CABEZA Y CUELLO

- **Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study**

INVESTIGADORES: Jong-Mu Sun, Lin Shen, Manish A Shah, Peter Enzinger, Antoine Adenis, Toshihiko Doi, Takashi Kojima, Jean-Philippe Metges, Zhigang Li, Sung-Bae Kim, Byoung Chul Cho, Wasat Mansoor, Shau-Hsuan Li, Patrapim Sunpaweravong, Maria Alsina Maqueda, Eray Goekkurt, Hiroki Hara, Luis Antunes, Christos Fountzilas, Akihito Tsuji, Victor Castro Oliden, Qi Liu, Sukrut Shah, Pooja Bhagia, Ken Kato, KEYNOTE-590 Investigators.

REVISTA Lancet 2021 Aug 28;398(10302):759-771. doi: 10.1016/S0140-6736(21)01234-4.

ABSTRACTO: Background: First-line therapy for advanced oesophageal cancer is currently limited to fluoropyrimidine plus platinum-based chemotherapy. We aimed to evaluate the antitumour activity of pembrolizumab plus chemotherapy versus chemotherapy alone as first-line treatment in advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer. Methods: We did a randomised, placebo-controlled, double-blind, phase 3 study across 168 medical centres in 26 countries. Patients aged 18 years or older with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer (regardless of PD-L1 status), measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1, and Eastern Cooperative Oncology Group performance status of 0-1, were randomly assigned (1:1) to intravenous pembrolizumab 200 mg or placebo, plus 5-fluorouracil and cisplatin (chemotherapy), once every 3 weeks for up to 35 cycles. Randomisation was stratified by geographical region, histology, and performance status. Patients, investigators, and site staff were masked to group assignment and PD-L1 biomarker status. Primary endpoints were overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 combined positive score (CPS) of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients. This trial is registered with ClinicalTrials.gov, NCT03189719, and is closed to recruitment. Findings: Between July 25, 2017, and June 3, 2019, 1020 patients were screened and 749 were enrolled and randomly assigned to pembrolizumab plus chemotherapy (n=373 [50%]) or placebo plus chemotherapy (n=376 [50%]). At the first interim analysis (median follow-up of 22·6 months), pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for overall survival in patients with oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more (median 13·9 months vs 8·8 months; hazard ratio 0·57 [95% CI 0·43-0·75]; p<0·0001), oesophageal squamous cell carcinoma (12·6 months vs 9·8 months; 0·72 [0·60-0·88]; p=0·0006), PD-L1 CPS of 10 or more (13·5 months vs 9·4 months; 0·62 [0·49-0·78]; p<0·0001), and in all randomised patients (12·4 months vs 9·8 months; 0·73 [0·62-0·86]; p<0·0001). Pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy for progression-free survival in patients with oesophageal squamous

cell carcinoma (6·3 months vs 5·8 months; 0·65 [0·54-0·78]; p<0·0001), PD-L1 CPS of 10 or more (7·5 months vs 5·5 months; 0·51 [0·41-0·65]; p<0·0001), and in all randomised patients (6·3 months vs 5·8 months; 0·65 [0·55-0·76]; p<0·0001). Treatment-related adverse events of grade 3 or higher occurred in 266 (72%) patients in the pembrolizumab plus chemotherapy group versus 250 (68%) in the placebo plus chemotherapy group. Interpretation: Compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy improved overall survival in patients with previously untreated, advanced oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma, PD-L1 CPS of 10 or more, and in all randomised patients regardless of histology, and had a manageable safety profile in the total as-treated population.

- **The Effects of Breastfeeding on Retinoblastoma Development: Results from an International Multicenter Retinoblastoma Survey**

INVESTIGADORES: Jasmeen K Randhawa, Mary E Kim, Ashley Polski, Mark W Reid, Kristen Mascarenhas, Brianne Brown, Ido Didi Fabian, Swathi Kaliki, Andrew W Stacey, Elizabeth Burner, Caitlin S Sayegh, Roy A Poblete, Xunda Ji, Yihua Zou, Sadia Sultana, Riffat Rashid, Sadik Taju Sherief, Nathalie Cassoux, Juan Garcia, Rosdali Diaz Coronado, Arturo Manuel Zapata López, Tatiana Ushakova, Vladimir G Polyakov, Soma Rani Roy, Alia Ahmad, M Ashwin Reddy, Mandeep S Sagoo, Lamis Al Harby, Nicholas John Astbury, Covadonga Bascaran, Sharon Blum, Richard Bowman, Matthew J Burton, Nir Gomel, Naama Keren-Froim, Shiran Madgar, Marcia Zondervan, Jesse L Berry.

REVISTA Cancers (Basel) 2021 Sep 24;13(19):4773. doi: 10.3390/cancers13194773. eCollection 2021 Oct 1.

ABSTRACTO: The protective effects of breastfeeding on various childhood malignancies have been established but an association has not yet been determined for retinoblastoma (RB). We aimed to further investigate the role of breastfeeding in the severity of nonhereditary RB development, assessing relationship to (1) age at diagnosis, (2) ocular prognosis, measured by International Intraocular RB Classification (IIRC) or Intraocular Classification of RB (ICRB) group and success of eye salvage, and (3) extraocular involvement. Analyses were performed on a global dataset subgroup of 344 RB patients whose legal guardian(s) consented to answer a neonatal questionnaire. Patients with undetermined or mixed feeding history, family history of RB, or sporadic bilateral RB were excluded. There was no statistically significant difference between breastfed and formula-fed groups in (1) age at diagnosis (p = 0.20), (2) ocular prognosis measures of IIRC/ICRB group (p = 0.62) and success of eye salvage (p = 0.16), or (3) extraocular involvement shown by International Retinoblastoma Staging System (IRSS) at presentation (p = 0.74), lymph node involvement (p = 0.20), and distant metastases (p = 0.37). This study suggests that breastfeeding neither impacts the sporadic development nor is associated with a decrease in the severity of nonhereditary RB as measured by age at diagnosis, stage of disease, ocular prognosis, and extraocular spread. A further exploration into the impact of diet on children who develop RB is warranted.

- **Biomarkers of human papillomavirus (HPV)-driven head and neck cancer in Latin America and Europe study: Study design and HPV DNA/p16 INK4a status**

INVESTIGADORES: Laura Sichero, Marta Tagliabue, Giana Mota, Silvaneide Ferreira, Rafaella A L Nunes, Carlos Arturo Castañeda, Miluska Castillo, Rita Mariel Correa, Sandra Perdomo, Paula A Rodríguez-Urrego, Leandro Luongo Matos, Ansarin Mohssen, Tarik Gheit, Massimo Tommasino, Susanna Chiocca, Luisa Lina Villa, HEADLAcE Study Group.

REVISTA: Head Neck 2021 Nov 2. doi: 10.1002/hed.26912.

ABSTRACTO: Background: Human papillomavirus (HPV)-driven head/neck squamous cell carcinomas (HNSCC) prevalence varies globally. We evaluated HPV DNA and p16INK4a in formalin fixed paraffin embedded (FFPE) HNSCC from Argentina, Brazil, Colombia, and Peru. Methods: HPV was genotyped by PCR-hybridization. All HPV DNA positive and some HPV DNA negative cases underwent p16INK4a immunohistochemistry. Results: HPV DNA was detected in 32.8%, 11.1%, and 17.8% of oropharyngeal (OPC), oral cavity (OCC) and laryngeal (LC) cancers, respectively. OPC HPV prevalence was higher in Colombia (94.7%), and Argentina (42.6%) compared to Brazil (10.6%) and Peru (0.0%). HPV-16 was the most detected. Other HPVs were found in LC. Higher rates of p16INK4a positivity were observed among HPV positive OPC/OCC cases compared to LC cases. Conclusions: Our results support a role for HPV-16 in a subset of HNSCC, corroborate the heterogeneity observed in samples from different countries, and contribute additional etiological and biomarkers information in tumors of significant impact worldwide.

- **Defining High-Risk Retinoblastoma: A Multicenter Global Survey**

INVESTIGADORES: Swathi Kaliki, Carol L Shields, Nathalie Cassoux, Francis L Munier, Guillermo Chantada, Hans E Grossniklaus, Hiroshi Yoshikawa, Ido Didi Fabian, Jesse L Berry, John D McKenzie, Kahaki Kimani, M Ashwin Reddy, Manoj Parulekar, Mika Tanabe, Minoru Furuta, Natalia Grigorovski, Patricia Chevez-Barrios, Patricia Scanlan, Ralph C Eagle Jr, Riffat Rashid, Rosdali Díaz Coronado, Sadia Sultana, Sandra Staffieri, Shahar Frenkel, Shigenobu Suzuki, Tatiana L Ushakova, Xunda Ji.

REVISTA: JAMA Ophthalmol 2021 Nov 11. doi: 10.1001/jamaophthalmol.2021.4732.

ABSTRACTO: Importance: High-risk histopathologic features of retinoblastoma are useful to assess the risk of systemic metastasis. In this era of globe salvage treatments for retinoblastoma, the definition of high-risk retinoblastoma is evolving. Objective: To evaluate variations in the definition of high-risk histopathologic features for metastasis of retinoblastoma in different ocular oncology practices around the world. Design, setting, and participants: An electronic web-based, nonvalidated 10-question survey was sent in December 2020 to 52 oncologists and pathologists treating retinoblastoma at referral retinoblastoma centers. Intervention: Anonymized survey about the definition of high-risk histopathologic features for metastasis of retinoblastoma. Main outcomes and measures: High-risk histopathologic features that determine further treatment with adjuvant systemic chemotherapy to prevent metastasis. Results: Among the 52 survey recipients, the results are based on the responses from 27 individuals (52%) from 24 different retinoblastoma practices across 16 countries in 6 continents. The following were considered to be high-risk features: postlaminar optic nerve infiltration (27 [100%]), involvement of optic nerve transection (27

[100%]), extrascleral tissue infiltration (27 [100%]), massive (≥3 mm) choroidal invasion (25 [93%]), microscopic scleral infiltration (23 [85%]), ciliary body infiltration (20 [74%]), trabecular meshwork invasion (18 [67%]), iris infiltration (17 [63%]), anterior chamber seeds (14 [52%]), laminar optic nerve infiltration (13 [48%]), combination of prelaminar and laminar optic nerve infiltration and minor choroidal invasion (11 [41%]), minor (<3 mm) choroidal invasion (5 [19%]), and prelaminar optic nerve infiltration (2 [7%]). The other histopathologic features considered high risk included Schlemm canal invasion (4 [15%]) and severe anaplasia (1 [4%]). Four respondents (15%) said that the presence of more than 1 high-risk feature, especially a combination of massive peripapillary choroidal invasion and postlaminar optic nerve infiltration, should be considered very high risk for metastasis. Conclusions and relevance: Responses to this nonvalidated survey conducted in 2020-2021 showed little uniformity in the definition of high-risk retinoblastoma. Postlaminar optic nerve infiltration, involvement of optic nerve transection, and extrascleral tumor extension were the only features uniformly considered as high risk for metastasis across all oncology practices. These findings suggest that the relevance about their value in the current scenario with advanced disease being treated conservatively needs further evaluation; there is also a need to arrive at consensus definitions and conduct prospective multicenter studies to understand their relevance.