for Non-squamous NSCLC

May 18, 2017 Atezolizumab for Urothelial Carcinoma

May 18, 2016 Atezolizumab for Urothelial Carcinoma

May 17, 2016 Nivolumab for cHL

Feb 2, 2017 Nivolumab for Urothelial Carcinoma

Feb 16, 2018 Durvumab for unresectable NSCLC
IMMUNOTHERAPY IN CANCER

TYPES OF IMMUNOTHERAPY

• **Immune checkpoint therapy**
  - Helps T cells mount a longer lasting response against cancer (blocks interaction of PD-1/PDL-1 which normally inhibits cancer cell death), CTLA-4
  - Pembrolizumab, Nivolumab, Atezolizumab, Cemiplimab, Durvalumab, Avelumab
  - Agonism of costimulatory molecules and others
  - Combinations

• **Adoptive cell therapy (manipulating T cells)**
  - Chimeric Antigen Receptor (CAR) T-cell therapy
    - Gives patients large amounts of T cells that are genetically engineered to find and fight cancer (from pts own cells)
    - Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel: Approved in DLBCL
  - Tumor infiltrating lymphocyte (TIL) therapy
  - Endogenous T cell therapy
  - Bispecific T-cell engager antibodies (BiTe) CD3-Specific target Ags

• **Cancer vaccines**: help the body recognize cancer cells and stimulate the immune system to destroy them (provenge)

• **Monoclonal antibodies**: attach to specific proteins on cancer cells and immune cells

• **Cytokine therapy**: Interferons, Interleukins (IL-2), (BCG), Lenalidomide, pomalidomide

• **Oncolytic viruses**: Infrct preferentially tumor cells, Tamilogene laheparevec (T-VEC)

• Other immune targets: NK cells, Anti-KIR Abs,, Macrophages, IDO
CAR-T cells are a form of genetically modified autologous immunotherapy that have shown activity against DLBCL cells. This customized treatment uses the patient's own T lymphocytes, which are genetically modified (transfected) with a gene that encodes a chimeric antigen receptor to direct the patient's T cells against the lymphoma cells. The T cells are genetically modified ex vivo, expanded in a production facility, and then infused back into the patient as therapy.
CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

(Axil-cel) Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma ZUMA-1 trial

NEJM Dec 28, 2018

- Phase II trial 111 patients with diffuse large B cell lymphoma with refractory disease to all prior therapies:
  - Objective response was 82%
  - Complete response was 54%
  - 42% had a sustained response at 15.4 months
IMMUNOTHERAPY IN CANCER
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Patient Apheresis

autologous cell product

antigen presenting cells (APCs) loaded with prostate antigen PA2024, a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF).

ADMINISTRATION OF THERAPY:

Weeks 0, 2, 4
Sipuleucel-T: Patient-Specific Therapy

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center

Dendreon

Doctor’s Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4

IMPACT Overall Survival: Primary Endpoint
Intent-to-Treat Population

\[ P = .032 \text{ (Cox model)} \]
\[ HR = 0.775 \text{ [95\% CI: 0.614, 0.979]} \]

Median Survival Benefit = 4.1 months

Sipuleucel-T (n = 341)
Median Survival: 25.8 months

Placebo (n = 171)
Median Survival: 21.7 months

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TYPES OF IMMUNOTHERAPY

- Monoclonal Abs
  - Rituxan
  - TDM-1
IMMUNOTHERAPY IN CANCER

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TOXICITIES ASSOCIATED WITH CHECKPOINT INHIBITOR IMMUNOTHERAPY

• Despite, important clinical benefits checkpoint inhibition is associated with a unique spectrum of side effects termed: Immune-related adverse events (irAEs)

• Dermatologic:
  • Rash/pruritis (30%), alopecia (1%), vitiligo
    • Lichenoid, eczematoid, psoriatic, morbilliform, neutrophilic (sweets sy), palmoplantar dysesthesias etc
  • Diarrhea/colitis: 30% with ipilimumab and 2% with antiPD1
  • Hepatotoxicity: asymptomatic elevated liver enzymes <10%
  • Pneumonitis: upto 5-16% of cases with a quarter being severe
  • Hypothyroidism or hyperthyroidism
  • Hypophysitis (headache and fatigue) adrenal insufficiency and hypothyroidism
  • Type 1 diabetes mellitus (incidence of 0.2%)
  • Nephritis, pancreatitis, myocarditis, Red cell aplasia, neutropenia, thrombocytopenia, uveitis, Inflammatory arthritis, myosistis
TREATMENT OF TOXICITIES ASSOCIATED WITH CHECKPOINT INHIBITOR IMMUNOTHERAPY

• Moderate toxicities: withholding treatment and resumed
• Severe or life-threatening toxicities: permanent discontinuation, High dose steroids with long taper
  • Infliximab (TNF blockers)
COMPETENCY QUESTIONS:

• Immunotherapy for lung cancer has improved lung cancer overall survival
  • True
  • False

• Immunotherapy has been approved for all the following cancer types except:
  • Lung cancer
  • Melanoma
  • Breast cancer
  • Prostate cancer
  • Sarcomas

• The common side effects of immunotherapy include which of the following:
  • Pneumonitis
  • Colitis
  • Thyroiditis
  • type I Diabetes