Rationale for a generic targeted therapy multi-drug regimen for NSCLC stage IIIB/IV patients without treatment options

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Common Principles of HIV-Infection and Cancer

HIV and cancer follow the principles of the Darwinian evolutionary system. Primary evolutionary drivers are the replication rate in HIV infections and the genetic heterogeneity in tumor development. The immune system and mono-therapies are unable to control the diseases because of similar mechanisms of escape and resistance. Despite these common principles only for HIV a breakthrough treatment is available (HAART). This therapy is successful because it is based on (i) high selectivity and (ii) multiple inhibition of disease-specific targets (Fig.1).

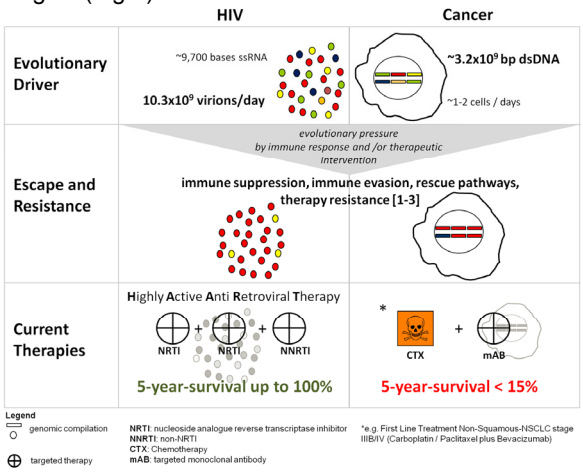

Figure 1: Comparison of HIV-infections and cancer: primary evolutionary drivers lead to similar mechanisms of escape mutants and therapy resistance by selectional pressure. Current therapies are effective for HIV- but not for cancer treatment (e.g. NSCLC IIIB/IV).

Implications for NSCLC Target Combination

Transferring the treatment concept of (i) high selectivity and (ii) multiple inhibition of disease-specific targets to NSCLC four signaling pathways appear to be suitable targets against which drugs are already marketed in different indications: VEGF/VEGFR2, EGF/EGFR, SDF1/CXCR4, and COX2/PGE2 are expressed in squamous and non-squamous NSCLC (Fig.1A) and are functional connected (Fig.1B).

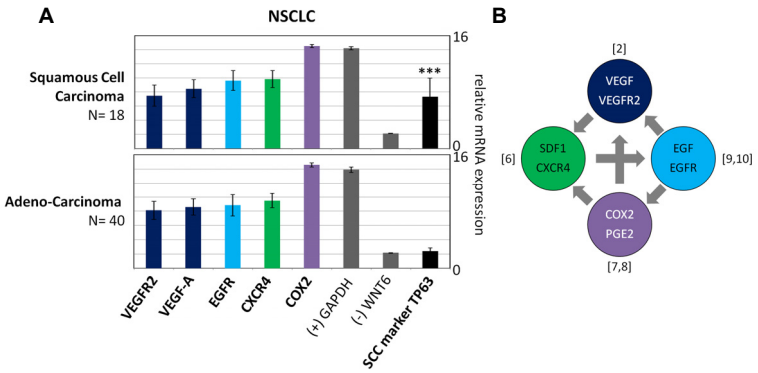

Figure 2: Expression and functional connection of targets in NSCLC. **A** mRNA expression of respective targets in 18 patients with squamous- and 40 patients with non-squamous NSCLC assessed by GEO Profiles database, GDS3627 [4,5]. Controls: GAPDH (positive), WNT6 (negative), TP63 as a specific marker for squamous NSCLC (***p< 0.0001 by unpaired student´s t-test; standard deviations shown by error bars). **B** Functional connection of pathways active in NSCLC identified from literature findings (may not be exhaustive).

The combined use of inhibitors against these targets such as Sunitinib, Plerixafor, Gefitinib and Etoricoxib blocks multiple receptor signaling pathways that are connected downstream and involved in tumor development and treatment resistance (Ras/Raf, PI3K/Akt, Jak/Stat, MAPK, PKC). Therefore this treatment may overcome covert resistance mechanisms to targeted therapy drugs seen for ineffective mono-therapies or in combination with chemotherapeutics (Fig.3).

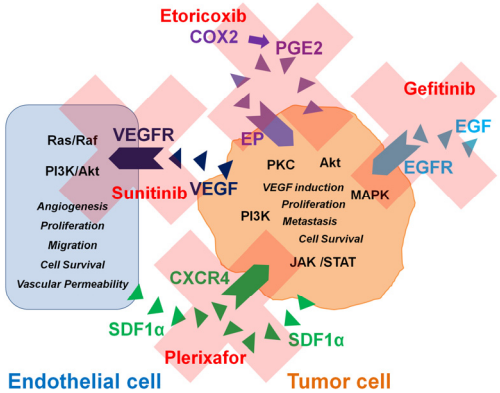

Figure 3: Overview of targeted therapy multi-drug regimen. Targeted therapy drugs such as Sunitinib, Gefitinib, Etoricoxib and Plerixafor are clinically evaluated and FDA approved. (PGE2: prostaglandin E2).

Drug Properties and Safety

The herein described drugs are approved for different indications, readily available and their clinical profiles are well known. None of them is a strong P450-Cyp inducer or inhibitor (Fig.4).

Drug	MoA	Label	IC50 in Cell Based Assays	Treatment Doses	Most Common Side Effects	P450-CYP Metabolism
Sunitinb (Sutent)	small molecule RTKi against VEGFR1-3 and others	GIST, mRCC, pNET	~ 0.01 µM (VEGFR2)	≤ 50 mg/ day	in >20% of patients: loss of appetite, dysgeusia hypertension, asthenia, gastrointestinal disorders, discoloration of the skin	no inducer or inhibitor (interaction with CYP3A4 metabolism)
Gefitinib (Iressa)	small molecule EGFR-TKI	NSCLC with EGFR-activating mutations	0.01-8.8 µM	250 mg/day	in >20% of patients: diarrhea, skin reactions	no inducer or inhibitor (interaction with CYP3A4 and CYP2D6 metabolism)
Plerixafor (Mozobil)	small molecule CXCR4 antagonist	mobilization of hemapoetic stem cells prior transplantation (Lymphoma, MM)	0.651 µM (inhibition of SDF-1 ligand binding)	0.24 mg/ kg /day (max. 40 mg/day)	≥ 1/10 diarrhea, nausea, skin reactions at infusion or injection sites	no inducer or inhibitor
Etoricoxib (Arcoxia)	small molecule COX-2 inhibitor	pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, Gout	1.1 µM (human whole blood assays in vitro)	30 -120 mg/day	≥ 1/10 abdominal pain	no inducer or inhibitor (no influence on hepatic CYP3A4)

Figure 4: Properties, indications, dosing, safety and metabolism of targeted therapy drugs.

Concluding Rationale

- The proposed drug combination is selective for multiple disease-specific targets (similar to principles of HAART)
- Respective drug targets are expressed in NSCLC
- May overcome non-responsiveness and resistance by breaking covert mechanisms mediated by rescue pathways
- Drug profiles seem to allow combined use for NSCLC patients without treatment options in an off-label setting or in a clinical trial

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