been approved for the treatment of adult and pediatric patients (pts) 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic PPGL who require systemic anticancer therapy. We have previously presented data showing improved biomarker responses in pts treated with HSA I-131 MIBG. Here we report the impact of biomarker status on the study primary endpoint and objective tumor response. **Methods:** Pts with iobenguane-avid PPGL who were ineligible for surgery, failed prior therapy or not candidates for chemotherapy, and on a stable antihypertensive medication regimen were treated. Pts received up to two therapeutic doses, each at ~18.5 GBq (or 296 MBq/kg for pts ≤62.5 kg), administered ~90 days apart. Biomarkers were analyzed at baseline and over a 12-month efficacy period. Confirmed biochemical responses (at least ≥ 50% decrease in abnormal tumor marker value for all hypersecreted biomarkers) required subsequent responses to be identical to or better compared with the previous assessment. The primary endpoint was clinical benefit, defined as the proportion of pts with at least 50% reduction of all antihypertensive medication(s) for ≥6 months beginning during the efficacy period. The secondary endpoint, confirmed objective tumor response by RECIST, was also evaluated. **Results:** 68 pts received at least one therapeutic dose of HSA I-131 MIBG. For all pts with hypersecretory tumors (with a baseline biochemical marker level of ≥1.5× ULN) (n=60), a comparison of biomarker response with antihypertensive therapy yielded a correlation coefficient of 0.35 (P = 0.006; Fisher exact P = 0.012). For pts with norepinephrine only-hypersecreting tumors (n=31), a correlation coefficient of 0.47 (P = 0.008; Fisher exact P = 0.015) was observed. The overall biomarker response also correlated with objective tumor response (n=55) yielding a correlation coefficient of 0.36 (P = 0.007; Fisher exact P = 0.012) for all pts with hypersecreted biomarkers. Pts who were not biochemical hypersecretors for any biomarker (n=6) had only one responder for the primary endpoint and no objective tumor responses. **Conclusions:** The biomarker data from this study establish a moderate but statistically significant correlation between biomarker response following treatment with HSA I-131 MIBG and objective tumor response and durable reduction of antihypertensive therapy. This correlation was improved with norepinephrine only-hypersecreting tumors in pts with unresectable, locally advanced or metastatic PPGL.

Adrenal

THERAPEUTIC TRIALS AND PROGNOSTIC MARKERS FOR ADRENAL DISEASES

Modified GRAS Score for Prognostic Classification of Adrenocortical Carcinoma: An ENSAT Multicentre Study

Yasir Elhassan, MD[1], Barbara Altieri, MD, PhD[2], Sarah Berhane, PhD[1], Deborah Cosentini, PhD[3], Anna Calabrese, PhD[4], Magalie Haissaguerre, PhD[5], Darko Kastelan, MD, PhD[6], Maria C. Fragoso, PhD,MD[7], Jerome Bertherat, MD,PhD[8], Eric Baudin, PhD[9], Harm Haak, MD,PhD[10], Maria Boudina, PhD[11], Letizia Canu, MD PhD[12], Paola Loli, MD[13], Mark Sherlock, MB, BCh, MD, PhD[14], Otilia Kimpel, PhD[15], Laganà Marta, PhD[3], Matthias Kroiss, PhD[15], Wiebke Arlt, MD DSc FRCP FMedSci[1], Massimo Terzolo, MD[16], Alfredo Berruti, PhD[2], Jonathan Deeks, PhD[1], Rossella Libe, PhD[17], Martin Fassnacht, MD[2], Cristina Lucia Ronchi, MD[1].

[1]University of Birmingham, Birmingham, United Kingdom, [2]University of Wuerzburg, Wuerzburg, Germany, [3]University of Brescia, Brescia, Italy, [4]University of Turin, Orbassano, Italy, [5]Service d'Endocrinologie - Diabète et Nutrition, Bordeaux, France, [6]University Hospital Zagreb, Zagreb, Croatia, [7]Universidade de São Paulo, Sao Paulo, Brazil, [8]Hopital Cochin, Paris, France, [9]Endocrine Oncology Gustave Roussy, Paris, France, [10]Maxima Medisch Centrum, Eindhoven, Netherlands, [11]Theagenio Cancer Hospital, Thessaloniki, Greece, [12]university of Florence, Florence, Italy, [13]Clinica Polispecialistica San Carlo, Milan, Italy, [14]Beaumont Hospital and Royal College of Surgeons in Ireland, Dublin, Ireland, [15]University of Würzburg, Würzburg, Germany, [16]University of Turin San Luigi Hospital, Orbassano, Italy, [17]Department of Endocrinology and Metabolic Diseases, Paris, France.

Background: Adrenocortical carcinoma (ACC) has an aggressive but heterogeneous behaviour. ENSAT stage and Ki67 proliferation index are used to predict clinical outcome but are limited in distinguishing patients with different risk of disease progress. We aimed to validate the prognostic role of a previously proposed points-based score (mGRAS) in a large ACC cohort.

Methods: We included ACC patients who underwent adrenalectomy between 2010 and 2019, had complete clinical and histopathological data, and did not participate in our previous studies (*Libe et al. Ann Oncol 2015; Lippert et al. JCEM 2018*). The mGRAS score was calculated as follows: age (<50yr=0; ≥50yr =1), symptoms (no=0; yes=1), ENSAT stage (1–2=0; 3=1; 4=2), resection status (R0=0; RX=1; R1=2; R2=3), and Ki67 (0–9%=0; 10–19%=1; ≥20%=2 points), generating scores from 0 to 9 and four mGRAS groups (scores 0–1, 2–3, 4–5, and 6–9). Progression-free survival (PFS) and disease-specific survival (DSS) were the primary and secondary endpoints, respectively. The discriminative performance of mGRAS was investigated using the Harrell's C-index and Royston-Sauerbrei's R^2_D statistic.

Results: A total of 942 ACC patients from 14 ENSAT centres were included (38% men; median age 50yrs (interquartile range 38, 61)). The four mGRAS groups showed superior prognostic discrimination compared to the individual clinical and histological parameters for both PFS and DSS (C-index 0.71, R^2_D=0.30 and 0.77, R^2_D=0.46, respectively); ENSAT staging was the second best discriminator (C-index 0.67, R^2_D 0.21 and 0.72, R^2_D=0.35, respectively). An even better prognostic discrimination was observed using the ten mGRAS scores individually (C-index 0.73, R^2_D=0.30, and 0.79, R^2_D=0.45 for PFS and DSS, respectively). The superiority of mGRAS was confirmed when separately considering patients treated or untreated with adjuvant mitotane (n=481 *vs* 314). In mitotane-treated patients, the four mGRAS groups showed better performance in predicting PFS than Ki67 index (C-index 0.66, R^2_D 0.18 *vs* C-index 0.62, R^2_D 0.12).

Conclusion: The prognostic performance of mGRAS is superior to that of ENSAT staging and Ki67. This simple score may guide personalised treatment decisions in patients with ACC, e.g. regarding the need for adjuvant therapy and frequency of monitoring.