A Case Study: Ipilimumab in Pre-treated Metastatic Melanoma

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Disclosure

- Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

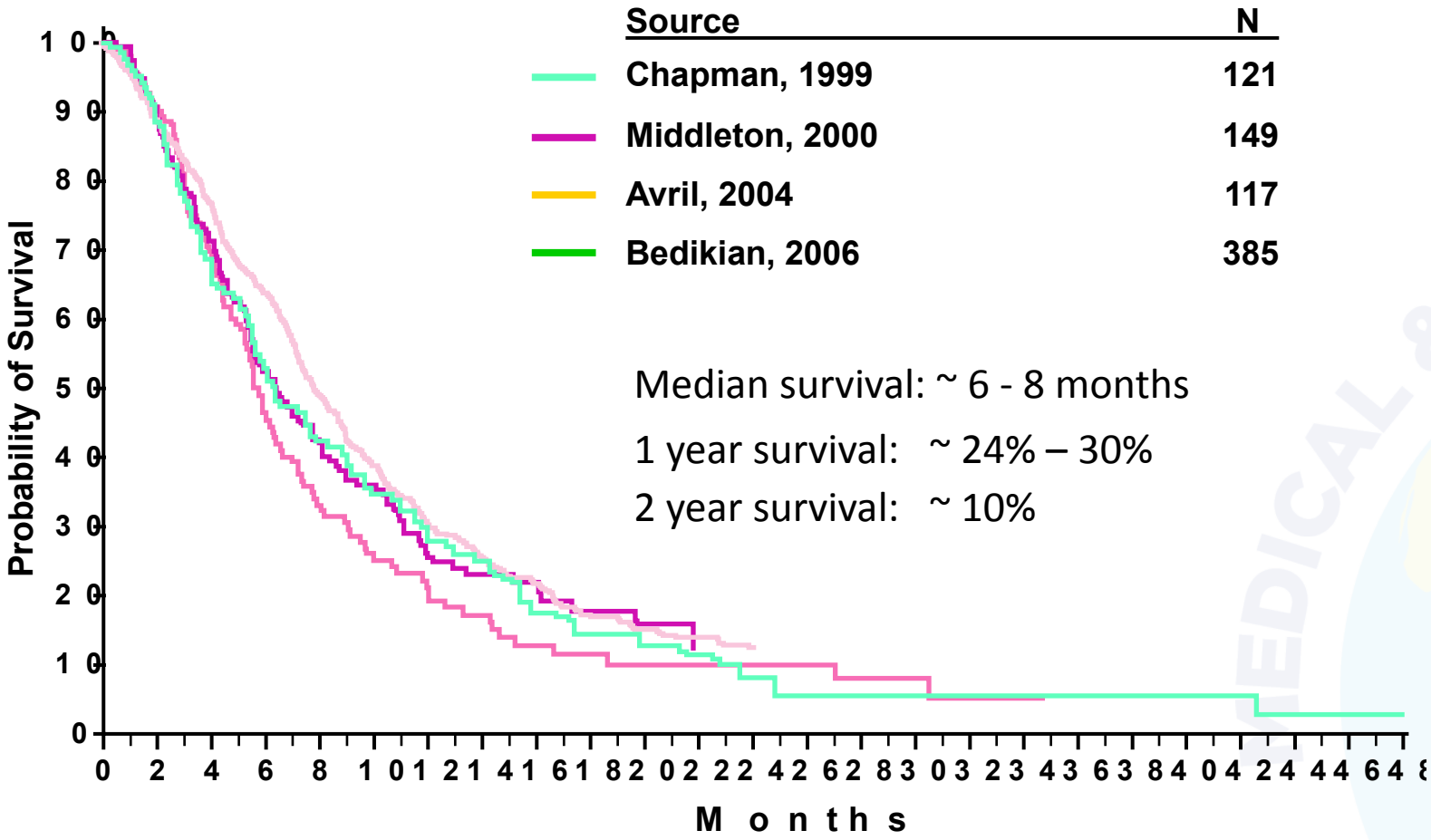
- The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb

Advanced Melanoma: Approved Agents Prior to 2011

	DTIC N=117	IL-2 N=270
Median Age (yrs)	55	42
Efficacy		
Median OS (months)	5.6	11.4
1 year survival (%)	24	43
2 year survival (%)	10	21
Safety (Grade 3-4 Toxicity)		
Hypotension (%)	—	45
Renal insufficiency (%)	—	39
Thrombocytopenia (%)	6	17

DTIC: Avril et al (2004) JCO.; IL-2: Atkins et al. (1999) JCO

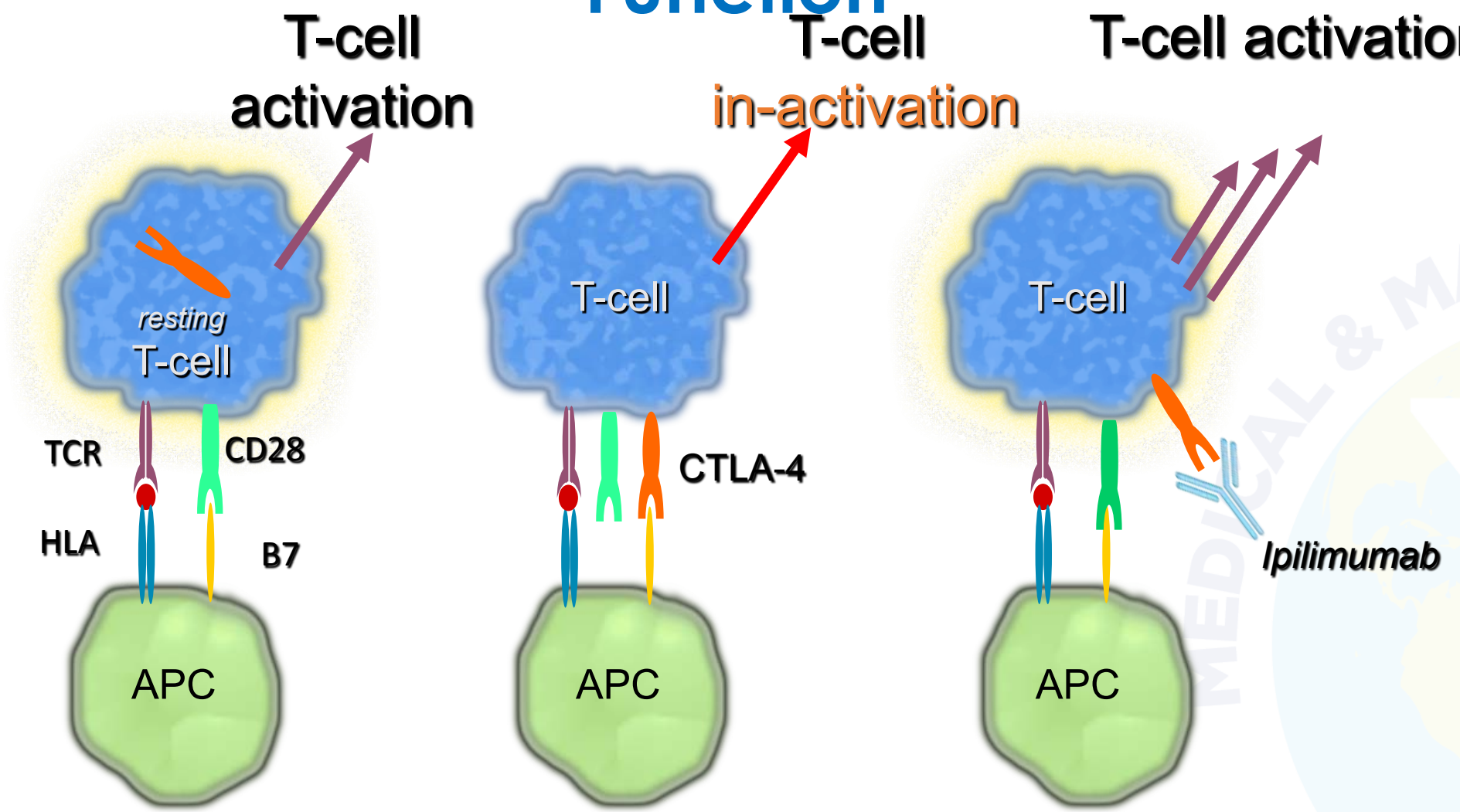
No Significant Improvement in OS on DTIC Over Time



Immunotherapy Approved in the US

- 1992
  - IL-2 for the treatment of renal cell cancer
- 1996
  - Interferon for the treatment of adjuvant melanoma
- 1998
  - BCG for the treatment of bladder cancer
  - IL-2 for the treatment of advanced melanoma
- 2009
  - Sipuleucel-T for the treatment of prostate cancer

Ipilimumab: Blocks CTLA-4, Potentiates T-Cell Function



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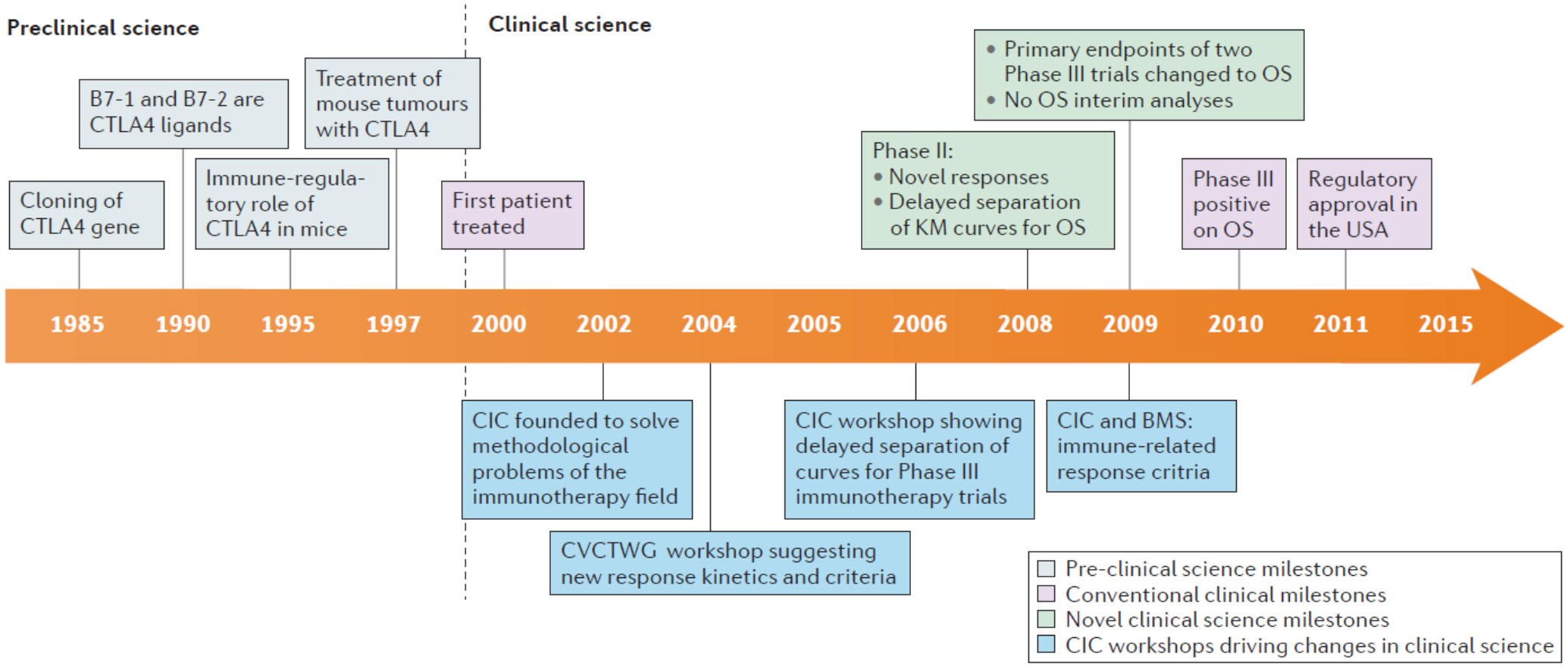
Ipilimumab Development Milestones



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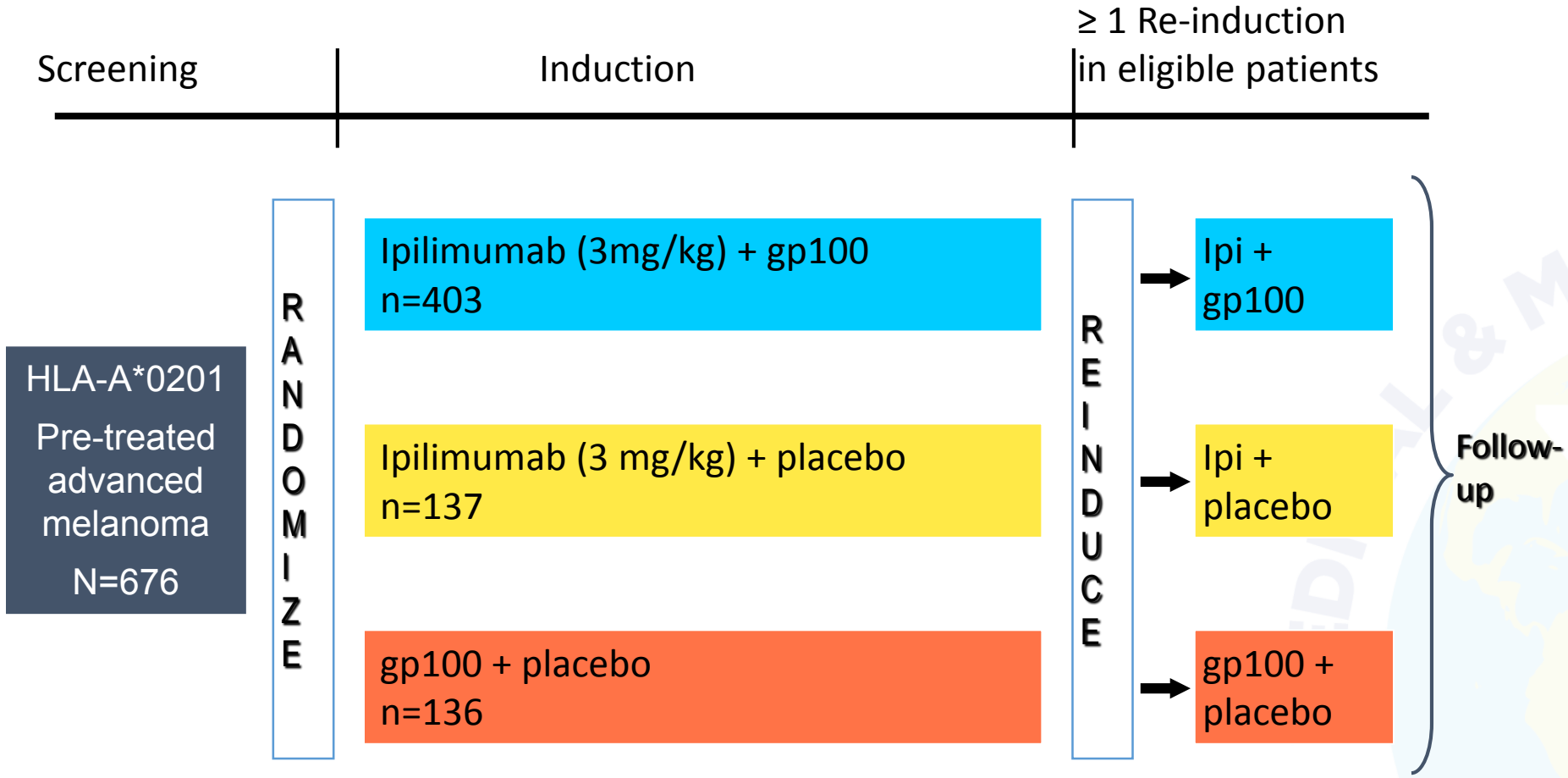
Ipilimumab Development Milestones (cont'd)

- MDX010-20 was the first trial that shows OS benefit in 30 years
- Previously treated and untreated metastatic melanoma
  - US approval: March, 2011
- Previously treated metastatic melanoma
  - EU approval: July, 2011
  - NICE appraisal: December, 2012
- Previously untreated metastatic melanoma
  - EU approval: November, 2013
  - NICE appraisal: July, 2014

MEDICAL & MARKET

Key Clinical Evidence
MDX010-20: Phase 3 Study Design



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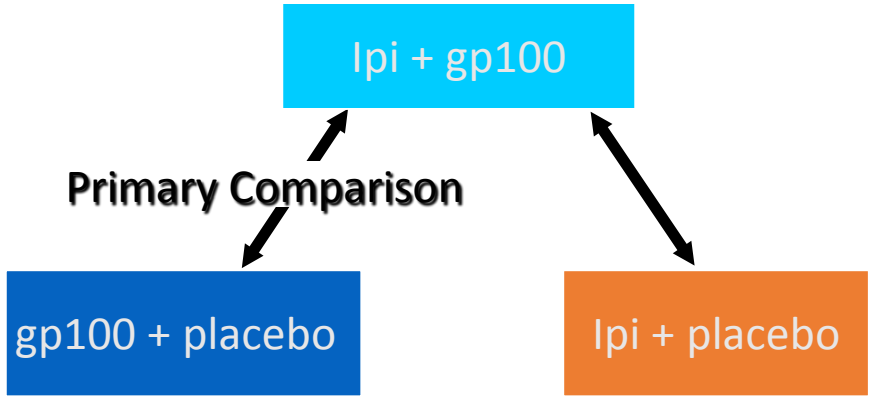
Key Clinical Evidence
MDX010-20 Study Design History

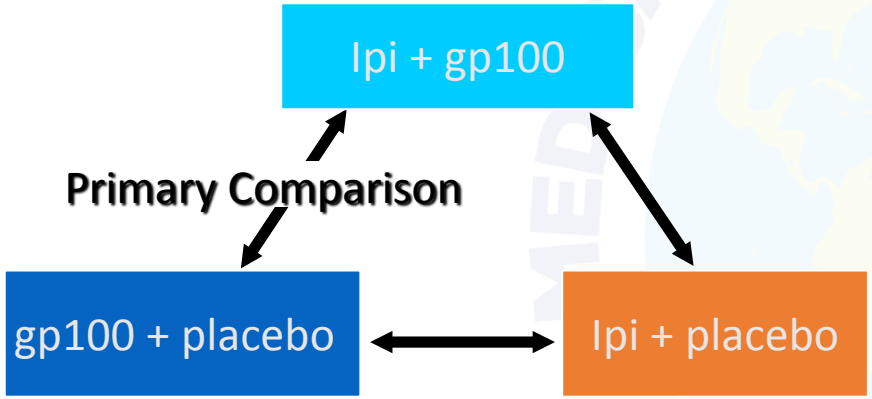
Original Study Design

- Contribution of components
  - Early phase II data
    - Durable responses
    - No OS data
  - Primary endpoint: BORR

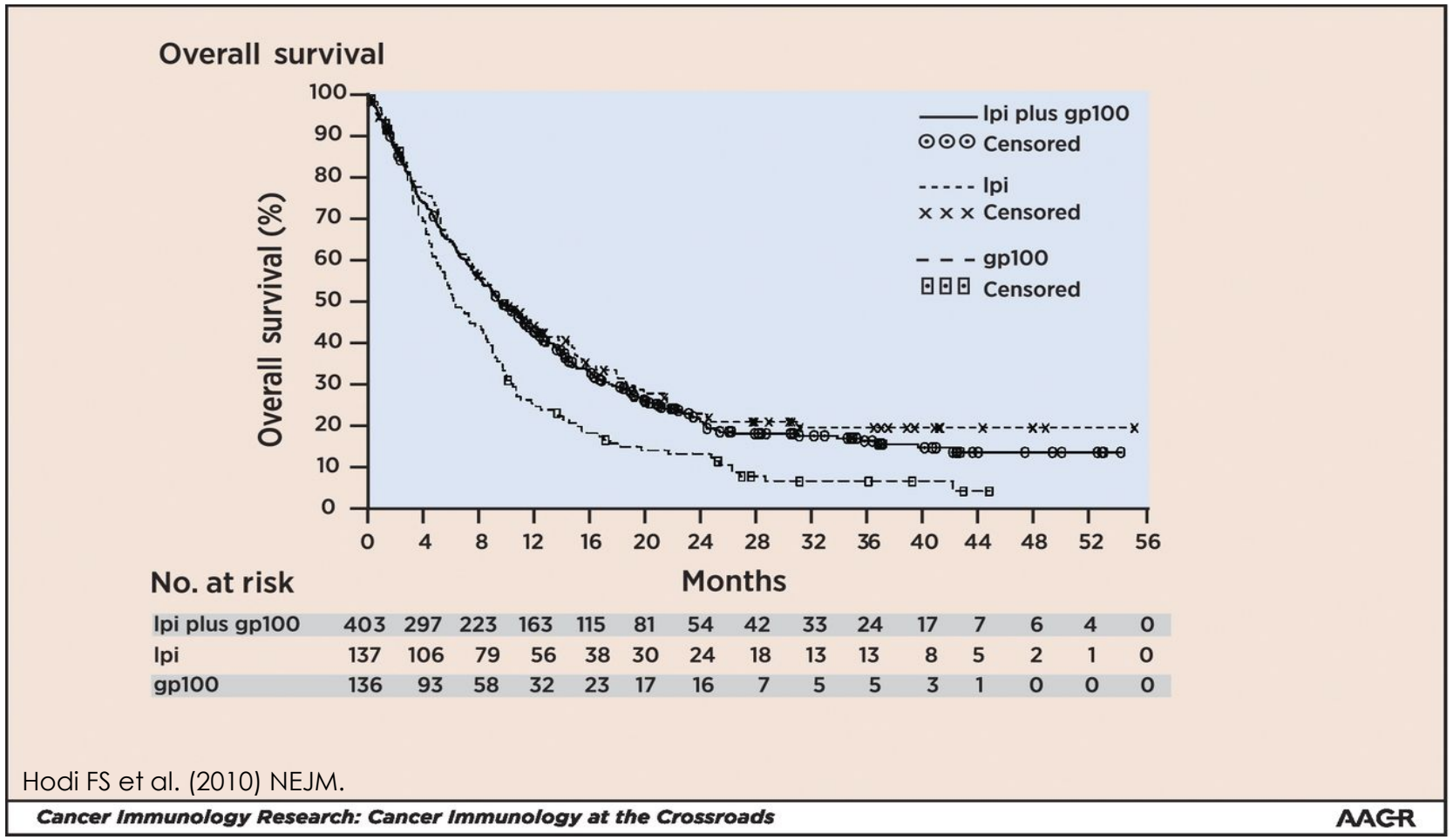


Revised Study Design (before unblinding)

- Survival superiority
  - Additional phase II data
    - BORR inadequate
    - Long-term survival
  - Primary endpoint: OS



MDX010-20 Ipilimumab in Previously Treated Stage III/IV Melanoma (Overall Survival)



Hodi FS et al. (2010) NEJM.

Cancer Immunology Research: Cancer Immunology at the Crossroads AACR

- Ipi/gp100 vs. gp100
  - HR: 0.68 (0.55,0.85)
  - P<0.001
- Ipi vs. gp100
  - HR: 0.66 (0.51,0.87)
  - P<0.003
- No added benefit of gp100

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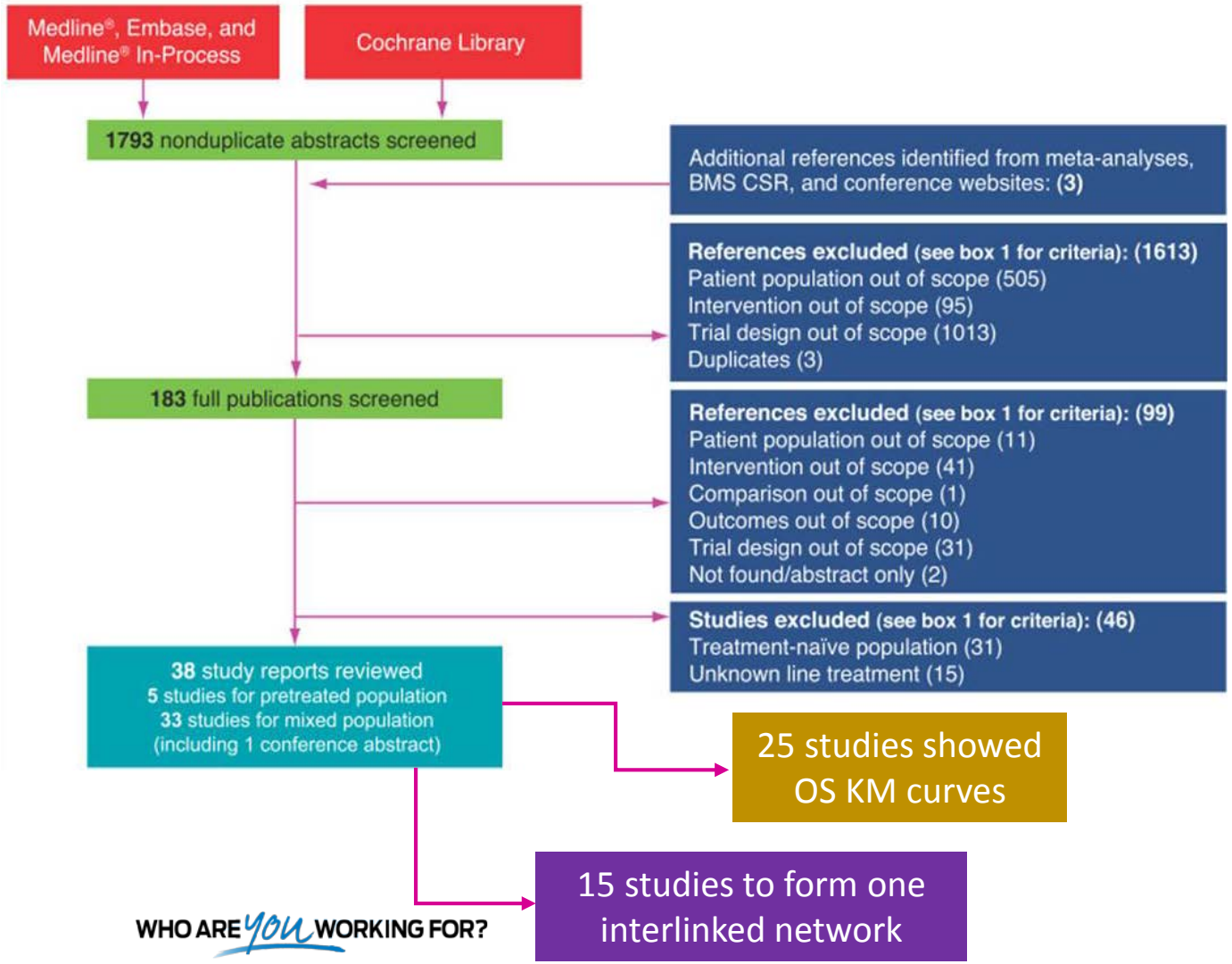
Challenges

- No direct comparison between ipilimumab and frequently used chemotherapies
- The standard of care for metastatic melanoma has been referral to clinical trials due to lack of efficacy
- Key clinical evidence compared ipilimumab 3 mg/kg to gp100
- In the absence of head to head comparison between ipilimumab 3 mg/kg against other therapies,
  - NMA was conducted to inform treatment selection
  - Additional analysis conducted to show similarity between gp100 and chemotherapy treatment effect

NMA: Study Selection



- A systematic literature review to synthesize available OS evidence of systemic therapies

Box 1. Scope of systematic literature review

Population: pretreated adult patients with unresectable (stage III/IV) melanoma, with or without BM. Studies which included a proportion of pretreated patients and systemic treatment-naïve patients (ie, mixed line population) were also included in order to maximize the evidence base

Interventions: ipilimumab, interferon-alpha (IFN-α)/IFN-α2b, interleukin-2 (IL-2), dacarbazine (DTIC), temolozomide, cisplatin, carboplatin, paclitaxel, fotemustine, melanoma vaccines, and placebo

Comparators: studies that compare the agents (listed under "Interventions") to each other as monotherapies, combination therapies with one another, combination therapies with another agent not listed under "Interventions" (ie, not of interest), or best supportive care

Outcomes: survival endpoints reported at interim time points such as median OS, percentage of patients alive, or hazard ratios

Study designs: RCTs, including open-label extensions and crossover studies; phase 2 and above. Full-text publications from peer-reviewed journal, clinical study reports (CSRs), or conference abstracts should be available, and in English

ASCO 2011

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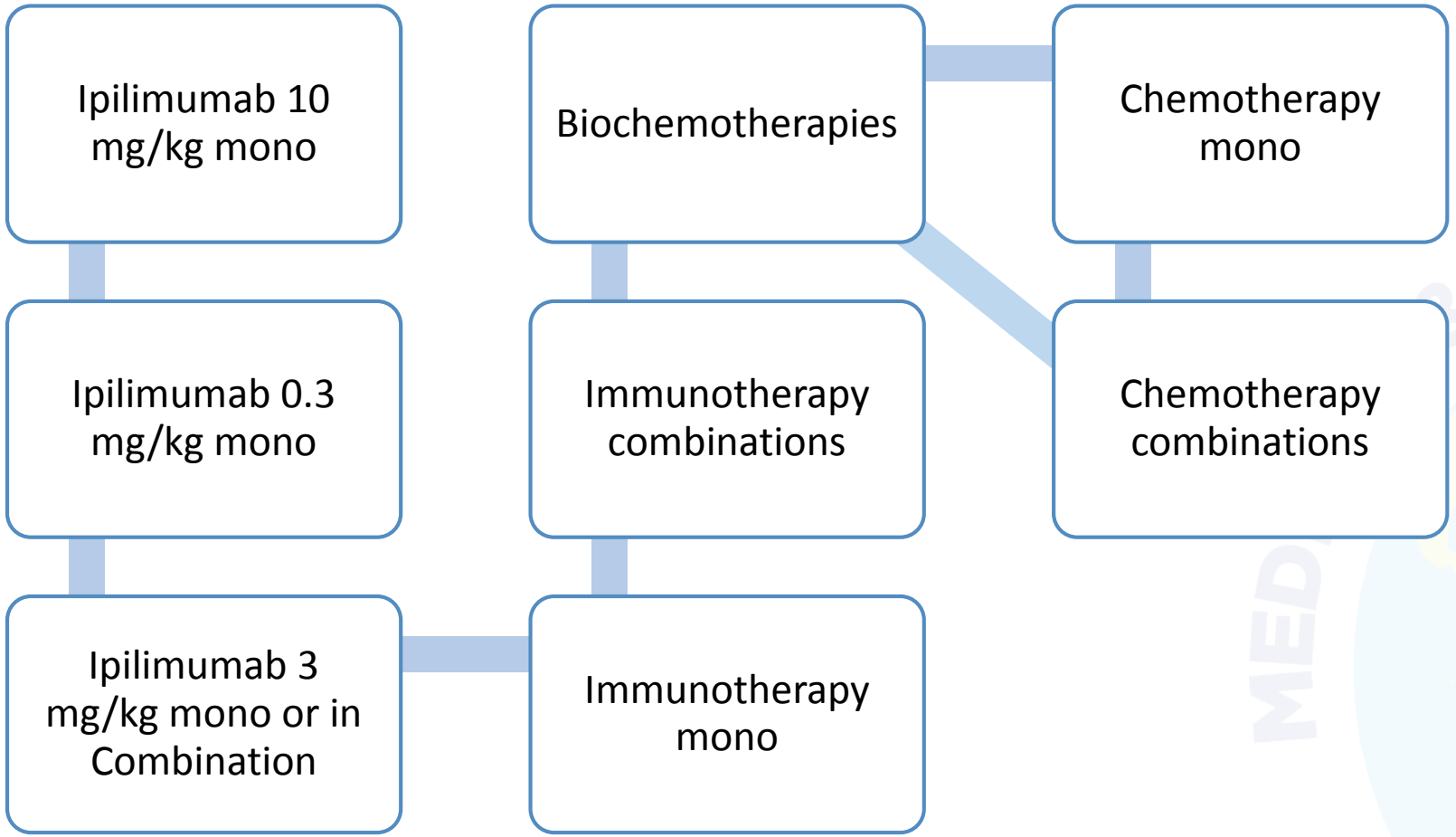
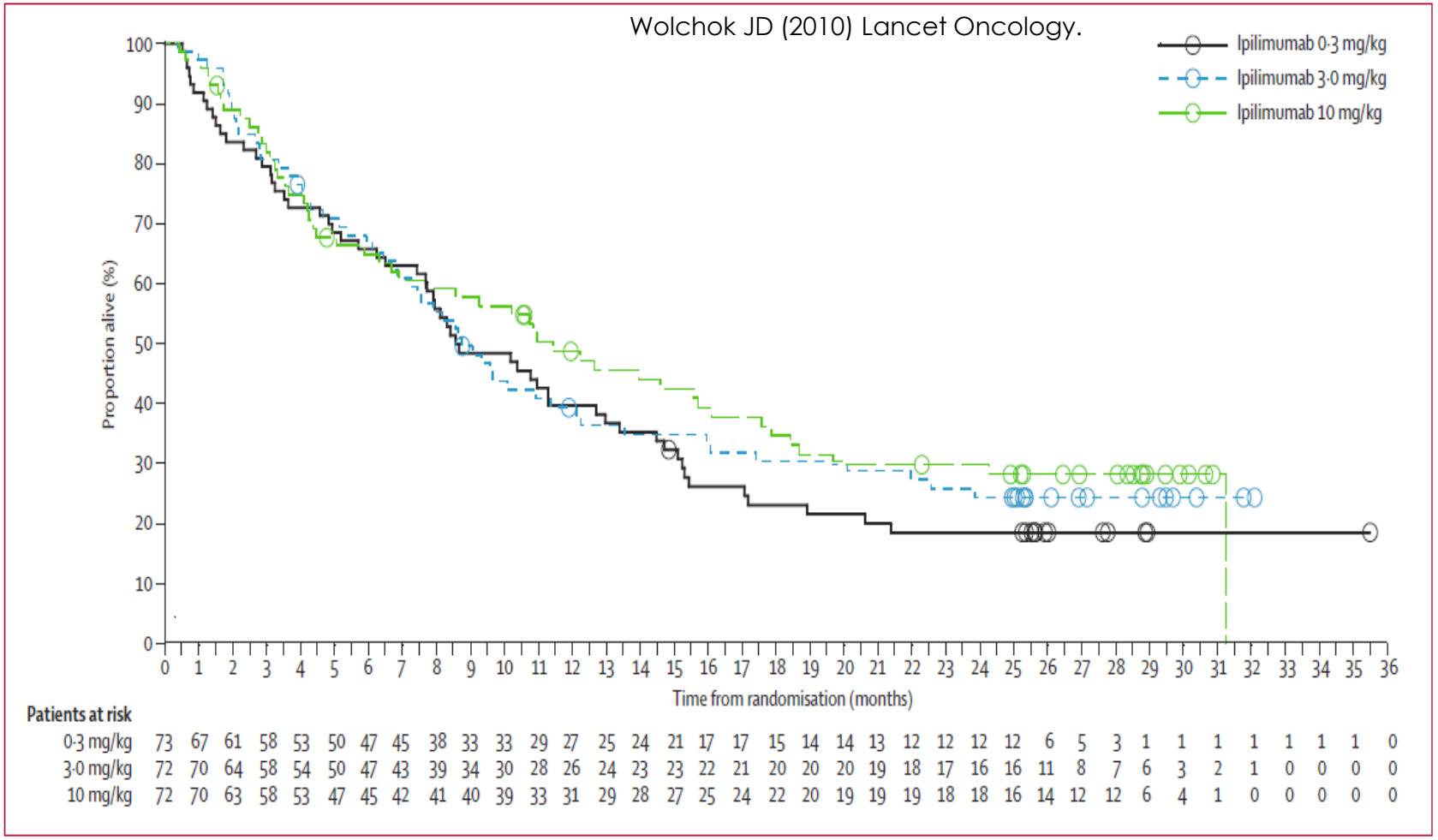
NMA: Network


Ipilimumab 10 mg/kg mono
Ipilimumab 0.3 mg/kg mono
Ipilimumab 3 mg/kg mono or in Combination
Biochemotherapies
Immunotherapy combinations
Immunotherapy mono
Chemotherapy mono
Chemotherapy combinations

Second Ipilimumab study included in the NMA: Ipilimumab in Patients with Previously Treated Advanced Melanoma

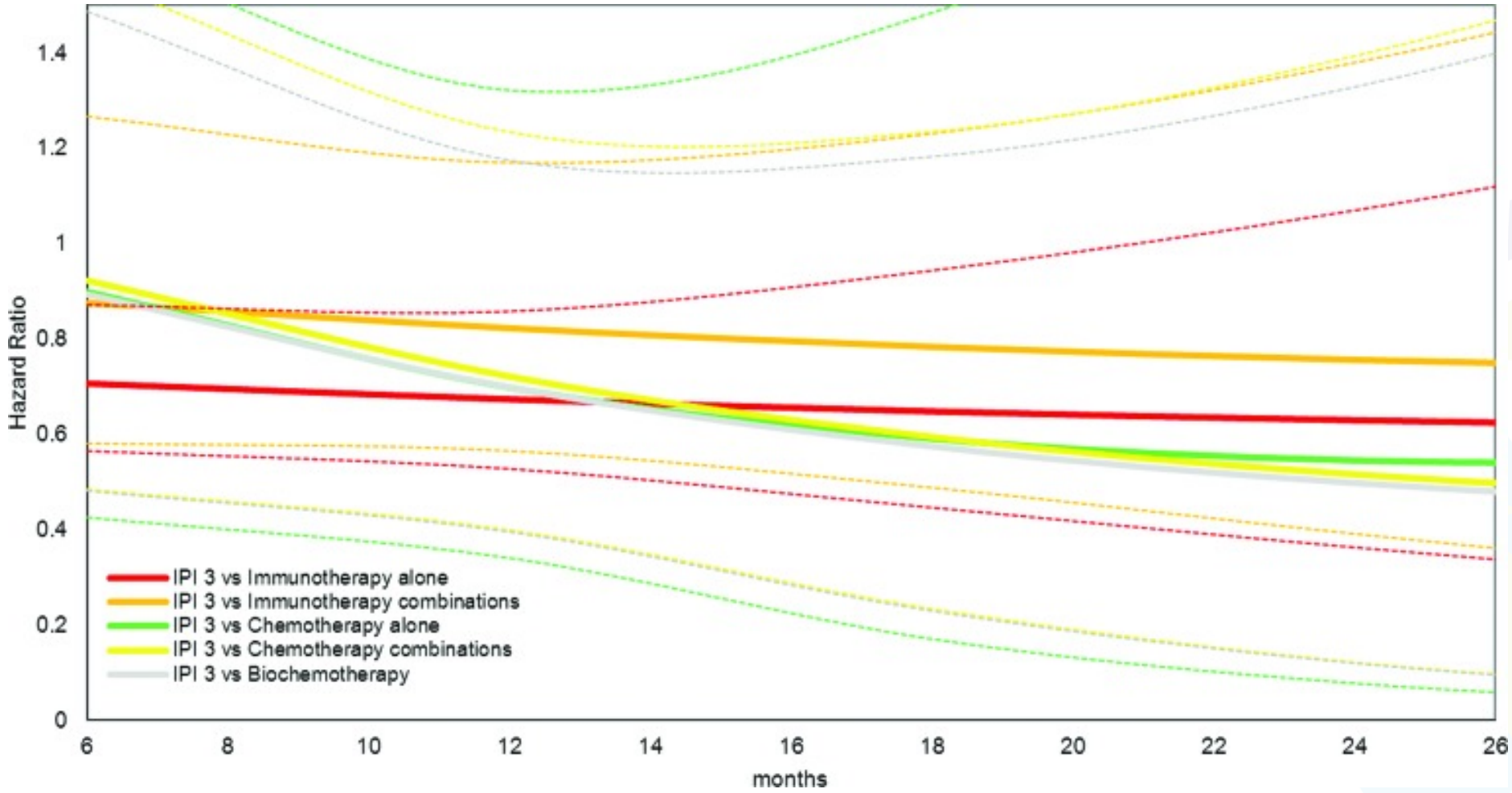
Wolchok JD (2010) Lancet Oncology.



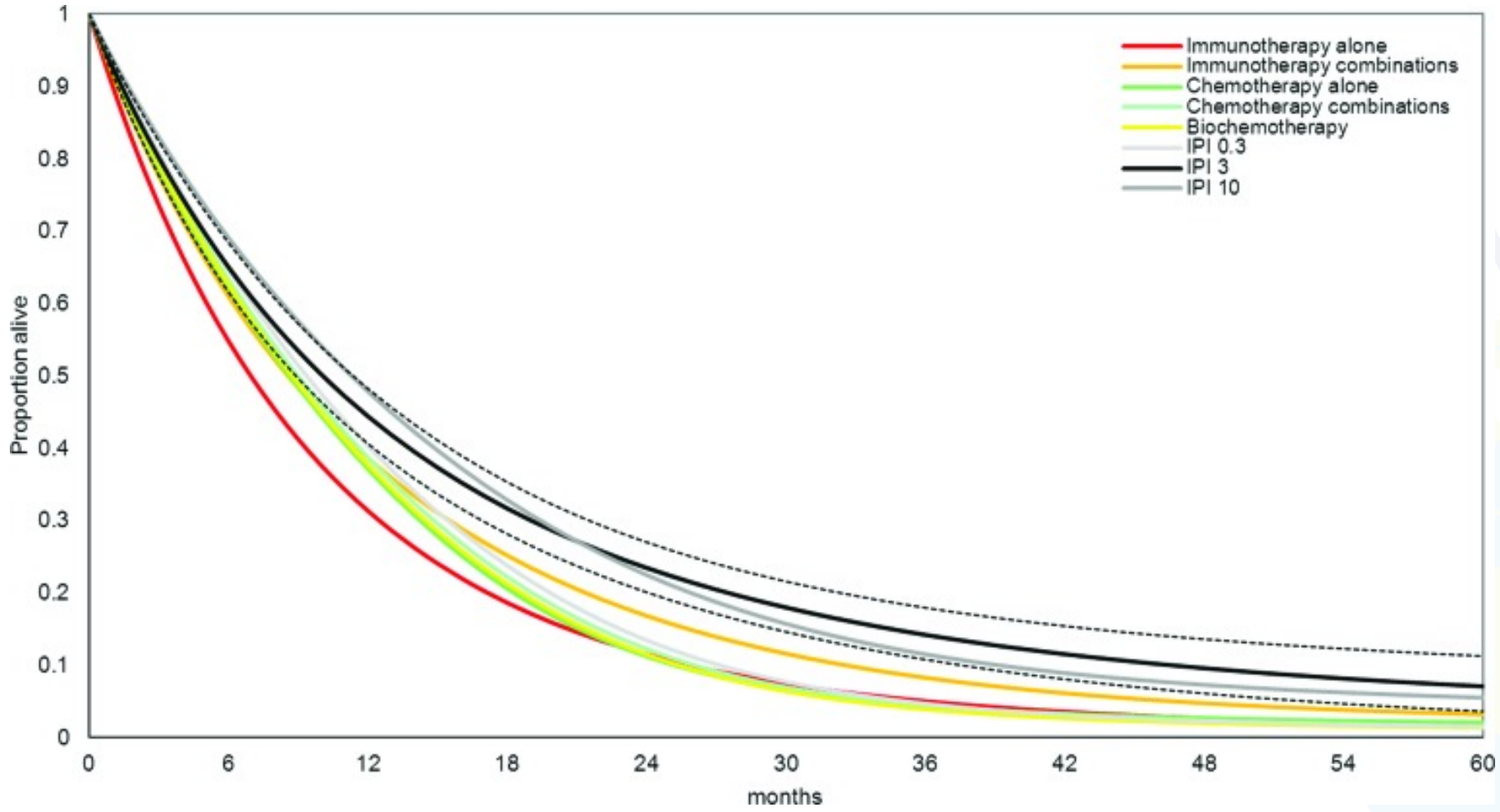
NMA Methodology

- Parametric network meta-analysis* (NMA) of treatment effect
  - Shape parameter
  - Scale parameter
- Parametric modeling potentially addresses non-proportionality
- Estimation of parameters was carried out using a fixed-effects and random-effects Weibull and Gompertz models
- Models were compared using Deviance Information Criterion (DIC)
- Fixed-effects Gompertz model was selected

Hazard Ratio Over Time: Fixed-Effects Gompertz NMA Model



Overall Survival: Fixed-Effects Gompertz NMA Model



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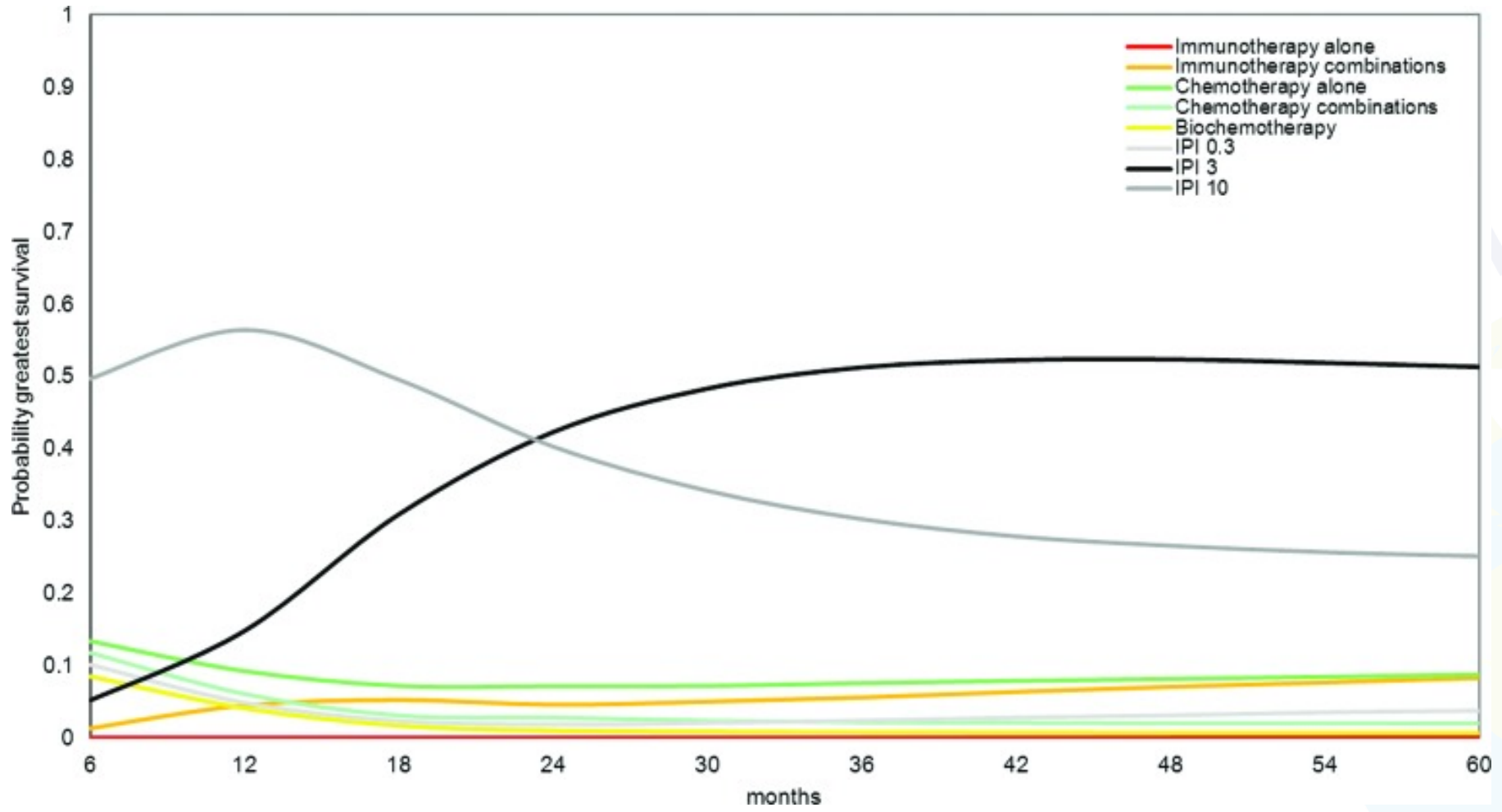
Probability of Greatest Survival Benefit Over time: Fixed-Effects Gompertz NMA Model



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Findings from NMA

- 3 mg/kg ipilimumab is expected to have greater OS compared to other existing therapies for the management of pretreated patients with unresectable stage III or IV melanoma

- Limitations
  - Compatibility of studies included in NMA
  - Inclusion and exclusion of studies in NMA
  - Grouping of studies by class in NMA

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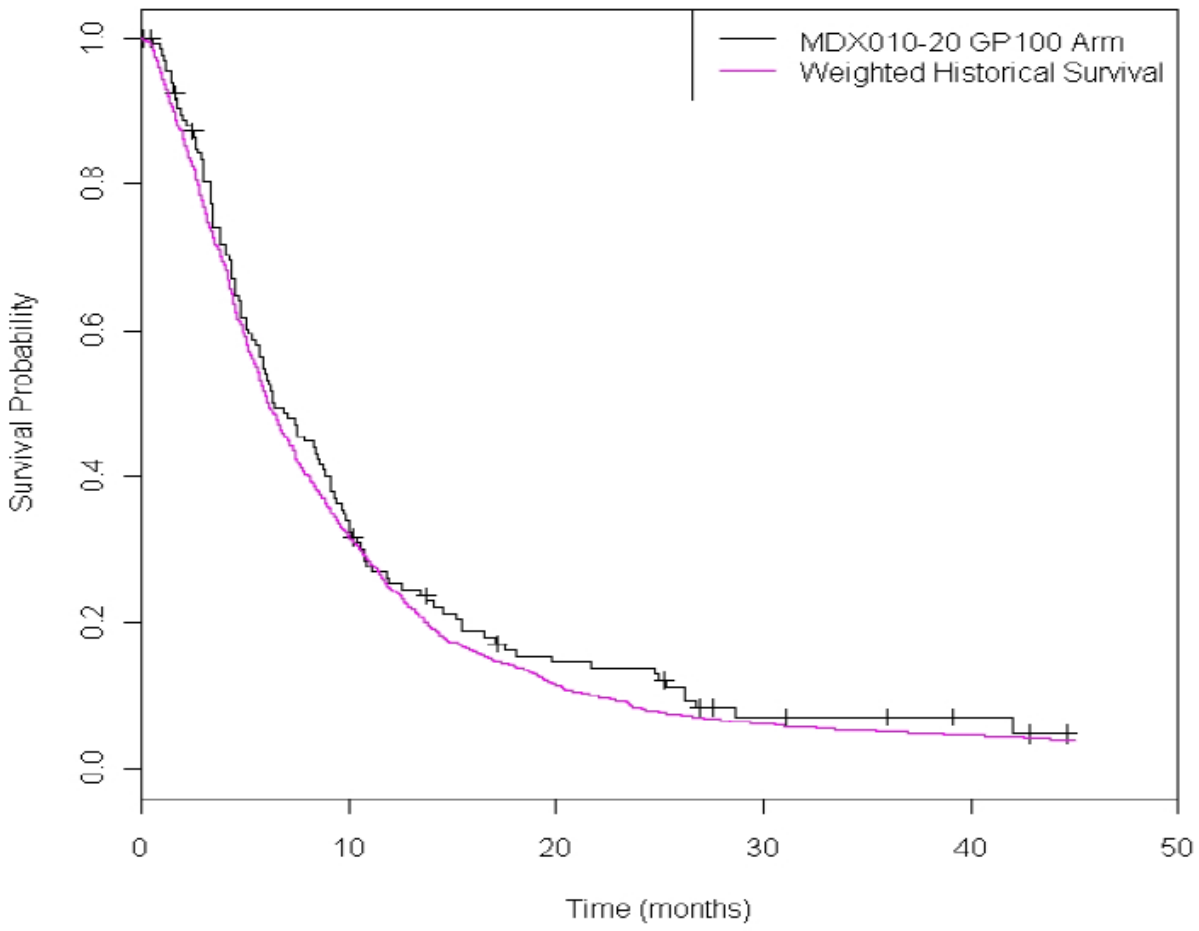
Key Question: GP100 Treatment Effect (OS)

- An analysis was performed by BMS
  - To understand the effect of gp100 on OS
  - To evaluate results in this arm relative to historical data for patients with advanced melanoma
- The objective of this analysis was to show that the observed OS in gp100 arm was representative of that from chemotherapies in the absence of a randomized comparison
- A prognostic model for advanced melanoma (Korn et al.) was adopted to estimate the OS had the same group of patients been treated with chemotherapies

Meta-Analysis Methodology (Korn et al.)

- Objective:
  - Develop benchmarks for OS and PFS for future studies
- Materials and Method:
  - 1278 patients in 42 cooperative group trials across different regiments from 1975 to 2005 were included
  - Multivariate analyses were performed to fit the key prognostic factors
- A multivariate analysis presented in the paper identified the following factors as predictors (key prognostic factors) for OS:
  - Individual patient baseline characteristics: performance status, presence of visceral metastases, and gender
  - Trial-level characteristics: the inclusion of central nervous system (CNS) metastases or not
- Reference curve was produced to allow prediction of OS based on the distributions of key prognostic factors

Predicted vs. Observed Overall Survival



- BMS applied the Korn model to generate the predicted OS curve for the gp100 arm of
- The resulting predicted survival curve was consistent with the observed OS data in the gp100 arm
- Survival results from this arm were not different from what would be expected in this population (one sample log-rank p = 0.25)

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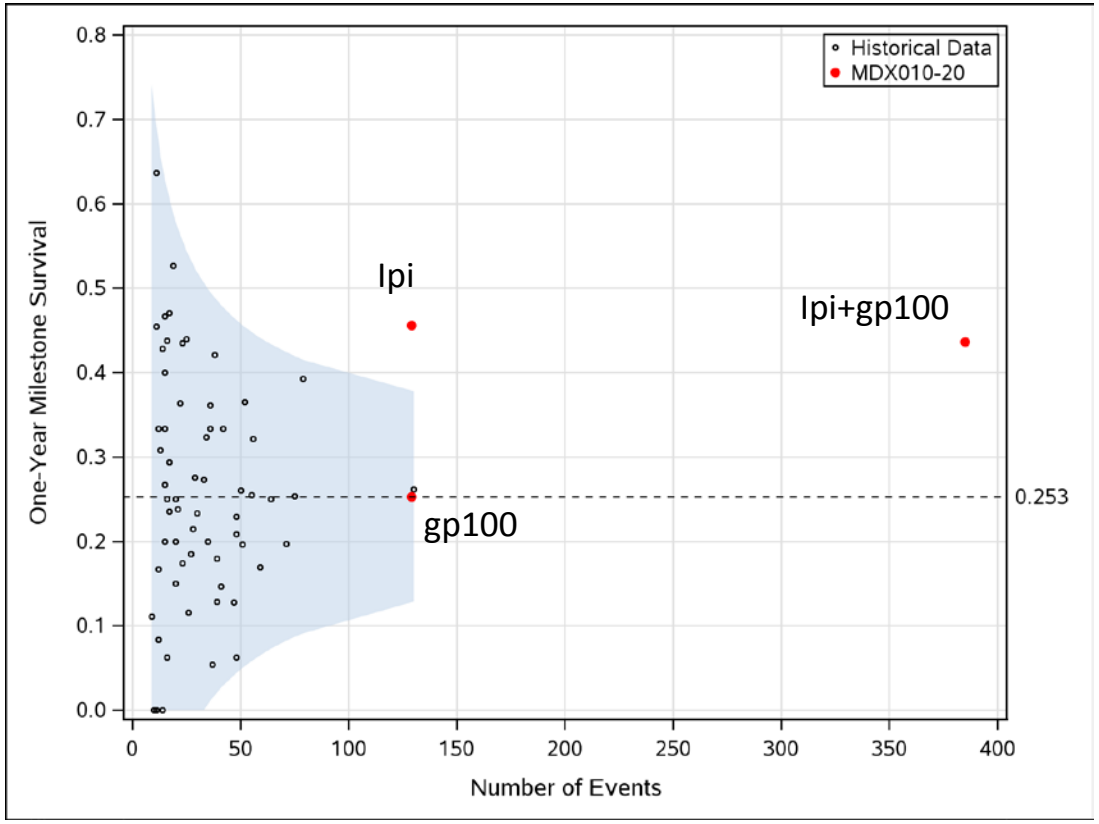
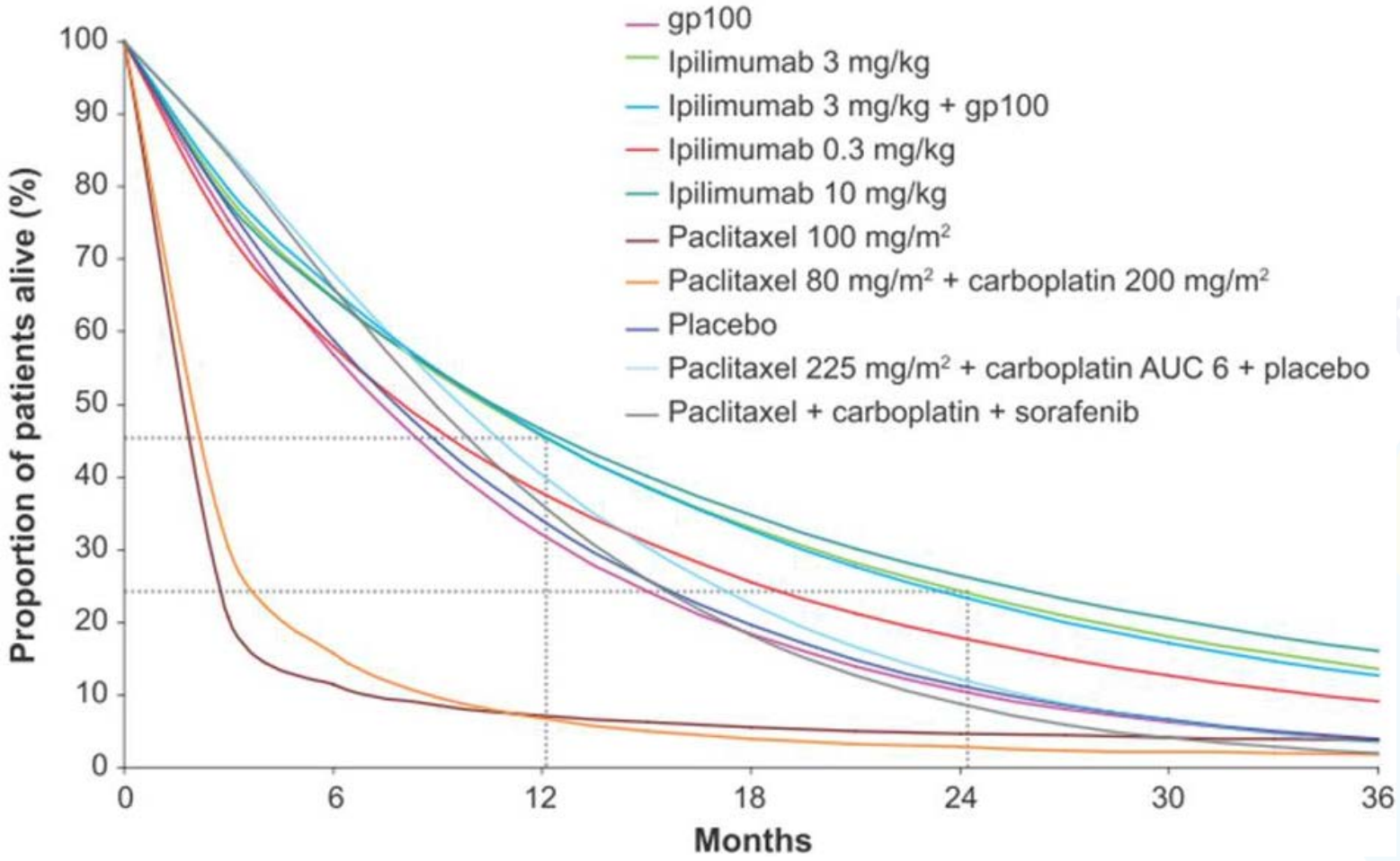
One-Year Milestone Survival



- The 95% confidence bounds suggest that no trial arm has a statistically different rate from the overall mean 1-year rate of 25% (524 of 2,075 patients).
- The 1-year milestone survival rate from MDX010-20
  - Ipilimumab+gp100: 0.436
  - Ipilimumab: 0.456
  - Gp100: 0.253

Estimated Overall Survival Adjusted for Prognostic Factors



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Estimated Expected Efficacy from 25 Studies

Treatment		Expected survival, months (95% CrI)	Median survival, months (95% CrI)	% patients alive at 12 months	% patients alive at 24 months
Pretreated population					
Ipilimumab 10 mg/kg[a]		18.3 (12.5, 26.7)	10 (7, 15)	46.5	26.4
Ipilimumab 3 mg/kg[a]		16.7 (12.8, 22.4)	10 (8, 13)	45.6	24.3
Ipilimumab 3 mg/kg + gp100		16.2 (11.4, 23.1)	10 (7, 14)	45.8	23.5
Ipilimumab 0.3 mg/kg		13.2 (8.6, 20.6)	8 (5, 11)	37.8	17.8
Paclitaxel 225 mg/m² + carboplatin AUC 6 + placebo		11.6 (9.6, 14.8)	9 (8, 11)	40.3	12.1
Ptacebo		10.5 (8.6, 13.6)	7 (6, 9)	34.0	11.3
Paclitaxel 225 mg/m² + carboplatin AUC 6 + sorafenib 400 mg		10.4 (8.8, 13.2)	8 (7, 10)	36.1	8.7
gp100 + placebo		10.1 (6.9, 14.9)	7 (5, 10)	32.1	10.6
Paclitaxel 80 mg/m² + carboplatin 200 mg/m²		2.9 (1.1, 12.8)	1 (0, 3)	6.7	2.8
Paclitaxel 100 mg/m²		2.1 (0.9, 24.3)	1 (0, 2)	7.1	4.7
Mixed (treatment-naïve and pretreated) population					
Ipilimumab combinations	Ipilimumab 3 mg/kg + DTIC 250 mg/m²	21.5 (12.9, 34.7)	14 (8, 24)	56.1	32.9
	Ipilimumab 10 mg/kg + budesonide 9 mg	14.2 (11.1, 18.9)	11 (8, 14)	47.4	19.2
Chemotherapy alone	DTIC 1200 mg/m²	12 (5.6, 37.5)	5 (0, 13)	30.8	16.3
	DTIC 250 mg/m²	8.5 (5.2, 19.9)	5 (2, 9)	25.7	9.3
Chemotherapy combinations	DTIC 220 mg/m² + cisplatin 35 mg/m² + carmustine 150 mg/m² + tamoxifen 20 mg/m²	17.7 (13.1, 26.4)	12 (9, 16)	50.1	26.7
	DTIC 220 mg/m² + cisplatin 25 mg/m² + carmustine 100 mg/m² + tamoxifen 40 mg	5.7 (4.2, 8.9)	4 (3, 6)	13.1	1.6
Biochemotherapy combinations	DTIC 220 mg/m² + cisplatin 35 mg/m² + carmustine 150 mg/m² + tamoxifen 20 mg/m² + IL-2 + IFN-α	16.3 (12.9, 21.8)	12 (9, 16)	52.6	24.2
	DTIC 220 mg/m² + cisplatin 25 mg/m² + carmustine 100 mg/m² + tamoxifen 40 mg + IL-2 + IFN-α	4.7 (3.8, 6)	4 (3, 5)	4.0	0.0
Immunotherapy alone	IL-2 720,000 MIU/m²	11.3 (7.8, 18.6)	9 (5, 13)	38.8	12.0
	IL-2 9 or 2 MIU/m²	8.6 (7.3, 10.3)	6 (5, 7)	27.2	6.3
Immunotherapy combinations	IL-2 4.5 MIU/m² + IFN-2a 3 MIU/m²	9.7 (7.1, 14.4)	6 (4, 9)	30.8	10.1
	IL-2 18 MIU/m² + IFN-α 10 MIU/m²	9.2 (7.7, 11.2)	8 (6, 9)	30.8	4.7

Conclusion

Network Meta-Analysis

- NMA was not included in NICE STA for Ipilimumab in previously treated melanoma patients
- Subsequent NMA was conducted by grouping 15 studies in 8 treatment classes
- Limitations of NMA include grouping of treatments and selection of studies

Benchmark Meta-Analysis Modeling (Korn et al.)

- Predicted OS adjusting for key prognostic factors showed OS benefit compared to chemotherapies
- Some key prognostic factors such as LDH not captured

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Reference (in chronological order)

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