# Merck ASCO 2015 Investor Briefing

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# Agenda

- **Opening Remarks:** Dr. Roger Perlmutter
- **Highlights from ASCO:** Dr. Roy Baynes
- **Concluding Remarks:** Dr. Roger Perlmutter
- **Q&A**

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# KEYTRUDA: Active in a Broad Range of Cancers

- Oncology is a priority area of focus for Merck

- Our strategy:
  - Build a broad foundation with monotherapy
  - Improve efficacy with selective combination therapy
  - Identify patients who are most likely to benefit from KEYTRUDA treatment

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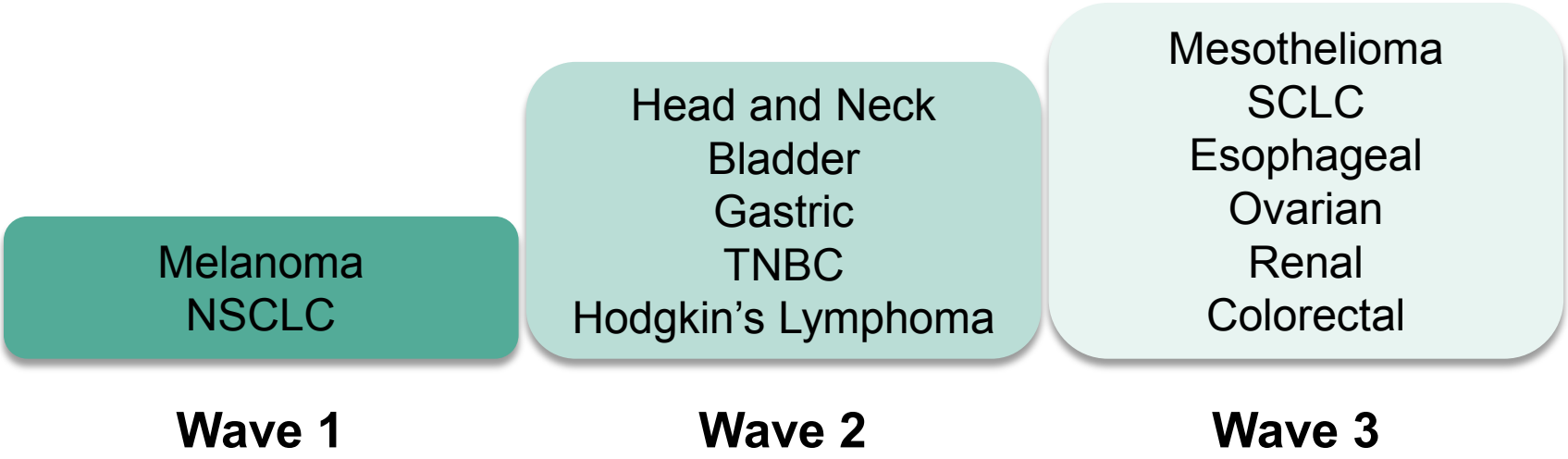
# Building a Foundation with Monotherapy




**Over 30 Different Tumor Types Under Investigation**

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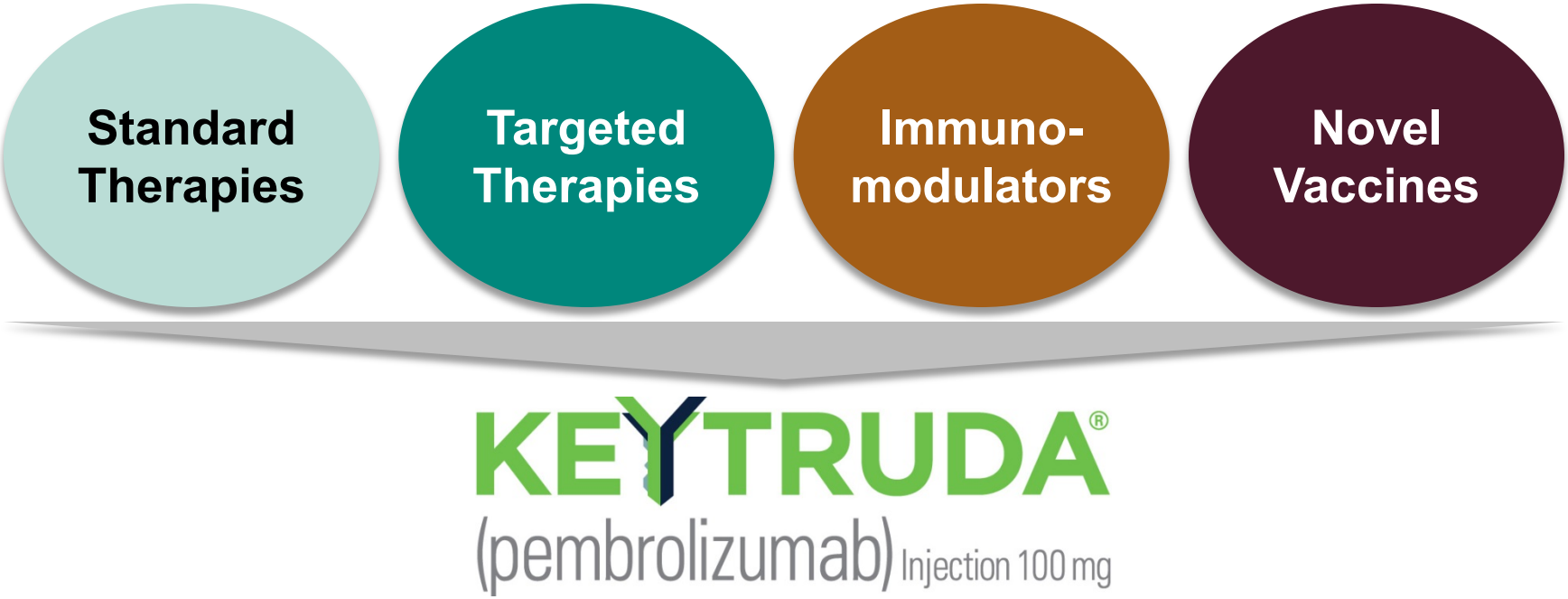
# Improving Efficacy with Selective Combination Therapy

## Combination Strategy
More than 40 Combinations Under Investigation

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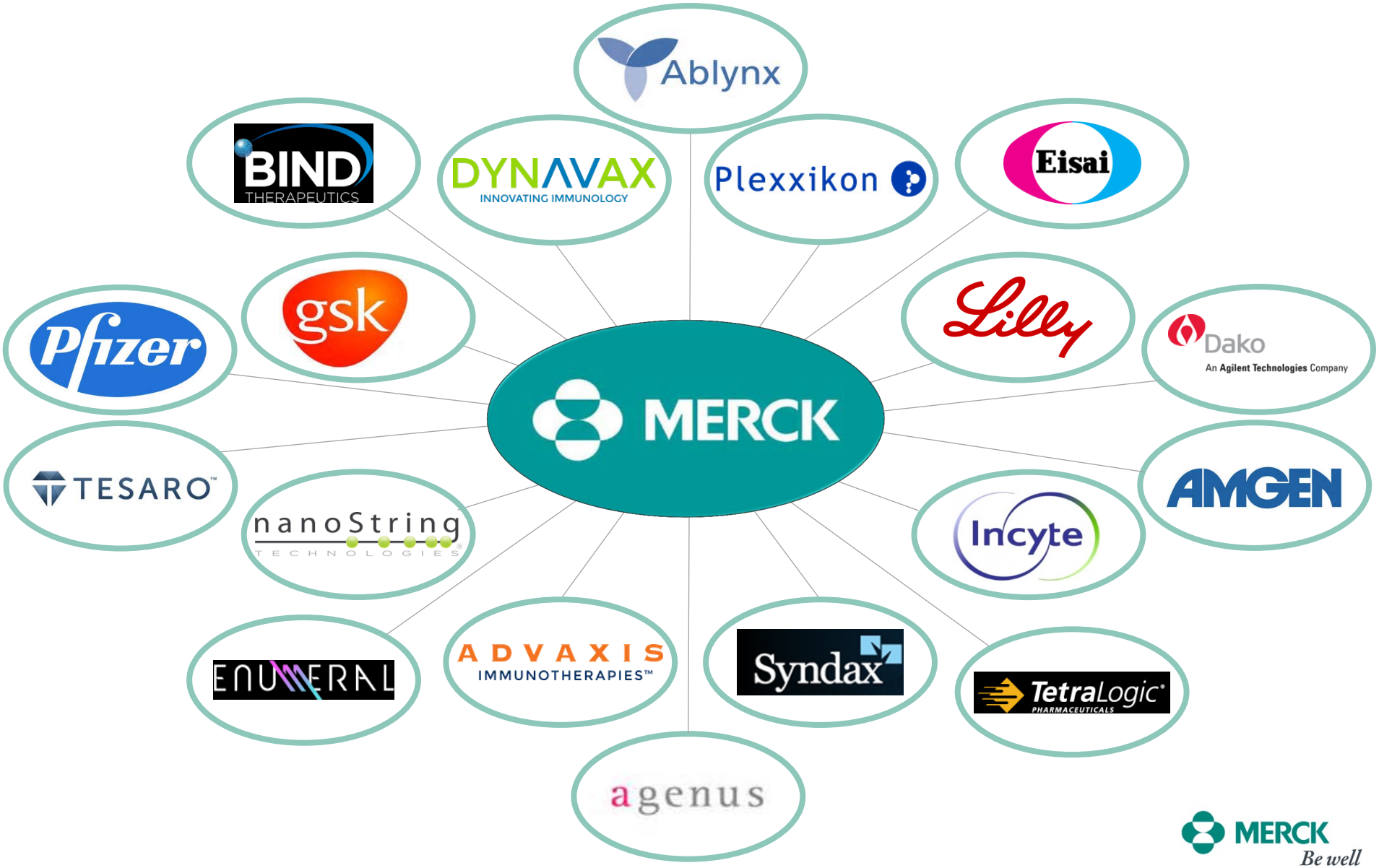
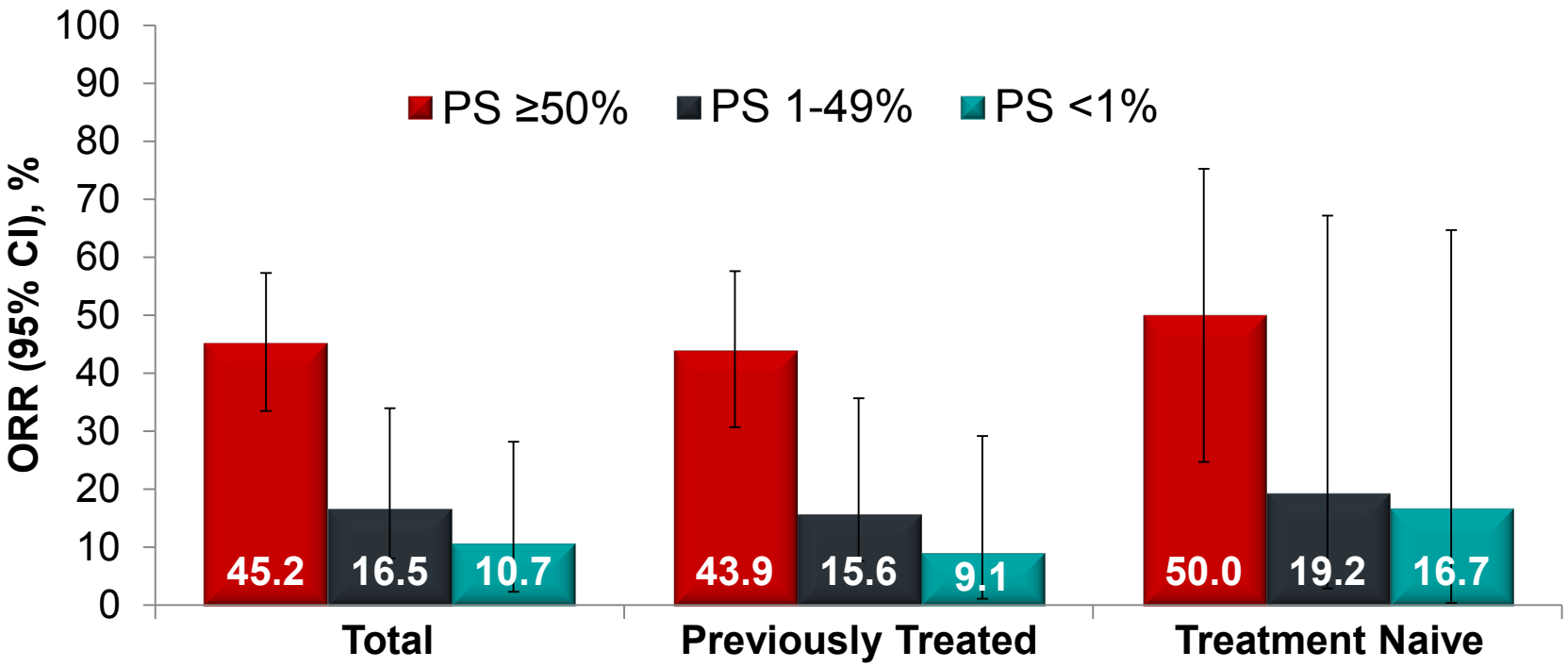
# Merck Oncology: Broad Universe of Partnerships



# Strategy Has Accelerated Melanoma and NSCLC Programs

## NSCLC File Accepted by FDA
### Priority Review Granted




**Overall Response Rate in Advanced NSCLC by PD-L1 Proportion Score (KEYNOTE-001)**

Adapted from presentation by Edward Garon, AACR 2015

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**Roy D. Baynes**
Senior Vice President
Global Clinical Development
Merck Research Laboratories

# Highlights from ASCO

KEYTRUDA® (pembrolizumab) Injection 100 mg

## Key Datasets

- New Data in Prior PoC Tumor Types
- Five New Tumor Types
- Early Combination Data
- Novel Biomarker Approaches

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# Head and Neck Squamous Cell Cancer

- Head and Neck Squamous Cell Cancer (HNSCC)
  - 5th most common cancer worldwide
- Recurrent/metastatic HNSCC remains poorly treatable with a median OS of 10 months in the first-line setting[1]
  - Commonly used agents: platinum, cetuximab, taxanes, 5-FU, methotrexate
- Median OS of 6-months in patients previously treated[2]
- Prominent immune escape observed in HNSCC[3,4]
  - T-cell inflamed phenotype (TILs + PD-L1 expression)
  - Present in both HPV(-) and HPV(+) tumors
  - HPV related “foreign” antigens present in HPV(+) tumors

Adapted from presentation by Tanguy Seiwert, ASCO 2015


1. Vermorken J et al. *N Engl J Med*. 2008;359(11):1116-27.
2. Stewart JSW, et al *J Clin Oncol*. 27:1864-1871.
3. Saloura V et al. *J Clin Oncol* 2014;32 (Suppl 5): Abstract 6009
4. Lyford-Pike S et al. *Cancer Res* 2013;73(6):1733-1741.


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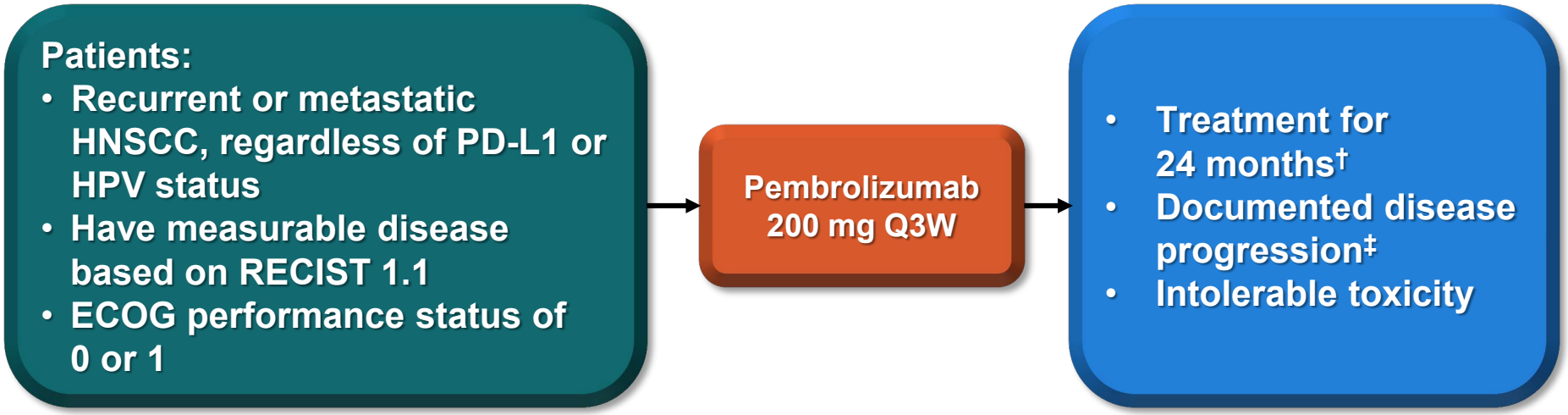
# HNSCC Expansion Cohort of KEYNOTE-012




**Response assessment**: Every 8 weeks

**Primary end points:** ORR per modified RECIST v1.1 by investigator review; safety

**Secondary end points:** PFS, OS, duration of response

Adapted from presentation by Tanguy Seiwert, ASCO 2015
*Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
†Treatment beyond progression was allowed.
‡Re-treatment was permitted.

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# HNSCC Overall Response Rate*

| Best overall response | Total N = 117† | | HPV+ n = 34 | | HPV− n = 80 | |
|---|---|---|---|---|---|---|
| | n (%) | 95% CI | n (%) | 95% CI | n (%) | 95% CI |
| ORR | 29 (24.8) | 17.3-33.6 | 7 (20.6) | 8.7-37.9 | 21 (26.3) | 17.0-37.3 |
| Complete Response | 1 (0.9) | 0.0-4.7 | 1 (2.9) | 0.1-15.3 | 0 (0) | 0-4.5 |
| Partial Response | 28 (23.9) | 16.5-32.7 | 6 (17.6) | 6.8-34.5 | 21 (26.3) | 17.0, 37.3 |
| Stable Disease | 29 (24.8) | 17.3-33.6 | 9 (26.5) | 12.9-44.4 | 20 (25.0) | 16.0-35.9 |
| Progressive Disease | 48 (41.0) | 32.0-50.5 | 13 (38.2) | 22.2-56.4 | 33 (41.3) | 30.4-52.8 |
| No Assessment | 9 (7.7) | 3.6-14.1 | 4 (11.8) | 3.3-27.5 | 5 (6.3) | 2.1-14.0 |
| Non-evaluable | 2 (1.7) | 0.2-6.0 | 1 (2.9) | 0.1-15.3 | 1 (1.3) | 0.0-6.8 |

Adapted from presentation by Tanguy Seiwert, ASCO 2015
*Unconfirmed and confirmed RECIST v 1.1 responses
†Includes patients who received ≥1 dose of pembrolizumab, had measurable disease at baseline and ≥1 postbaseline scan or discontinued due to PD or DRAE
HPV status missing for 3 patients
Data cutoff date: March 23, 2015.

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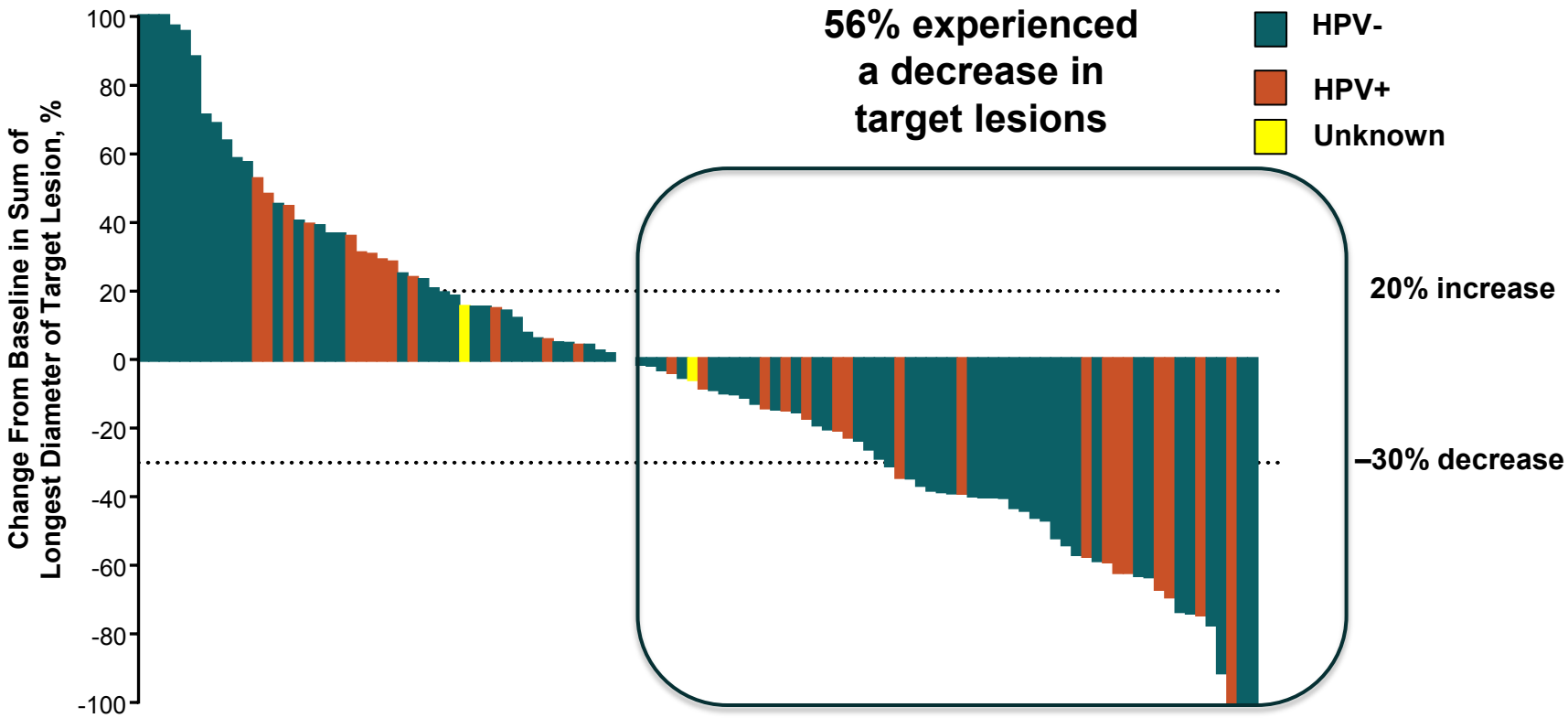
# HNSCC Tumor Shrinkage




Adapted from presentation by Tanguy Seiwert, ASCO 2015
Analysis includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and had ≥1 post-baseline tumor assessment (n = 106)
Unconfirmed and confirmed RECIST v 1.1 responses by site radiology review
*2 oropharynx cancer patient are HPV unknown. Cancers outside the oropharynx are considered HPV negative by convention
Data cutoff date: March 23, 2015.

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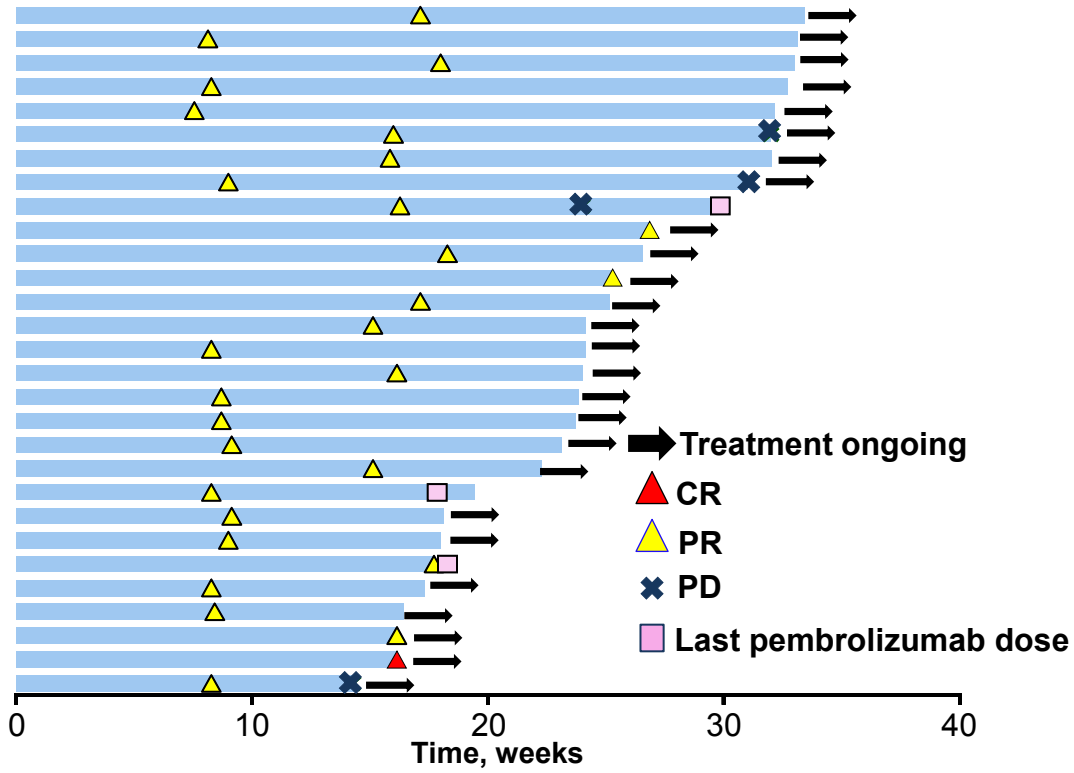
# HNSCC Treatment Exposure and Response Duration




- Median follow-up duration:
  - 5.7 (0.2 – 8.7) months
- Median time to response:
  - 9.0 (7.6−18.0) weeks
- Median duration of response was not reached
  - Range: 7.3+ − 25.1+ weeks
- 40 patients remain on therapy
- **86% (25/29) of responding patients remain in response**

Adapted from presentation by Tanguy Seiwert, ASCO 2015
Unconfirmed and confirmed RECIST v 1.1 responses
Data cutoff date: March 23, 2015.

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# HNSCC Conclusions

- Significant experience of immunotherapy in head and neck cancer
  - 56% of patients experienced any decrease in target lesions
  - Response rate of 25%
  - Broadly active in both HPV(+) and HPV(-) patients
  - Active in heavily pretreated population
  - Responses were durable → 86% of responding patients remain in response
- The 200 mg every 3 weeks dosing schedule is currently being evaluated in multiple phase III trials to investigate the clinical benefit of pembrolizumab vs standard of care chemotherapy
- Ongoing registration studies KEYNOTE-040, -048, -055

Adapted from presentation by Tanguy Seiwert, ASCO 2015

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# Refining the Biomarker Strategy

## Identifying patients who are most likely to benefit from KEYTRUDA treatment

### PD-L1 Expression

- Many tumors evade immune response through the PD-1/PD-L1 checkpoint
- Enrichment approach in clinical program across several tumors
- Not an absolute marker of responsiveness

### Immune-Related Gene Expression Signatures

- Several immune-related signatures established in melanoma patients treated with KEYTRUDA
- Broadening investigation to other solid tumors
- Early results consistent with hypothesis that response to PD-1 blockade occurs in patients with a pre-existing, IFN-mediated adaptive immune response

### DNA Mismatch Repair Deficiency

- Mutations have been shown to encode proteins that are immunogenic
- Average tumor has dozens of somatic mutations
- Mismatch repair deficient tumors harbor thousands of mutations
- Early signals of correlation in colorectal and other solid tumors

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# Mismatch Repair Deficiency / Microsatellite Instability

- Mutations have been shown to encode proteins that are immunogenic
- Average tumor has dozens of somatic mutations. Mismatch repair (MMR) deficient tumors harbor thousands of mutations
- Microsatellite instability in tumor cells is due to deficient DNA mismatch repair
- Colorectal cancer (CRC):
  - 15% of sporadic colorectal carcinomas
- Other tumor types with deficient DNA mismatch repair: endometrial, gastric, small bowel, ampullary, cholangiocarcinoma, pancreatic, sarcoma, prostate, esophageal, and others

Adapted from presentation by Dung Le, ASCO 2015

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# Mismatch Repair Study Design

**Colorectal Cancers**

**Non-Colorectal Cancers**

Cohort A
**Deficient in Mismatch Repair (n=25)**

Cohort B
**Proficient in Mismatch Repair (n=25)**

Cohort C
**Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based method for detection of microsatellite instability

Adapted from presentation by Dung Le, ASCO 2015

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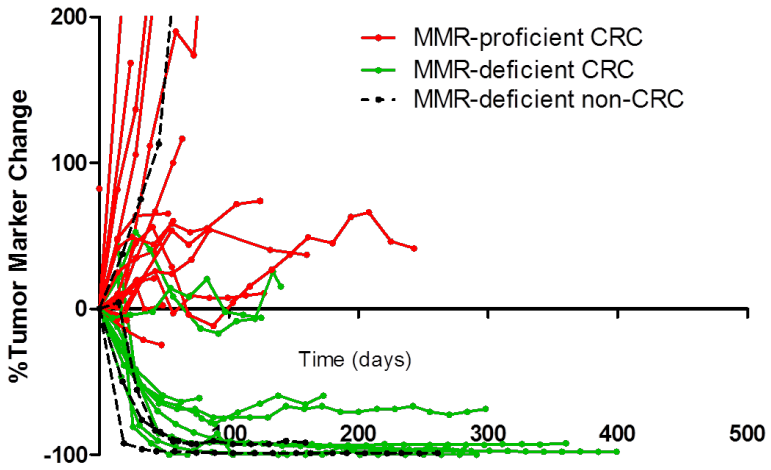
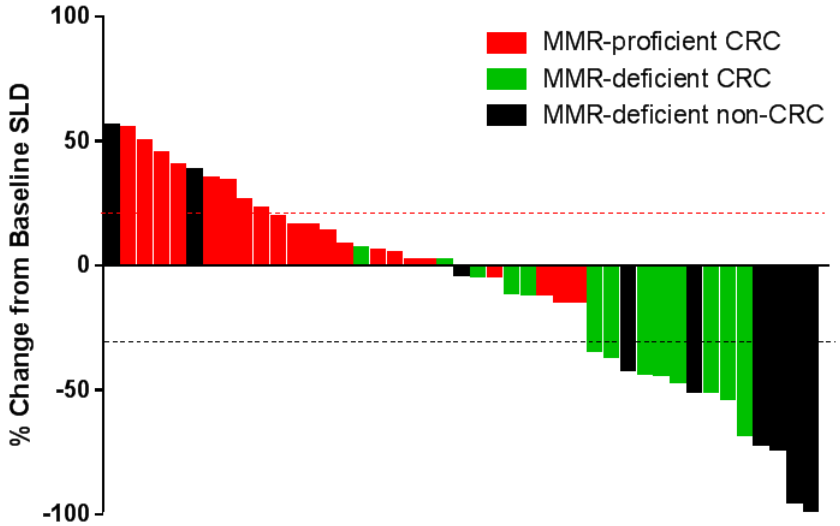
# MMR Status Predicts Responses to KEYTRUDA treatment

| | MMR-deficient CRC | MMR-proficient CRC | MMR-deficient non-CRC |
|---|---|---|---|
| ***N*** | 13 | 25 | 10 |
| **Objective Response Rate** | 62% | 0% | 60% |
| **Disease Control Rate** | 92% | 16% | 70% |

## Biochemical Responses




## Objective Responses




Adapted from presentation by Dung Le, ASCO 2015

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# Mismatch Repair Summary

- Mismatch repair deficient tumors are highly responsive to checkpoint blockade with anti-PD1.
- Biochemical response correlates with radiographic response as well as PFS and OS.
- Mismatch repair deficient tumors are highly mutated and are rich in $CD8^+$ T cells and PD-L1 expression at the tumors' invasive front.
- Results published in *The New England Journal of Medicine*
- Planned Registration Study KEYNOTE-164

Adapted from presentation by Dung Le, ASCO 2015

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**Roger M. Perlmutter**
**Executive Vice President and President**
**Merck Research Laboratories**

# Broad Pipeline is Advancing Rapidly

| EARLY CLINICAL DEVELOPMENT | REGISTRATION | |
|---|---|---|
| Over 30 Different Tumors<br><br>Over 40 Different Combinations | **Melanoma**<br>• 1L (KN006)<br>• 2L (KN002)<br>• Adjuvant (KN054)<br>• T-Vec combination (Amgen)* | **Head and Neck**<br>• 1L + chemo/cetuximab (KN048)<br>• 2L (KN040)<br>• 3L (KN055) |
| | **NSCLC**<br>• 1L (KN024)<br>• 1L (KN042)<br>• 2/3 L (KN010) | **Triple Negative Breast**<br>• 2L (KN086)<br><br>**RRcHL**<br>• 3L (KN087) |
| MK-8628 (BET inhibitor): Solid tumors, hematologic malignancies | **Gastric**<br>• 2L (KN061)<br>• 3L (KN059) | **Bladder**<br>• 1L (KN052)<br>• 2L (KN045) |
| MK-4166 (Anti-GITR): Solid tumors | **Colorectal**<br>• 3L MSI-high (KN164)* | |
| MK-1966 (anti-IL-10) + SD-101 (Dynavax): Solid and hematological tumors* | | |

KEYTRUDA NME's *Planned

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# What to Expect from Merck Oncology in 2015

- Anticipated approval in NSCLC in U.S. and melanoma in E.U.
- Anticipated full approval from KEYNOTE-002 submission in U.S. for ipilimumab-refractory melanoma
- Filing of KEYNOTE-006 data for ipilimumab-naïve melanoma
- Multiple additional registration trials to begin
- Proof of concept data in other tumor types
- Ongoing melanoma launch in U.S. and other global markets

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SVP, Global Clinical Development
Merck Research Laboratories

**Roger M. Perlmutter**
Executive Vice President and President
Merck Research Laboratories

**Frank Clyburn**
President Merck Oncology

# Q&A

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