What to expect on I-O Resistance at ASCO 2019?

RAS Lifescience Solution

Circulating tumor DNA to predict response and resistance by anti-PD-1 therapy in Chinese relapsed/refractory classic Hodgkin lymphoma.

Abstract No: 7534
Poster Board Number:Poster Session (Board #288)

Background: *A large fraction of patients with relapsed/refractory (r/r) Classic Hodgkin Lymphoma (cHL) enjoy a beneficial response induced by PD-1. However, no reliable predictive biomarkers for response or resistance are available. Sintilimab, an anti-PD1 agent, has recently demonstrated efficacy and safety in a multi-center, single-arm, phase II study of Chinese patients with r/r cHL (ORIENT-1). The predictive value of circulating tumor DNA (ctDNA) in longitudinal samples from patients in ORIENT-1 was investigated.*

Methods: *A total of 192 plasma samples were collected from 75 patients prior to treatment and during therapy. After ctDNA extraction next-generation sequencing (NGS) was performed using the HiSeq Sequencing System to assess either a 619 or 659 gene panels at an average sequencing depth of 1260×. The panels include frequently mutated genes in cHL and other hematological malignancies. DNA from paired granulocytes was sequenced as presumptive germline control.*

Results: *The genomic profiling of baseline ctDNA revealed a mean allele mutation frequency of 5.47%. Among the most frequently mutated genes in these cHL patients, $PCLO$ and $LRP1B$ are likely unique to Chinese r/r cHL patients. Truncating mutation of $B2M$, $DNMT3$, $TNFRSF14$ and $KDM2B$ were found in patients with acquired resistance, of which $TNFRSF14$ and $KDM2B$ have not been reported before and need to be confirmed in further study. The baseline ctDNA level was significantly different between objective response group (CR+PR, n = 41, median = 8.72) and non-responder group (SD+PD, n = 9, median = 2.9) (p= 0.0070) Patients with ctDNA high achieved response earlier than others (p< 0.05). A drop of 40% in ctDNA after three cycles of therapy confirmed as best cut-off to predict progression associated with clinical benefit, demonstrating 100% specificity. Patients with ctDNA drop ≥40% achieved response significantly earlier (median = 71 days) than others (median = 216 days, p= 0.0074).*

Conclusions: *Our study demonstrated that ctDNA could serve as valuable biomarker for prediction of response or resistance to anti-PD1 immunotherapy.*

Progression and hyperprogression after anti-PD1 therapy for unresectable stage III or IV melanoma patients.

Abstract No: e21021

Background: *Primary progression (PP) and secondary progression (SP) to anti-PD1 therapy (APD) are poorly described in advanced melanoma in real life practice. Hyperprogression with a deleterious effect is reported in many cancers but is poorly assessed in advanced melanoma.*

Methods: *Characteristics of 793 patients treated by APD (nivolumab or pembrolizumab) between July 2014 and May 2018 were collected from MelBase, a prospective French biobank (NCT02828202).We considered:* ***group A*** *(progressive disease as best response),* ***group AHP*** *(hyperprogression) within group A patients (progression/death within 3 months with normal initial LDH and ECOG at baseline, and either ECOG increased from 0 to 3-4, either LDH*

increased from normal to elevated or both), ***group B SP*** *(response or stable disease then progression). Characteristics for all and survival for patients alive at progression (AAP) were also described.*

Results: *Median follow-up was 11.3 months (Q1-Q3 4.8–23.6). Characteristics at baseline are in the table. In group A, 14% patients died at progression; within 262 patients AAP, 17% continue APD (the same or switch), 15.1% (CI_{95} 11.1-20.6) were alive 1-year after progression (1YAP); 20.5% for patients in first line and 11.5% for pretreated. In group AHP, 41% patients died at progression; within 48 patients AAP, 12% continue APD, 11.1% (CI_{95} 7.8-13.6) were alive 1YAP. In group B, 11% patients died at progression; within 88 patients AAP, 36% continue APD, 10.3% (CI_{95} 5.2-20.1) were alive 1YAP, 15.9% for patients in first line and 7.0% for pre-treated.*

Conclusions: *Our study shows that PP and SP to APD differ at baseline, but have similar survival rates at progression, while mechanisms involved might be different, providing important landmarks to build second line trials. This study thus highlights the existence of hyperprogressors among which 41% patients died within 3 months, as well as describes their associated characteristics.*

Tumor growth rate as an early indicator of the efficacy of anti-PD-1 immunotherapy in advanced melanoma.

Abstract No: e21050

Background: *As immunotherapeutics take longer time to show clinical efficacy compared with chemotherapy and targeted therapy, it is critical to select patients with low tumor growth rate (TGR) prior immunotherapy as to get sufficient time for immunotherapeutics to play functions. However, which threshold of TGR before immunotherapy may be associated with good outcome remains unknown.*

Methods: *Medical records from patients with advanced refractory melanoma prospectively treated in clinical trials (NCT02836795 and NCT03013101) of anti-PD-1 antibody toripalimab were analyzed. TGR was computed during the pretreatment period (reference) and the treatment period (treatment). Associations between TGR and objective response at the first evaluation, progression free survival (PFS), overall survival (OS) were computed.*

Results: *We analyzed a total of 142 patients enrolled in these two clinical trials. Excluded for no measurable lesions in pretreatment period or incomplete imaging data through the pretreatment/treatment periods, a total of 90 patients could be explored for the relationship of TGR and the efficacy of anti-PD-1 antibody. TGR and hyperprogression were defined as Champiat S. used to make. The distribution of TGR is as follows: median 63.7 (range: -51~720). A total of 15 (16.7%), 41 (45.6%), 34 (37.8%) and 0 patients exhibited PR, SD, PD, CR, respectively. An association between lower TGR (TGR ≤55) and objective response was observed (P≤0.001). Among evaluable patients at week 8, 83.9% (13+34/56) and 26.5% (2+7/34) showed PR/SD from baseline tumor measurements for the group of TGR≤55 and TGR > 55, respectively. Median PFS was 5.5 0.9m in the group of TGR≤55 compared 1.8 0.4m in the group of TGR > 55 (P≤0.001). Median OS was not reached in the group of TGR≤55 group and was 15.9 1.8m in the group of TGR > 55 (p = 0·02). Two patients were confirmed pseudoprogression in the follow-up. The TGR of these two patients was lower than 55. Five patients experienced hyperprogression. The TGR of each patient was 9, 12, 54, 56, 78, respectively.*

Conclusions: *Melanoma patients with TGR≤55 prior anti-PD-1 antibody therapy are more likely to benefit from this regimen. However, it could not predict patients who may develop hyperprogression after anti-PD-1 antibody therapy. Clinical trial information: NCT02836795 and NCT03013101*

Clinical implication of inflammation-based serologic biomarkers and tissue biomarkers on hyperprogression in

NSCLC patients receiving immune checkpoint blockers in real world.

Abstract No: e20633

Background: *Although immune checkpoint blockades (ICBs) therapy can lead to favorable and durable results by reinvigorating the anti-tumor immune response in some patients, many other patients experience poor prognosis and even tumor overgrowth can be seen in real practice. We aimed to assess these hyperprogressive disease (HPD) in patients who underwent ICB therapy.*

Methods: *We retrospectively reviewed medical records of non-small cell lung cancer patients (n = 243) treated with anti-PD-1 or anti-PD-L1 monotherapy. HPD was defined as a tumor growth kinetics ratio > 2 during anti-PD-1/PD-L1 therapy and a time-to-failure of less than 2 months. We analyzed the association of Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and CRP-albumin ratio (CAR) with HPD and the difference of immune composition in TME by multiplex IHC.*

Results: *Overall, 231 patients were included. The median age was 64.2 years; most patients were male (74.9%) and smokers (70.1%, n = 162). 25 patients (10.8%) met the criteria for HPD. Oncogenic drive mutant status was significantly associated with HPD (18.6% vs 9.04%; P = 0.001). Kaplan Meier overall survival estimates showed a clear trend toward worse outcomes for patients with HPD (median, 5.6 months; P < 0.001) than for those without (median, 7.4 months). We also analyzed the association of NLR, PLR and CAR with HPD. Serologic markers at the time of first response evaluation (post 6 weeks, i.e.,) showed a prognostic value for HPD after ICB use (P< 0.001, 0.008, 0.017). In multiplex IHC, there was no difference in T cell related immune marker of CD 3/4/8/45RO and FOXP3, dendritic cell, NK cell and other co-inhibitory signal markers between two groups. However, the key point was the M2 polarized tendency in the HPD group when the macrophage M1 / 2 markers of CD68, CD163, CD206 and CCR7 were observed. This suggests that changes in the AXL pathway and EMT features associated with reinvigorating anti-tumor immunity in M2 polarized cells may lead to changes in poor prognosis to HPD.*

Conclusions: *Despite improved recognition of HPD, its etiology and predisposing factors remain unclear, but it is clear that the prognosis becomes poor when it occurs. We observed that some serologic biomarkers (NLR, PLR and CAR. i.e.,) can be used to predict HPD. Multiplex IHC can be used not only to predict HPD, but also to validate its mechanism. Furthermore, we undergo whole exon sequencing and multiplex IHC to understand mechanism of Hyperprogression.*

Association between MDM2/MDM4 amplification and PD-1/PD-L1 inhibitors-related hyperprogressive disease: A pan-cancer analysis.

Abstract No: 2557

Poster Board Number: Poster Session (Board #201)

Background: *Immune checkpoint inhibitors have demonstrated a clear survival benefit in various tumor types. However, accelerated disease progression, documented as hyperprogressive disease (HPD), was reported in a subset of patients treated with PD-1/PD-L1 inhibitors. Until now, the mechanisms underlying HPD have not been elucidated. Previous studies have demonstrated that MDM2/MDM4 amplification were associated with HPD. In the present study, we evaluated the relationship between MDM2/MDM4 amplification and HPD.*

Methods: *We reviewed extensive clinical trials of PD-1/PD-L1 inhibitors in advanced solid tumor patients updated to January 2019, and estimated the incidence of HPD, which was defined as time-to-treatment failure (TTF) < 2 months,*

and > 50% increase in tumor burden compared with pre-immunotherapy imaging in this study. The proportions of MDM2/MDM4 amplification across different cancer types were obtained from The Cancer Genome Atlas (TCGA) and our own database respectively. Then we plotted the incidence of HPD and the corresponding proportion of MDM2/MDM4 amplification across various cancer types in TCGA.

Results: *Overall, 19 published clinical trials of 1318 patients treated with PD-1/PD-L1 inhibitors were included for analysis, covering 12 types of solid cancers. The incidences of HPD among these studies were ranging from 1.58% in renal clear cell carcinoma to 24.3% in sarcoma. Correspondingly, the proportions of MDM2/MDM4 amplification for these cancer types in TCGA were 0.74% in renal clear cell carcinoma to 20.38% in sarcoma. In our database, in total, 60 patients with MDM2/MDM4 amplification were identified in 2931 patients with the highest proportion of MDM2/MDM4 amplification in sarcoma (22 of 152, 14.5%). A significant correlation was detected between the incidence of HPD and the corresponding proportion of MDM2/MDM4 amplification in TCGA across various cancer types ($P < 0.001$, $R^2 = 0.67$).*

Conclusions: *Our results suggest that MDM2/MDM4 amplification may be associated with rapid disease progression in patients receiving PD-1/PD-L1 inhibitors among various tumor types. The exact mechanisms underlying HPD are needed to be further evaluated.*

Hyperprogressive disease in advanced triple-negative breast cancer (aTNBC) treated with immunotherapy (IO).

Abstract No: 1086
Poster Board Number: Poster Session (Board #167)

Background: *Hyperprogression of disease (HPD), a rapid acceleration of tumor growth rate (TGR) has been reported with IO in other tumor types. Here, we explore HPD in aTNBC.*
Methods: *A retrospective chart review identified aTNBC patients who consented for IO clinical trials at Princess Margaret Cancer Centre between June 2013 and June 2018. Demographic data, medical history, details of trial enrolment and RECIST 1.1 response to study treatment were recorded. Patients with RECIST 1.1 measurable disease on CT scans or physical examination before trial entry, at trial baseline and at protocol-defined interval following IO start were evaluable for TGR as defined by Champiat et al. Clin Cancer Res 2017.* ***HPD defined as a ≥2-fold increase in TGR between baseline and on-trial restaging assessment****. Univariable logistic regression used to identify variables [age, co-morbidity index, prognostic index, performance status, distant disease-free interval (dDFI), lactate dehydrogenase, no. of metastatic sites, visceral disease and no. of prior treatment lines] associated with HPD. Overall survival (OS) curves were estimated with the Kaplan-Meier method and compared by the log-rank test.*

Results: *99 patients with aTNBC consented for 15 IO clinical trials, 60% IO monotherapy, 22% chemotherapy+/-IO and 18% IO combinations. Median age 52 (range 25-78), median no. of lines of prior systemic therapy for advanced disease 1 (range 0-8). 15% had de-novo metastatic disease, 58% recurred after a dDFI of < 3 years and 25% after a dDFI of > 3 years. 61% had < 3 metastatic disease sites, and 71% had metastases involving the viscera. 66 received IO treatment, 40 patients (20 monotherapy, 7 IO combination, 13 chemotherapy+/-IO) were evaluable for TGR. Median TGR pre-IO was 74.3 (range -17 – 1680) and post-IO was 2.5 (-71.4 – 223). 4 patients (10%) met criteria for HPD. All 4 treated with monotherapy PD1 inhibitor and received at least 2 further lines of therapy post-trial; 1 patient treated with IO as first-line therapy, 3 in the second or later lines. There was no significant difference in the overall OS of patients with HPD and patients who did not meet definition for HPD HR 0.89, (95% CI: 0.26-3.01; p = 0.41). Univariable analysis did not identify factors associated with HPD.*

Conclusions: *HPD was observed in 10% of aTNBC treated on IO clinical trials. HPD was not associated with worse survival outcomes or known prognostic factors in our analysis.*

CDKN2A/B gene loss and MDM2 alteration as a potential molecular signature for hyperprogressive disease in advanced NSCLC: A next-generation-sequencing approach.

Abstract No: e20628

Background: *Hyperprogressive disease (HPD) incidence ranges from 8% to 21% in patients treated with anti-PD-1/PD-L1 mAbs in NSCLC and is associated with poor survival. Previously published data underlined a link between HPD across different cancers types and specific genetic alterations, such as MDM2 amplification and EGFR aberrations. We present a single-center cohort of patients with NSCLC and PD-L1 > 50% treated with 1st-line pembrolizumab. We performed NGS, IHC and FISH analysis to evaluate genetic correlations with the clinical phenotype.*

Methods: *Clinical data from 20 patients with diagnosis of advanced NSCLC treated with 1stline immunotherapy pembrolizumab were retrospectively collected. HPD was defined by Time to Treatment Failure ≤2 months and raising in Tumor Burden ≥50% compared with basal CT-scan. MDM2 amplification was investigated by FISH on FFPE tissue sections using the MDM2/CON12 break apart FISH Probe. Positive cases were defined as those with > 10% positive tumor cells. We performed IHC for MDM2 protein on FFPE tissue sections. The staining was semi-quantitatively graded for the intensity as: 0, negative; 1+, weak positive; 2+, moderately positive; 3+, strongly positive, and for the extent as 0–< 1% (negative), 1–50% (focal), and > 50% (diffuse). We also performed NGS analysis (FoundationOne CDX, Foundation Medicine Inc.) on 324 preidentified genes.*

Results: *We identified 5 cases of HPD; all five cases showed MDM2 amplification by FISH analysis and a focal protein expression by IHC with the strongest nuclear staining observed in the cases showing a higher degree of MDM2 amplification (8/9 dots) and a weaker expression in those with a lower MDM2amplification (4/5 dots). NGS analysis showed MDM2amplification in 1/5 HPD patient and a loss of CDKN2A/B in 4/5 patients. None of the non-HPD patients had IHC expression of MDM2 or amplification of the gene. Among the non-HPD patients no genetic alterations regarding MDM2 and/or CDKN2A/B were found on NGS analysis.*

Conclusions: *Our data suggest a potential role of CDKN2A/B gene loss and alteration of MDM2 on the establishment of HPD in NSCLC patients treated with immunotherapy. Because the HPD logic is not yet clear, more data is needed to better understand the link between this genomic signature and the development of HPD.*

Clinical implications of hyperprogression with immune checkpoint inhibitors in patients with head and neck squamous cell carcinoma (HNSCC).

Abstract No: 6034
Poster Board Number: Poster Session (Board #23)

Background: *Hyperprogressive disease (HPD) refers to paradoxical acceleration of tumor growth kinetics (TGK) after initiation of treatment with anti- PD-1/PD- L1 agents and has been reported across tumor types in 4-29% of patients using different definitions. Preliminary data suggest that HPD might affect response to subsequent therapies.*

Methods: *We compared TGK prior and TGK upon immunotherapy (IO) in 62 patients (pts) with recurrent/metastatic (R/M) HNSCC treated with PD-1/PD-L1 inhibitors. The TGK ratio (TGKR, ratio of tumor growth velocity before and upon treatment) was calculated. The first imaging assessment was performed 3 months (mo) after IO initiation. HPD was defined as 1. Radiological HPD (TGKR≥2) or 2. Clinical HPD (Disease-related rapid clinical deterioration post IO).*

Results: *After median follow-up of 12.3 mo (range, 0.4-28.1), 43 pts progressed and 38 died. Median PFS was 2.8 mo (95%CI, 2.2-3.4) and median OS 8.6 mo (95%CI, 4.2-12.9). HPD was observed in 16 pts (25.8%), while 15 pts had early PD (Time to Treatment failure, TTF < 3 mo) and 31 late PD (TTF > 3mo). Among 16 pts with HPD, 11 had radiological HPD and 10 had clinical HPD. 4 pts had both clinical and radiological HPD. Pts with late PD had median OS 11.3 mo (95%CI, 9.3-13.3), those with early PD 5.2 mo (95%CI, 3.1-7.3 months) and those with HPD 5.1 mo (95%CI, 4.4-5.9) (p < 0.005). Regarding post-progression OS, pts with late PD had median 11.3 mo (95%CI 0-22.8), those with early PD 2.5 mo (95%CI 0.6-4.4) and those with HPD 4.2 mo (95%CI 1.7-6.7) (p = 0.001). Pts with HPD had a trend for longer median post-progression OS compared to pts with early PD (p = 0.121). Median PFS with chemotherapy after immunotherapy failure was 3.0 mo (95%CI 2.4-3.6) for pts with late PD, 2.1 mo (95%CI 0.9-3.4) for pts with early PD and 6.1 mo (95%CI 3.0-9.3) for those with HPD (p = 0.040). HPD was associated with longer median PFS with chemotherapy compared to pts with early PD (p = 0.016), while the difference in median PFS with chemotherapy between pts with HPD and late progressors was non-statistically significant (p = 0.260).*

Conclusions: *Radiological or clinical HPD was observed in 25.8% of patients with R/M HNSCC treated with IO. Early progression to immunotherapy is an important predictor of short survival, while HPD was associated with improved PFS to subsequent chemotherapy.*

Hyperprogressive disease (HPD) in head and neck squamous cell carcinoma (HNSCC) patients treated with immune checkpoint inhibitors (ICI).

Abstract No: 6029
Poster Board Number: Poster Session (Board #18)

Background: *HPD was described in 9% of cancer patients (pts) treated in phase I trials, in 13.8% of advanced non-small cell lung cancer and 29% of 34 HNSCC pts upon ICI. A better definition of the hallmarks and survival outcomes of HPD pts in a larger cohort of HNSCC is still lacking.*

Methods: *We retrospectively analyzed all advanced HNSCC pts treated with ICI at our Institution between October 2014 and December 2018. Three scans, performed before ICI, at baseline and at first evaluation during ICI, were assessed according to RECIST 1.1. Tumor Growth Kinetics (TGK) pre- (TGKpre) and post-baseline (TGKpost) were measured as previously reported (Saâda-Bouzid E, Ann Oncol 2017). Pts were defined HPD if they had progression at first radiological evaluation and TGKpost/TGKpre ≥2. Correlation between HPD and clinical characteristics was performed by Fisher or t-student test. Median overall survival (mOS) and progression free survival (mPFS) were estimated using the Kaplan-Meier method and compared between HPD and non-HPD using the log-rank test.*

Results: *Ninety pts were eligible: 18% were female, 4% had ECOG PS ≥ 2, 73% smoking history, 37% oropharyngeal cancer (61% HPV+), 65% locoregional disease (89% previously irradiated), 54% received combined immunotherapy, 75% in ≥ 2nd line. Two out of 90 pts had TGKpre = 0 and were not evaluable for TGK ratio. HPD was observed in 7.9% (7/88) of pts. HPD pts were significantly younger compared to non-HPD pts (median age 53 ± 3.7 vs 63.3 ± 0.9 years, p = 0.002) and had a significantly higher median neutrophil-lymphocyte ratio (NLR) (11.5 ± 3.5 vs 6.4 ± 0.4, p = 0.004). Overall, mOS and mPFS were 7.5 (95% CI: 4.2-10.8) and 2.2 months (95% CI: 0.9-3.4), respectively. At a median follow-up of 20.9 months (95% CI: 19-22.8), HPD pts had a significantly worse mPFS compared to non-HPD pts [1.8 (95% CI: 1.5-2.2) vs 3.5 (95% CI: 2.2-4.8) months; p = 0.001]. HPD correlated with a not significant trend in lower mOS compared to non-HPD group [3.7 (95% CI: 2.4-5.1) vs 8.3 (95% CI: 4.1-12.5) months; p = 0.348]. Three (43%) out of 7 HPD pts early switched to chemotherapy after PD to ICI having a mOS of 8.1 months (range 3.7-25.3). Excluding these 3 pts, HPD correlated with a significantly worse mOS compared to non-HPD [2.6 (95% CI: 1.9-3.3) vs 8.3 (95% CI: 4.1-12.5) months; p = 0.006].*

Conclusions: *HPD was identified in 7.9% of HNSCC and correlated with younger age and higher NLR. HPD pts who did not receive a subsequent treatment had poorer mPFS and mOS. The assessment of HPD in a control cohort of advanced HNSCC upon standard chemotherapy is ongoing.*

Hyperprogressive disease in patients with recurrent high grade gliomas treated with immune checkpoint inhibitors or other therapies.

Abstract No: e13575

Background: *Hyperprogressive disease (HPD) has been described in solid tumor patients treated with immune checkpoint inhibitors (ICI). HPD is defined as a ≥2-fold increase in tumor growth rate (TGR) following initiation of ICI. HPD has not been explored in patients with high grade gliomas (HGG) on ICI or standard cytotoxic regimens. In advanced cancer patients receiving ICI, MDM2/4 amplification or EGFR alterations, both found in HGG, correlated with HPD. We compared the rate of HPD in recurrent HGG patients receiving ICIs to those treated with non-immunotherapy agents.*

Methods: *Patients with HGG on ICIs for 1st or 2nd recurrence were compared to a control group receiving other therapies at 1st recurrence. Patients with prior or concurrent bevacizumab or anti-VEGFR were excluded due to pseudo-response and decreased enhancement with these drugs. HPD was calculated by comparing TGR immediately before and after treatment.*

Results: *49 patients met inclusion criteria (27 ICI, 25 control). 25/27 patients treated with ICIs and 20/22 patients in the control group had complete imaging and were eligible for analysis. In the ICI group, 60% were men (15/25) and 88% (22/25) had a diagnosis of GBM. 68% were treated at first progression (17/25). Controls were 80% male (16/20) and all had a diagnosis of GBM. 30% (6/20) were 65 years or older at diagnosis in the control group compared to 28% (7/25) in the ICI group. In total, 7/25 patients met criteria for HPD in the ICI group (28%) compared to 4/20 patients in the control group (20%). 10/25 patients (5/7 with HPD) in the ICI group and 8/20 patients (2/4 with HPD) in the control group had next generation sequencing of their tumors. EGFR alterations and MDM2/4 amplifications were not associated with HPD whereas PTEN mutations were more common in the HPD group (71% HPD vs. 33.3% no HPD).*

Conclusions: *HPD is observed in patients with HGG treated with ICI at comparable rates to those with other cancers, but was also observed in 20% of patients receiving other therapies. While the numbers are small, PTEN mutations may be associated with HPD in patients with HGG. In contrast to other solid tumors, EGFR alterations and MDM2/4 amplifications were not associated with HPD in HGG.*

Clinical outcomes of EGFR+ NSCLC pts treated with immune checkpoint inhibitors (ICI).

Abstract No: 9069
Poster Board Number: Poster Session (Board #392)

Background: *ICIs have limited efficacy in EGFR+ NSCLC with ORR ~10% if PDL1 > 25% in ATLANTIC, yet ICIs are often used in later lines of therapy as pts and providers feel there may be little risk. The impacts of ICI in this setting are poorly understood. We describe our institutional experience of ICI use in EGFR+ NSCLC.*

Methods: *MGH pts with advanced EGFR+ NSCLC treated with ICI (any line) were retrospectively reviewed for demographics, PDL1, treatment duration and patient outcomes. Disease flare was defined as hospital/hospice admission due to progression or death (Chaft CCR 2011) within 30d of ICI.*

Results: *40 pts with EGFR+ NSCLC (22 del19, 11 L858R, 5 ins20, 2 other) received ICI between 7/2012-12/2018. 13 were on a clinical trial. 4 had SCLC transformation. Median # of prior therapies = 3 (range, 0-8). Of 16 with PDL1 quantified, 8 had PDL1 > 25%. ICI regimens were: nivolumab (nivo; n = 16), pembrolizumab (pembro; 9), atezolizumab (atezo; 3), ipilimumab/nivo (7), carboplatin/pemetrexed (pem)/pembro (3), pem/pembro (1), paclitaxel/atezo (1). 18 pts stopped TKI ≤21d prior to ICI start. Median duration of treatment (DOT) was 25 days*

(range, 1-1482). DOT was > 1 yr for 2 pts (5%), treated with 1st-line nivo/erlotinib (erlo) and 3rd-line nivo. All 8 pts with PDL1 > 25% had DOT < 2 mos. Disease flare within 30d of ICI occurred in 16/40 (40%) overall, 8/18 (44%) who stopped TKI ≤21d of ICI start, and 14/26 (54%) who received ICI in 4th line or later. 8 pts had concurrent TKIs (4 erlo/nivo, 2 erlo/pembro, 1 erlo/atezo, 1 osimertinib (osi)/nivo); 3/8 discontinued ICI for toxicity (all 3 treated first-line). 5 pts received osi immediately post-ICI. There was no pneumonitis on osi post-ICI; 1 pt developed gr3 LFTs and gr4 hypoNa.

Conclusions: *In this real world cohort of EGFR+ NSCLC, clinical benefit from ICI (assessed by DOT) was rare, including pts with high PDL1. 5% had durable benefit (both pts received ICI in earlier lines of therapy). A previously underappreciated negative outcome of ICI is that admission to hospital, hospice or death within 30d of ICI occur in up to 54% pts. This may be related to disease flare or hyperprogression and suggests that use of ICI in heavily pretreated EGFR+ NSCLC may negatively impact outcomes at end-of-life and should be used with caution.*

Identification of clinically actionable mutations and immunotherapy biomarkers in Chinese esophageal squamous cell carcinoma patients.

Abstract No: e15576

Background: *Esophageal squamous cell carcinoma (ESCC), the major esophageal cancer histological type in East Asia, has limited therapeutic options and is associated with poor prognosis. Here, we identified clinically actionable genomic alteration (GA) for potential targeted and immunotherapy in Chinese ESCC patients by next generation sequencing (NGS).*

Methods: *Clinical data were collected from 150 ESCC patients from March 2011 to December 2018, with a median follow-up of 34 months. NGS-panel sequencing of 466 cancer genes was performed on FFPE tumor and matched blood sample. Tumor mutational burden (TMB) was assessed in all patients by standard NGS algorithms. PD-L1 expression was evaluated in 61 samples by IHC (28-8 Ab).*

Results: *Overall, 75.5% of ESCC patients harbored at least one clinically actionable GAs with the most frequent being CCND1 (40%), CDKN2A (40%), CDKN2B (24%), PIK3CA (14%) and FGFR1 (8%). Most clinically actionable GAs occurred in genes involved with cell cycle (61%) and with PI3K pathway (23%). Clinically actionable GAs also distributed in BRCA2 (5%), ATM (3%), MET amp (3%), KIT (3%), EGFR mut (2%), PDGFRA (2%) and ERBB2 amp (1%). The lowest 25% (TMB-L), median and highest 25% TMB (TMB-H) value was 4.6, 6.9 and 9.2 muts/Mb, respectively. Compared with younger patients, patients ≥50 years had higher TMB (p= 0.047). Compared with TMB-L ESCCs, frequencies of NOTCH2 (15.9% vs 0%, p= 0.015), PIK3CA (22.7% vs 2.8%, p= 0.019) and KMT2D (25.0% vs 5.6%, p= 0.031) were significantly higher in TMB-H. Notably, amplification in 11q13 region, MDM2/MDM4 and EGFR, which potentially relates to immunotherapy hyperprogression, accounted for 48% of TMB-H. Eleven patients (18%) showed PD-L1≥1%, in which 7 pts were also TMB-H.*

Conclusions: *In Chinese ESCCs, clinically actionable GAs were detected in most patients, which highlights the promise of molecularly directed therapies. Patients with PD-L1 positive/TMB-H/both, who could potentially benefit from immunotherapy, accounted for 41%. Older age, NOTCH2, PIK3CA and KMT2D mutations correlated with TMB-H.*

BIOLUMA: A phase II trial of nivolumab in combination with ipilimumab to evaluate efficacy and safety in lung cancer and to evaluate biomarkers predictive for response—Preliminary results from the NSCLC cohort.

Abstract No:
e20550

Background: *Patient selection, dosing regimens and resistance mechanisms for immune checkpoint inhibitor combination therapy remain unmet medical needs in lung cancer. Combining blockade of PD-1 and CTLA-4 can be more effective than monotherapy but is accompanied by an increase in toxicity. Thus, to circumvent unnecessary toxicity it is of great interest to identify patients who will benefit from PD-1/PD-L1 blockade alone and to add ipilimumab only in case of primary or secondary progression. We present interim data from the non-small-cell lung cancer (NSCLC) cohort of the ongoing BIOLUMA trial which evaluates efficacy and safety of nivolumab and ipilimumab in lung cancer with a broad translational program to identify potential biomarkers predictive of response and/or resistance including whole exome sequencing (WES) of serial biopsies, functional analysis of peripheral T-cells and gut microbiome analyses.*

Methods: *BIOLUMA is a multicentre non-randomised phase II trial in 2nd line patients with non-squamous NSCLC. Patients are treated with nivolumab 240 mg until disease progression and subsequently with a combination therapy of nivolumab 3 mg/kg q2w and ipilimumab 1mg/kg q6w. Primary endpoint is overall response rate (ORR) after addition of ipilimumab to nivolumab treatment. Analysis of sequential tumor biopsies, blood and gut microbiome is performed at different timepoints.*

Results: *To date, 26 patients have been enrolled and 9 patients were transferred to the combination therapy after progression on nivolumab monotherapy. Drop-out rate between the treatment arms is high, mainly due to rapid disease progression and adverse events which don't allow addition of ipilimumab. ORR is available for 8 of these patients: 6 patients (75%) had PD as best response, and 1 (12.5%) each had a stable disease and partial response, respectively. The patient who achieved a PR had experienced primary tumor progression on nivolumab monotherapy before. Toxicity rate was similar to what has been reported from other trials.*

Conclusions: *In NSCLC, addition of ipilimumab to nivolumab in nivolumab refractory patients seems to be safe, but the response rate is low and the drop out between the treatment parts high. Given these data, early termination of this cohort is currently discussed. Clinical trial information: NCT03083691*

Blood-based genomic profiling of cell-free DNA (cfDNA) to identify microsatellite instability (MSI-H), tumor mutational burden (TMB) and Wnt/B-Catenin pathway alterations in patients with gastrointestinal (GI) tract cancers.

Abstract No: 3552
Poster Board Number: Poster Session (Board #44)

Background: *MSI-H cancers are responsive to immune checkpoint blockade (ICB), but nearly half of all patients experience primary or early treatment resistance. Activation of the WNT/B-Catenin pathway can lead to immune exclusion and may drive resistance to ICB.*

Methods: *12 patients had stage III (N = 1) or IV (N = 11) MSI-H GI tract (small bowl, colon, or rectal) cancers. Blood samples were obtained after (N = 5) or during (N = 5) ICB. 2 patients did not receive ICB. Blood samples from 8 patients with microsatellite stable (MSS) metastatic colorectal cancer were included as controls. The Guardant Health (Redwood City, CA) Omni 2.0 mb panel was used to analyze cfDNA. We analyzed MSI-H status, TMB, and mutations within the WNT/B-Catenin pathway, including APC, RNF43 and CTNNB1.*

Results: *Of 12 patients with MSI-H GI cancers, 1 sample failed enrichment due to hemolysis. MSI-H was not detected in 2 patients with a history of MSI-H in tissue; however these patients had a complete response to ICB at the time of blood collection. The Omni panel identified MSI-H in the remaining 9 patients with MSI-H disease in tissue. Among 8 control patients with MSS disease in tissue, MSI-H was not detected. Median TMB (mutations/Mb) was greater for MSI-H specimens (109; range 30-807) than for MSS specimens (13; range 6-24). All 8 patients with MSS GI cancers were identified to have APC mutations, and none were found to have CTNNB1 or RNF43 mutations. Of 9 evaluable MSI-H GI cancers, 2 had APC mutations alone. The remaining 7 carried RNF43 mutations (G659fs). All patients with*

RNF43 mutations were found to have disease progression while on ICB. Among these 7 patients with RNF43 mutations, 6 had additional mutations in APC or CTNNB1.

Conclusions: *Blood based genomic profiling can identify MSI-H cancers. Patients with MSI-H cancers resistant to ICB in this cohort have mutations in RNF43 as well as additional mutations in APC or CTNNB1, suggesting that co-activation of the WNT/B-Catenin pathway may be biologically important. Further study of the role of WNT/B-Catenin pathway activation in ICB resistance will be pursued using tumor tissue from this cohort.*

Epigenetic alternate promoter utilization and association with PD-L1 expression in Epstein–Barr virus positive gastric cancer.

Abstract No: e15509

Background: *We recently elicited the role of epigenetic promoter alterations as a mechanism of immune-evasion and primary resistance to immune checkpoint inhibition in gastric cancer. High prevalence of epigenetic modifications are known to occur in Epstein-Barr virus associated gastric cancer (EBVaGC). EBVaGC has high response rates to anti-PD-1 immune checkpoint inhibitors and is associated with high levels of PD-L1 expression. However, not all EBVaGC express PD-L1 and mechanisms that mediate these phenomena are unknown.*

Methods: *We performed NanoString profiling and PD-L1 immunohistochemistry (using Dako PD-L1 IHC 22C3) on tissue from gastric cancer patients undergoing primary tumor resections at Samsung Medical Centre, South Korea. NanoString panel was designed for 90 recurrent somatic alternate promoter-related genes, and immune-related genes including PD-L1. EBV status was determined using EBV-encoded RNA in situ hybridization and categorized as EBVaGC and EBV-negative. Samples in the top-quartile of alternate promoter utilization were classified as AP_{high} and the remaining AP_{low}.*

Results: *A total of 272 samples (EBVaGC n = 79; EBV-negative n = 193) were included in this study. EBVaGC had significantly higher PD-L1 expression ($p < 0.001$) compared to EBV-negative samples. AP_{high} group (n = 67) consisted of 61 EBV-negative and 6 EBVaGC samples. EBVaGC AP_{high} tumors had significantly lower PD-L1 transcript expression compared to EBVaGC AP_{low} tumors ($p = 0.011$, Wilcoxon-rank sum). Similar correlation was also found with PD-L1 IHC combined positive score (CPS)(median CPS score 1 vs 8, $p = 0.047$). There was a trend towards poorer survival for EBVaGC AP_{high} tumors (vs EBVaGC AP_{low}; HR 0.23, 95% CI: 0.046 – 1.23, $p = 0.087$). EBV-negative AP_{high} tumors also had lower PD-L1 expression (vs EBV-negative AP_{low}; $p = 0.046$, Wilcoxon-rank sum).*

Conclusions: *Increased utilization of epigenetic alternate promoter isoforms correlates with lower transcriptomic and protein expression of PD-L1 in EBVaGC. Here we describe a potential mechanism of immune-evasion to explain low immune-infiltration and PD-L1 expression that occurs in a group of EBVaGC that is traditionally considered highly immunogenic.*

Myeloid immunosuppressive state as a predictor of rapidly progressive phenotype and poor survival in advanced non-small cell lung cancer (NSCLC) patients treated with PD-1/PD-L1 inhibitors

Abstract No: e20594

Background: *Immune subpopulations within the tumor microenvironment (TME) play a central role in determining response to checkpoint inhibitors. Myeloid derived suppressor cells, a heterogeneous population of immature myeloid cells, have a predominantly immunosuppressive role by stimulating T regulatory cells. We hypothesize that elevated*

myeloid-to-lymphocyte measures in the peripheral blood predict for greater numbers of myeloid derived suppressor cells in the TME and worse outcomes.

Methods: *In advanced NSCLC patients who received immunotherapy between 2010-2018, baseline characteristics collected retrospectively included age, sex, histology, stage, smoking status, ethnicity, PD-L1 expression and tumor genotype. Pre-treatment neutrophil/lymphocyte (NLR) and monocyte/lymphocyte ratios (MLR) were log transformed and analyzed using cox and logistic regression models.*

Results: *Among 219 eligible patients, a high NLR was associated with shorter time-to-treatment-failure (HR 1.38, 95%CI 1.09-1.75, p = 0.008) and poorer OS (HR 1.62, 95%CI 1.23-2.14, p < 0.001), independent of PD-L1 levels. Disproportionate increases in NLR and MLR were highly correlated (Spearman's rho = 0.78). Further, higher NLR (p = 0.09) or MLR (p = 0.06) tended to associate with best overall response (BOR) to immunotherapy, with higher rates of progressive disease (PD) and lower rates of clinical response. A high NLR (p = 0.01) and MLR (p = 0.02) were associated with a rapidly progressive phenotype defined by PD as the BOR and duration of therapy ≤2 months. This remained significant after adjusting for confounders in a multivariate model (p = 0.03 for NLR and p = 0.03 for MLR). No associations were observed between high myeloid counts and other clinical prognostic factors such as liver metastases.*

Conclusions: *A myeloid immunosuppressive state characterized by a disproportionate increase in peripheral immune myeloid populations is significantly associated with primary refractory disease, rapidly progressive phenotype, and poorer survival. Further investigation into myeloid mediated mechanisms of resistance is warranted.*