Clinical Study Report Synopsis	
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SUPREME-HN

A Retrospective Cohort Study of PD-L1 in Recurrent and Metastatic Head and Neck Squamous Cell Carcinoma(s) (HNSCC)

Study dates: First subject enrolled: 15 September 2015
Last subject last visit: 14 November 2016

Phase of development: Not Applicable – Observational study

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[redacted]

Study centre(s)

The study was implemented in a total of 19 sites in the US, Asia (Japan, South Korea) and Europe (Germany, Greece, Italy and Spain).

Publications

Pai S, Cohen EE, Lin D, Fountzilas G, Kim E, Mehlhorn H, et al.
A retrospective study of tumoral PD-L1 expression as a prognostic biomarker in patients with R/M HNSCC who were treated with first-line or second-line standard of care therapy chemotherapy. Tumoral PD-L1 expression was examined with OS or PFS after first-line and second-line therapy.
European Society for Medical Oncology (ESMO) 2017 Congress, Madrid, Spain, 8-12 September 2017. Poster Discussion. Abstract #1048PD.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	To determine the prognostic value of programmed death ligand 1 (PD-L1) status in terms of overall survval (OS) in patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) not amenable to local therapy. Overall survival after diagnosis of recurrent/metastatic HNSCC not amenable to local therapy was assessed in PD-L1 high and PD-L1 low or negative patients and in predefined sub-groups.	Overall survival; hazard ratios
Secondary	To describe the relevant demographic and clinical characteristics of patients, stratified by PD-L1 status.	Descriptive statistics
	To describe first line HNSCC treatment choices, and where available, subsequent treatment choices.	Descriptive statistics
	To describe investigator-assessed tumor response for first line and second line of therapy (if any), including: best response, duration of response where applicable, and objective response rate (ORR).	Descriptive statistics
	To describe investigator-assessed progression-free survival (PFS) for first line and second line of therapy (if any).	Progression-free survival; hazard ratios
[redacted] d	[redacted]	[redacted]

Study design

This was a retrospective international, multi-center, non-interventional cohort study based on the use of data derived from established medical records and a secondary analysis of archival tumor samples. The study aimed to describe the patient characteristics, patterns of treatment, and clinical outcomes in association with PD-L1 status in a retrospective cohort of patients with recurrent/metastatic HNSCC treated according to the current clinical practice. The date of diagnosis of recurrent/metastatic disease not amenable to local therapy was used as the index date. The patient selection period extended from 01 March 2011 to 30 June 2015. All patients with a diagnosis of recurrent/metastatic squamous cell carcinoma (SCC) of the oral cavity (tongue, gum, floor of mouth, and other/unspecified part of the mouth), oropharynx, hypopharynx, or larynx during that period were considered for inclusion in the study. Patients were identified and followed up through their medical records until death or end of data collection. PD-L1 status was determined by IHC using a validated assay, the Ventana SP263 PD-L1 assay, at an approved central testing laboratory, using archived tissue samples, including samples from the primary tumor site, lymph nodes or distant metastatic sites. PD-L1 high expression was defined as ≥25% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

Target subject population and sample size

Consented adult patients (≥ 18 years old) with histologically confirmed HNSCC of the oral cavity (tongue, gum, floor of mouth, other/unspecified part of the mouth), oropharynx, hypopharynx or larynx and recurrent or metastatic HNSCC not amenable to local therapy. Patients had a mandatory archival tissue sample (less than five years old) from the primary site, a lymph node, or a distant metastatic site. Patients had not received treatment for HNSCC with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, or any other antibody with known immunomodulatory effect.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Not Applicable

Statistical methods

Descriptive analyses of patient characteristics, treatment choices, and treatment outcomes were performed for the whole cohort (defined as all patients meeting the eligibility criteria) stratified by PD-L1 status, and for predefined subgroups (age, race, smoking history, heavy alcohol consumption, anatomical sub-site of primary tumor, performance status at index date, metastatic disease at index date, types of treatment regimens, HPV status). Missing data were not imputed.

Time to event data (OS, PFS) were described using the Kaplan-Meier method. Two-sided 95% confidence intervals (CIs) were provided for the main statistical estimators. Overall survival and PFS were compared between PD-L1 high and PD-L1 low/negative subgroups using the log-rank test, at a 5% level of significance. The prognostic value of PD-L1 status in

terms of OS and PFS was investigated using a Cox proportional hazards model, where selected covariates are included in the model for univariate and multivariate analysis.

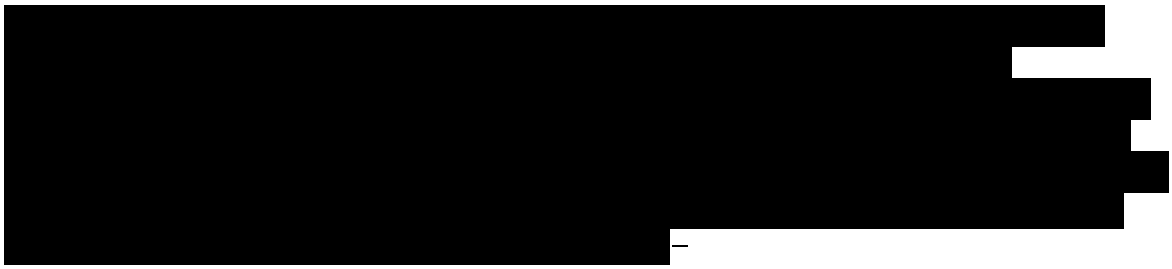
Subject population

Patient Disposition

Nineteen sites in seven countries (US, Germany, Greece, Italy, Spain, Japan, South Korea) screened 513 patients with recurrent/metastatic HNSCC tumors for inclusion, from which 412 patients (80.3%) met the eligibility criteria. From the 412 patients in the Full Analysis Set (FAS), 213 (51.7%) were located in the US, 174 (42.2%) in Europe, and 25 (6.1%) in Asia. The total cohort was comprised of 132 patients (32.0%) with PD-L1 high status, 264 patients (64.1%) with PD-L1 low/negative status, and 16 patients with unknown PD-L1 status (3.9%; due to technical issue).

Tissue Samples

The majority of the 412 patients (n=400, 97.1%) provided one tissue sample; 12 patients provided two samples, for a total of 424 samples. The sample was obtained from the primary tumor in 162 cases (n=162/424, 38.2%), from recurrent disease in 179 cases (n=179/424, 42.2%) and from a metastatic location in 83 cases (n=83/424, 19.6%). The proportion of samples with high PD-L1 expression (n=132/424, 32.1% overall) did not vary with the source of tissue sample, and amounted to 32.1% (n=52/162, primary tumor), 31.8% (n=57/179, recurrent site), and 32.5% (n=27/83, metastatic site), respectively.



Demographics

In the total cohort, patients' median age was 62.0 years (range: 28.0-93.0, n=411); 176 patients (n=176/411, 42.8%) were less than 60 years old. The median age was 62.0 years in either subgroup, with 41.7% of patients with PD-L1 high status and 42.6% of patients with PD-L1 low/negative status under 60 years of age.

The majority of patients were male (n=329/412, 79.9%) and of White race (n=350/397, 88.2%). The proportion of females was 25.8% (n=34/132) in the PD-L1 high subgroup, and 17.0% (n=45/264) in the PD-L1 low/negative subgroup. With this exception, demographic characteristics did not vary by PD-L1 status.

HNSCC Characteristics

In the total cohort, the median time from initial diagnosis of HNSCC to the index date was 13.3 months (range: 0.0-475.9, n=412). It was roughly similar across PD-L1 subgroups, with

medians of 11.4 months (range: 0.0-475.9 months, n=132) in the PD-L1 high subgroup, and 14.7 months (range: 0.0-349.8 months, n=264) in the PD-L1 low/negative subgroup.

The main tumor locations at initial diagnosis (available for 409 patients, three patients were missing information) were the oral cavity (n=143/409, 35.0%), the larynx (n=137/409, 33.5%), and the oropharynx (n=91/409, 22.2%). In the PD-L1 high subgroup, 48.5% (n=64/132) of patients exhibited tumors of the oral cavity, 30.3% (n=40/132) presented with tumors in the larynx region, and 15.2% (n=20/132) had tumors of the oropharynx. Among the patients in the PD-L1 low/negative subgroup, the most common location was the larynx (n=91/261, 34.9%), followed by the oral cavity (n=76/261, 29.1%), and the oropharynx (n=65/261, 24.9%).

Stage at initial diagnosis (available for 378 patients, 34 patients were missing information) was similarly distributed across PD-L1 subgroups, with approximately 90% of patients initially diagnosed at stage IVA or below. Overall, 35% of the patients (n=144/412) had cervical lymphadenopathy at the time of initial diagnosis. Among the 341 patients with tumor stage data available at the index date, 69.8% (n=238/341) presented with tumors at stage IVC at the index date (in similar proportion across PD-L1 subgroups), followed by Stage IVA (n=63/341, 18.5%) and IVB (n=22/341, 6.5%). The most common metastatic sites were the lung (n=80/412, 19.4%) and bones (n=30/412, 7.3%).

Treatment History Post Index Date

Among the 266 patients that received first line chemotherapy regimens in the advanced setting (before or after the index date, excluding neoadjuvant and adjuvant therapies), 238 patients (n=238/412, 57.8%) received at least first line chemotherapy, and 84 patients (84/412, 20.4%) received second line chemotherapy after the index date. A limited number of patients received third line (n=28/412, 6.8%), fourth line (n=11/412, 2.7%), and fifth line (n=3/412, 0.7%) chemotherapy treatments. Additionally, 123 patients (n=123/412, 29.9%) underwent palliative surgical interventions, and 113 patients (n=113/412, 27.4%) received palliative radiotherapy treatments.

The 266 patients treated by first line chemotherapy regimens were comprised of 77 patients with PD-L1 high expression, 177 patients with PD-L1 low/negative status, and 12 patients with unknown PD-L1 expression. The most common first line chemotherapy agents were cetuximab (n=132/266, 49.6%) and cisplatin (n=119/266, 44.7%), followed by 5-fluorouracil (n=97/266, 36.5%), carboplatin (n=84/266, 31.6%), paclitaxel (n=67/266, 25.2%), and docetaxel (n=43/266, 16.2%). Cetuximab, platinum-based therapy and taxanes were used in similar proportions in patients with high or low/negative PD-L1 expression. Finally, 5-fluorouracil was administered to 45.5% (n=35/77) and 31.6% (n=56/177) of patients in the PD-L1 high and low/negative subgroups, respectively.

Among the 90 patients who received second line chemotherapy regimens (comprised of 25 patients with PD-L1 high status, 60 with PD-L1 low/negative status, and five patients with unknown PD-L1 status), the most common chemotherapy agents were cetuximab (n=30/90, 33.3%), followed by paclitaxel (n=25/90, 27.8%), carboplatin (n=20/90, 22.2%), docetaxel

(n=18/90, 20.0%) and 5-fluorouracil (10/90, 11.1%). Cetuximab, carboplatin and taxanes (paclitaxel and docetaxel) were used in similar proportions in the PD-L1 high and low/negative subgroups.

Treatment Response to First Line Chemotherapy

A total of 98 patients had tumor response evaluated according to the Response Criteria In Solid Tumors (RECIST), with assessments based on computerized tomography (CT), magnetic resonance imaging (MRI), or fluorodeoxyglucose positron emission tomography (FDG-PET) scan imaging (the latter is used per RECIST to identify new lesions). Among these 98 patients, one patient (n=1/98, 1.0%) had a complete response, and 42 patients (n=42/98, 42.9%) experienced a partial response. The complete response was observed in a PD-L1 low/negative patient. The distribution of partial responses was comparable in the two PD-L1 subgroups. The ORR (sum of complete and partial responses) based on RECIST and measured by CT, MRI, or FDG-PET Scan was 43.9% (95% CI: 33.9% - 54.3%) overall, 40.0% (95% CI: 21.1% - 61.3%) among patients with PD-L1 high status, and 44.3% (95% CI: 32.4% - 56.7%) among patients with PD-L1 low/negative status. The median duration of response, when available, was 13.1 weeks overall (n=34), 10.6 weeks in patients with PD-L1 high status (n=8) and 15.3 weeks in patients with PD-L1 low/negative status (n=24).

Best overall tumor response evaluated according to any criteria and assessed by any measurement method was available for 246 patients. Thirteen patients (n=13/246, 5.3%) had a complete tumor response and 62 patients (n=62/246, 25.2%) had a partial response. The distribution of complete and partial responses was comparable in the two PD-L1 subgroups. The ORR (sum of complete and partial responses) for first line chemotherapy based on any evaluation criteria and measurement method was 29.8% (95% CI: 24.2% - 35.8%) overall, 28.8% (95% CI: 18.8% - 40.6%) in the PD-L1 high subgroup, and 29.8% (95% CI: 23.0% - 37.3%) in the PD-L1 low/negative subgroup. The median duration of response, when available, was 13.4 weeks (n=49) for all patients, 11.0 weeks (n=11) among patients with PD-L1 high status, and 14.7 weeks (n=36) among patients with PD-L1 low/negative status.

Treatment Response to Second Line Chemotherapy

Among the 30 patients with best overall response evaluated according to RECIST, and measured by CT, MRI or FDG-PET scan, four patients (n=4/30, 13.3%) had a partial response, including two patients (n=2/10, 20.0%) with PD-L1 high status, one patient (n=1/18, 5.6%) with PD-L1 low/negative status, and the last patient with unknown PD-L1 status (n=1/2, 50%). The median duration of response, available for these four patients was 10.6 weeks (range: 1.3-27.0). The ORR for second line chemotherapy evaluated according to RECIST, and measured by CT, MRI or FDG-PET scan was 13.3% (95% CI: 3.8% - 30.7%) overall, 20.0% (95% CI: 2.5% - 55.6%) in the PD-L1 high status subgroup, and 5.6% (95% CI: 0.1% - 27.3%) in the PD-L1 low/negative status subgroup.

Best overall tumor response evaluated to any criteria and by any measurement method was available for 82 patients. One patient (n=1/82, 1.2%) had a complete tumor response; this patient had a PD-L1 low/negative status. Nine patients (n=9/82, 11.0%) had a partial response, including two patients (n=2/24, 8.3%) with PD-L1 high status, and six patients (n=6/53,

11.3%) with PD-L1 low/negative status; the last patient had unknown PD-L1 expression. The median duration of response, available for eight patients, was 11.1 weeks (range: 1.3-30.1). The ORR (sum of complete and partial responses) for second line chemotherapy based on any evaluation criteria and measurement method was 11.9% (95% CI: 5.9% - 20.8%) overall, 8.3% (95% CI: 1.0% - 27.0%) among patients with PD-L1 high status, and 12.7% (95% CI: 5.3% - 24.5%) among patients with PD-L1 low/negative status.

Progression-Free Survival

Among all patients with data for PFS (n=253) from the initiation of first line chemotherapy (whether administered before or after index date), the median PFS was 4.6 months (95% CI: 4.0 - 5.0). Median PFS was 4.2 months (95% CI: 2.6 - 4.8) in patients with PD-L1 high expression, and 4.8 months (95% CI: 3.9 - 5.8) in patients with PD-L1 low/negative status (log-rank test; p=0.37). [redacted]

Among all patients with data for PFS from the initiation of second line chemotherapy (n=88), the median PFS was 2.8 months (95% CI: 1.9 - 4.4). Median PFS amounted to 4.1 months (95% CI: 2.8 - 7.1) in patients with PD-L1 high expression (n=25), and 2.2 months (95% CI: 1.6; 4.0) in patients with PD-L1 low/negative status (n=58). The difference in median PFS between the two PD-L1 subgroups was statistically significant (log-rank test; p=0.04).

Overall Survival

The proportion of patients who died during the study period was 70.4%. The median OS estimate from the index date for the 412 patients in the FAS was 9.6 months (95% CI: 8.3 - 10.8). The median OS amounted to 8.2 months (95% CI: 6.3 - 10.6) in the PD-L1 high subgroup (n=132) and to 10.1 months (95% CI: 8.3 - 12.2) in the PD-L1 low/negative subgroup (n=264). There was no statistically significant difference between the two PD-L1 subgroups in terms of OS (log-rank test; p=0.55). [redacted]

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Cox Proportional Hazard Model for Death

In the multivariate analysis three independent factors reduced the hazard for death compared to their reference group, and one factor had a detrimental effect in this regard:

- Age: patients ≥ 60 years old had a lower hazard for death, with a hazard ratio (HR) for death of 0.710 (95% CI: 0.551 - 0.915, p<0.01) compared to patients less than 60 years old.
- Platinum-based therapy was associated with a lower hazard for death, with a HR for death of 0.703 (95% CI: 0.524 - 0.942, p=0.02), compared to patients who did not receive platinum-based therapy.
- Anatomical sub-site of larynx was associated with a lower hazard for death, with a HR for death of 0.626 (95% CI: 0.458 - 0.856, p<0.01), compared to anatomical sub-site of oral cavity.
- Metastatic disease at the index date increased the hazard for death, and was associated with a HR for death of 1.424 (95% CI: 1.098 - 1.848, p<0.01), compared to patients who were not at a metastatic stage at the index date.

PD-L1 status was not identified as a significant covariate (HR: 1.047, 95% CI: 0.796 – 1.377, p=0.74) in the multivariate analysis.

Cox Proportional Hazard Model for Disease Progression or Death

The only covariate associated with the hazard for disease progression or death from the initiation of first line chemotherapy was the patient's race. Patients from all other races (Black, Asian; n=35) had a lower hazard for disease progression or death, with a HR of 0.586 (95% CI: 0.379 – 0.904, p=0.02), relative to White patients (n=212). However, the interpretation of the Cox proportional hazard model was impaired by the low number of observations available from non-White patients (n=35).

No significant covariates for the hazard of disease progression or death from second line chemotherapy at a p ≤0.05 level of significance were identified. PD-L1 high expression was associated with a non-significant HR of 0.556 (95% CI: 0.283 – 1.094, p=0.09).

Summary of safety results

Not applicable.

Conclusion(s)

The SUPREME-HN study, based on the retrospective review of patient medical records, described the clinical characteristics, patterns of clinical management, and treatment outcomes of 412 patients with recurrent/metastatic HNSCC not amenable to local therapy, enrolled from

the US, Europe and Asia, and assessed the prognostic value of the PD-L1 status in terms of OS and PFS. The overall proportion of patients with PD-L1 high expression was 32.0%.

The proportion of tissue samples with high PD-L1 expression did not vary with the source of tissue sample, and amounted to 32.1% (primary tumor), 31.8% (recurrent site), and 32.5% (metastatic site), respectively.

Based on the final analysis of the SUPREME-HN retrospective cohort study, the PD-L1 status assessed by staining of tumor cells on archival tissue (where PD-L1 high was defined as ≥25% tumor cells with membrane staining at any intensity) does not appear to be prognostic of OS as measured from the index date, defined as the time of the first diagnosis of recurrent/metastatic HNSCC not amenable to local therapy.

The Cox proportional hazards model identified four covariates associated with the hazard for death. Three covariates reduced the hazard for death compared to their reference group, including age ≥60 years, platinum-based therapy, and anatomical sub-site of larynx, compared to anatomical sub-site of oral cavity. Metastatic disease at the index date increased the hazard for death.

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