IMMUNO-ONCOLOGY CHANGING PATIENT LIVES

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DISCLOSURES

- **Relationships with financial sponsors:**
  - **Other:** Novartis, Janssen (Advisory Board)

- **Potential for conflict(s) of interest:**
  - No speakers present any conflicts with sponsoring organization
  - No products discussed in this program present a conflict

Melanoma in Chemotherapy Era

- Survival of Stage 4 melanoma poor.
- 10 yr survival < 10%.
- Mainly due to resection of solitary mets.
- Multiple chemo agents and regimen – Response rates poor 5-20%.
- Did not extend survival.

Older Immunotherapy

- HIGH DOSE IL-2 [lymphokine that stimulate T-cells]
- Benefits small but substantial
- Durable response in some patients
- Too toxic – needed hospitalizations and ICU management
- INTERFERON: R.R – 20%
- Severe side effects

Current Agents - Immunotherapy

- IPILIMUMAB [Yervoy]
- NIVOLUMAB [Opdivo]
- PEMBROLIZUMAB [Keytruda]
- (all the above are checkpoint inhibitors)

- COMBINATION OF 1&2

- If b-raf mutated → has other targeted therapy options.

IPILIMUMAB

- Monoclonal Antibody that helps immune system to fight cancer cells
- T-cells have surface proteins called CTLA-4 which tell cells when to switch off
- Ipi blocks CTLA-4 protein
- T-cells switched on and can attack cancer cells

Precautions

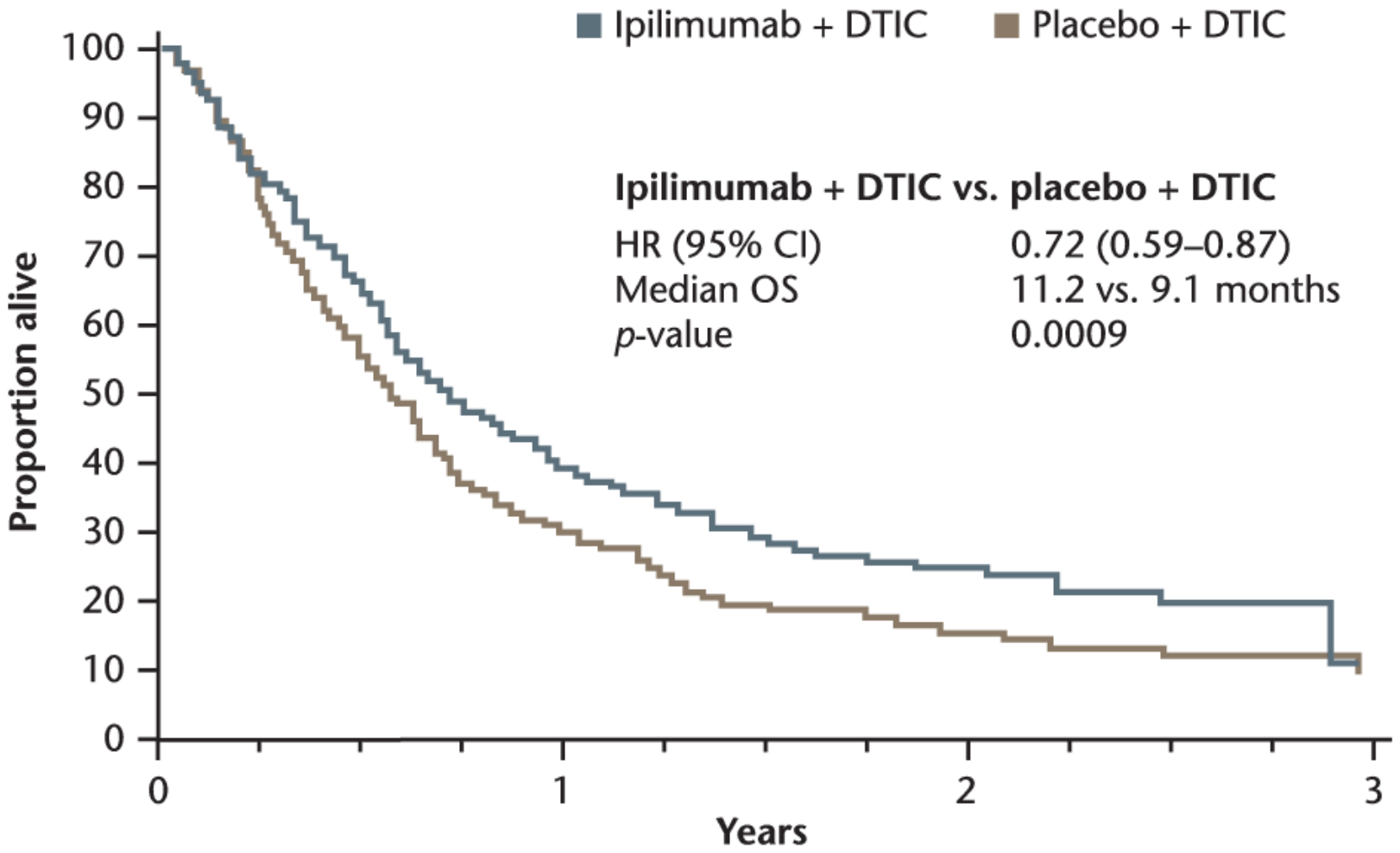
- Vaccines: Don’t have live vaccines during therapy and 6 months after. (rubella, mumps, measles, shingles, BCG)
- Can have other vaccines, may not be as effective
- Can have flu vaccine

- FERTILITY: Might affect fertility.

CONTRAINDICATIONS

- Active, life threatening auto-immune disease
- Organ transplant where discontinuation of immune-suppression can be life threatening.

Figure 1. Overall survival



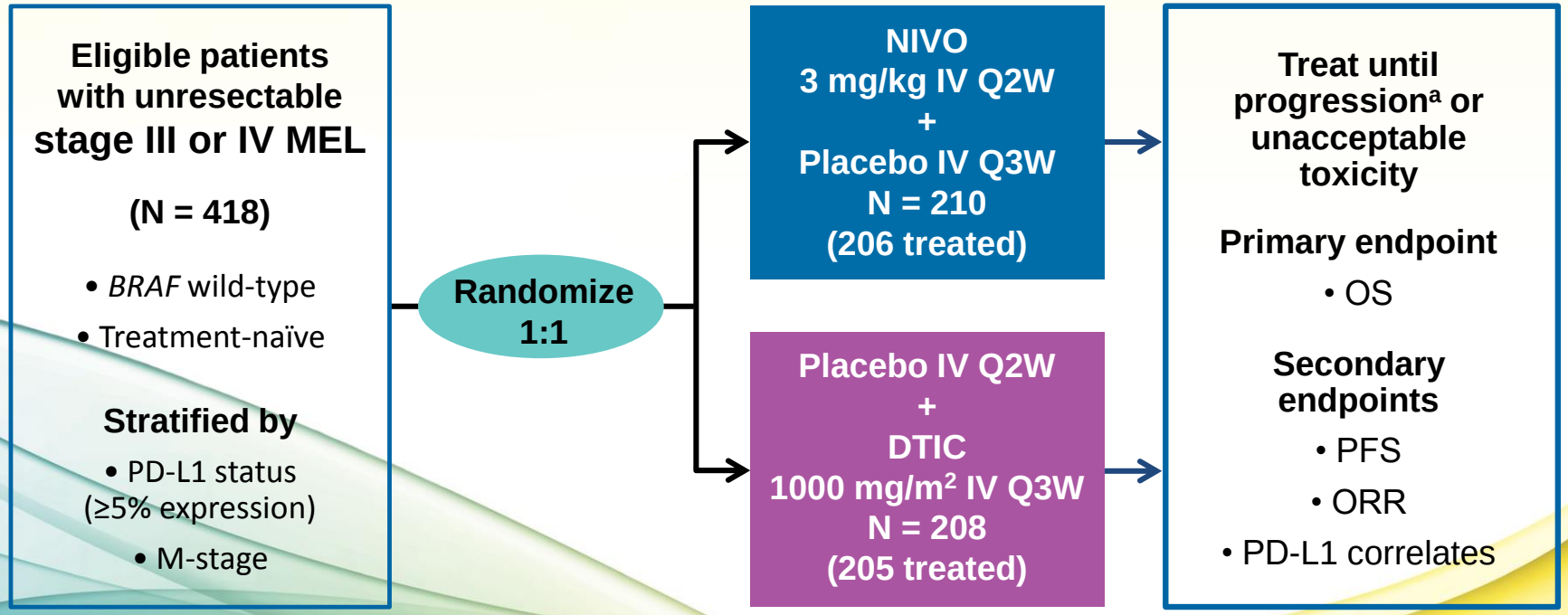
95% CI = 95% confidence interval; DTIC = dacarbazine; HR = hazard ratio; OS = overall survival

NIVOLUMAB

- IgG4 – anti PD-1 monoclonal antibody
- Checkpoint inhibitor
- Blocks signal that would have prevented T-cells from attacking cancer cells
- Targets programmed cell death receptor of lymphocytes

CheckMate 066: Study Design

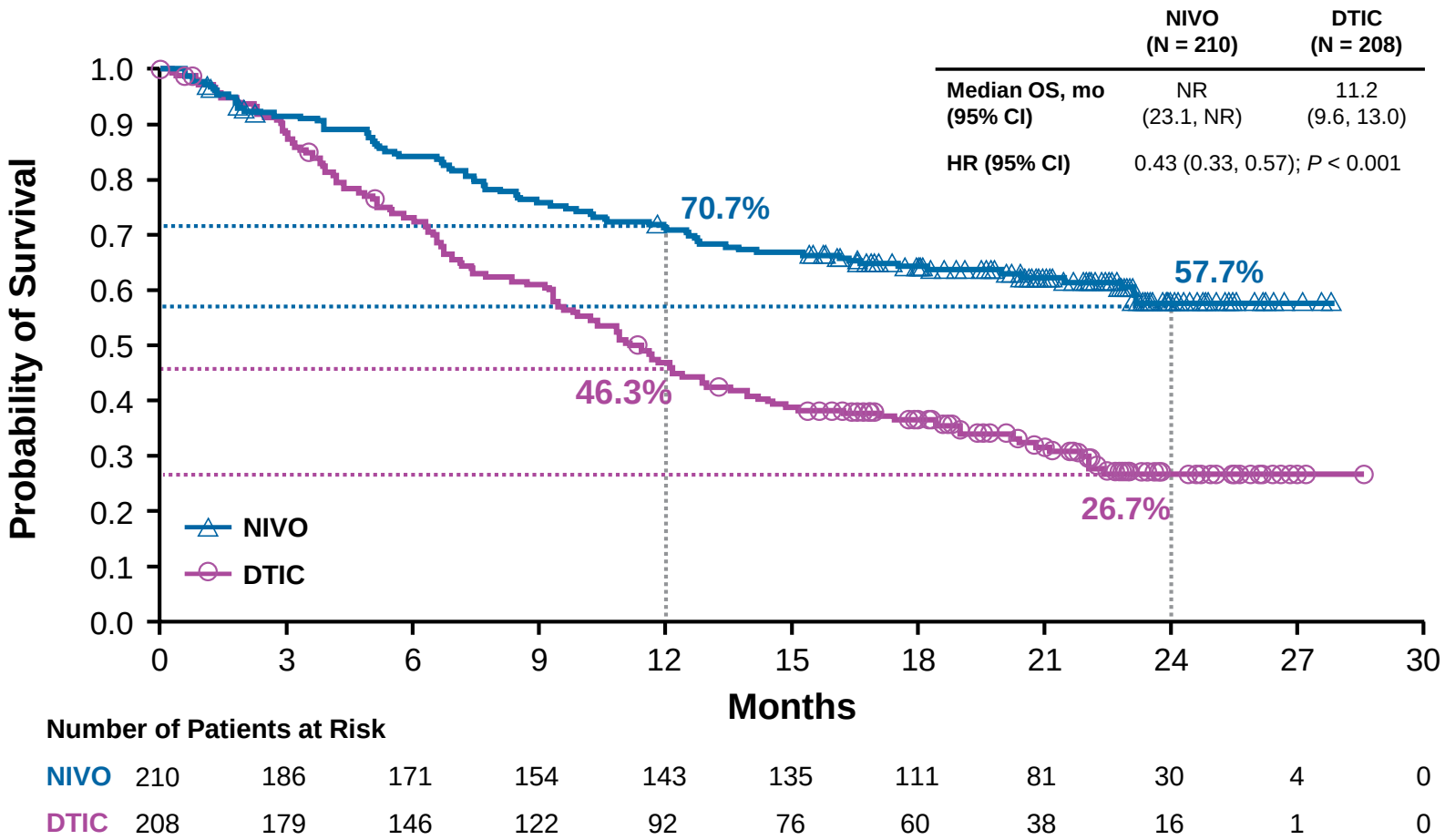
Randomized, double-blind, phase 3 study to compare NIVO to DTIC



[a]Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug

IV = intravenous; Q2W = twice weekly; Q3W = three times a week

Overall Survival – NIVO vs DTIC

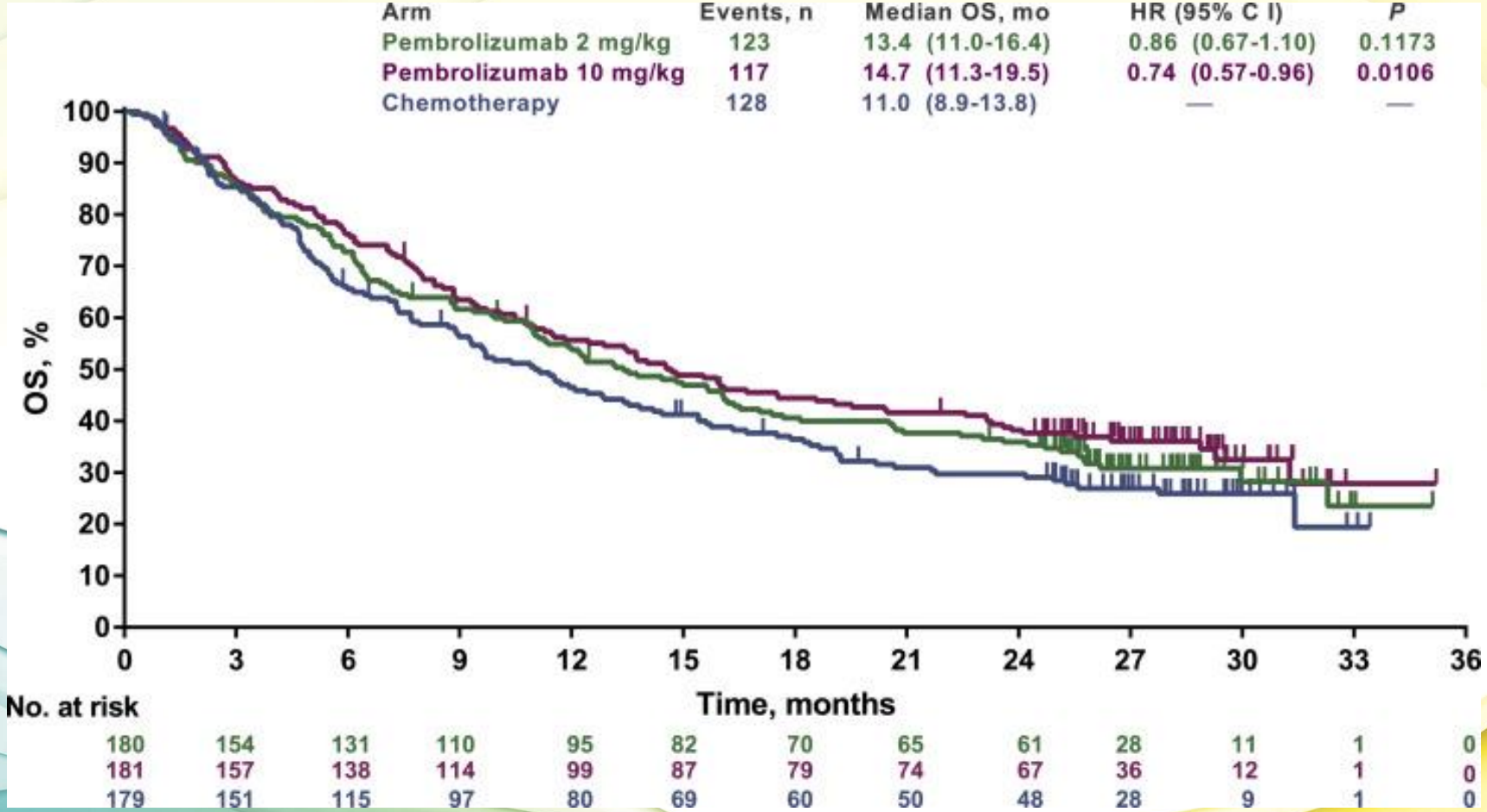


- Median follow-up was 18.5 months for NIVO and 10.9 months for DTIC (2 year OS rates are estimated)
- Database lock was on July 15, 2015

CI = confidence interval, HR = hazard ratio; mo = month

PEMBROLIZUMAB

- Humanized antibody used in cancer immunotherapy.
- Anti PD-1



WINDSOR REGIONAL HOSPITAL
OUTSTANDING CARE – NO EXCEPTIONS!

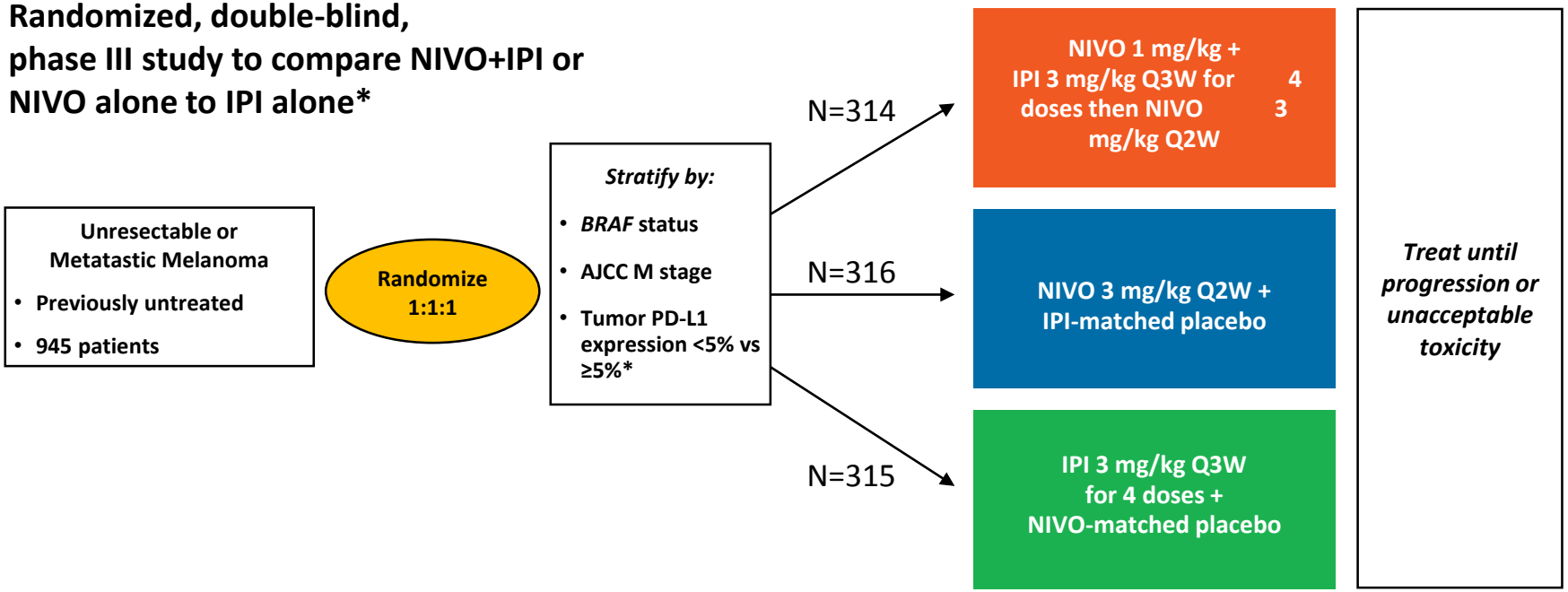
COMPASSION is our PASSION

COMBINATION: IPI + NIVO

- Synergistic mechanism of action
- More benefits – PFS and OS
- More toxicities

CheckMate 067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*



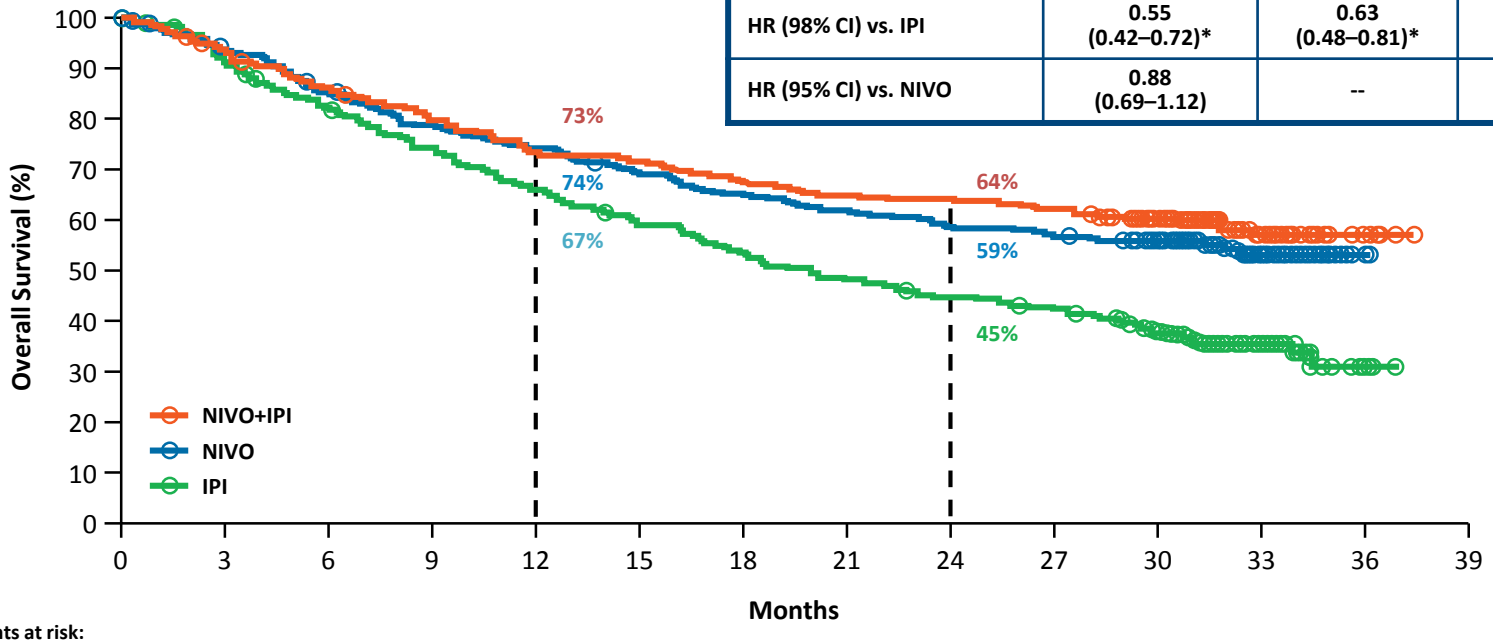
Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

**The study was not powered for a comparison between NIVO and NIVO+IPI*

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*$P<0.0001$



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

Key Principles of imAR Management

Patient education essential

Stay alert: continuous monitoring[1,2]
- Most imARs occur during treatment
- Monitor after the last dose; imARs can occur week to months later

Robust, proven management guidelines available[2]

Early identification[1,3]

Timely intervention[1,3]

Patients must report new, persistent or worsening symptoms[1-3]

Evaluate differential diagnoses per standard practice[1,2]
- Consider noninflammatory etiologies
- Consider all signs and symptoms

Individualized patient follow-up and counseling[3]

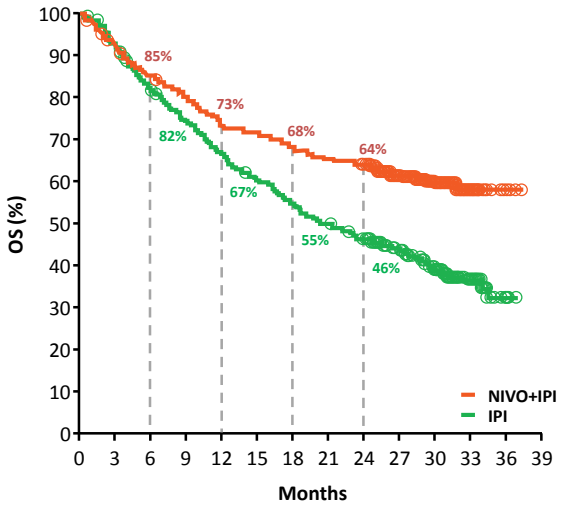
Systemic high-dose corticosteroids may be needed for severe events[2]

1. Yervoy Risk Evaluation and Mitigation Strategy. http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_IMMUNE%20MEDIATED%20ADVERSE%20REACTION%20MANAGEMENT%20GUIDE.pdf. Accessed January 2016. 2. http://www.opdivohcp.bmscustomerconnect.com accessed March 2016. 3. Ledezma B, et al. *Cancer Manag Res*. 2014;6:5-14.

Analysis of Overall Survival in Patients with GI irAEs and who used High Dose CS (CM069/067)[1]

All Treated Patients

	NIVO+IPI	IPI
Events, n/N	162/407	217/357
Median OS, mo (95% CI)	NR	20.21 (17.68, 25.72)
HR (95% CI) vs IPI	0.58 (0.47, 0.71)[a]	–



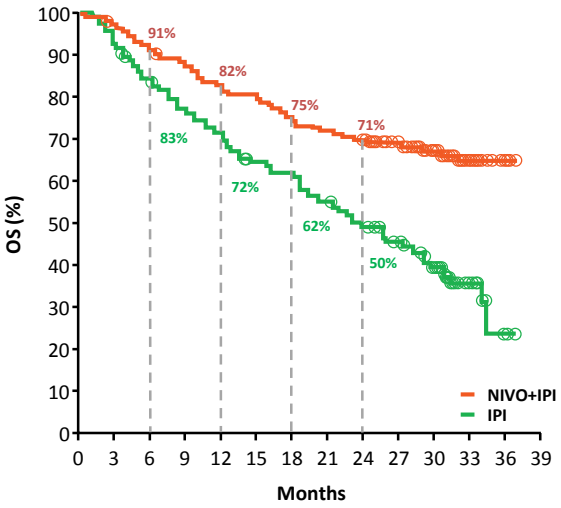
Patients at risk

NIVO+IPI	407	373	341	320	294	287	273	262	254	197	169	49	7	0
IPI	357	325	289	261	234	209	190	174	158	132	104	34	4	0

[a]*P*<0.0001

Patients With Select GI irAEs

	NIVO+IPI	IPI
Events, n/N	64/195	81/132
Median OS, mo (95% CI)	NR	23.20 (18.56, 29.40)
HR (95% CI) vs IPI	0.44 (0.32, 0.61)[a]	–

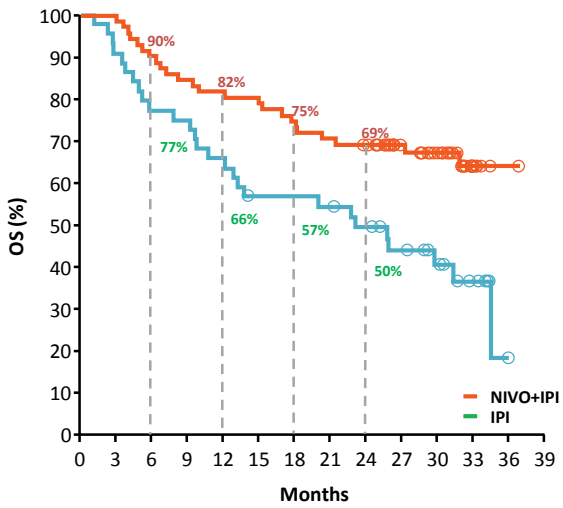


	195	188	177	169	158	154	144	139	133	105	87	28	5	0
	132	122	108	99	92	82	79	70	62	52	40	16	2	0

[a]*P*<0.0001

High-dose CS

	NIVO+IPI	IPI
Events, n/N	24/72	27/44
Median OS, mo (95% CI)	NR	23.03 (10.71, 34.43)
HR (95% CI) vs IPI	0.44 (0.26, 0.77)[a]	–



	72	71	65	61	59	57	54	51	49	36	29	7	1	0
	44	40	34	33	29	24	24	23	20	16	12	6	0	0

[a]*P*=0.0031

Database lock: February 2016, minimum follow-up 24 months (CheckMate 069), and September 2016, minimum follow-up 28 months (CheckMate 067)

CI = confidence interval; HR = hazard ratio; NR = not reached

1. Adapted fromWeber J, et al. Presented at ASCO 2017; abstract 9523

Immune-mediated Adverse Reactions

- Result from increased or excessive immune activity
- Can be severe or life-threatening, affecting various organs

GASTROINTESTINAL

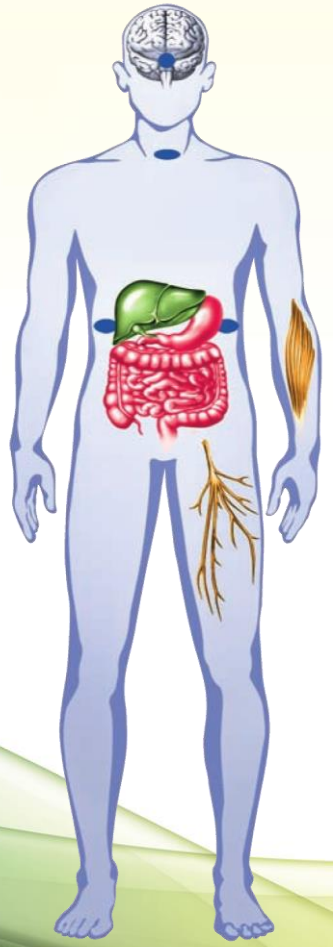
Signs and symptoms such as
- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus

LIVER

Signs such as
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

SKIN

Symptoms such as
- Pruritus
- Rash



NEUROLOGIC

Symptoms such as
- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

ENDOCRINE

Signs and symptoms such as
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

OTHER ADVERSE REACTIONS, including ocular manifestations

Please see each organ system section for related guidance.

Adapted from Yervoy Risk Evaluation and Mitigation Strategy. http://www.accessdata.fda.gov/drugsatfda_docs/rems/Yervoy_2012-02-16_IMMUNE%20MEDIATED%20ADVERSE%20REACTION%20MANAGEMENT%20GUIDE.pdf. Accessed January 2016.

Toxicity - Grades

- 1:Mild – can often continue - monitor
- 2: Hold – can restart with resolution
- 3: Hold – treat – with immunosupression
- 4: Severe- life-threatening- needs hospitalization - Discontinue

Immunotherapy Toxicity Management Guidelines

- **Cancer Care Ontario** – Immune Checkpoint Inhibitor side-effect toolkit
- **ASCO Guidelines** – Management of immune related adverse events.
- **ESMO** – Management of toxicities of immunotherapy.
- Society of Immunotherapy working group guidelines.

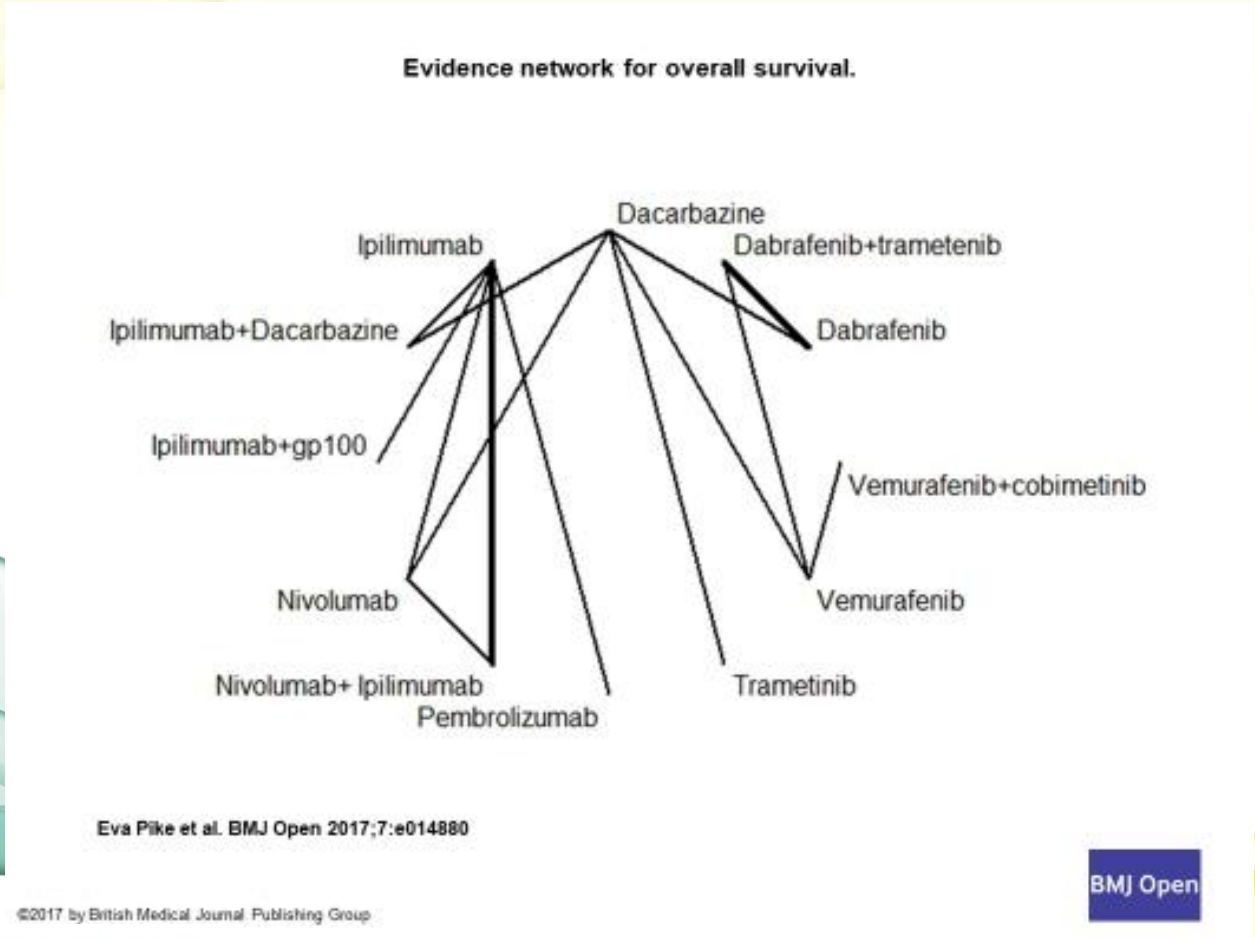
Immunosuppressive Agents (Beyond Corticosteroids)

Agent	irAE Category where IMM considered
Infliximab	GI[1,2,3], Cardiac[3], Ocular[3], Pulmonary[2,3,4]
MMF	Pulmonary[3,4], Hepatic[1,2,3,4] Myositis[3], Renal[3], GI[4], Neurological[4] Cardiac[3,4]
IVIG	Neurological[1,3,4], Pulmonary,[2,3] Dermatological[3], Myositis[3]
Methotrexate	Rheumatological[2,3]
Cyclophosphamide	Pulmonary[2,3]
Vedolizumab	GI[2,3]
Anti-cytokine Therapies (TNFi, anti-IL6 etc.)	Rheumatological[2,3,4], Ocular (TNFi) [4], Musculoskeletal (anti-IL6)[3]
Rituximab	Neurological[4] Hematological[3]
ATG	Hematological[3], Cardiac[3], Hepatic[4]
Cyclosporine	Neurological[4], Hematological[3]
Tacrolimus	Cardiac[4], GI[4], Hepatic[4]

List is not exhaustive; this is an area of emerging research, the agents identified here have been noted in BMS algorithms and/or consensus recommendations/ working group guidelines for management of specific irAEs within irAE the categories; Consult references for more details on supporting evidence in specific irAEs when considering their use

1. BMS Algorithms: a. OPDIVO [product monograph]. Canada; 2016. b. Postow MA et al. *N Engl J Med*. 2015;372:2006-2017 [supplementary appendix].
c. Larkin J et al. *N Engl J Med*. 2015;373:23-34. [protocol]. 2.*SITC* Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95 3. *ASCO-NCCN* Brahmer, J. et al. J Clin Oncol. 2018 Feb 14:JCO2017776385 4. *ESMO* Haanen,J et. Al., Ann Oncol (2017) 28 (suppl 4): iv119–iv142

Comparison of Agents in Melanoma



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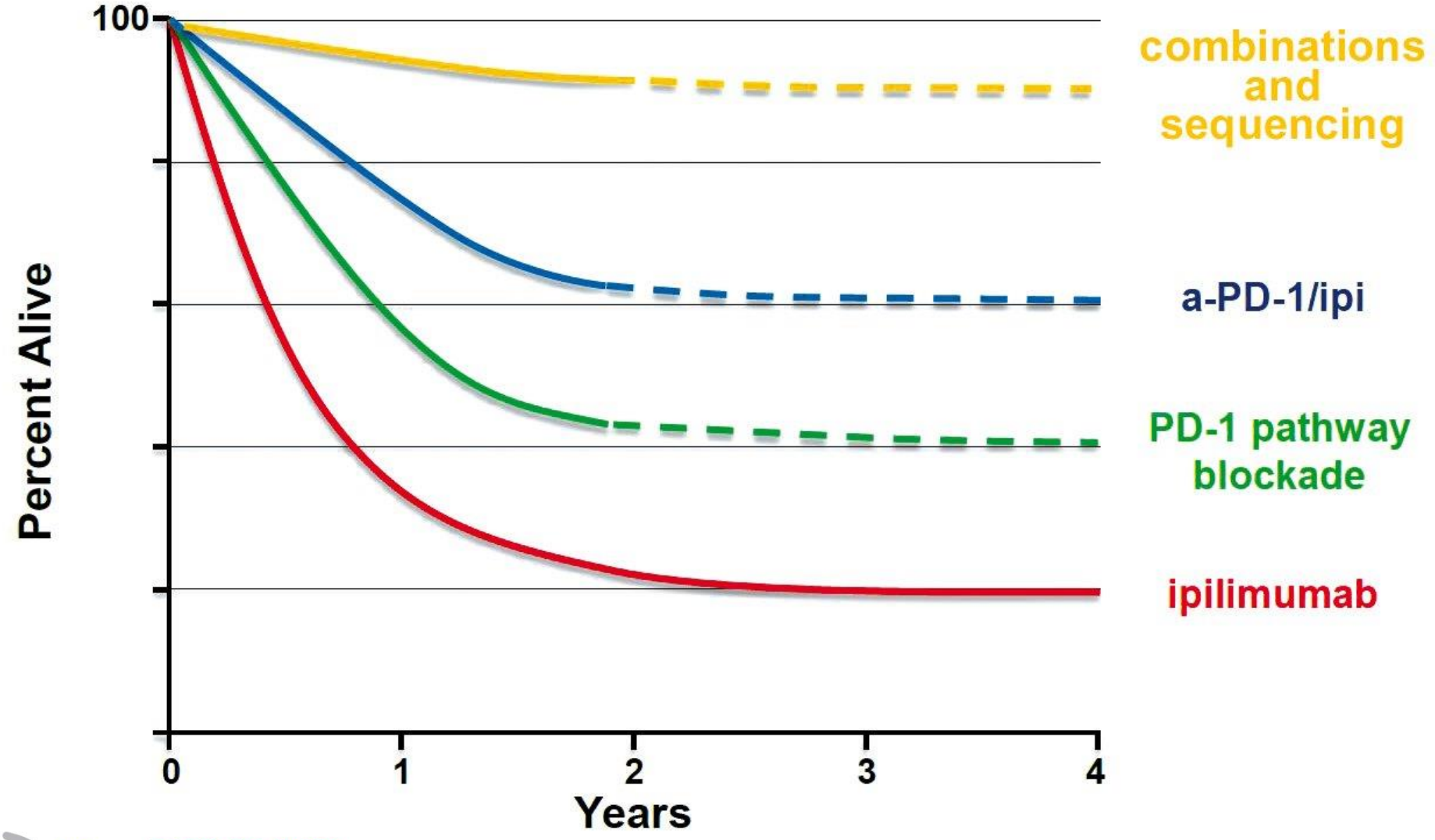

THANKS!

- FOR YOUR ATTENTION

Immunotherapy For Hodgkin's Lymphoma

Mohammad Jarrar, MD

Introduction-1

- Hodgkin's Lymphoma is a highly curable malignancy with cure rates ranging from 90-100% in early stage disease and 60-90% in advanced stage disease. These results are achieved utilizing either chemotherapy alone or a combination of chemotherapy and radiation therapy.
- Patients with refractory or relapsed disease can be salvaged using second line chemotherapy followed by high dose chemotherapy and autologous stem cell transplant.

Introduction-2

- Patients who relapse after autologous transplant have inferior outcome with more limited treatment options.
- Immunotherapy using conjugate anti CD30 antibody-drug conjugate Brentuximab Vedotin and PD-1 inhibitors Nivolumab and Pembrolizumab have shown promising results for relapsed and refractory patients and more recently incorporated in frontline therapy for high risk disease.

Brentuximab Vedotin (BV)

- BV is antibody-drug conjugate that conatins anti CD30 antibody along with microtubule disrupting agent monomethyl auristatin E (MMAE). The antibody component binds to the CD30 receptor expressed on HRS cells which enables the MMAE molecule to be internalized to the cell which results in cell cycle arrest and apoptosis.

Brentuximab Vedotin (BV)-Cont.

- BV was initially approved for HL patients who relapse after autologous transplant. In this patient population it produced overall response rate of 75% with 35% of patients achieving CR.
- Subsequent study (AETHERA trial) showed that patients at high risk of relapse (refractory disease, relapse within 12 months or extranodal disease) benefit from maintenance therapy with BV given for 16 cycles post auto transplant.

Brentuximab Vedotin (BV)-Cont

- In the AETHERA trial patients who received VB maintenance had a 2-year EFS of 65% compared 45% in those who received placebo.
- Several studies have used BV either as a single agent or in combination with Nivolumab or chemotherapy as a first salvage for refractory or relapsed patients before auto transplant with CR rates ranging from 61-93%.

Brentuximab Vedotin (BV)-Cont

- BV was used recently in the frontline therapy for early unfavorable or advanced HD in combination with ABVD and AVD chemo with CR rates of 95%. EFS at 5 years was 92% and OS was 100%. Pulmonary toxicity was significant when BV was used with bleomycin, therefore BV-AVD was recommended for further studies.

Brentuximab Vedotin (BV)-Cont

- Based on the previous phase I study, a phase III randomized study (ECHELON-1), compared BV-AVD to ABVD in high risk patients. 2-yr EFS for BV-AVD arm was 82.1% and 72.2% in the ABVD arm. Of note that this was a non-PET adapted study and required GCSF support for the BV-AVD arm.
- BV was combined with BEACOPP like regimens (BrECAPP or BrECADD) and produced 95% CR rate.

Brentuximab Vedotin (BV)-Cont

- BV was also used as an initial therapy in elderly patients or patients with multiple comorbidities with promising results.
- BV was also tested in early stage patients in an effort to decrease chemo or radiation exposure with results being similar to standard therapy.
- Main toxicities reported with BV include: Peripheral neuropathy, hyperglycemia, fatigue, fever. neutropenia and diarrhea.

Brentuximab Vedotin (BV)-Cont

- Incidence of neuropathy is up to 67%. It may require treatment delay or dose reduction. It tends to resolve after drug discontinuation and in those patients where it persists it is usually grade 1-2.
- In summary, BV is FDA approved for patients who relapse post auto transplant, as maintenance therapy post auto for high risk patients and as a frontline therapy in combination with AVD for advanced stage patients. In Ontario it is currently funded for the first indication only.

Immune Checkpoint Inhibitors

- Three drugs fall in this category:PD-1 inhibitors Nivolumab and Pembroluzumab and PDL-1 inhibitor Avelumab.
- PD-1 is a protein that is expressed on the surface of T-lymphocytes. PDL-1 is expressed on surface of normal cells. When PD-1 detects PDL-1 on another cell, it inhibits T-cell from attacking that cell.
- Hodgkin's RS cells frequently (>95% of the time) express PDL-1 on their surface and this helps them to escape destruction by the immune system.

Immune Checkpoint Inhibitors-Cont.

- Phase 1 CHECKMATE 039 study tested the efficacy of PD-1 inhibitor Nivolumab in heavily pretreated HD patients (including auto transplant). ORR was 87% and CR rate was 17%.
- Phase 1 KEYNOTE 013 study tested the efficacy of PD-1 inhibitor Pembrolizumab in heavily pretreated patients. ORR was achieved in 65% and CR was achieved in 16%.

Immune Checkpoint Inhibitors-Cont.

- Further studies on PD-1 inhibitors documented overall response rate of 70% and CR rate of 20% in patients with refractory or relapsed HD regardless of treatment previously received.
- PFS with PD-1 inhibitors compared favorably to BV in this patient population. Even patients who showed stable disease had increased PFS.
- PDL-1 inhibitor Avelumab showed ORR of 55% and CR rate of 7%.
- Only 5% of the patients had severe side effects.

Immune Checkpoint Inhibitors-Cont.

- Nivolumab was tested in combination with BV in patients with first relapse. ORR of 80% and CR rate of 61% were achieved.
- Nivolumab was tested in combination with AVD in frontline therapy for advanced stage HD. ORR of 84% and CR rate of 67% were achieved.
- Side effects profile observed in these combinations was similar to those observed when Nivolumab was used as monotherapy.

Immune Checkpoint Inhibitors-Cont.

- Disease response evaluation in the context of using checkpoint inhibitors is tricky. A phenomenon known as “pseudoprogression” is commonly seen, where the tumor size may increase or new lesions may appear due to interaction between immune system and tumor cells. Follow up of these patients has shown that patients who were continued on treatment beyond this pseudoprogression had better OS when compared to those who stopped treatment.

Immune Checkpoint Inhibitors-Cont.

- Side effects observed with checkpoint inhibitors include: Fatigue, fever, cough, skin rash, itching, joint pain, diarrhea, decreased appetite, constipation, nausea.
- Immune related adverse effects are also seen and can be severe in about 5% of the patients.
- Treatment is usually given IV every 2-3 weeks.

Immune Checkpoint Inhibitors-Cont.

- US FDA has approved use of Nivolumab in adult patients who relapsed after autologous transplant and BV.
- US FDA has approved Pembrolizumab for the treatment of children and adults who have failed previous three lines of treatment.
- In Ontario, neither of the two medications are currently funded pending Health Canada approval.

Immunotherapies Generic & Trade Names

- Below are the drugs that relate to the Immune Checkpoint inhibitor toxicity management tool from CCO:
  - Ipilimumab (Yervoy) – CTLA-4 inhibtior
  - Nivolumab (Opdivo) – PD-1 inhibitor
  - Pembrolizumab (Keytruda) – PD-1 INhibitor
  - Durvalumab (Imfinzi) - PD-L1 inhibitor
  - Atezolizumab – (Tecentriq) PD-L1 inhibitor