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

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Outline

- Pembrolizumab P001 study - example of multiple expansion cohorts in a first-in-human study
- Pembrolizumab single arm trials with registrational intent in new indications with high unmet medical need

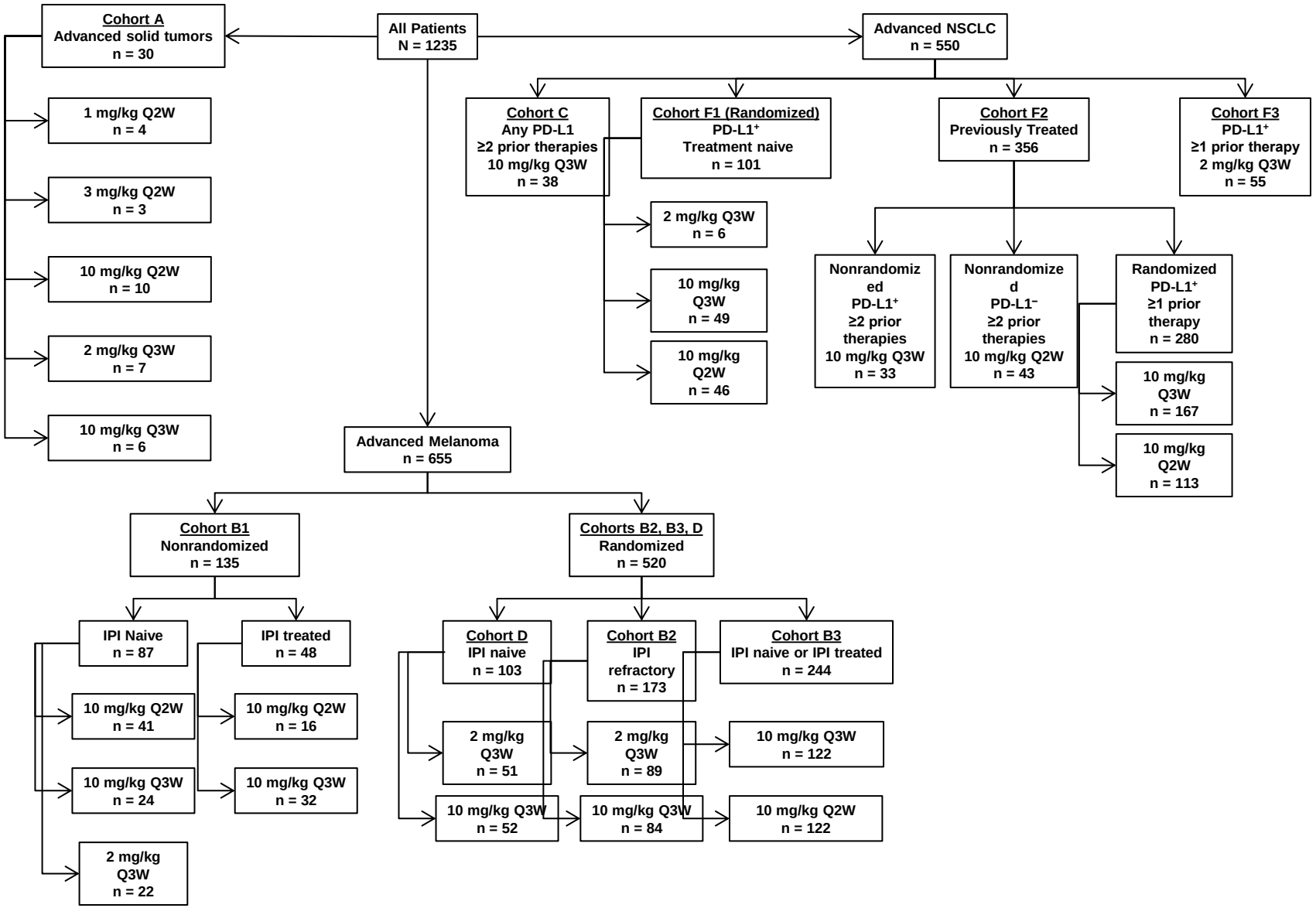
History of Pembrolizumab P001 Study

- 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 P001 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

P001 Treatment Cohorts



Benefits of Multiple Expansion Cohorts Approach

- 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
- 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

Additional Single Arm Trials of Pembrolizumab with Registrational Intent

- Several single arm trials ongoing in high unmet medical need populations
- In these trials the level of benefit could be evidenced by
  - High response rates, related to underlying biology
    - relapsed/refractory classical Hodgkins disease
    - mismatch repair deficient (MSI-H) colorectal and other cancers
  - Durable effect, e.g. in squamous cell cancer of head and neck

Relapsed or Refractory (rr) Classical Hodgkin Lymphoma (cHL) – KN087

Study design

- KEYNOTE-087 is a multicenter, single-arm, nonrandomized study of pembrolizumab, 200 mg Q3W, in 3 cohorts of patients with relapsed or refractory cHL
  - **Cohort 1**: patients with relapsed or refractory cHL that progressed after autologous stem-cell transplantation and subsequent brentuximab vedotin therapy
  - **Cohort 2**: patients with relapsed or refractory cHL who progressed after salvage chemotherapy and were ineligible for ASCT and progressed after brentuximab vedotin therapy
  - **Cohort 3**: patients with relapsed or refractory cHL after autologous stem-cell transplantation but not treated with brentuximab vedotin posttransplantation

RRcHL – KN087

High ORR per investigator review

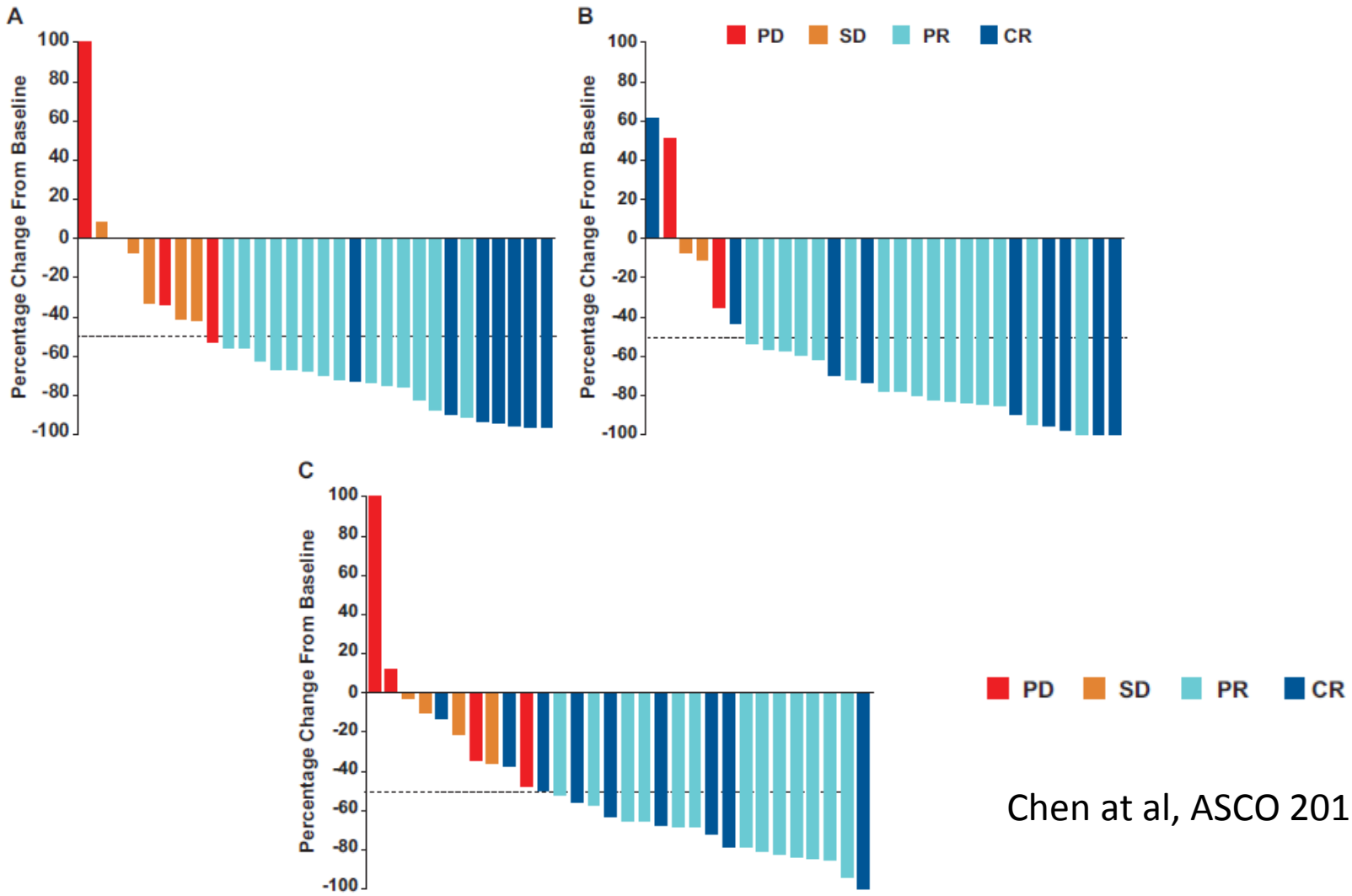
	Cohort 1 Progressed After ASCT and Subsequent BV Therapy n = 30 % (95% CI)	Cohort 2 Failed Salvage Chemotherapy, Ineligible for ASCT and Failed BV Therapy† n = 30 % (95% CI)	Cohort 3 Failed ASCT and Not Treated With BV Transplantation n = 30 % (95% CI)	Primary Refractory Disease‡ n = 37 % (95% CI)
Overall response rate	73 (54-88)	83 (65-94)	73 (54-88)	78 (62-90)
Complete remission§	27 (12-46)	30 (15-49)	30 (15-49)	35 (20-53)
Partial remission	47 (28-66)	53 (34-72)	43 (26-63)	43 (27-61)
Stable disease	17 (6-35)	7 (1-22)	13 (4-31)	11 (3-25)
Progressive disease	10 (2-27)	7 (1-22)	13 (4-31)	8 (2-22)

Chen at al, ASCO 2016

ASCT = autologous stem-cell transplantation; BV = brentuximab vedotin.
†1 patient in cohort 2 had no postbaseline assessment. The patient had symptomatic deterioration, with subsequent clinical progression.
‡Defined as failure to achieve complete or partial remission to frontline therapy. §For complete remission, a posttreatment residual mass was permitted as long as it was negative on PET scanning.

RRcHL – KN087

Change From Baseline in Tumor Size

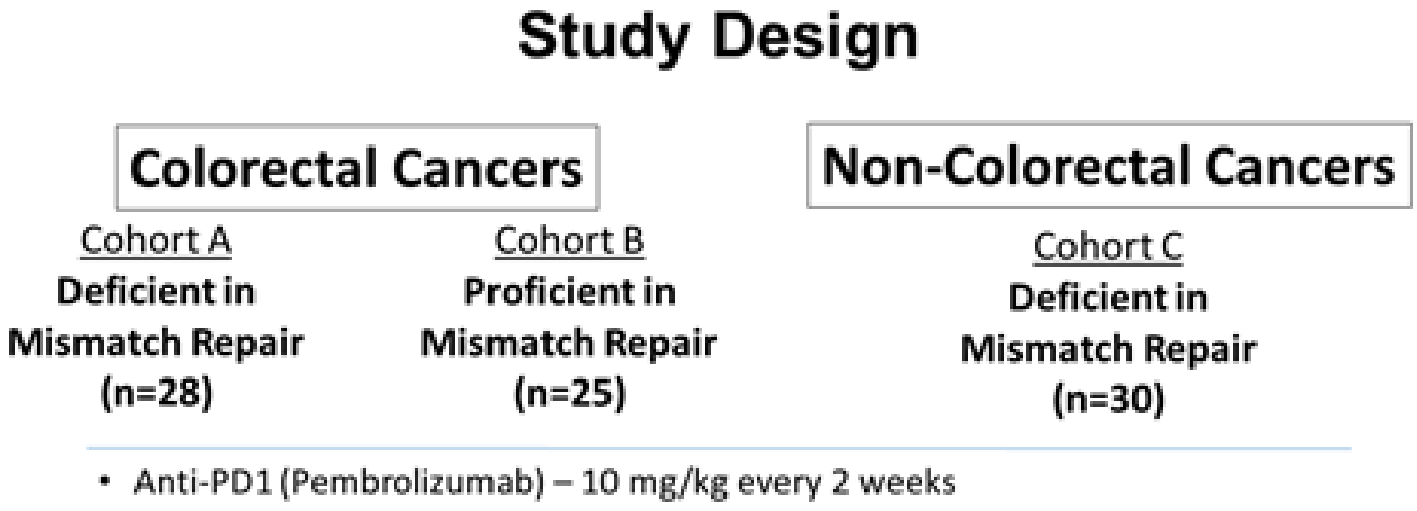


Chen at al, ASCO 2016

CR = complete remission; PD = progressive disease; PR = partial response; SD = stable disease.

[†]The patient in cohort 2 with a 60% increase in tumor size had thymic hyperplasia, and pathologic CR was confirmed.

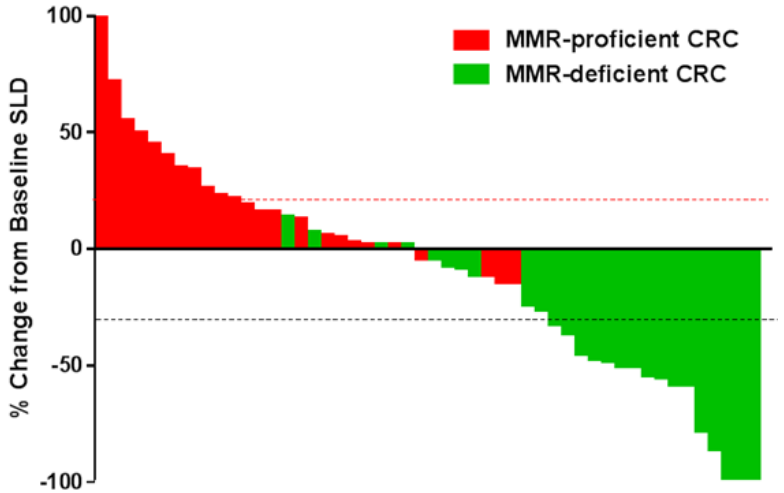
Microsatellite Instability-High Colorectal Carcinoma – KN016



Le at al, ASCO 2016

MSI-H CRC – KN016

High Response Rate

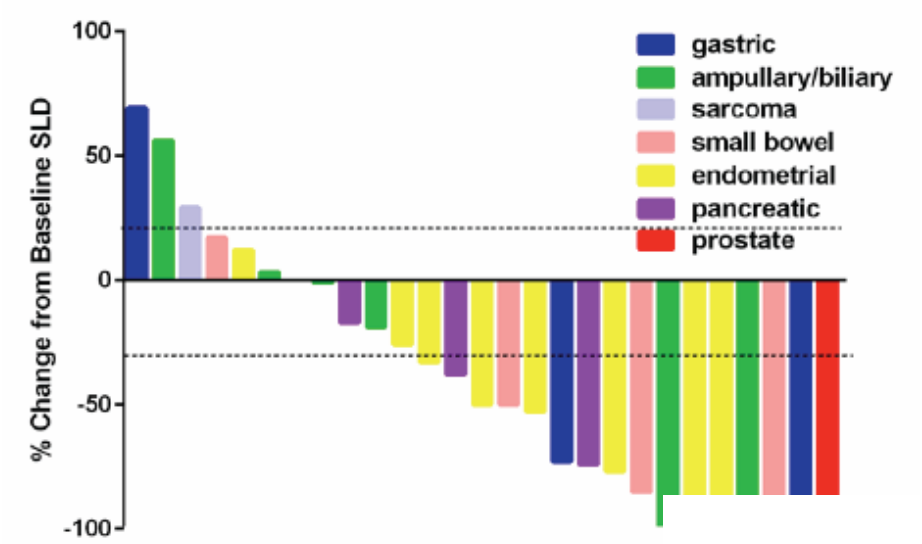


Type of Response-no (%)	MMR-deficient CRC n=28	MMR-proficient CRC n=25
Objective Response Rate (%)	57%	0%
Disease Control Rate (%)	89%	16%
Progression-free Survival (mos)	Not Reached	2.3
Overall Survival (mos)	Not Reached	5.98

Le at al, ASCO 2016

MSI-H non-CRC – KN016

High Response Rate

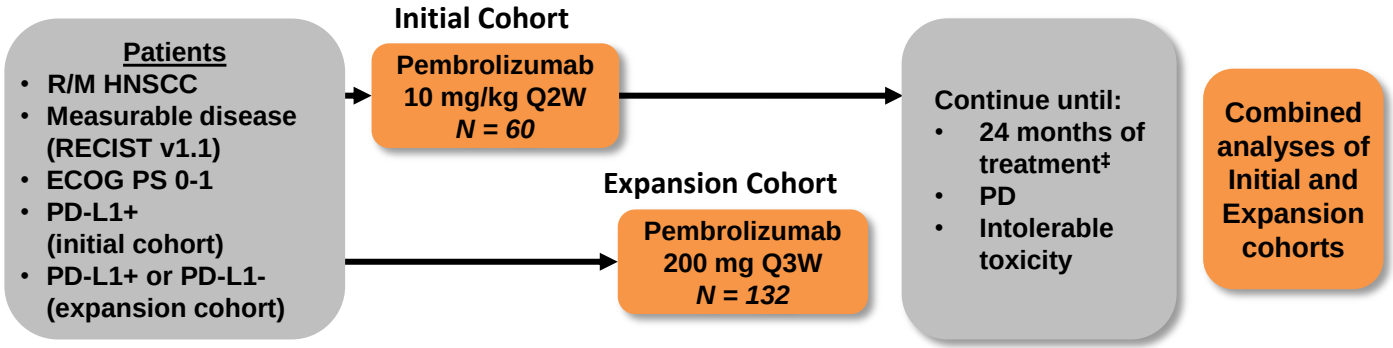


Type of Response-no (%)	MMR-deficient non CRC n=30
Complete Response	9 (30)
Partial Response	7 (23)
Stable Disease (Week 12)	5 (17)
Progressive Disease	7 (23)
Not Evaluable[1]	2 (7)
Objective Response Rate (%)	16 (53)
95% CI	36-70
Disease Control Rate (%)	21 (70)
95% CI	52 - 83
Median Follow Up	10 mos

[1]Patients were considered not evaluable if they did not undergo a 12 week scan

Le at al, ASCO 2016

Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma – KN012



Response assessment: Every 8 weeks

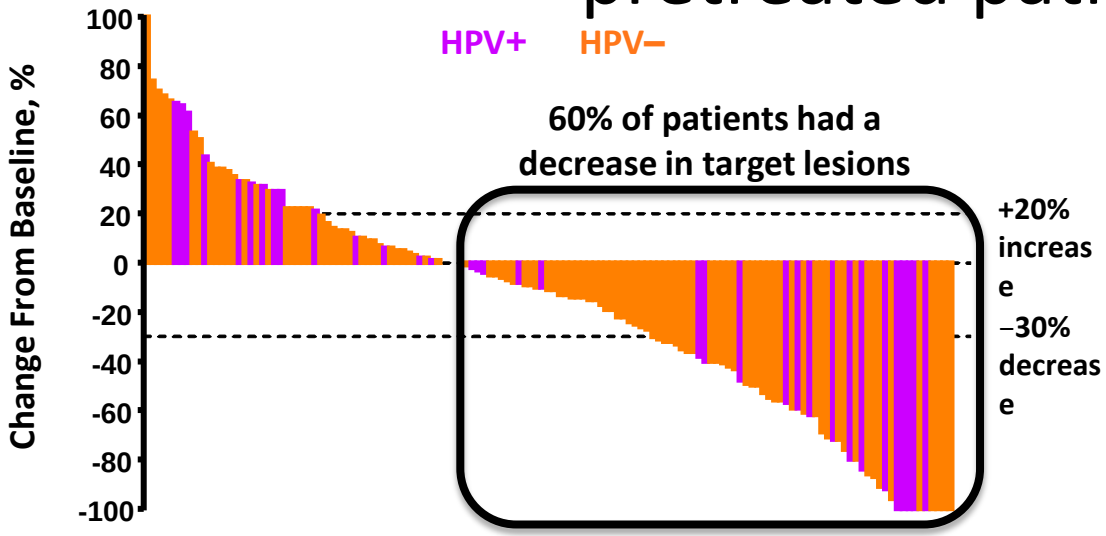
Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients[§]

[†]Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
[‡]Treatment beyond progression was allowed.
[§]Initial cohort only.

R/M HNSCC – KN012

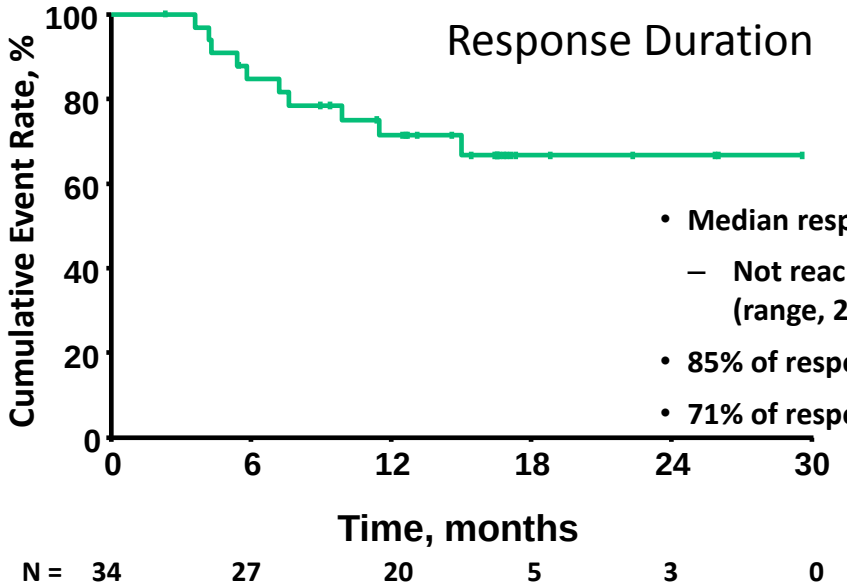
Robust, durable antitumor activity in heavily pretreated patients



Data cutoff date: Apr 26, 2016. Based on RECIST v1.1 per central imaging vendor review (waterfall plot). Includes patients who received ≥1 dose of pembrolizumab, had a baseline scan with measurable disease per RECIST v1.1, and a postbaseline assessment (n = 140).

ORR

- Overall, 18%;
- Pts with prior platinum, 17%
- Pts with prior platinum and cetuximab, 15%



Data cutoff date: Apr 26, 2016. Based on patients with confirmed response per RECIST v1.1 by central imaging vendor review.

Mehra et al, ASCO 2016

Benefits of Approval Based on Single Arm Trials

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

Challenges in EU Regulatory Environment

- In EU, the conditional marketing authorization scheme is currently limited to initial marketing authorization applications and not applicable to Type II variations (e.g. for new indications)
  - In contrast to FDA, which offers breakthrough designation/ accelerated approval for new indications of existing product in case of high unmet medical need and/or orphan indications
- Specific issue for immunotherapies that are expected to show efficacy in a large number of different tumor types