negative and high KI-67. v Clinical (PR):43 patients majority of them had topo IIA overexpression. fig (9–10) 2-Non responders: 4(8%) patients all had negative (TOPOII/HER2), low KI-67 and 2 had hormonal receptor positive and another 2 had hormonal receptor negative.

Conclusions: Our data support a correlation between topoisomerase II-α expression in locally advanced breast cancer patients and improved clinical benefit with neoadjuvant anthracyclines based therapy.

P03.02

MiRNA set dysregulation in breast cancer cells can contribute to both primary and acquired resistance to immune checkpoint blockade

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Background: One of the main immune escape mechanisms used by tumors is the exploitation of immune checkpoints – receptors on surface of immune cells, which, after binding their ligands, can suppress immune response. Consequently, immune checkpoint blockade is considered as promising approach for cancer treatment. However, currently available anti-CTLA-4 and anti-PD-1/anti-PD-L1 drugs have shown limited efficiency against many common cancer types (e.g. breast cancer). This research aims to identify in what way the shifts in miRNA expression pattern can contribute to the resistance of breast cancer cells to the immune checkpoint inhibitors and to the weakening of their efficiency during treatment.

Materials and methods: miRNA targets within gene transcripts were predicted *in silico* using the TargetScan software.

Results: Targets of miRNAs miR-15/16, miR-34, miR-140, miR-141/200, miR-145, miR-148/152, miR-199, miR-200, miR-202, miR-214, miR-302, miR-320 and miR-520 were found in *PDL1* (*CD274*) gene transcript. Down-regulation of these miRNAs is characteristic to the breast cancer cells and, therefore, can allow reactivation and hyperexpression of gene encoding PD-1 ligand. Moreover, multiple targets of down-regulated miRNAs let-7, miR-1/206, miR-15/16, miR-22, miR-26, miR-29, miR-31, miR-34, miR-124, miR-125, miR-128, miR-129, miR-133a/b, miR-138, miR-140, miR-141/200, miR-143, miR-145, miR-148/152, miR-149, miR-194, miR-199, miR-204, miR-205, miR-214, miR-218, miR-302, miR-326, miR-449, miR-506, miR-520 and miR-655 were revealed in transcripts of genes encoding other immune checkpoint ligands – PDL2 (PDCD1LG2), B7-H3 (CD276), B7-H4 (VTCN1), HHLA2, galectin 9 (LGALS9), HVEM, PVR (Necl-5), PVRL2 (Nectin 2) and CD200.

Conclusions: Down-regulation of tumor-suppressive miRNAs can be responsible for overexpression of genes encoding the key immune checkpoint ligands. As a result, breast cancer cells can escape immune detection and ensure immune privilege via anergy and apoptosis of helper and cytotoxic T cells involved in antitumor immunity. Initial overexpression of the immune checkpoint ligands predetermines primary resistance to their blockade. Moreover, this resistance is multiple, because the shifts in miRNAome can cause hyperexpression of many immune checkpoint ligands at one time. Inhibition of one of the immune checkpoint axes may be easily overcome by the most profound down-regulation of the miRNA expression that is well-known phenomenon during the tumor progression and drug administration. Probably, this explains the long-term failure of immunotherapy.

P04. THERAPEUTIC MODULATION OF IMMUNE CHECKPOINTS

P04.01

Complete clinical remission of stage IV breast cancer with liver, lung, bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia and metronomic low-dose chemotherapy

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Advanced stage inoperable breast cancer has a poor prognosis and patients rarely enjoy durable complete response to treatment; progression free survival often is limited.

Materials and methods: We previously reported complete remission of far advanced lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016 and complete remission of inoperable esophageal Cancer ITOC4 (Prague) 2017; here we report a similar successful treatment. **FD: 09/2014** grade 3 invasive ductal adenocarcinoma of the left breast, ER+++, PR neg., Her2-neu neg.; neoadjuvant chemo radiation ACT and initial resection (02/2015), followed by aromatase inhibitor Arimidex. **07/2016** New Onset of very large bone metastasis left scull, infiltrating the dura mater; the patient underwent initial radiation; also new onset of previously not diagnosed pulmonary metastasis. **08/2016** Patient was started on Ibrance and aromatase inhibitor Letrozol: PD. **09/2016** Palliative Radiation of the cervical spine and T2. **10/2016** Restaging with CT of the thorax and abdomen demonstrated stable lung metastasis but increasing pleural nodules; first onset of disseminated liver metastasis with index lesions between 2.1, 3.1 and 1.3 cm; also new lytic osseous lesions; also acute sigmoid colonic diverticulitis. Further restating of the skull with MRI indicated massive PD of the previously radiated left sphenoid lesion as well as PD of further lesions in the skull base and mandible. Bone scan indicates PD of all innumerous bony lesions. The patient initially presented with far advanced stage IV breast cancer pT3 pN2 M1 (bone, liver, lung) with Karnofsky index of 50% with serious neurological deficits from the large progressive skull metastasis which had started expanding and infiltrating the Dura Mater in spite of previous radiation. She underwent immunotherapy as described previously combining low-dose checkpoint inhibitor ipilimumab-nivolumab in combination with low dose interleukin (IL-2) treatment parallel to local regional and whole-body hyperthermia. Additionally low-dose metronomic chemotherapy was performed with Topotecan (0.5–1.0mg/m^2) and Capecitabine 1000mg bid, 2w on/1w off following chemo sensitivity testing.

Results: PET CT in 08/2017 as well as comprehensive restaging clinically and laboratory markers in 10/2017 demonstrated complete remission.

Conclusion: The unexpected remission of far advanced metastatic breast cancer following complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemotherapy warrants further clinical studies.