Banner MD Anderson Cancer Center

Making Cancer History®

Immunotherapy
Cancer's Checkpoint Inhibitors, Checkmate?

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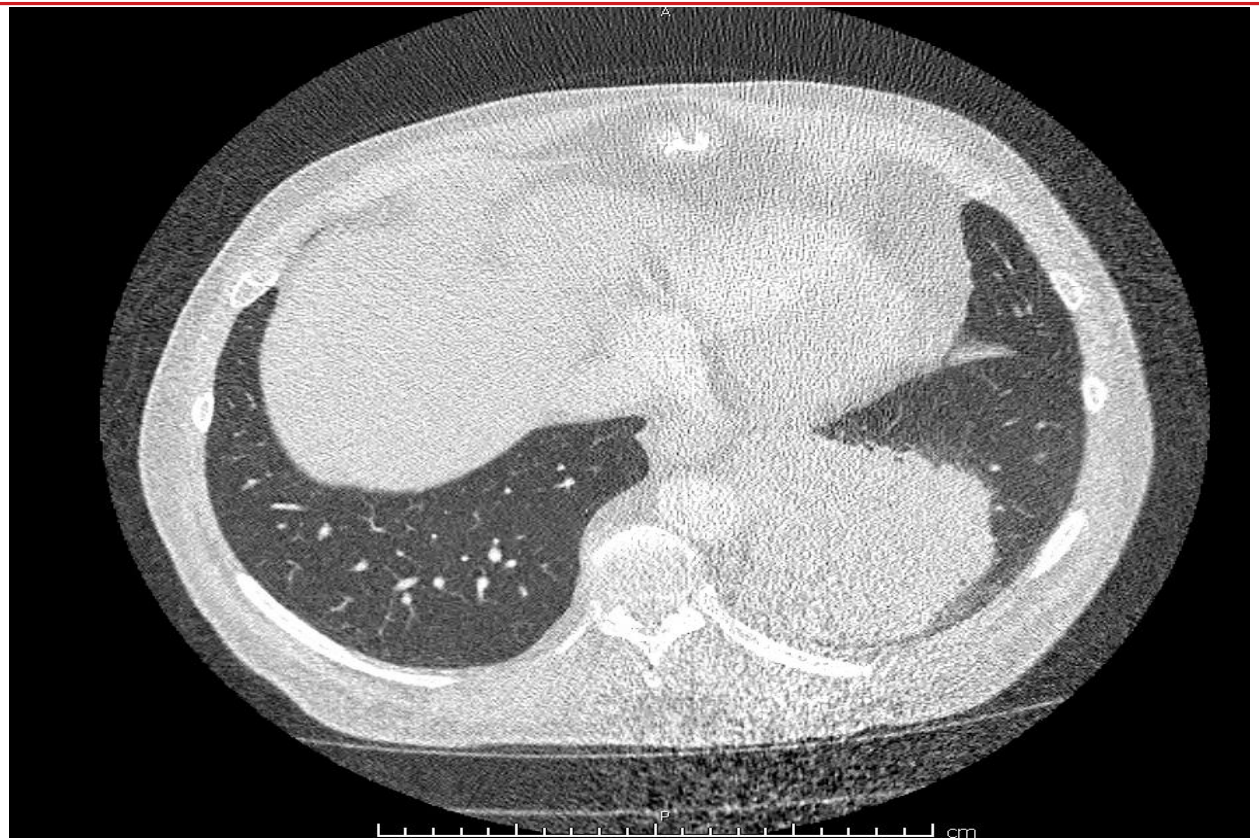
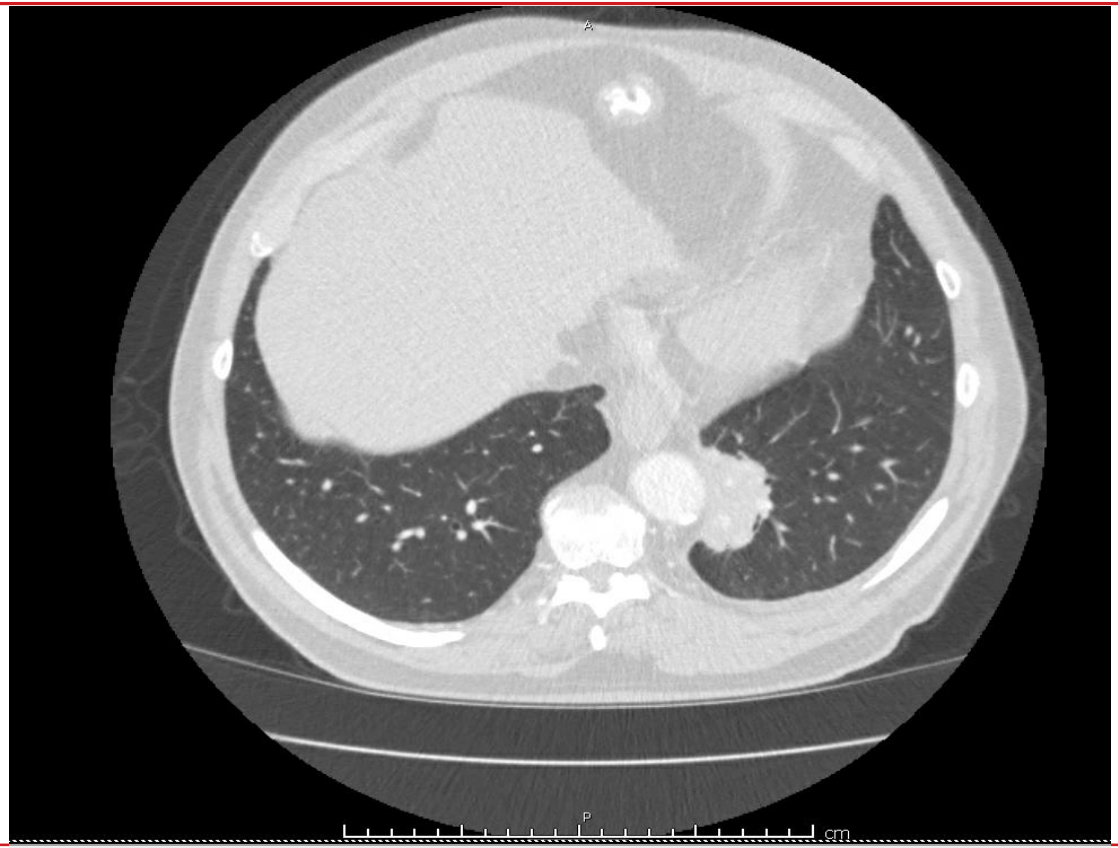
Case presentation: Stage IV Malignant Melanoma

- 72 y.o. Caucasian gentleman with a hx of Stage Unknown Malignant Melanoma resected L neck 1999
- No prior relapses or other hx of malignancies. Negative FH
- He presents in September 2016 with nausea and abdominal pain radiating to his back. He was found to have a 10 cm AAA needing emergent endograft repair.
- Incidental findings: 9 mm L occipital lobe lesion, 11 cm LLL mass, and 2 N2 LNs confirmed on PET/CT
- CT guided needle Bx of LLL mass: Metastatic Melanoma (BRAF mutation negative)


A
P
cm

Treatment

- Stereotactic Radiosurgery (SRS) to solitary brain lesion, 5 fractions (35Gy)
- Pembrolizumab IV q 3 wks Dec 2016-Feb 2018
- Toxicity: progressive NCI grade 2 rash treated with topicals and breaks from treatment
- Serial CT scans of chest to monitor response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Diagnosis:

A. Left subcarinal lymph node:

- **One lymph node, negative for metastatic disease.**

B. Lung, left lower lobe, lobectomy specimen:

- **Necrotic mass, 4.6 cm with surrounding fibrosis and inflammation, including overlying pleural fibrosis; negative for residual melanoma (100% tumor necrosis).**
- **Bronchovascular resection margin, negative for neoplasm.**
- **Three attached lobar lymph nodes, negative for metastatic disease.**

C. Left inferior pulmonary ligament lymph node specimen:

- **Two lymph nodes, negative for metastatic disease.**

D. Left posterior hilar lymph node specimen:

- **Four lymph nodes, negative for metastatic disease.**

E. Left carinal lymph node #2:

- **One lymph node with microscopic focus of necrosis consistent with necrotic neoplasm (100% tumor necrosis); negative for viable metastatic disease.**

F. Left peribronchial lymph node specimen:

- **Two lymph nodes, negative for metastatic disease.**

Practice changing advances in last 25 years

- Tyrosine kinase inhibitors (TKIs): small molecules that target signal transduction pathways inside cell and not dependent on cell cycle: imatinib (BCR/ABL), erlotinib (EGFR), crizotinib (ALK), ibrutinib (Bruton's tk)
- Cladribine for hairy cell leukemia
- Monoclonal antibodies: rituximab (CD20), trastuzumab/pertuzumab (Her 2 neu family)
- Checkpoint inhibitors: for the first time, treatment that was tumor agnostic with broad implications and potential applicability: nivolumab (PD-1), durvalumab (PDL-1), ipilimumab (CTLA-4)

Immunotherapy

- Nonspecific immunotherapies: alpha interferon, IL-2
- Monoclonal antibodies:
  - Targets: trastuzumab (her2) that alters downstream signaling
  - Flags: rituximab (CD20), daratumumab (CD38) that initiates A-DCC/C-DC
  - T cell immune tolerance interference: check point inhibitors
- Oncolytic viral therapy: T-VEC (viral replication inside cell) and subsequent antigen release
- T cell therapy: CAR-T that involves genetically altering patient's WBCs with chimeric antigen receptors that can recognize pt's cancer cells
- Cancer vaccines: sipuleucel-T for prostate CA as treatment, or HPV/HepB for prevention of associated malignancies

Checkpoint Inhibitors: how do they work?

- Immune checkpoint blockade removes inhibitory signals of T cell activation which enables tumor reactive T cells to overcome regulatory mechanics and mount an effective antitumor response.
- Regulatory mechanisms exist within a certain physiologic range to prevent autoimmunity.
- Malignant cells co-opt immune suppressive and tolerance mechanisms to avoid immune destruction.
- Basic bench research postulated that blocking these immune checkpoints would lead to increased T cell activation.

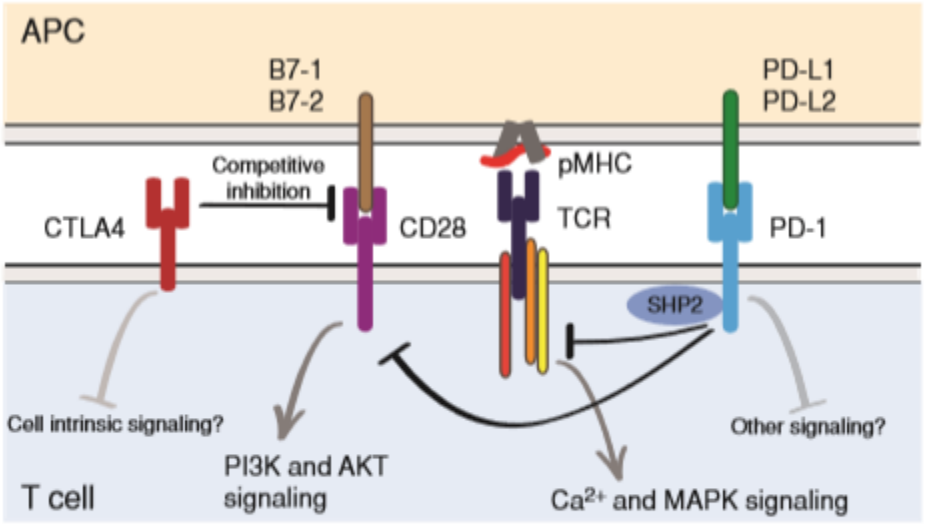


Figure 1. Molecular mechanisms of CTLA4 and PD-1 attenuation of T-cell activation. Schematic of the molecular interactions and downstream signaling induced by ligation of CTLA4 and PD-1 by their respective ligands. The possibility of additional downstream cell-intrinsic signaling mechanisms is highlighted for both CTLA4 and PD-1.

PD-1, PDL-1 and CTLA-4 are the current targets but not the whole story. Downstream signaling may be the next rich area to explore. Aside from the blockade effect directly seen with ipilumumab on CTLA-4, it also depletes regulatory T cells contributing to effect and toxicity.

Current FDA approved checkpoint inhibitors

PD-1 (Programmed Cell Death) Inhibitors (checkpoint on T cells):

- Cemiplimab (Libtayo)
- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)

PDL-1 (Programmed Cell Death Ligand) Inhibitors (checkpoint on CA):

- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinizi)

CTLA-4 (Cytotoxic T lymphocyte-associated antigen 4) Inhibitors:

- Ipilimumab (Yervoy)

Summary of Tumor types currently approved

- Melanoma
- NSCLC
- SCLC
- RCC
- Hodgkins Lymphoma
- Urothelial Carcinoma
- MSI High of any histology
- HCC
- Gastric CA/GE junction
- Breast CA
- H&N (SCC)
- Merkel Cell CA

Toxicity profiles

Many factors at play in determining degree of toxicity:

1. Type of cancer and its site (melanoma, rash and colitis and less pneumonitis. Lung/RCC, more pneumonitis)
2. Dose (PD-1 & PDL-1 std, low vs high in CTLA-4)
3. Combinations (PD-1/PDL-1 alone vs combos with CTLA-4)
4. Agent specific (PD-1: hypothyroid, pneumonitis, CTLA-4: colitis, hypophysitis, rash)

Toxicity Profiles

- In general: “ the itis’ “
- Fatigue
- Infusion rxns
- Dermatologic (especially in combo, 60%)
- Gastrointestinal (diarrhea)
- Liver (transaminitis)
- Endocrine (often permanent)
  - Thyroid, pituitary, adrenal, pancreas

Toxicity Profiles

- Pulmonary (cough, DOE, O2 requirements, exercise tolerance)
- Rheumatologic (A/M)
- Neuro (HA, encephalopathy, meningitis)
- Ocular (keratitis, uveitis)
- Renal
- Heme (anemia, cytopenias)
- Cardiac (myocarditis, pericarditis)

Toxicity profile: treatment

- Mild: Close observation
- Moderate to severe:
  - Treatment cessation
  - Steroids, topical, prednisone (0.5-1 mg/kg), IV
  - Hospitalization (fluids, IV steroids, IVIG)
  - Infliximab
  - Other immune modulators
- Opportunistic infections
- Cancer specific efficacy maintained, same for pts with autoimmune histories and treatments (excludes transplant pts)

PDL-1 expression

- Immunohistochemical testing (IHC)
- Highly variable expression that may or may not predicative or prognostic
- Differing stains and kits
- Tumor vs immune cell expression in result
- Difficult deciding threshold “positives” on results
- Only 1/3 of pts with NSCLC express $\geq$ 50%
- We may learn of better alternative biomarkers

PDL-1 expression and response

Crit Rev Oncol Hematol. 2016 Apr;100:88-98. doi: 10.1016/j.critrevonc.2016.02.001. Epub 2016 Feb 10.

PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis.

Gandini S[1], Massi D[2], Mandalà M[3].

Meta-analysis of 20 RCT that included Melanoma, NSCLC, RCC in pts receiving anti PD-1/PDL-1 agents

1. +PDL-1 expression Melanoma: 53% risk reduction in mortality, RR 45% v 27%, correlation with expression increase and anti PD-1 agents
2. RR for nonsquamous NSCLC 29%(+) v 11% (-), squamous cell NSCLC RR equal for + or -

Landmark Clinical Trials

- Hodi et al, NEJM Aug 2010
  - 676 pt with Stage IV Melanoma randomized (3:1:1) Ipilimumab with GP100 vaccine, to GP100 vaccine, or ipilimumab
  - Best RR: 10.9% Ipi alone with 60% having disease stability of 2 years
  - 10 mos survival with IPI alone or combination vs 6 months vaccine ($p<0.001$)
  - Toxicity severe in some patients: 60% all grades, 10-15% Grade 3/4
  - First trial to demonstrate improved survival in Stage IV Melanoma with a check point inhibitor. Difficult to demonstrate with any agent.

Landmark Clinical Trials

- Checkmate 003: 2012 ASCO
  - Phase I Escalation Study of MDX-1106 (nivolumab) with NSCLC, Melanoma, CRPC, RCC, CRC
  - Increased RR with increased dose in NSCLC up to 32%, response duration 24 weeks, Grade 3/4 toxicity 14%
  - First trial to demonstrate activity of checkpoint concept in NSCLC
- Keynote 001: Garon et al, NEJM, May 2015
  - Phase I Dose Escalation Study of Pembrolizumab in NSCLC only
  - Overall RR 19% but **45%** if PDL-1 expression $\geq$ 50%
  - Grade 3/4 Toxicity 9.5%

Landmark Clinical Trials (Melanoma)

- Robert et al, NEJM June 2015
  - RCT of 418 pts with Stage IV Melanoma (nivolumab vs dacarbazine)
  - 72.9% OS vs 42% at 1 year in favor of nivolumab
  - 40% RR vs 13.9%
- CHECKMATE 238 (3 yr updated results ESMO Sept 2019)
  - RCT of resected 906 Stage III/IV melanoma pts of Nivolumab (3mg/kg) vs Ipilimumab (10 mg/kg) for 1 year adjuvant treatment
  - Superior RFS for N at 36 mos: 58% v 45% ($p<0.001$); Gr 3/4 toxicity: 14% vs 46%
  - N effects were superior regardless of Stage, PDL-1 expression or BRAF mutation status
- KEYNOTE 006 Schacter et al, Lancet Aug 2017
  - RCT of 834 Stage IV Melanoma (pembrolizumab q2wks, q3wks or ipilimumab at 3mg/kg)
  - 3yr f/u: Median survival not yet reached (P), 16 mos IPI. 24 mos OS: 55%, 55%, 43%

Landmark Clinical Trials: Melanoma

- CHECKMATE 067 5yr data (ESMO Sept 2019/Larkin et al NEJM Oct 2019)
  - RCT of 945 untreated, BRAF – Stage III/IV pts (Nivolumab-3, Ipilimumab-3, or N-1/I-3)
  - Toxicity: Grade 3/4 treatment related events, 59% N/I, 28% I, 23% N
  - RR: 58% combo, 45% Nivolumab and 19% Ipilimumab
  - Median OS: Combo, not reached; 36.9 months N and 19.9 mos I
  - 5 yr OS: Combo, 52%, 44% N, and 26% I
- CHECKMATE 511 Lebbe' et al, JCO April 2019
  - Phase III RCT of untreated Stage IV Melanoma pts with Nivo1/Ipi3 vs Nivo3/Ipi1
  - 1 year f/u thus far with similar efficacy as original (50.6% RR vs 45.6%)
  - Grade 3/4 toxicity down to 34% vs 48%

Summary of Checkpoint Inh. Melanoma Trials

- Stage III Adjuvant: Nivolumab frontline (category 1), 1 year
- Stage IV Metastatic or Resected:
  - Nivolumab alone frontline (category 1)
  - Pembrolizumab alone frontline (category 1)
  - Nivolumab plus Ipilimumab (4 doses) frontline (category 1)

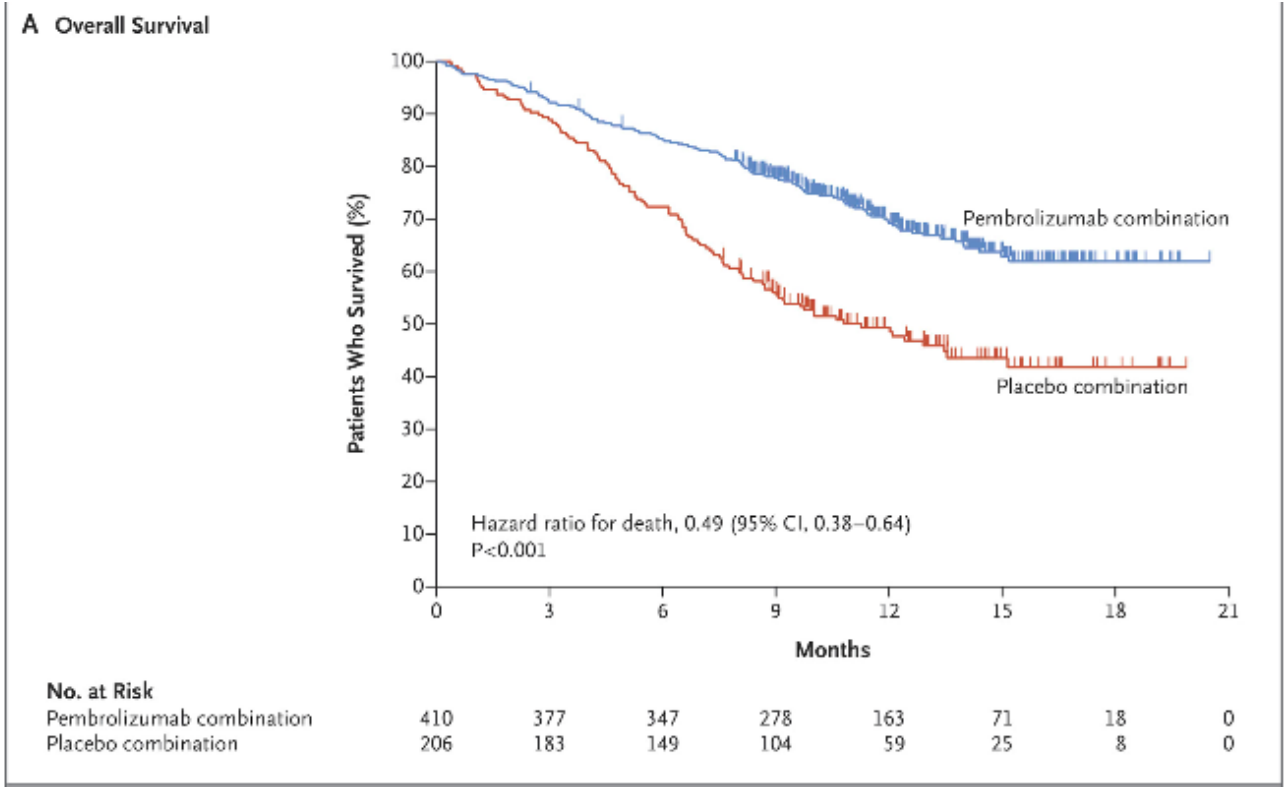
    Duration? Continue until toxicity or progression of disease, 2 years?

    BRAF mutated? Who goes first?

Landmark Clinical Trials NSCLC

- Gandi et al NEJM May 2018
  - 2:1 RCT 616 Pts with Stage IV nonsquamous, non-mutated to platinum analogue/pemetrexed plus pembrolizumab or placebo, followed by pembro or placebo plus pemetrexed as maintenance
  - Primary endpoints: PFS and OS; Secondary Endpoints: RR, resp duration and safety
  - Overall survival at 1 year: 69% vs 49% (p, 0.001); PFS 8.8 mos vs 4.9 mos (p< 0.001) both were regardless of PDL-1 expression
  - RR 47.6% vs 18.9% in favor of pembrolizumab (p<0.001)
  - Grade 3 or higher toxicity was 69% but only 9% attributed to immune system related events

Landmark Clinical Trials NSCLC



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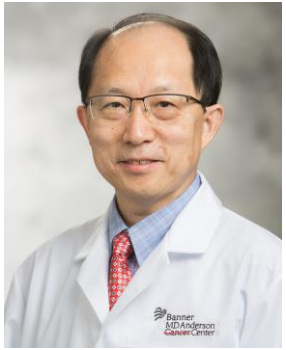
Landmark Clinical Trials NSCLC

- Antonia et al, NEJM Dec 2018
  - RCT 713 Pts Stage III unresectable NSCLC following definitive concurrent chemo/RT to durvalumab (PDL-1) or placebo x 1 year
  - Primary endpoints: OS and PFS
  - At 24 months: OS 69% vs 55% ($p<0.005$); PFS 17.2 mos vs 5.6 mos
  - Grade 3/4 Toxicity at 30% overall but individual categories including immune related events < 5%. Mild rashes and pulm sx were most common

Future Directions

- Increased trials with Ipilumumab using lower doses (1mg/kg)
- Exploring earlier use of these active agents in adj settings
- Combinations of checkpoint inhibitors
  - With other inhibitors (Ipi +)
  - With chemo
  - With targeted agents
- Bench research investigating downstream signals from T cell receptor
- Search of other biomarkers to identify receptive cancers

Medical Oncology



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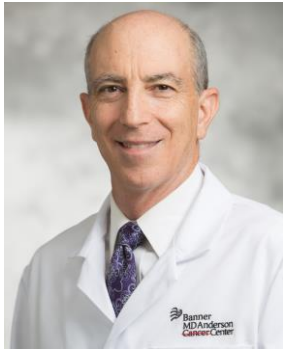

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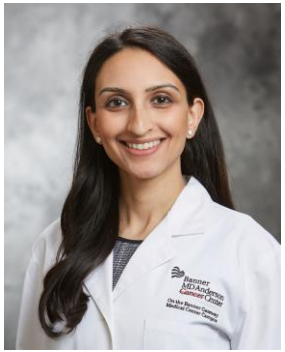
Melissa Yap, NP

Radiation Oncology



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Then & Now

2011

2019

Vital Statistics

	2012	2019*
Providers	20	160
Visits	53000	230000
Admits	1000	2800
Surgery	708	2770

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