Conclusions: There was no significant difference in survival between RAS/BRAF mutant patients treated with doublet plus anti-EGFR agent or doublet plus anti-VEGF agent. However, one of the BRAF mutant patients was also MSI-high (MSI-H) and treated with doublet plus anti-VEGF therapy; the survival time was significantly longer than that of the other BRAF mutant patients at 28 months ($p < 0.05$). According to the literature, Ras-wild patients were initially treated with doublets plus anti-EGFR agents. In our study, according to the RAS analysis, no treatment option had a statistically significant effect on survival. The overall survival of 47 KRAS mutant patients was 32 months, shorter than that of KRAS wild-type patients (P=0.66). While the patients in the RAS/BRAF wild group were observed to live longer than the other, no statistical significance was detected (36 months ± 13.7 x 30.5 months ± 10.5, p=0.728). The use of intensive chemotherapy regimens in BRAF mutant and MSI-H patients with a low incidence and poor prognosis of mCRC, the inclusion of anti-VEGF therapy in the first-line treatment, and the selection of new targeted therapies based on new genomic discoveries can increase effectiveness.

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50P KRAS mutation, the molecular landscape of lung adenocarcinoma in the Portuguese population

C.F.P. Trabulo[1], J. Gramaça[2], N.D. Girão[3], J.L. Mendes[4], R. Gameiro Dos Santos[2], J.C.N. Gonçalves[2], I.C. Gomes Fernandes[5], S. Alfarroba[6], P. Winckler[7], I.M.C. Guerreiro[8], I.M. Matos Pina[9], R.J.M. Da Luz[4]

[1]Departamento Oncologia Medica, Hospital Nossa Senhora do Rosário (Centro Hospitalar Barreiro Montijo, EPE), Barreiro, Portugal; [2]Medical Oncology Department, Hospital Nossa Senhora do Rosário (Centro Hospitalar Barreiro Montijo, EPE), Barreiro, Portugal; [3]Pathologic Anatomy, Centro Hospitalar de Lisboa Central (CHLC)-Hospital de Santo António dos Capuchos (HSAC), Lisbon, Portugal; [4]Medical Oncology Department, Centro Hospitalar de Lisboa Central (CHLC)-Hospital de Santo António dos Capuchos (HSAC), Lisbon, Portugal; [5]Dept. Oncologia Médica, Hospital Nossa Senhora do Rosário (Centro Hospitalar Barreiro Montijo, EPE), Barreiro, Portugal; [6]Pneumology, Centro Hospitalar de Lisboa Central (CHLC)-Hospital de Santo António dos Capuchos (HSAC), Lisbon, Portugal; [7]Medical Oncology, Centro Hospitalar de Lisboa Central (CHLC) - Hospital Sao Jose (HSJ), Lisbon, Portugal; [8]Medical Oncology, Centro Hospitalar de Lisboa Central (CHLC)-Hospital de Santo António dos Capuchos (HSAC), Lisbon, Portugal; [9]Medical Oncology, Hospital Nossa Senhora do Rosário (Centro Hospitalar Barreiro Montijo, EPE), Barreiro, Portugal

Background: Activating mutations in Kirsten rat sarcoma viral oncogene homologue (KRAS) are detected in over 1/3 of non—small-cell lung cancer (NSCLC) subtype, representing the most prevalent genomic driver event. Mostly located in codons 12 and 13, the most frequent is the p.Gly12Cys (c.34G.T) (G12C), representing about 20-25% of KRAS drive mutations in NSCLs, but remains scarce. The impact of them on prognosis is currently subject to debate, as is their impact on the response to chemotherapy and EGFR tyrosine kinase inhibitors. Our goal was to stratify our population, reporting the KRAS mutation frequency in a series of Portuguese NSCLC cases, in order to observe the incidence and impact of change of practice.

Methods: Retrospective study included NSCLC samples submitted for KRAS testing at one Portuguese center in Lisbon, between 1/1/2027 and 31/12/2021. Data cut-off was 1/9/2022. KRAS mutational status was evaluated from tumor biopsy using a new generation sequencing technique on DNA obtained to detect the most common mutations of the KRAS gene. The Oncomine™ Focus Assay panel was used in the IPATIMUP laboratory. Data was obtained from pts' clinical files and analyzed with SPSSv26.0.

Results: 101 pts with NSCLC were included in our analysis, median age of 66 years (44-87), 70% male, with good performance status (70% ECOG PS 0-1). Concerning tobacco consumption, 80% were active smokers. Regarding tumor characteristics, all cases were adenocarcinomas, with 46% N1 at diagnosis and 56% of pts M1 ad initium. 10% were relapses. PDL1 status was positive in 40% of pts, and unknown in 2%. Mutation KRAS G12C was the status most frequent, identified in 36,6% of the population including c.34G>T p.Gly12Cys (36 pts) and c.35G>A p.Gly12Cys (1 pt). Followed by c.35G>T p.Gly12Val in 21,7% (22pts), c.35G>A p.Gly12Asp in 13,8% (14pts) and c.35G>C p.Gly12Ala in 6,93% (7). 1,98% (2pts) had 2 KRAS different mutation observed c.34G>T p.Gly12Cys+c.37G>A p.Gly13Ser and c.35G>T p.Gly12Val+c427G>A p.Glu143Lys where the combinations.

Conclusions: Our representative population presented a slight raise in the frequency of the G12C mutation, showing that approximately 36% of Portuguese pts with NSCLC harbor the G12C variant, thus potentially responsive to the new anti-KRAS agents.

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51P Toxicity profile in early clinical trials with fibroblast growth factor receptor (FGFR) inhibitors (FGFRi): 10-years experience of a drug development unit

K.I. Rojas Laimito[1], M. Vieito Villar[1], B. Fullana Grimalt[2], R. Berché[1], C. Hierro Carbo[3], O. Saavedra Santa Gadea[1], I. Braña[1], G. Alonso Casal[1], V. Galvao de Aguiar[1], M.J. Lostes Bardaji[1], M. Oliveira[1], H. Verdaguer[1], R. Morales Barrera[1], C. Garcia Duran[1], E. Zamora[1], J. Carles Galceran[1], T. Macarulla[1], J. Tabernero[1], E. Garralda Cabanas[1]

[1]Medical Oncology Department, Vall d'Hebron Institute of Oncology (VHIO)-Cellex Center, Barcelona, Spain; [2]Medical Oncology Department, Hospital Mutua de Terrassa, Terrassa, Spain; [3]Medical Oncology Department-Early Drug Development, GI Tumours and Melanoma Group, ICO - Institut Català d'Oncologia Badalona (Hospital Universitario Germans Trias i Pujol), Badalona, Spain

Background: FGFRi have been in clinical development for over 10 years, with recent approvals in patients (pts) with cholangiocarcinoma and urothelial tumors with FGFR alterations. Management of toxicity is still challenging with 10-20% of pts experiencing at least one dose reduction, especially hyperphosphatemia. The purpose of our work was to evaluate biomarker inclusion and toxicity profile of pts treated with FGFRi.

Methods: FGFRi-naïve pts included in early clinical trials with FGFRi in VHIO's Early Drug Development Unit were included in the analysis. Adverse events were evaluated using CTCAE 4.03.

Results: A total of 72 eligible pts were treated between 2012-2022 with 6 different FGFRi. Median age was 56y, 73% female, main tumor types were breast cancer(37%) and colorectal cancer(14%). Most pts(85%) were included based on a biomarker (47% FGFR amplification, 4% FGFR mutation, 3% FGFR fusion and 22% FGFR overexpression/ligand overexpression). Most common alterations occurred in FGFR1(40%), FGFR2(19%), FGFR3(7%), FGFR4(1.7%) and 2.7% with two or more isoforms. Pts treated with panFGFRi (1-4) (76%) had statistically higher % of G2-3 toxicity than pts treated with FGFR1-2-3i(56%)($p<0.01$). The commonest ≥G2 toxicity in both groups was hyperphosphatemia (7% G3 and 43% G2), fatigue (17%;G2-3), skin and nail changes (10%;G2-3), ocular/corneal toxicity(8%;G2-3) and diarrhea(6%;G2-3). 40% of pts experiencing G2-3 hyperphosphatemia needed at least 1 dose reduction, and 51.5% had to interrupt treatment. The % of G3 toxicity was statistically superior in pts treated at doses >RP2D than at doses ≤RP2D ($p<0.01$). Among 16 pts that received doses >RP2D, 68% exhibited G3 toxicity, 75% underwent a dose interruption, and 50% needed dose reduction. Among 56 pts treated at ≤RP2D doses 20% exhibited G3 toxicity, 25% had at least 1 dose interruption and 23% needed dose reduction.

Conclusions: Toxicity management with FGFRi remains challenging with a high proportion of pts requiring dose reductions or interruptions even at the RP2D. FGFRi that spare FGFR4 were associated with lower G3 toxicity. The impact of hyperphosphatemia highlights the potential role of more specific inhibitors.

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52P Antitumor efficacy of polypyrrole-polyethyleneimine nanocomplex to target B-cell lymphoma

T.T. Nguyen[1], E-Y. Chuang[2], P-C. Tseng[3], M-K. Jhan[3], C-L. Chen[4], C-F. Lin[5]

[1]International Ph.D Program in Medicine, College of Medicine, TMU - Taipei Medical University, Taipei City, Taiwan; [2]College of Biomedical Engineering, TMU - Taipei Medical University, Taipei City, Taiwan; [3]Department of Microbiology and Immunology, School of Medicine, College of Medicine, TMU - Taipei Medical University, Taipei City, Taiwan; [4]School of Respiratory Therapy, College of Medicine, TMU - Taipei Medical University, Taipei City, Taiwan; [5]Core Laboratory of Immune Monitoring, Office of Research & Development, TMU - Taipei Medical University, Taipei City, Taiwan

Background: Traditional administration of standard lymphoma treatment can lead to poor pharmacokinetics and poor biological distribution. Recently, the nanomaterial system shows tremendous potential for therapy with a high drug-loading efficiency, good biosafety, improved bioavailability, and active targeting. This study aimed to report novel and intelligent therapeutics with particular and targeted B-cell killing in aggressive B-cell lymphoma based on nanotechnology.

Methods: A synthetic polypyrrole-polyethyleneimine nanocomplex (PPY-PEI NC) was constructed and characterized to provide its interaction with specific target B-cell lymphoma. We further investigated cell apoptosis of PPY-PEI NC in Raji cells in vitro and Raji xenograft mice models and the loss of mitochondrial transmembrane potential by Propidium iodide, Annexin V, and Rhodamine 123 staining, respectively. In

addition, protein analysis identified activation of the apoptotic signaling pathway (GSK-3β, Bax, Bcl-2, Mcl-1, PARP, caspase 3) and were examined to clarify their roles.

Results: An earlier engulfment of PPY-PEI NC rapidly targeted B-cell lymphoma in clathrin-dependent endocytosis. PPY-PEI NC effectively caused B-cell lymphoma inhibition in an intrinsic pathway of apoptosis in vitro. PPY-PEI NC decreased anti-apoptotic Bcl-2 family proteins and caused classical caspase substrate activation. PPY-PEI NC induced loss of MTP while stabilizing MTP and inhibiting caspase protected B-cells from mitochondrial apoptosis. In addition, PPY-PEI NC-activated GSK-3β and inhibiting GSK-3β prevented MTP loss and mitochondrial apoptosis. In Raji subcutaneous xenograft mice model, PPY-PEI NC not only significantly inhibited the effect on tumor growth but also demonstrated no noticeable adverse effects on the treated nude mice.

Conclusions: The PPY-PEI nanocomplex strongly showed in vitro and in vivo antitumor activities. These results suggest that PPY-PEI NC has a promising application prospect as an innovative, safe and effective anti-lymphoma agent.

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53P Characterization of the non-ATP competitive PI3Kdelta inhibitor IOA-244 in lymphoma models: From single agent to combination screen and clinical investigation

F. Bertoni[1], C. Tarantelli[1], F. Spriano[1], L. Cascione[1], E. Civanelli[1], E. Cannas[1], A.A. Mensah[1], A.J. Arribas[1], S. Napoli[1], A. Rinaldi[2], A. Stathis[3], K. Niewola[4], G. Di Conza[4], M. Lahn[5], A. Santoro[6], C. Carlo-Stella[6]

[1]Lymphoma Genomics, Institute of Oncology Research, Faculty of Biomedical Sciences, USI, Bellinzona, Switzerland; [2]Genomics Facility, Institute of Oncology Research, Faculty of Biomedical Sciences, USI, Bellinzona, Switzerland; [3]Medical Oncology, EOC - Ospedale Regionale Bellinzona e Valli - Istituto Oncologico della Svizzera Italiana (IOSI), Bellinzona, Switzerland; [4]Translational Research Department, IOnctura SA, Geneva, Switzerland; [5]Oncology Department, IOnctura SA, Geneva, Switzerland; [6]Oncology and Haematology, Humanitas University and IRCSS Humanitas Research Hospital, Rozzano, Italy

Background: IOA-244 is a highly selective PI3Kδ inhibitor with a differentiated chemical mechanism of action from other PI3K inhibitors. IOA-244 is currently being investigated in patients with solid tumors and lymphoma (NCT04328844). Here, we present preclinical and initial clinical data in lymphomas.

Methods: Anti-proliferative activity by MTT assay at 72h. Transcriptome analysis by total and targeted RNA-Seq on Illumina platform. Follicular lymphoma patients (pts) were treated at 20 mg and 80 mg QD continuous dosing and assessed for safety.

Results: IOA-244 showed moderate dose-dependent anti-proliferative activity, measured as area under the curve, across 66 human B and T cell lymphoma models, with IC50s $<$ 10 mM in 18 cell lines. The activity correlated with PI3Kδ expression as measured by total RNA-Seq (R^2=0.18, P=0.0009; 59 B and T cell lymphomas) or by HTG EdgeSeq Oncology Biomarker panel (R^2=0.13, P=0.028; 36 B cell lymphomas). In MCL SP53 cells, IOA-244 (5µM; 24, 48, 72h) downregulated BCR, MYD88, NF-κB, MTOR and NOTCH signaling and upregulated cell cycle arrest genes (adj.P$<10^{-10}$). Changes overlapped with signatures obtained with other PI3K and BTK inhibitors (adj.P $<10^{-10}$). IOA-244 was then combined with 474 compounds (each given at 5µM) in two cell lines (MCL, SP-53; cutaneous T cell lymphoma, HH) and increased anti-proliferative activity was observed for combinations with inhibitors of other kinases, chemotherapy as well as metabolic and nuclear targets. NHL-FL pts treated with 20mg QD (4/4; 2 female and 2 males) and 80mg QD daily (4/4; 3 female and 1 male) had no DLT. Transient platelet reduction (G3) (N=1), AST/ALT elevation (G2) and Neutropenia (G3) (N=1) were observed in 3/8 pts, which returned to baseline without dose modifications.

Conclusions: Single-agent IOA-244 has moderate activity in vitro in lymphoma, correlated with PI3Kδ expression. Given its favorable monotherapy safety profile, IOA-244 may be used in combination with drugs identified in the present pharmacological screen.

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54P Inhibition of ATM vs ATR in combination with radiotherapy affects cellular toxicity and expression of immune checkpoint molecules differently in HNSCC

T. Jost

Translational Radiobiology, Universitätsklinikum Erlangen - Strahlenklinik, Erlangen, Germany

Background: Treatment of human papilloma virus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) is still challenging, regarding its radio resistance and sparing of healthy surrounding tissue when applying radiotherapy (RT). Small molecules kinase inhibitors (smKI), targeting components of the DNA damage repair (DDR) pathway such as ATM and ATR, in combination with RT are promising to overcome these challenges. We hypothesized that inhibition von ATM vs. ATR concomitant to RT increases cellular toxicity and leads to diverse immune surface marker expression on HNSCC cells.

Methods: The effect of smKIs AZD0156 (ATMi) and VE-822 (ATRi) in combination with RT on HPV-pos. and HPV-neg. human HNSCC was analyzed. Colony formation (Co, smKI, RT, smKI+RT), immunogenic and non-immunogenic cell death (necrosis, apoptosis) were measured using Annexin/PI staining (flow cytometry). Immune-stimulating (ICOS-L, OX40-L, TNFSFR9, CD70) and immune-suppressive (PD-L1, PD-L2, HVEM) surface-marker were measured after 48h of treatment of HNSCC cells (HSC4, Cal33, UM-SCC-47, UD-SCC-2).

Results: Colony forming was significantly inhibited by smKI+RT in cancer cells, while sparing toxicity in healthy fibroblasts. Effects were more prominent in HPV-pos. compared to HPV-neg. HNSCC cells. Furthermore, ATRi demonstrated stronger cellular toxicity by inducing cell death at 0.1 µM compared to 1 µM ATMi. In contrast, ATMi only in combination with RT led to significant increase of apoptosis. After treatment with ATRi, upregulation of immune-suppressive checkpoint molecules on the cell surfaces was observed predominantly, but less influence on immune-stimulatory surface marker was found. Of note, ATMi treatment w/o RT led to even increased expression of both suppressive and stimulatory immune checkpoint molecules.

Conclusions: Inhibition of ATR shows greater toxicity, but ATM inhibition has stronger influence on the expression of immune checkpoint molecules. Taken together, combined treatment has the potential to be a therapeutic option that could improve tumor control without increasing toxicity in HNSCC.

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55P The SOS inhibitor BAY293 contributes to amplified vertical inhibition of the MAP kinase pathway in human melanoma cells

M. Hohenegger, R. Mirzahi, N. Szorger, M. Ambrosio, G. Hamilton

Pharmacology, Medical University Vienna, Vienna, Austria

Background: The driver mutation $Braf^{V600E}$ in human melanoma has been successfully targeted by vemuarfenib and successors. Since then vertical inhibition of the mitogen-activated protein (MAP)-kinase pathway by dual inhibition of B-Raf and MAP-kinase kinase (MEK)1/2 has been introduced in the therapy of advanced melanoma. Here we investigated in vitro inhibition of the guanine nucleotide exchange factor Son of Sevenless (SOS) by BAY293 in order to identify possible synergism with Braf or/and MEK1/2 inhibitors in human melanoma cell lines.

Methods: The 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) assays and wound healing assays were used to monitor viability, proliferation and migration in human melanoma cell lines from the early (WM35, WM278, and WM793b) and the metastatic growth phase (A375 and 518a2), all harbouring the driver mutation $Braf^{V600E}$, but wild type NRAS. Apoptosis and kinase signalling were investigated by caspase assays and Western blot analyses.

Results: The SOS inhibitor BAY293 inhibited basal ERK1/2 phosphorylation in a dose dependent manner in human metastatic A375 and 518a2 melanoma cells. Importantly, viability was not affected in these cells following BAY293 exposure times below 24h. Longer incubation times enhanced cell death and reduced gap closure in a wound healing assay. Co-application of BAY293 with inhibitors of B-Raf and/or MEK1/2 augmented these effects significantly. Concomitantly, ERK1/2 phosphorylation was significantly reduced by these drug combinations. Similar effects were seen in early stage melanoma cells so that no stage dependent differences were observed.