Immuno-Oncology Applications

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Concept of immunotherapy to treat cancer has been around for over a century

1890s

William Coley observed a cancer patient with complete remission following infection from the bacteria *Streptococcus pyogenes*

- Dr. Coley injected streptococcal cultures – “Coley’s Toxin” - into patients and observed some cases with tumor regression
- Most patients had inoperable sarcomas; cure rate was over 10%

Studies like Dr. Coley’s led to the use of bacilli Calmette-Guerin (BCG) which is used today to treat bladder cancer

(source: Parish, 2003)

Immunosurveillance theory supports the view of an immune response against tumors

1960s

Sir Frank Burnet publishes his **immunosurveillance** theory: lymphocytes eliminate malignant cells via recognition of tumor-associated antigens (TAA) (proposed earlier by Paul Erlich; refines views held by Lewis Thomas)

Sir Frank Burnet
(taken from Parish, 2003)

Mid-1970s

Spontaneously arising tumors not recognized by the immune system

Mid to Late 1980s

T cells can be recruited to respond to transformed cells; identifications of many TAAs; cytokine approved by FDA to treat cancer

(sources: Parish, 2003; Lee and Margolin, 2011)

The New Era of Cancer Treatments: Immunotherapy

1990s to the 2000s

- Major advances in molecular biology, cell-signaling pathways, identifications of antigens, and targeted therapies/monoclonal antibodies as cancer therapies
- Immuno-deficient mice and tumor incidence
- Modified thinking about how tumors evade immune detection

2010 to Present:

- Immunotherapies result in impressive tumor responses:
  - Immunotherapy vaccine
  - Checkpoint inhibitors
  - Other immunotherapies in development; combination regimens

Immunotherapy has become a standard of care in cancer

Examples of Immuno-oncologic agents:

Cytokines (mid-1980s)

- **elicit an immune response against the tumor; examples of include interferons (e.g. interferon alfa-2b (1986) and interleukins (aldesleukin (1992))**

Vaccines (mid-1980s, 2010)

- **introduce the immune system to tumor-associated antigens; immune system recognizes and attacks tumor cells associated with the antigen (e.g. Bacillus Calmette-Guerin (mid-1980s) sipuleucel-T (2010))**

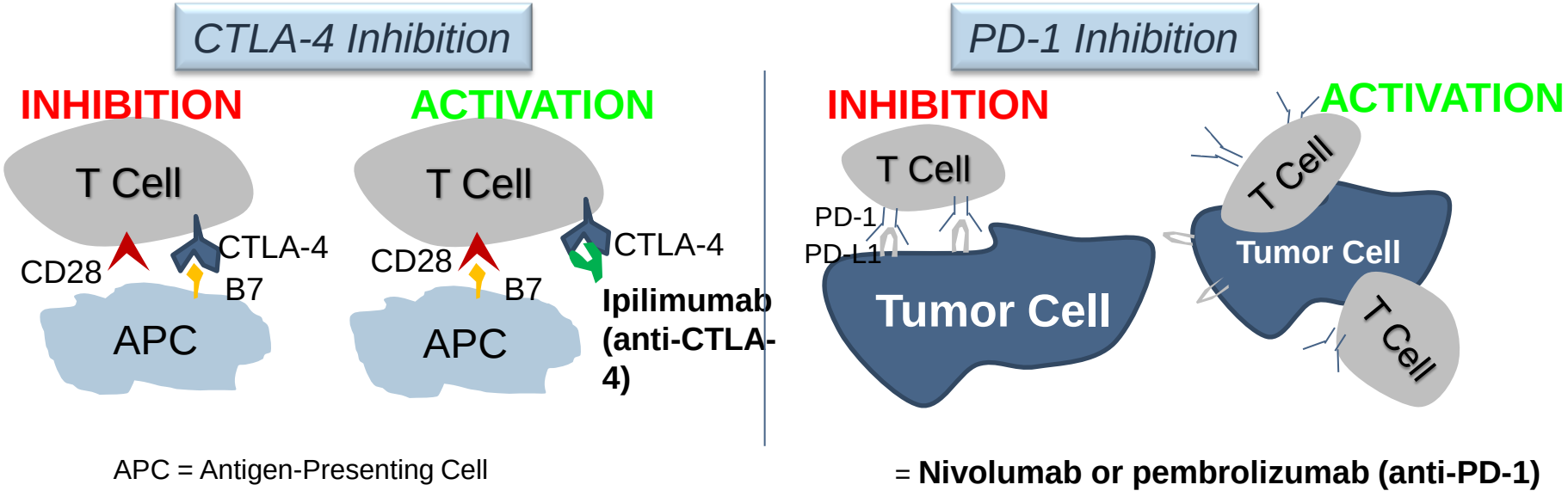
Checkpoint Inhibitors (2011)

- **Tumors escape detection from the immune system by expressing "checkpoint" proteins on their cell surface; targeting and inhibiting these cell surface proteins enhances the immune response to the tumor (e.g. ipilimumab (2011), nivolumab (2014), pembrolizumab (2014))**

Others: Cell therapies (e.g. CAR T cells), Monoclonal antibodies (e.g. alemtuzumab)

Checkpoint Inhibitors: Mechanisms of Action

Checkpoint inhibitors:



APC = Antigen-Presenting Cell

= **Nivolumab or pembrolizumab (anti-PD-1)**

Immuno-oncology agents such as checkpoint inhibitors are changing the treatment paradigm for many oncology disease states

The CTLA-4 inhibitor ipilimumab dramatically improved survival for patients with advanced melanoma

Patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin:

HLA-A2*0201 genotype**	**ipilimumab + gp100* (n=403)**	**ipilimumab (n=137)**	**gp100 (n=136)**
Overall Survival (OS), median	10 months	10 months	6 months

** gp100 is an investigational peptide vaccine*

*** facilitates immune presentation of the investigational peptide vaccine*

(source: Yervoy (ipilimumab) FDA approved label, Bristol-Myers Squibb

Pembrolizumab and nivolumab demonstrated impressive response rates for patients with metastatic melanoma experiencing disease progression

Pembrolizumab:

- Unresectable or metastatic melanoma with progression of disease, refractory to: two or more doses of ipilimumab, disease progression within 24 weeks following the last dose of ipilimumab, if BRAF V600 mutation-positive, refractory to a BRAF or MEK inhibitor.

Results:

89 patients taking the 2mg/kg dose of pembrolizumab	**pembrolizumab (2 mg/kg)**
Overall Response Rate (ORR)	24% (one complete response, 20 partial responses)

Nivolumab:

- Progression of disease on or following ipilimumab treatment and if BRAF V600 mutation positive, a BRAF inhibitor

Results – interim analysis:

120 patients taking 3 mg/kg dose of nivolumab	**nivolumab (3 mg/kg)**
Overall Response Rate (ORR)	32% (four complete response, 34 partial responses)

(sources: Keytruda (pembrolizumab) FDA approved label, Merck; Opd (nivolumab) FDA approved label, Bristol-Myers Squibb)

Nivolumab was approved earlier this year as subsequent therapy in patients with metastatic NSCLC

Approval for squamous NSCLC was based on two studies:

- Phase III (n=272), nivolumab (3 mg/kg) vs. docetaxel (75 mg/m^2); metastatic squamous NSCLC, disease progression during or after one prior platinum doublet based chemotherapy
  - Median Overall Survival (OS) = 9.2 months on nivolumab (n=132) vs. 6.0 months on docetaxel (n=137)
- Phase II, single-arm, nivolumab (n=117); progression after a platinum-based therapy and at least one additional systemic treatment

  ORR = 15%, all partial responses, median time to onset of response = 3.3 months

  76% (13 of 17 patients) with a confirmed response had ongoing responses, 10 of the 17 had durable responses of 6 months or longer

Nivolumab is also recommended for subsequent therapy use in patients with metastatic non-squamous NSCLC:

Phase III, previously treated advanced non-squamous NSCLC	Nivolumab 3 mg/kg (n=292)	Docetaxel 75 mg/m2 (n=290)
Median Overall Survival	12.2 months	9.4 months
Objective Response Rate	19%	12%
Median Duration of Response	17.2 months	5.6 months

(sources: Opdivo (nivolumab) FDA approved label, Bristol-Myers Squibb; Rizvi, et al., 2015; : Paz-Ares et al., 2015)

Immuno-oncology agents are being developed as both monotherapy and in combination with other agents to treat a number of tumor types

- Bladder
- Breast
- Colorectal
- Esophageal
- Gastric
- Head and Neck
- Hepatocellular
- Leukemia
- Lung
- Lymphoma
- Melanoma
- Ovarian
- Pancreatic
- Prostate
- Renal Cell Carcinoma

Considerations for healthcare providers when using immunotherapy to treat patients with cancer:

Response patterns to immunotherapy may differ compared to the responses observed with cytotoxic agents

Novel therapies with novel mechanisms of action can result in specific treatment-related adverse events (i.e. immune-related Adverse Events (irAEs))

The unique MOA of immuno-oncology agents requires modified tumor response criteria

Conventional RECIST guidelines may not provide a complete assessment of immunotherapy tumor response:

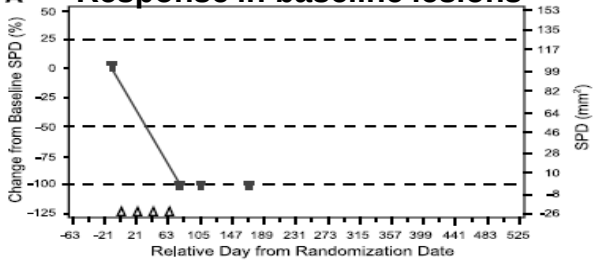
- Anti-tumor response to immunotherapy may take longer compared to cytotoxic agent response
- Clinical response to immune therapies can manifest after conventional progressive disease (PD) – "pseudoprogression"
- Discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed
- Allowance for "clinically insignificant" PD (e.g., small new lesions in the presence of other responsive lesions) is recommended
- Durable stable disease may represent antitumor activity

(source: Wolchock et al., 2009)

Patterns of response observed in patients with advanced melanoma treated with ipilimumab

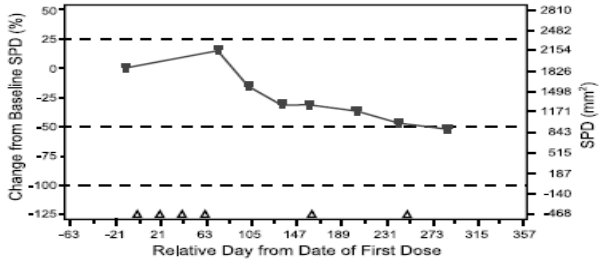
CONVENTIONAL TUMOR RESPONSES

A **Response in baseline lesions**



“stable disease” with slow, steady decline in total tumor volume

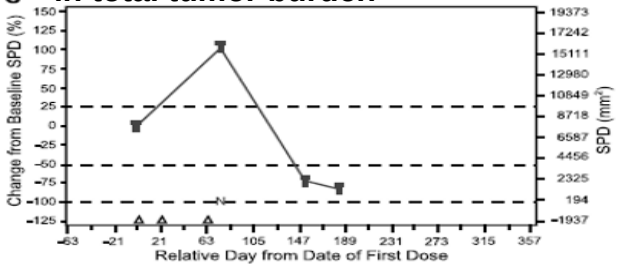
B



TUMOR RESPONSES THAT GO AGAINST STANDARD CRITERIA

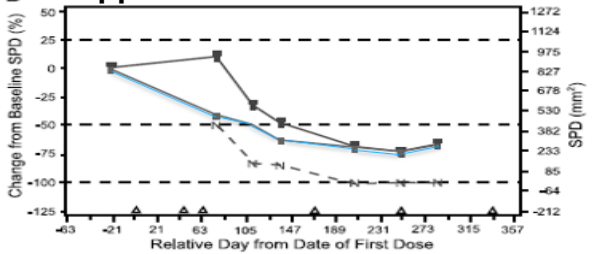
Responses after an initial increase in total tumor burden

C



Reduction in total tumor burden during or after the appearance of new lesions

D



SPD = sum of the product of perpendicular diameters; Triangles = ipilimumab dosing time points; N=tumor burden of new lesions

(source: Wolchock et al., 2009)

Differences between WHO (World Health Organization) classification and irRC

	WHO	irRC
New Measurable lesions (> 5 x 5 mm)	Always represent PD	Incorporated into total tumor burden
New non-measurable lesions (<5 x 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining best overall response	Contribute to defining irCR

Application of immune-related Response Criteria

- **irCR** — Complete disappearance of all lesions and no new lesions; confirmation by a repeat consecutive assessment no less than 4 weeks from the date first documented
- **irPR** — decrease in tumor burden ≥50% relative to baseline confirmed by repeat consecutive assessment at least 4 weeks later
- **irSD** — not meeting criteria for irCR or irPR in absence of irPD
- **irPD** — increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmed by repeat consecutive assessment at least 4 weeks later

Healthcare providers will need to recognize and manage irAEs related to immunotherapy

Adverse Events differ in patients taking cytotoxic agents versus patients taking immunotherapy checkpoint inhibitors

irAEs associated with checkpoint inhibitors* :	Dermatologic Toxicities
	Enterocolitis / Gastrointestinal related
	Endocrinopathies
	Hepatotoxicities
	Pneumonitis

**discussed in more detail during the 11:30am session*

Immuno-Oncology: Challenges & Considerations

- Rapid approval of immunotherapies for on- and off-label indications
  - Payers may struggle to “keep up” with the amount of supporting clinical data constantly being published; this could affect coverage

- Increasing use of immunotherapies in combination (e.g. chemo, targeted biologics, other immuno-oncologic agents) may drive cost upwards resulting in tighter payer-management of these agents (Pre-cert, step therapy, use of biomarkers (e.g. PD-L1 expression)

- Requirement of resources
  - Involvement of the entire multidisciplinary team (physicians, pharmacists, nurses) and patients: Communication/coordination, education, updating protocols
  - Reimbursement staff

Summary

- *Concept of immunotherapy has been around for over a century; today, immunotherapy is changing the treatment paradigm for many oncology disease states with impressive tumor responses in hard-to-treat cancers*

- *Immuno-oncology agents are being developed to treat a number of tumor types (monotherapy and in combination with other agents or other immunotherapies)*

- *Healthcare providers will need to consider response patterns and immune-related adverse events when using checkpoint inhibitors to treat patients with cancer*

- *A number of challenges have the potential to affect immunotherapy utilization: reimbursement related issues, administrative hassles, utilization of resources, etc.*

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Panel Discussion

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