Use of Single-Arm Cohorts/Trials to Demonstrate Clinical Benefit for Breakthrough Immunotherapies

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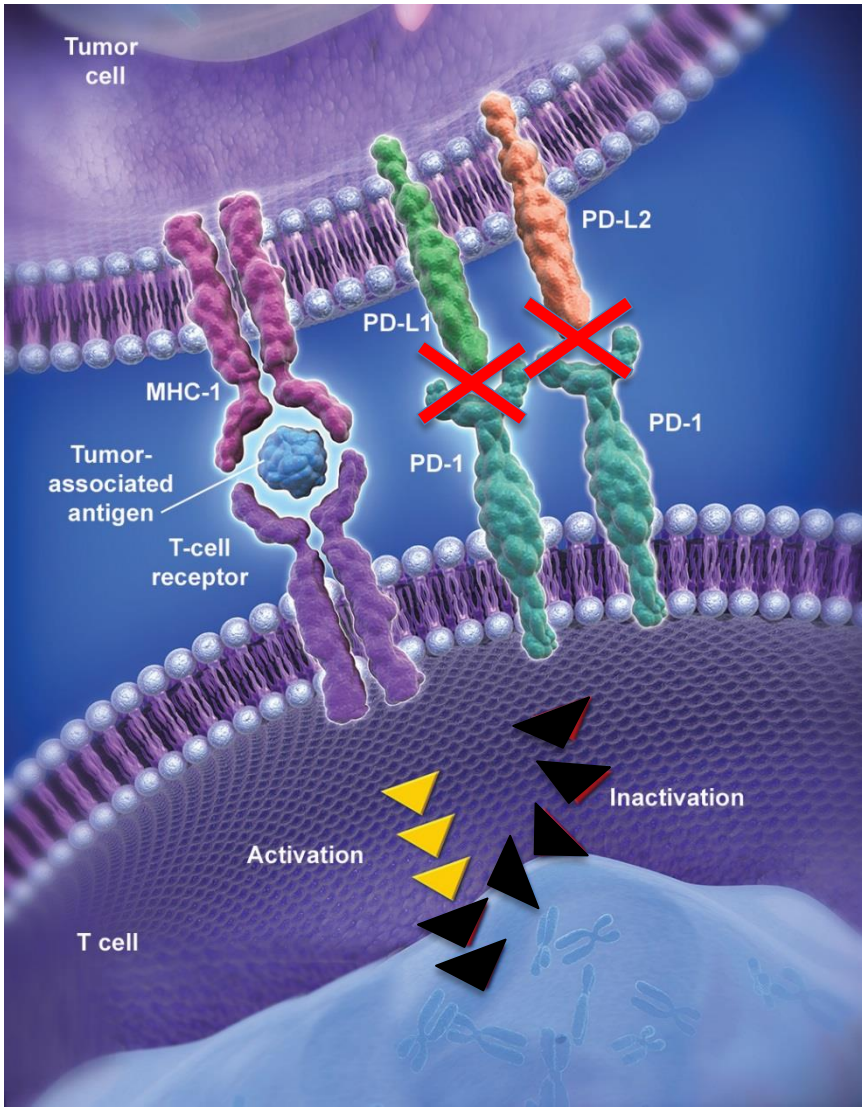
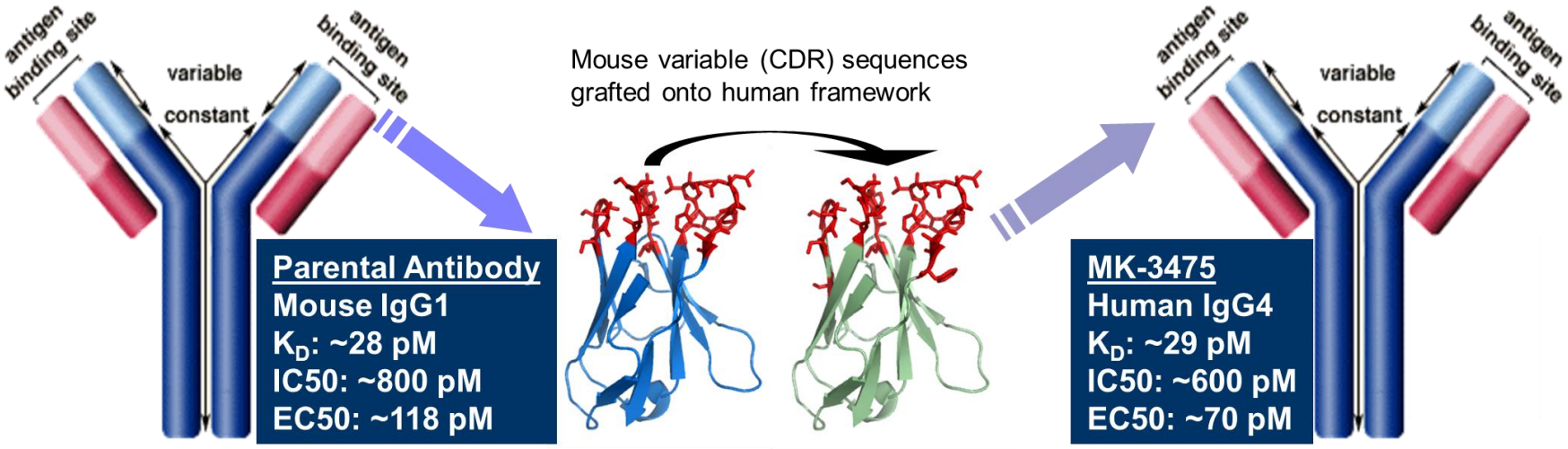
PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy reactivates anti-tumor immunity and results in tumor destruction



Topalian et al. *N Engl J Med*. 2012.
Garon et al. *N Engl J Med*. 2015.
Robert et al. *Lancet.* 2014.

Pembrolizumab is a Humanized IgG4, High-Affinity Anti-PD-1 Antibody



- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics supportive of dosing every 3 weeks
- Low occurrence of anti-drug antibodies and no impact on pharmacokinetics

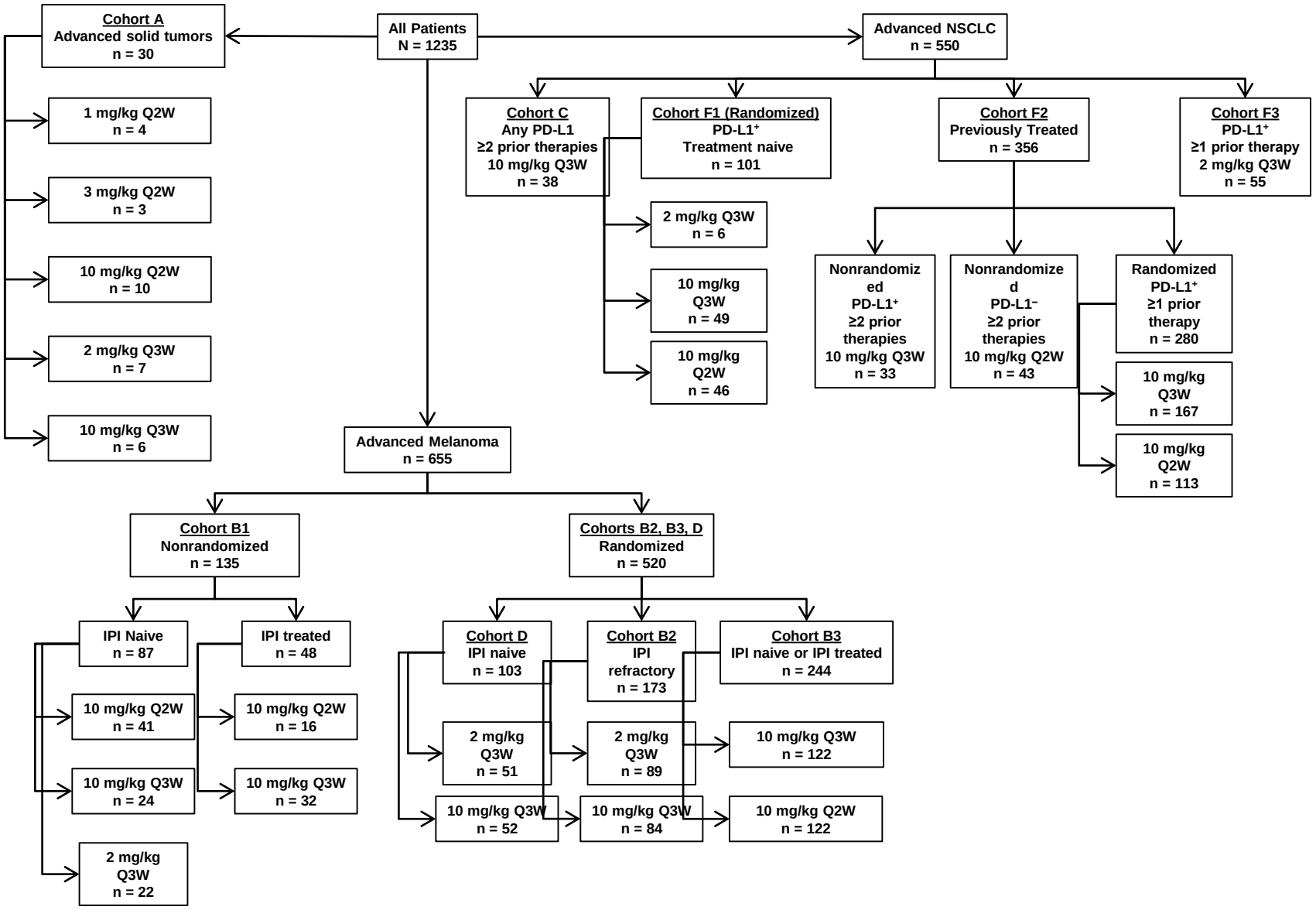
History of Pembrolizumab KN-001 Study

- First-in-human study initiated 2011
  - 3+3 dose escalation with expansion cohort in melanoma, estimated sample size 32
- Striking responses observed in initial melanoma patients enrolled in dose escalation cohort
  - Led to increase in expansion cohort sample size to 60, including ipi-naïve and ipi-treated patients
  - 97% power to exclude null hypothesis of 10% ORR and 30% DCR in ipi-naïve patients, with alternative hypothesis of 30% ORR or 55% DCR (Hochberg), one-sided p= 0.05
  - Included interim futility analysis after evaluation of 11 ipi-naïve patients
- Added 35 patient cohort of previously treated NSCLC patients based on suggestion of potential for efficacy in this population
  - 80% power to exclude null hypothesis of 9% ORR with alternative hypothesis of 22%, one-sided p=0.10

History of Pembrolizumab KN-001 Study

- Given preliminary evidence of activity in ipi-treated patients, addition of 40 patient ipi-refractory cohort to evaluate efficacy in a strictly defined population with high unmet need
  - 98% power to exclude null hypothesis of 5% ORR, with alternative hypothesis of 25%, one-sided p= 0.05
- Randomized cohorts in melanoma (n=520) and NSCLC (n=381) added to investigate dose (2 mg/kg vs 10 mg/kg Q3W and 10 mg/kg Q3W vs 10 mg/kg Q2W) and to provide training and validation sets for PD-L1 expression test in NSCLC patients
  - All with pre-specified statistical hypotheses
  - With registrational intent after discussions with FDA
- Ultimately 1235 patients treated, with enrollment completed in July 2014

KN-001 Treatment Cohorts

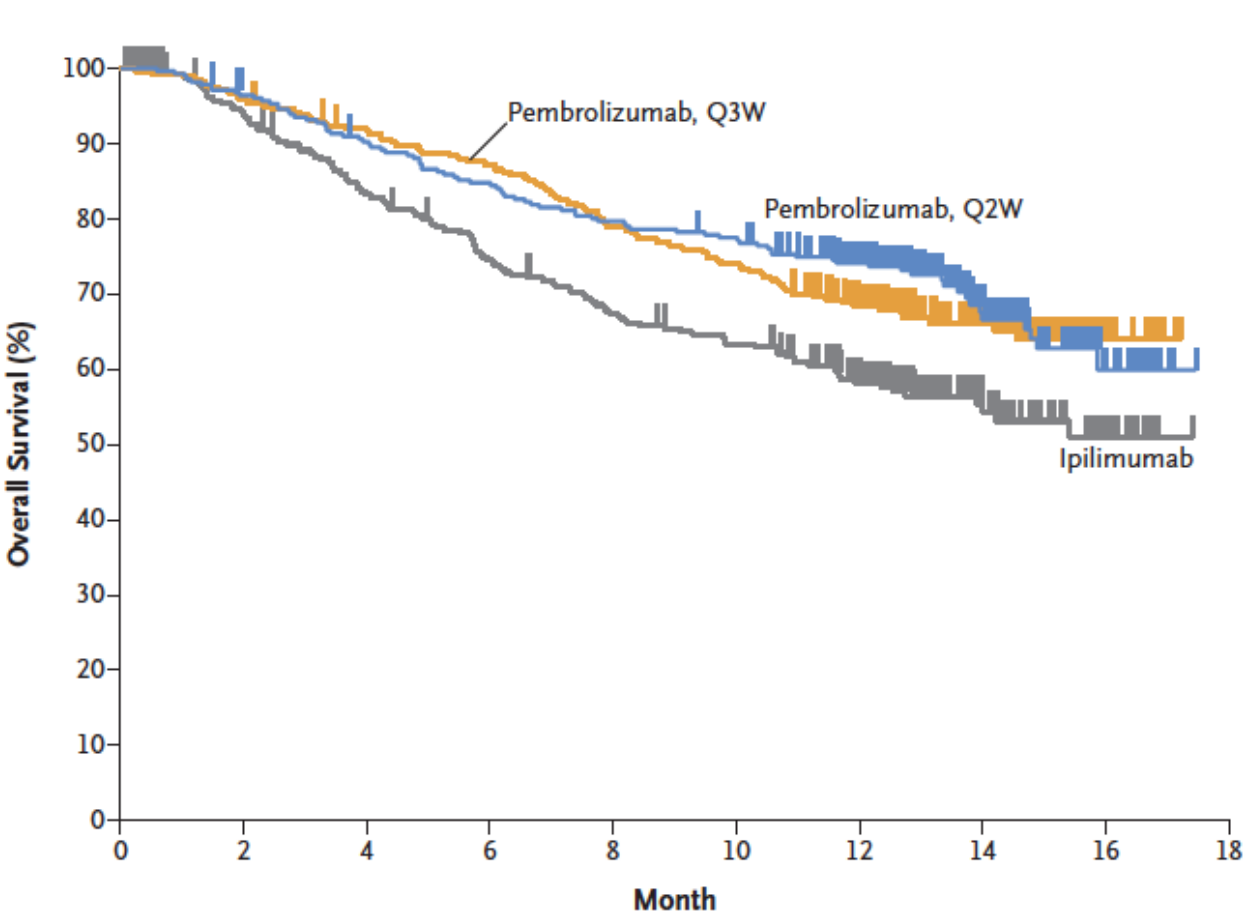


First FDA Approval of Pembrolizumab

- Approval in melanoma was based upon positive risk/benefit demonstrated in KN-001
- Efficacy based on cohort B2: 173 IPI-refractory patients, with 89 patients treated at the 2 mg/kg recommended dose
  - Overall response rate 24% (1 complete response and 20 partial responses)
    - Responses durable
- Safety profile acceptable
- Received accelerated approval on Sept 4, 2014
  - Two confirmatory trials (KN-002 (IPI-treated) and KN-006 (IPI-naïve)) were conducted to confirm safety and efficacy

KN006 Results

HR 0.63 for Q2W vs Ipi
HR 0.69 for Q3W vs Ipi



No. at Risk										
Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

Robert C., et al., NEJM 2015

Overall KN-001 Results

This adaptive “phase 1” study was the basis for 3 FDA approvals:

1. Accelerated approval for patients with IPI-refractory melanoma
2. Accelerated approval for patients with previously treated NSCLC with tumors that express PD-L1 (≥50% tumor proportion score)
3. Dako PD-L1 IHC 22C3 pharmDx test, the first companion diagnostic approved for a cancer immunotherapy

Benefits of Multiple Expansion Cohorts Approach in an Early Study

- Efficiently address multiple hypotheses with appropriate type 1 error control
  - Population, dose, and biomarker development
- Aligned with single-arm trial design as one of the accepted approaches to seeking accelerated approval in US
- Can be performed with sufficient rigor to support regulatory filings (e.g. central independent review of efficacy)
- Accelerates development and approval for drugs that are transformative in nature based on early and strong efficacy signals
  - Avoids delay in initiating multiple separate trials replicating the initial findings
  - Makes transformative therapies available to patients at earliest opportunity, particularly where effective therapies do not exist

Challenges

- Ultimate study design not predicted at study inception
  - Would be difficult to use this approach for all new agents in a fully pre-specified manner at study inception
- Operational burden on sites and sponsor due to rapid accrual in multiple separate cohorts
  - Addition of specific tumor types (or pediatric patients) may require additional sites or investigators
- Multiple amendments generate protocol complexity and potential protocol adherence issues
- Complexity of analysis and interpretation of data supporting multiple hypotheses tested simultaneously rather than sequentially
  - E.g. dose hypotheses evaluated in NSCLC simultaneously with melanoma, rather than waiting for melanoma dose data
  - Must ensure statistical rigor
- Multiple database locks during an ongoing study
  - Programming challenges to “isolate” one cohort for submission purposes
- Difficult for manufacturing to keep up with demand
- While adequate for initial approval in the US, Canada, and Australia, not deemed sufficient in EU, where randomized controlled data were expected to be provided before approval

Benefits of Approval Based on Single-Arm Trials

- For breakthrough immunotherapies, which may be expected to have remarkable efficacy across multiple tumor types, allows earlier access for patients with high unmet medical need and/or rare tumor types
  - After initial demonstration of substantial efficacy in single-arm studies, randomized studies in these patient populations may not be feasible
  - May be supported by “real world” data