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Review

Inhibition of Akt and other AGC kinases: A target for clinical cancer therapy?

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ABSTRACT

AGC kinases have been identified to contribute to cancer development and progression. Currently, most AGC inhibitors in clinical development are Akt inhibitors such as MK-2206 or GDC-0068, which are known to promote cell growth arrest and to sensitize cancer cells to radiotherapy. Response rates in clinical trials with single agent Akt inhibitors are typically low. The observed adverse events are within the expected limits for compounds inhibiting the PI3K-mTOR axis. Preclinical and early clinical data for combination therapies are accumulating. Based on these data, several Akt inhibitors are about to enter phase 3 trials. Besides drugs that target Akt, p70S6K inhibitors have entered clinical development. Again, the response rates were rather low. In addition, relevant toxicities were identified, including a risk for coagulopathies with these compounds. Multi-AGC kinase inhibitors are also in early clinical development but the data is not sufficient yet to draw conclusions regarding their efficacy and side-effect profile. PKC inhibitors have been tested in the phase 3 setting but were found to lack efficacy. More trials with isoform-specific PKC inhibitors are expected. Taken together, therapies with AGC kinase inhibitors as single agents are unlikely to meet success. However, combination therapies and a precise stratification of patients according to the activation of signaling axes may increase the probability to see relevant efficacy with these compounds. The emergence of onco-immunotherapies holds some new challenges for these agents.

1. The rationale for AGC kinase-directed therapy in clinical cancer care

AGC kinases are a subgroup of Ser/Thr protein kinases. Based on the structure of their catalytic kinase domain, kinases are related to cAMP-dependent protein kinase 1 (PKA), cGMP-dependent protein kinase (PKG) and protein kinase C (PKC), building the acronym AGC [1]. The AGC family contains 60 of the 518 humain protein kinases and 42 possess functional domains other than the kinase core, which are mostly involved in regulating kinase activity and localization [2].

Recent studies have identified around 1100 cancer drivers, both oncogenes and tumor suppressor genes. Roughly 10% of those cancer drivers correspond to protein kinases, making this group of enzymes a prime target for cancer therapy. Although some of these kinases are mutated at high frequency (> 10% in a given cancer entity), the mutation rate of most cancer drivers is low. The most common genetic aberration of protein kinases are somatic mutations, followed by copy number aberrations and gene fusions. Of the eight main classes of kinases, by far the most frequent genomic aberrations have been identified in tyrosine kinases (TK), followed by tyrosine-like kinases (TLK) and homologues of yeast sterile 7 (STE).

Cancer driving genomic alterations of AGC kinases are less frequent. However, a number of AGC kinases have been identified to contribute to cancer development and progression, including Akt 1, Akt 3, PRKCI, PRKCZ, RPS6KB1, and SGK1 [3]. The role of those kinases in tumorigenesis and cancer progression depends on the context in which a mutation occurs. In cervical cancer for example, tumor cells only become dependent from SGK2 upon loss of p53 [4]. This has implications for the development of clinical biomarkers.

2. Predictive biomarkers in oncology

True predictive markers are able to estimate the likelihood of clinical benefit of a specific therapy in an individual. Predictive markers can be genetic by nature but markers based on RNA arrays or protein expression have been validated in the clinic as well. Examples for predictive markers in oncology include Her2 amplification as well as the expression of the estrogen and progesterone receptor in breast

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Table 1
Recent clinical trials with AGC kinase inhibitors. The most advanced clinical studies were selected.

Target	Subunit	Compound	Name	Company	Mechanism	Phase	Indication	Combination	Comparator	NCT	Start	Status
AKT	pan-AKT	MK-2206	–	Merck	Allosteric	Phase 2	Platinum-Resistant Ovarian, Fallopian Tube, or Peritoneal Cancer	–	–	NCT01283035	2011	Completed
						Phase 2	Metastatic Neuroendocrine Tumors	–	–	NCT01169649	2010	Completed
						Phase 2	Relapsed Acute Myelogenous Leukemia	–	–	NCT01253447	2010	Completed
						Phase 2	Relapsed Lymphoma	–	–	NCT01258998	2010	Completed
						Phase 2	Relapsed Diffuse Large-B Cell Lymphoma	–	–	NCT01481129	2011	Completed
						Phase 2	Advanced Gastric and Gastroesophageal Junction Cancer	–	–	NCT01260701	2011	Completed
						Phase 2	Refractory Biliary Cancers	–	–	NCT01425879	2011	Completed
						Phase 2	Non-small Cell Lung Cancer Progredient After Erlotinib Therapy	Erlotinib	–	NCT01294306	2011	Completed
						Phase 2	Metastatic Pancreatic Cancer After Prior Chemotherapy	AZD6244	mFOLFOX	NCT01658943	2012	Completed
						Phase 2	Recurrent and Metastatic Nasopharyngeal Carcinoma	–	–	NCT01370070	2011	Ongoing
						Phase 2	Progressive, Recurrent/ Metastatic Adenoid Cystic Carcinoma	–	–	NCT01604772	2012	Ongoing
						Phase 2	Recurrent or Advanced Endometrial Cancer	–	PIK3CA Mutation Stratified	NCT01307631	2011	Ongoing
						Phase 2	Previously Treated Metastatic Colorectal Cancer Patients Enriched for PTEN Loss and PIK3CA Mutation	–	–	NCT01802320	2013	Ongoing
						Phase 2	Patients With Advanced Breast Cancer Who Have Tumors With a PIK3CA Mutation, or an AKT Mutation, and/or PTEN Loss/ PTEN Mutation	–	–	NCT01277757	2011	Ongoing
						Phase 2	Refractory Renal Cell Carcinoma	–	Everolimus	NCT01239342	2011	Ongoing
						Phase 2	Clinical Stage 2 or 3 PIK3CA Mutant Estrogen Receptor Positive and HER2 Negative Invasive Breast Cancer	Anastrozole if Postmenopausal, Anastrozole and Goserelin if Premenopausal	–	NCT01776008	2013	Ongoing
						Phase 2	Prostate with Rising PSA at High-Risk of Progression After Primary Therapy	Bicalutamide	–	NCT01251861	2010	Ongoing
		GDC-0068	Ipatasertib	Genentec	Allosteric	Phase 2	Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	Fluoropyrimidine Plus Oxaliplatin	–	NCT01896531	2013	Ongoing
						Phase 2	Paclitaxel	Metastatic Triple-Negative Breast Cancer	–	NCT02162719	2014	Ongoing
						Phase 2b	Glioblastoma/Gliosarcoma	–	MK–3475 (Pembrolizumab)	NCT02430363	2015	Recruiting
						Phase 2	Early Stage Triple Negative Breast Cancer	Paclitaxel	–	NCT02301988	2015	Recruiting
		GSK2110183	Afuretesib	GSK	ATP-	Phase 2	Relapsed and Refractory Chronic	GSK2110183	–	NCT01532700	2012	Ongoing

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