Antitumor Activity and Safety of Pembrolizumab in Patients with PD-L1–positive Nasopharyngeal Carcinoma: Interim Results From a Phase 1b Study

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Disclosures

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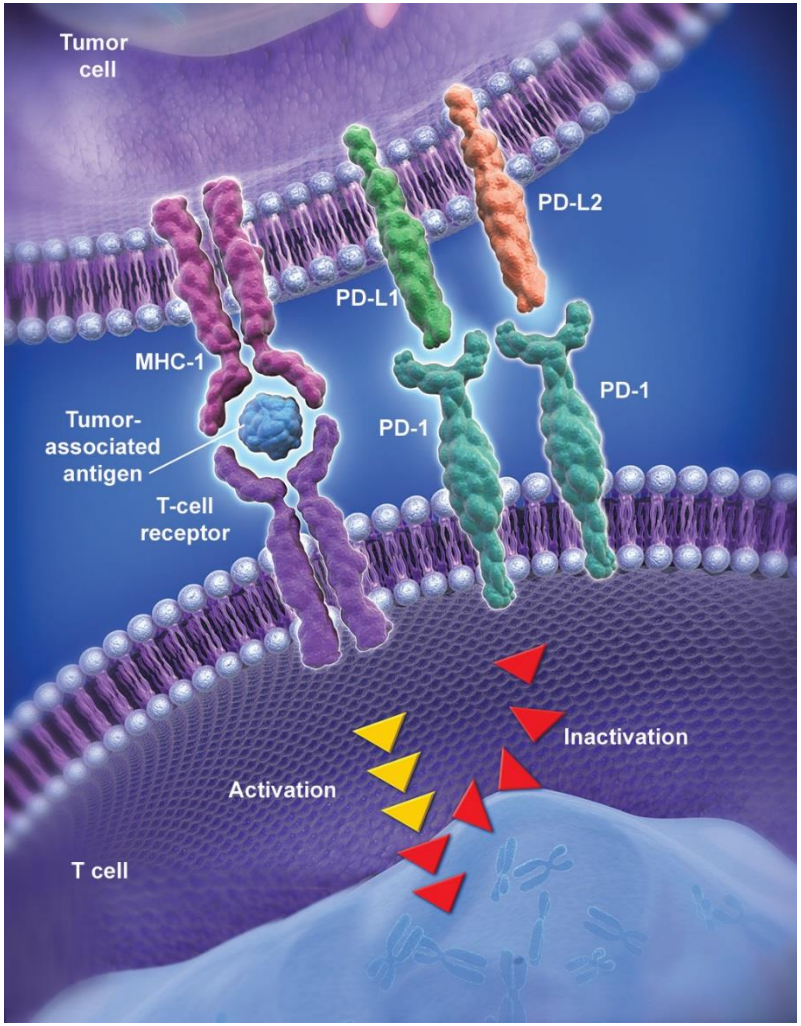
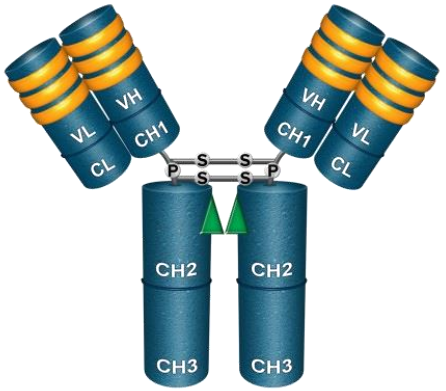
Programmed Cell Death 1 (PD-1)

- Inhibitory receptor expressed primarily on the surface of activated T cells
- Binding of PD-1 to one of its ligands, PD-L1 or PD-L2, protects healthy cells from autoimmunity
- Tumors can exploit this pathway to escape immune surveillance



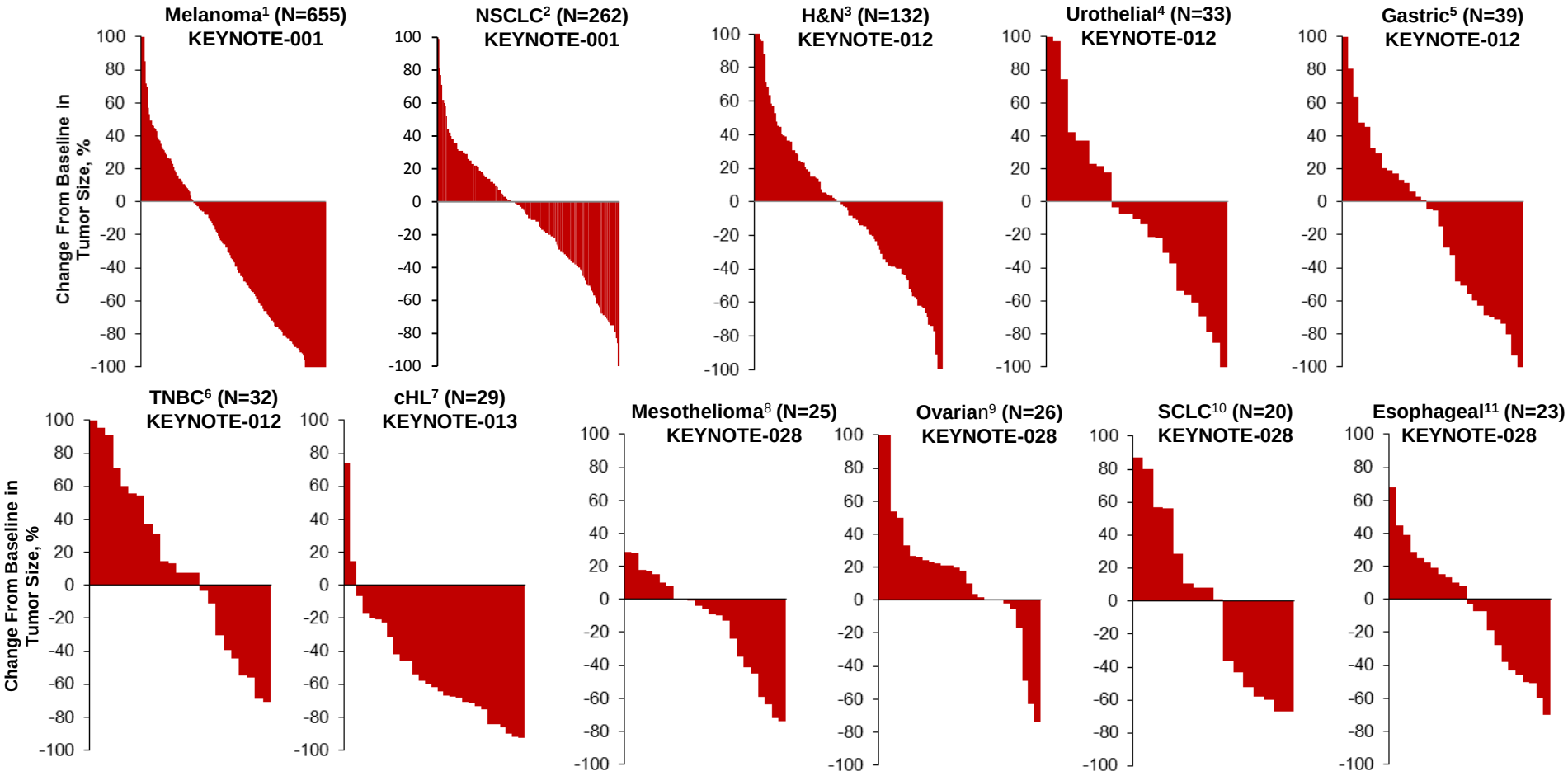
Pembrolizumab

- High-affinity humanized monoclonal antibody against programmed cell death 1 (PD-1) receptor
- Prevents PD-1 from binding to its ligands, PD-L1 and PD-L2, helping to restore antitumor immune surveillance
- Currently in development as monotherapy and as combination therapy in ≥30 tumor types
- Approved for the treatment of advanced melanoma and non-small cell lung cancer



- **Humanized IgG4 S228P**
- **K_D ~ 29 pM**
- **IC50 ~600 pM**
- **EC50 ~70 pM**
- **$t_{1/2}$ of 14-21 days**

Pembrolizumab Antitumor Activity



cHL = classical Hodgkin's lymphoma; H&N = head and neck; NSCLC = non-small cell lung cancer; TNBC = triple-negative breast cancer.

1. Daud A et al. 2015 ASCO; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. 2015 ASCO; 4. Plimack E et al. 2015 ASCO; 5. Bang YJ et al. 2015 ASCO; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR; 9. Varga A et al. 2015 ASCO; 10. Ott PA et al. 2015 ASCO; 11. Doi T et al. 2015 ASCO.

Nasopharyngeal Carcinoma (NPC)

- Incidence
  - Relatively rare in US (<1 case/100,000[1]) and Europe (0.1-2.2 per 100,000[2])
  - More common in some parts of Asia (26.9 per 100,000 in Southern China[2])

- Front-line curative therapy options[3,4]
  - Stages I Radiation therapy (RT)
  - Stages IIA, IIB, III, IVA/B: Chemoradiation (cisplatin is standard)

- Treatment options for recurrent/metastatic disease
  - Palliative chemotherapy, commonly with platinum-based combination regimens
  - Median survival time of patients with advanced NPC[3]
    - 5-11 months

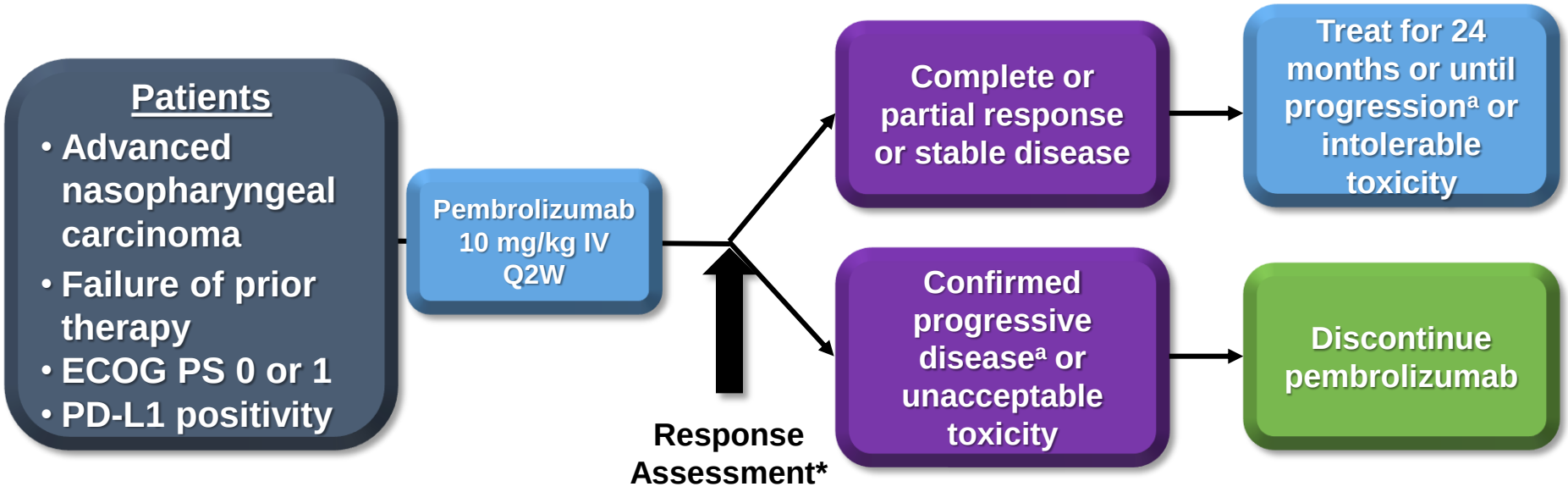
1. www.cancer.org; 2. Chan ATC et al. (2009) *Ann Oncol* 20 (Suppl 4): iv123–iv125; 3. Zhang L et al. (2013) *Drug Des Devel Ther* 7:37–52.
4. NCCN Guidelines for the Treatment of Head and Neck Cancers V1.2015.

PD-L1 Expression in Nasopharyngeal Carcinoma

- High PD-L1 expression is common in Epstein-Barr virus (EBV) associated cancers such as NPC[1]
- PD-L1 expression in NPC is upregulated by EBV-induced activation of LMP1 and IFN-γ pathways[2]
- PD-1 and PD-L1 expression may correlate with poor prognosis in patients with NPC[3]

1. Chen BJ et al. (2013) *Clin Cancer Res* 19(13):3462–34732
2. Fang W et al. (2014) Oncotarget 5(23):12189-202.
3. Zhang J et al. (2015) *Med Oncol* 32(3):86.

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors



***Response assessment**: Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end point: ORR per RECIST v1.1

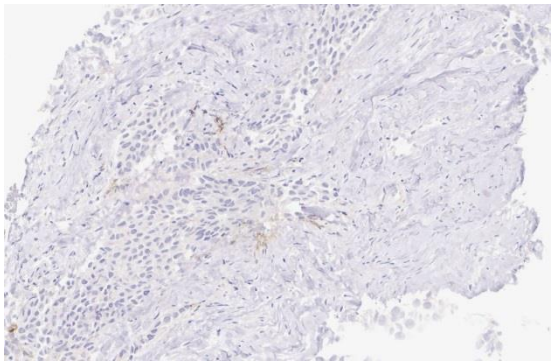
Secondary end points: PFS, OS, duration of response, and safety

[a]If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy is received.

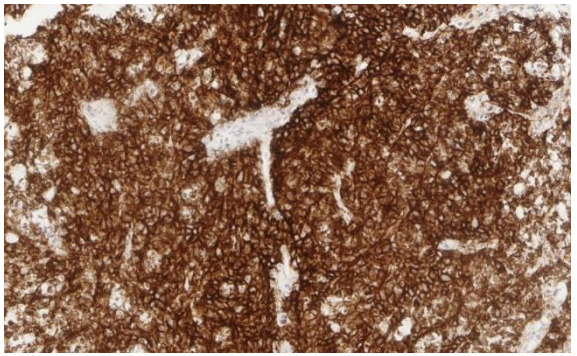
Analysis of PD-L1 Expression

- Tumor samples: archival or newly obtained core or excisional biopsy of non-irradiated lesion
- Immunohistochemistry: assessed at a central laboratory using a prototype assay (QualTek) and 22C3 antibody clone (Merck)
- Positivity: membranous PD-L1 expression in ≥1% of cells in tumor and stroma
- 41 of 44 (93.2%) patients with nasopharyngeal carcinoma who provided tissue had PD-L1–positive tumors

Examples of PD-L1 Staining in Nasopharyngeal Carcinoma Specimens



PD-L1 Negative



PD-L1 Positive

Baseline Characteristics

Characteristic, N (%)	N = 27
Median age, years (range)	52 (18–68)
Female, n (%)	6 (22.2)
Race, n (%)	
Asian	17 (63.0)
White	5 (18.5)
Black or African American	2 (7.4)
American Indian or Alaska Native	1 (3.7)
Not specified	2 (7.4)
ECOG performance status, n (%)	
0	7 (25.9)
1	20 (74.1)
Histology at baseline, n (%)	
WHO Class 1	6 (22.2)
WHO Class 2/3	18 (66.6)
Other	3 (11.1)

Characteristic, N (%)	N = 27
Adjuvant or neoadjuvant systemic therapy, n (%)	8 (29.6)
Prior lines of therapy for advanced disease, n (%)	
0	2 (7.4)
1	3 (11.1)
2	3 (11.1)
3	8 (29.6)
4	2 (7.4)
≥5	9 (33.3)
Patients with prior therapies, n (%)	
Cisplatin	25 (92.6)
Fluorouracil	22 (81.4)
Gemcitabine	14 (51.9)
Carboplatin	11 (40.7)
Docetaxel	10 (37.0)
Cyclophosphamide	7 (25.9)
Paclitaxel	6 (22.2)
Capecitabine	5 (18.5)

Data cutoff date: July 1, 2015.

Treatment-Related Adverse Events

Any Grade Occurring in ≥2 Patients	N = 27 N (%)
Pruritus	7 (25.9)
Fatigue	5 (18.5)
Hypothyroidism	5 (18.5)
Hepatitis	3 (11.1)
Herpes zoster	3 (11.1)
Pneumonitis	3 (11.1)
Rash	3 (11.1)
Maculo-papular rash	3 (11.1)
Anemia	2 (7.4)
Cough	2 (7.4)
Diarrhea	2 (7.4)
Myalgia	2 (7.4)

Grade 3-5 AEs Occurring in ≥1 Patient	N = 27 N (%)
Hepatitis	2 (7.4)
Pneumonitis	2 (7.4)
Anemia	1 (3.7)
Facial pain	1 (3.7)
Increased blood creatine phosphokinase	1 (3.7)
Proteinuria	1 (3.7)
Sepsis	1 (3.7)

Data cutoff date: July 1, 2015.

AEs of Interest Based on Immune Etiology

Event, N (%)	Grade 1-2	Grade 3	Grade 4
Any	6 (22.2)	3 (11.1)	1 (3.7)
Hypothyroidism	5 (18.5)	0 (0)	0 (0)
Hepatitis	2 (7.4)	1 (3.7)	1 (3.7)
Pneumonitis	1 (3.7)	2 (7.4)	0 (0)

- 1 treatment-related death due to bacterial sepsis
- 4 discontinuations due to treatment-related AEs: proteinuria, pneumonitis, increased blood creatine phosphokinase, hepatitis

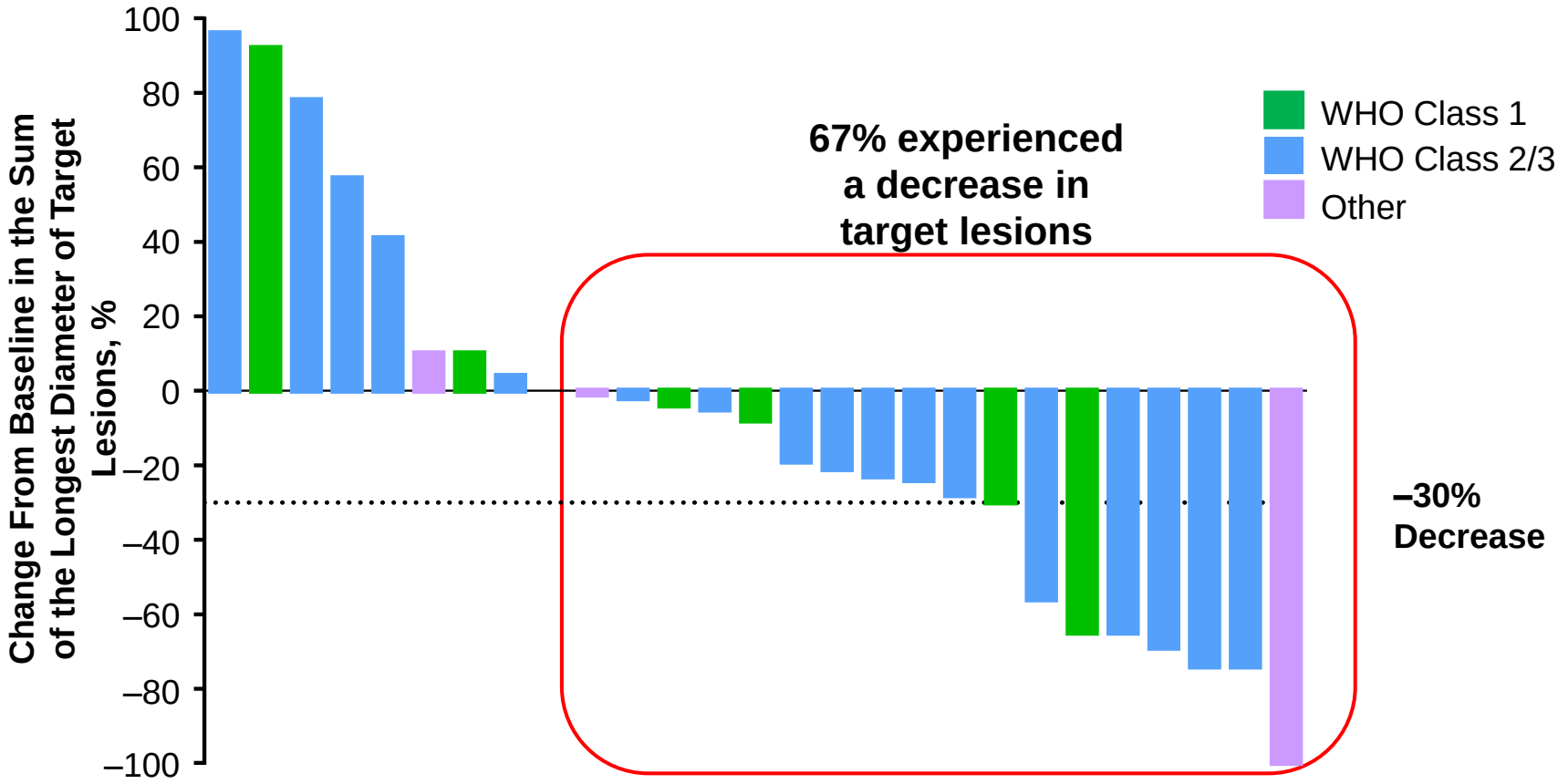
Data cutoff date: July 1, 2015.

Antitumor Activity

	N = 27		
Response evaluation	n	%	95% CI
ORR	6	22.2	8.6−42.3
Complete response	0	0	0−12.8
Partial response	6	22.2	8.6−42.3
Stable disease	15	55.6	35.3−74.5
Progressive disease	6	22.2	8.6−42.3
Disease Control Rate*	21	77.8	57.7−91.4

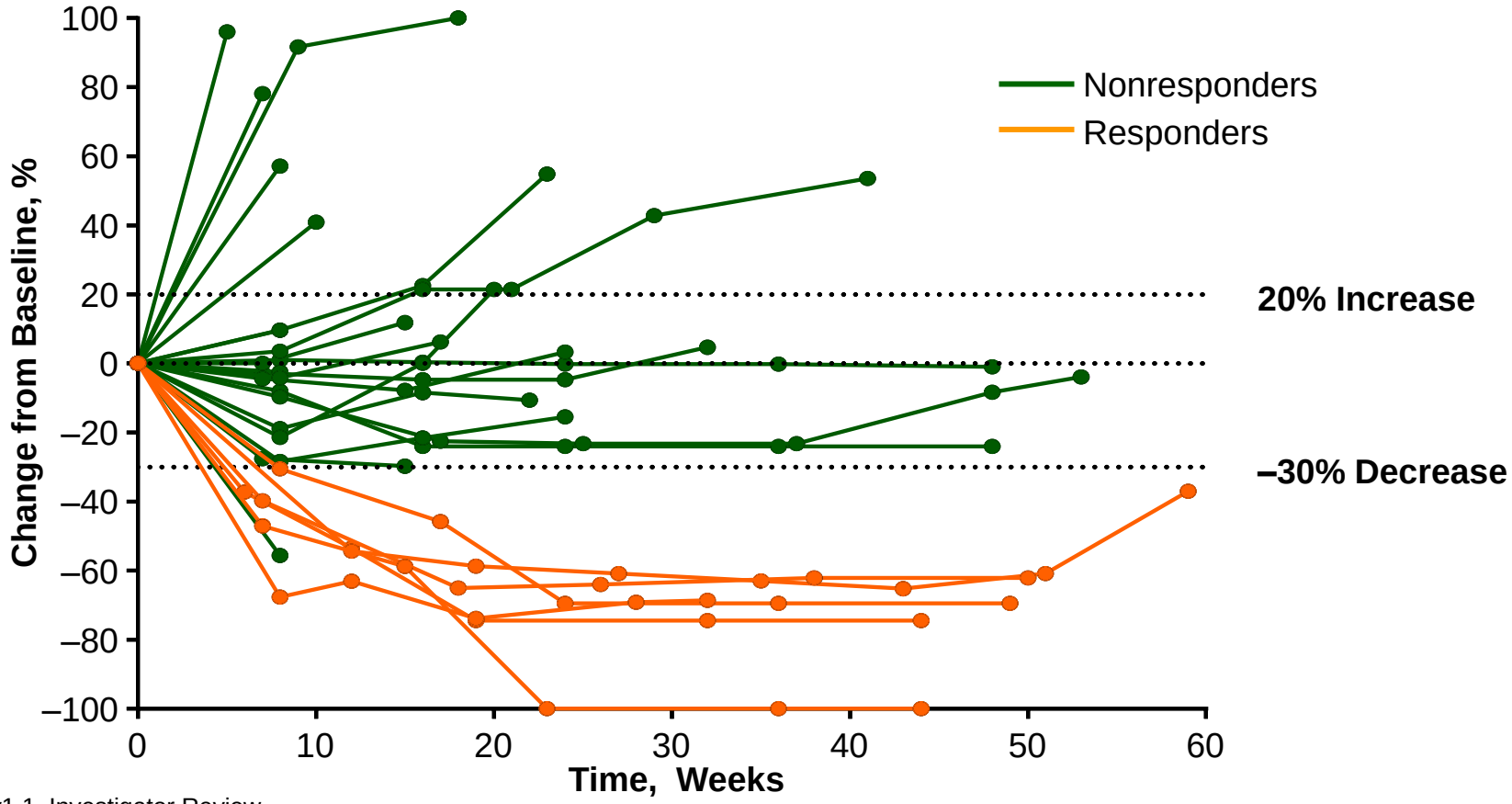
*Disease Control Rate = CR + PR + SD.
RECIST v1.1, Investigator Review. Only confirmed responses are included.
Data cutoff date: July 1, 2015.

Change from Baseline in Tumor Size: Waterfall Plot



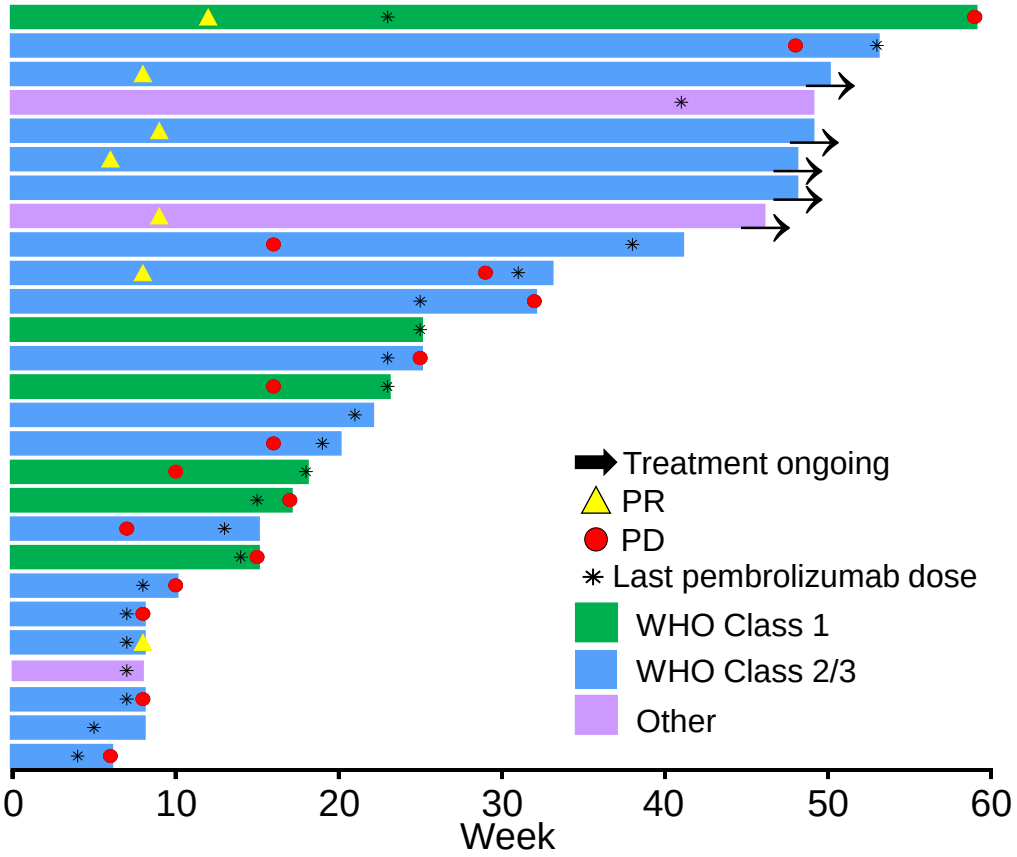
RECIST v1.1, Investigator Review.
Data cutoff date: July 1, 2015.

Longitudinal Change From Baseline in Tumor Size



RECIST v1.1, Investigator Review.
Data cutoff date: July 1, 2015.

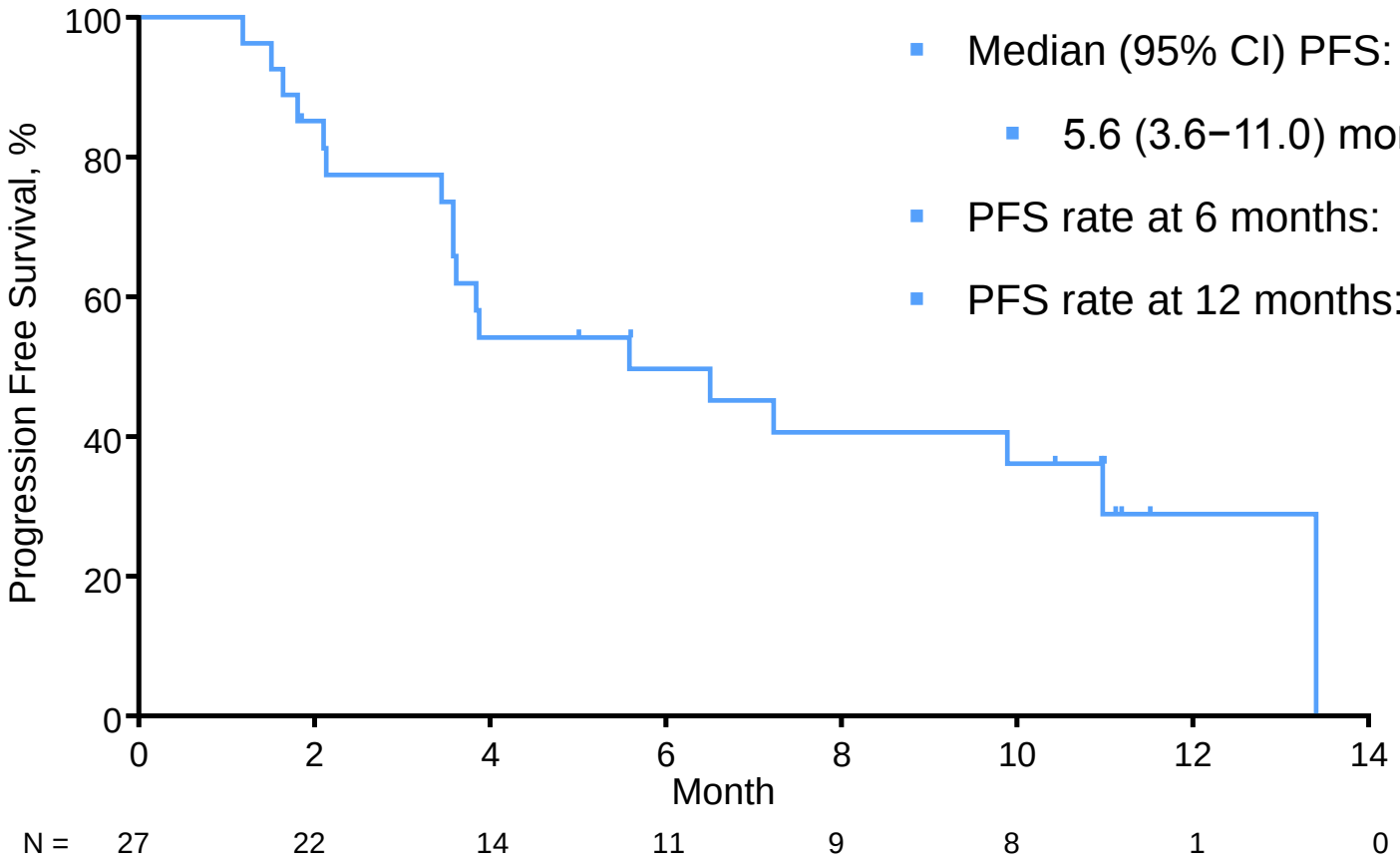
Treatment Exposure and Response Duration



RECIST v1.1, Investigator Review.
Data cutoff date: July 1, 2015.

- Median (range) follow-up duration:
  - 12.9 (2.2−15.0) months
- Median (range) time to response:
  - 1.8 (1.4−2.6) months
- Median (range) response duration:
  - 10.8 (4.8- 10.8) months
- Median SD duration (range):
  - 5.6 (1.7+ - 11.1+) months

Progression-Free Survival

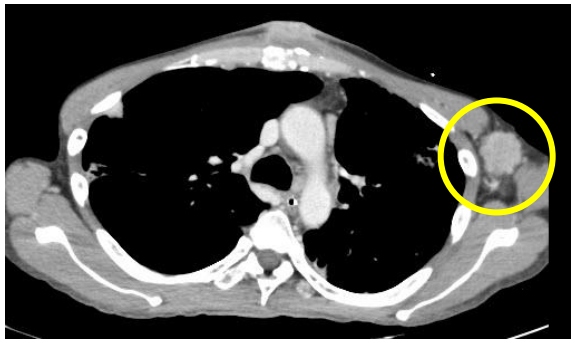
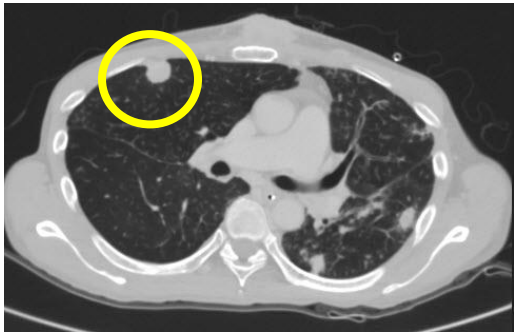
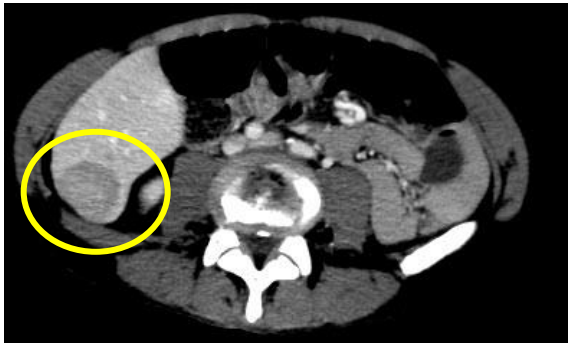


- Median (95% CI) PFS:
  - 5.6 (3.6−11.0) months
- PFS rate at 6 months: 49.7%
- PFS rate at 12 months: 28.9%

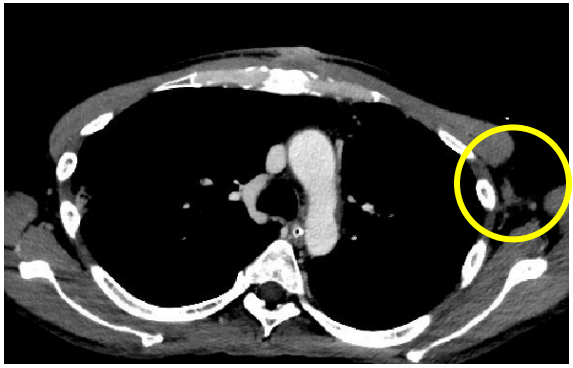
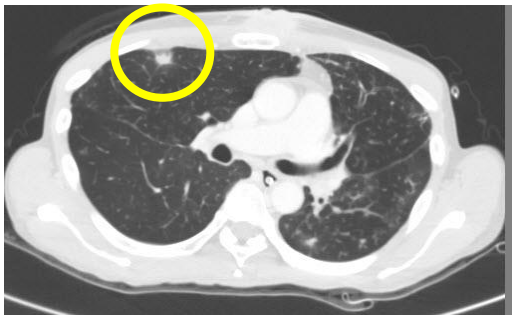
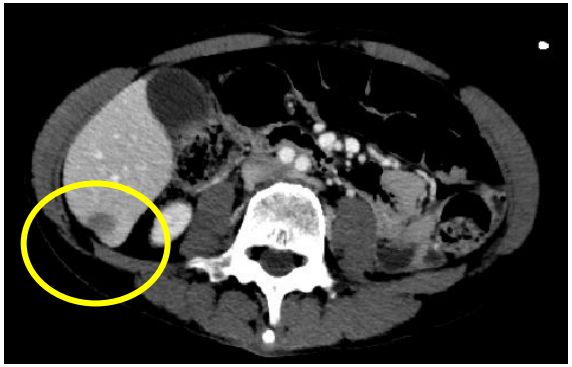
RECIST v1.1, Investigator Review.
Data Cutoff Date: July 1, 2015

Example of Response in Nasopharyngeal Carcinoma (WHO Class 2/3)

Baseline

First time point post baseline

Conclusions

- This study is the first demonstration of robust clinical activity of a PD-1 inhibitor in patients with recurrent/metastatic nasopharyngeal carcinoma
- Pembrolizumab demonstrated antitumor activity in patients with NPC:
  - ORR was 22.2%
  - Median duration of response was 10.8 months
- Pembrolizumab showed a manageable safety profile
- Further investigation is planned
  - Phase II study of pembrolizumab monotherapy versus chemotherapy in platinum pre-treated, recurrent/metastatic nasopharyngeal carcinoma (KEYNOTE-122, NCT02611960)

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