Targeting the PI3K/AKT Pathway for the Treatment of Gastric Cancer

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Abstract

Gastric Cancer (GC) is the fourth most common malignancy and the second leading cause of cancer deaths, accounting for 10% of global cancer mortalities. Despite the progress made in recent years, the prognosis for patients with advanced-stage GC remains poor. In the metastatic setting, chemotherapy is the primary choice for palliative therapy and results in Objective Response Rates (ORRs) of only 20-40% and median Overall Survivals (OSs) of 8–10 months. Emerging evidence suggests that the aberrant activation of phosphatidylinositol 3-kinase (PI3K)/AKT signaling is one of the most common molecular events involved in the resistance to current systemic therapies for GC.A number of small molecule inhibitors targeting the PI3K/AKT pathway are currently under clinical evaluation for the treatment of various malignancies, including GC. In this paper, we review the current clinical practice and discuss the potential use of inhibitors targeting the PI3K/AKT pathway, either alone or in combination with current therapies for the treatment of advanced GC.

Introduction

Gastric Cancer (GC) is one of the most common malignancies and the second leading cause of cancer deaths [1].The estimated global incidence and mortality for GC were 990,000 and 737,000, respectively, in 2011, which accounted for approximately 8% of total cancer cases and 10% of annual cancer deaths worldwide [2,3].Geographically, GC is more prevalent in developing countries, especially those in Eastern Asia, Central and Eastern Europe, and South America, than in the rest of world. The current treatments for GC include surgery, chemotherapy,radiotherapy, and targeted therapy against the HER-2-positive segment n GC [4]. Although the prognosis for GC has been improved significantly in certain nations, such as Japan and Korea, with national early screening, the five-year survival rate remains poor. The genome-wide profiling of genetic aberrations in primary tumor samples from GC patients revealed a number of potential targets, such as FGFR, Met, and PI3K, for the development of next-generation therapies for GC [5].Selective inhibitors of these potential targets are being developed at various clinical stages for the treatment of cancers, including GC. In this paper, we review the current clinical practice for the systemic treatment of advanced GC, the role of the activation of the PI3K/AKT pathway, and the potential of targeting the PI3K/AKT pathway for treatment of advanced GC.

Current Treatments for Advanced GC

The treatment of GC requires multidisciplinary approaches that incorporate surgery, chemotherapy, targeted therapy, and radiotherapy. For patients with operable tumors, surgery and chemotherapy remain the primary curative treatments. Although the 5-year survival rate has been improved in certain nations, such as

Japan (57%) and Korea (64.3%), it still remains poor globally, ranging between 20 and 25% [6,7].

In the United States, patients with GC are often diagnosed at advanced stages due to lack of routine endoscopic screening. Overall, 5-year survival rates are less than 10% [8].The implementation of additional combined strategies, including neoadjuvant and adjuvant therapy (pre- or postoperative chemo/radiotherapy or perioperative chemotherapy), led to 5-year survival rates of only 30-35% and pathologically Complete Responses (pCRs) in no more than 20-30% of patients [8-10].In metastatic GC, chemotherapy is the mainstay of palliative therapy and results in objective response rates (ORRs) of only 20–40% and a median Overall Survival (OS) of 8–10 months [11]. The recurrence of GC after undergoing surgical treatment has been reported in approximately 45% of cases in western countries and in about 22% of cases in Korea and Japan [12].

Although no standard adjuvant or palliative chemotherapy regimen has been internationally approved for patients with advanced GC, a number of chemo agents have been widely used alone or in combination as the first-line therapy, with demonstrated benefits. These include fluoropyrimidine (5-FU, S-1, or capecitabine), platinum (cisplatin or oxalipatin), taxane (docetaxel or paclitaxel), epirubicin, and irinotecan. A systemic meta-analysis based on aggregate data revealed that in patients with advanced GC, palliative chemotherapy is more beneficial in terms of the improvement of OS and the relief of symptoms than treatment with the best supportive care (BSC) [13]. The combination of docetaxel/cisplatin/5-FU (DCF), ECF, and fluoropyrimidine (5-FU or capecitabine), as well as cisplatin, as a category 1 treatment has been recommended by the NCCN guidelines. The response rates to this combination regimen range from 25% to 54%, suggesting intrinsic resistance to these therapies [13].

In January of 2010, trastuzumab was approved as the first targeted therapy for the treatment of patients with HER2-positive GC. The

HER family consists of four members: HER-1 (epidermal growth factor receptor (EGFR), HER-2, HER-3, and HER-4. HER-1, HER-3, and HER-4 are all activated via ligand binding, whereas HER-2 does not require a ligand for activation. The activation of these receptors triggers phosphorylation cascades and the subsequent activation of a number of signaling transducers, thus activating both the PI3K/AKT and Ras/Raf pathways, which are important in cancer cell proliferation and survival [14,15]. Trastuzumab is a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of HER-2, thereby blocking its downstream signaling.

HER-2 amplification or over-expression is observed in about 15% to 25% of GC cases [16].HER-2 over-expression is more common in intestinal-type and gastroesophageal junction (GEJ) tumors than in diffuse-type and gastric tumors [16,17]. The Phase III ToGA trial found that 22% of advanced and metastatic GC patients overexpressed HER-2 via an immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) methodology. The addition of trastuzumab to chemotherapy also led to a significantly higher ORR, 47% versus 35% (p=0017); significantly longer progression-free survival (PFS) intervals, 6.7 months versus 5.5 months (p=0002); and significantly longer OS duration, 13.8 months versus 11.1 months (p=0046) [18].In Korea, a combination therapy of trastuzumab and CF is recommended in patients with HER-2-over-expressing adencarcinoma. The greatest benefit was seen in patients with high levels of HER-2 expression. To date, trastuzumab is the first and only targeted agent for GC approved by both U.S. and European authorities. However, a significant proportion patients withHER-2 positive breast cancer either do not respond or eventually become resistant to trastuzumab [19], suggesting the existence of both intrinsic and acquired resistance.

The PI3K/AKT Pathway

PI3K is a family of intracellular lipid kinases involved in the signaling network that regulates cell survival, proliferation, differentiation, migration, and metabolism [20]. PI3Ks can be categorized into three classes (I–III) according to their substrate preferences and sequence homologies. The activation of receptor tyrosine kinases (RTKs), such as EGFR, IGFR, and HER2, activates class IA PI3Ks. The binding of the p85 regulatory subunit of PI3K to phosphotyrosine residues on activated RTKs leads to a conformational change in p85, releasing the inhibition of the catalytic subunit p110 (α, β, and δ isoforms) of PI3K.PI3K localizes to the plasma membrane and catalyzes the formation of phosphatidylinositol 3,4,5-trisphosphate (PIP3) through the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2). PIP3 is a critical activator of the serine/threonine kinase AKT (also known as protein kinase B). The binding of PIP3 to AKT leads to the membrane recruitment of AKT and its subsequent phosphorylation by PDK1 (3-phosphoinositide-dependent kinase) and PDK2 [20,21].Activated AKT translocates to the cytoplasm and nucleus and activates the downstream targets involved in cell survival, proliferation, cell cycle progression, growth, migration, and angiogenesis [21,22] (Figure 1). PIP3 levels are tightly controlled by stringent PI3K regulation and via PTEN PIP3 phosphatase and SHIP (SH2-containing inositol5-phosphatase), which converts PIP3 back to phosphatidylinosito 4, 5-bisphosphate.

Cell apoptosis is a normal function that controls excessive proliferation. Cancer cells utilize a variety of mechanisms to down-regulate cell apoptosis and prolong survival. An important function of the activated PI3K/AKT pathway in cells is the inhibition of apoptosis. AKT is a good candidate for mediating these PI3K-dependent cell-

survival responses. A large number of AKT's direct downstream substrates have been identified, which include the pro-apoptotic Bcl-2 family members Bad, Bax, caspase-9, and GSK-3 and the forkhead family transcription factors (FoxO1).Activated AKT inhibits Bad's function through direct phosphorylation and suppresses the expression of Bim and FasL via the indirect phosphorylation of FoxO1 [23]. In addition, it is reported that AKT can phosphorylate iKKs, which promote cIAP expression for the inhibition of cell apoptosis. Recently, Jeong et al. proposed that AKT has a role in the activation of pro-survival pathways, possibly through NF-kB activation and the inhibition of p53 transcription activity [24].
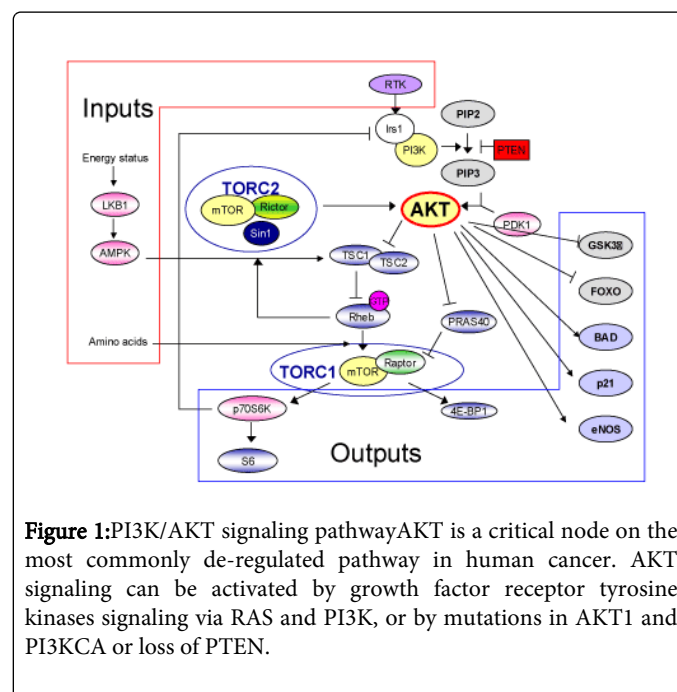

Figure 1:PI3K/AKT signaling pathwayAKT is a critical node on the most commonly de-regulated pathway in human cancer. AKT signaling can be activated by growth factor receptor tyrosine kinases signaling via RAS and PI3K, or by mutations in AKT1 and PI3KCA or loss of PTEN.

Activation of the PI3K/AKT Pathway in GC

The dysregulation of the PI3K/AKT/mTOR pathway is a common phenomenon in many human cancers, including GC [25].It can be triggered by a variety of mechanisms, including PI3KCA-activating mutations, loss of PTEN function, overexpression or activating mutations of AKT, and the overexpression of upstream receptors, such as IGFR, EGFR, and HER-2 [26].PI3KCA is a gene that encodes for the p110-alpha subunit of PI3K.PI3KCA-activating mutations occur in exome 9 and 20 of the PI3K gene and have been reported in GC by several groups. Mutation frequencies range from 10.6% to 15.9% [27,28] in Caucasian and 4.3% to 7.1% in Asian GC cases [29,30].Recently, we screened 127 GC samples from Chinese patients and detected PI3KCA hotspot mutations in 2.7% of cases (4/127) [31]. This apparent discrepancy between the western and eastern populations may be due to geographical differences or the sample size, or it could be related to disease stage and genomic instability status. PTEN phosphatase is a novel tumor suppressor that negatively regulates the PI3K/AKT signaling network [32].Loss of PTEN function can be attributed to inactivating gene mutations, chromosomal deletions, and promoter methylation, which are implicated in multiple cancer types, including GC [33].In comparison to PI3KCA mutations, the lack of detectable PTEN protein expression via IHC staining was more frequently observed in GC cases, with reported rates of between 20 and 36% [34,35].Consistent with these observations, our recent data

indicated that the loss of PTEN protein expression, detected via IHC, was found in 23% (14/61) of the samples from Chinese GC patients [31].On the other hand, the increased phosphorylation of AKT and mTOR was observed in 80% [36] and 47%-64% of GC patients, respectively [37-39], suggesting that additional factors, such as activation of RTKs (e.g., HER2, IGFR), must be responsible for the activation of the PI3K/AKT pathway.

Activation of the PI3K/AKT Pathway and Resistance to Chemo and Anti-HER2 Therapies

Drug resistance is a major problem for the treatment of metastatic and recurrent GC. The involvement of the PI3K/AKT/mTOR pathway in the resistance to chemotherapies in GC has been documented by several studies [29,40]. When primary tumor tissues from GC patients were tested for their chemotherapeutic sensitivity in vitro, the association between activated AKT and increased resistance to multiple chemotherapeutic agents, including 5-fluorouracil, doxorubicin, mitomycin C, and cisplatin, was found [41]. Consistently, the reduction of basal AKT activity via the ectopic expression of PTEN sensitized GC cells to anti-cancer chemotherapy agents. These data suggest that the activation of the PI3K/AKT pathway has a direct role in resistance to chemotherapy in GC cases. The combination of PI3K/AKT pathway inhibitors with chemotherapy has successfully attenuated chemotherapeutic resistance in GC cell lines [42]. Recently, we tested the anti-tumor activity of a novel AKT kinase inhibitor, AZD5363, in a patient-derived GC xenograft (PDGCX) model with PTEN loss. This indicated that AZD5363 and taxotere monotherapies were ineffective, but significant anti-tumor activity was observed when AZD5363 was combined with taxotere. Similarly, Lin et al. showed that the administration of another AKT kinase inhibitor, GDC-0068, in combination with taxotere induced tumor regression in a PC-3 prostate xenograft model with a homozygous deletion of PTEN [43]. Because the doses used for each single agent only caused modest tumor growth delay in the study, these results suggest a new strategy to sensitize GC with PTEN loss to chemotherapy by targeting the PI3K/AKT pathway [31].

In addition to its involvement in resistance to chemotherapies, the role of the activation of the PI3K/AKT pathway in resistance to anti-HER-2 agents has been well-studied in HER-2-positive breast cancer [31,44]. In a HER-2-positive BT474 model, a combination of AZD5363 and taxotere led to complete tumor regression.A recent study by Linos et al. indicated that PTEN was lost in the majority of HER-2-positive GC cases [45]. These observations provide a possible explanation for the observed clinical resistance of HER-2-positive breast cancer patients to current anti-HER-2 therapies, including trastuzumab and lapatinib.

The mechanisms of the AKT pathway in chemo resistance are multifold.First, activated AKT suppresses apoptotic cell death via the inhibition of cytochrome c's release from the mitochondria or via its regulatory effect on various downstream effectors, e.g., NF-κB, Bcl-2-family proteins, FOXO transcription factors, and MDM2 [23,24]. In addition, AKT activation mediates cell cycle progression through the inhibition of GSK-3, opposing the action of p21WAF1 and p27Kip1, and via the phosphorylation of mTOR kinases [46]. Geng et al. showed that Bcl-2 expression was significantly associated with chemo resistance. The over-expression of Bcl-2 may predict decreased chemotherapy efficacy in patients with GC [47]. Chemotherapy promotes the activation of NFkB, which regulates various genes involved in angiogenesis, metastasis, and the suppression of apoptosis

[48]. The PI3K/AKT pathway is involved in the activation of NF-kappa B via tumour necrosis factor [49,50] and plays a role in chemo resistance in GC [51]. The PI3K inhibitor LY294002 was able to decrease the expression of MDR1/Pgp, Bcl2, and XIAP and to up-regulate the expression of Bax and caspase3, thereby enhancing chemo sensitivity by inhibiting a drug pump and inducing apoptosis. These results suggest an approach to enhance chemo sensitivity by direct targeting PI3K in human GC [52].

Agents Targeting the PI3K/AKT Pathway in Clinical Development

A number of inhibitors of PI3K, AKT, and mTOR have being developed and are now at various stages of clinic evaluation (Table 1).Because mTOR is one of the downstream effectors of PI3K and AKT, it is expected that inhibitors of mTOR will have more selective effects and better safety profiles. At present, the mTOR inhibitor everolimus is the only one approved for the treatment of malignancies, including breast cancer, neuroendocrine tumors of pancreatic origin, and subependymal giant cell astrocytoma.

Agents	Manufacturer	Target	Indications	Stage
mTOR inhibitors				
Everolimus	Novartis	mTORC1	RCC, HCC, lymphoma, mBC, and GBM	Approved for RCC, PNET and SEGA
Temsirolimus	Pfizer	mTORC1	Various tumors	Approved for CRC
Ridaforolimus	Merck	mTORC1	Sarcoma, EC, mBC, prostate cancer, Her2+ mBC, NSCLC	Phase III
OSI-027	OSI	mTORC1/2	Solid tumors and lymphoma	Phase I
AZD8055	AstraZeneca	mTORC1/2	Gliomas, HCC and solid tumors	Phase I
AZD2014	AstraZeneca	mTORC1/2	mBC, RCC and solid tumors	Phase I/II
INK128	Millennium	mTORC1/2	mBC, NHL, MM, and solid tumors	Phase I
CC-223	Celgene	mTORC1/2	NHL, NSCLC and MM	Phase I
DS-30786a	Daiichi Sankyo	mTORC1/2	Solid tumors and lymphoma	Phase I
PI3K inhibitors				
BKM120	Novartis	Pan-PI3K	Solid tumors, prostate cancer, CRC, ER+ mBC, Her2+ mBC, GBM, hematologic malignancies, NSCLC, thyroid Cancers and EC	Phase I/II/III
XL147	Sanofi-aventis	Pan-PI3K	GBM, EC, OC, NSCLC, Her2+ breast cancer,	Phase I/ II

			lymphoma, and solid tumors	
PX866	Oncothyreon	Pan-PI3K	GBM, NSCLC, CRC, HNSCC, prostate cancer, and solid tumors	Phase II
GDC-0941	Genentech	Pan-PI3K	ER+ mBC, Her2+ mBC, NSCLC, NHL, and solid tumors	Phase I/II
GSK2126458	GSK	Pan-PI3K	Pulmonary fibrosis, lymphoma and solid tumors	Phase I
BAY 80-6946	Bayer	Pan-PI3K	Solid tumors, lymphoma	Phase I/II
BYL719	Novartis	PI3K p110α	Solid tumors, mBC, CRC, GC	Phase I/II
GS-1101 (CAL-101),	Gilead	PI3K p110δ	CLL, NHL, and hematologic malignancies	Phase II
AMG319	Amgen	PI3K p110δ	CLL, NHL, and hematologic malignancies	Phase I
BEZ235	Novartis	PI3K/ mTOR	RCC, prostate cancer, Leukemia , solid tumors and mBC	Phase I/II
XL765	Sanofi-aventis	PI3K/ mTOR	GBM, BC, NSCLC, and solid tumors	PhaseIb/II
GDC-0980	Genentech	PI3K/ mTOR	mBC, NHL, RCC,EC, prostate cancer and solid tumors	Phase I/II
SF1126	Semafore	PI3K/ mTOR	Solid tumors	Phase I
AKT inhibitors				
Perifosine (KRX-0401)	Keryx	AKT	CRC, MM, glioma, hematologic malignancies, lymphoma, OC, BC, NSCLC, RCC, sarcoma, and solid tumors	Phase II/III
AZD5363	AstraZeneca	AKT	BC, OC, CC, prostate cancer, solid tumors	Phase I/II
GDC-0068	Genentech	AKT	Prostate cancer, GC, Solid tumors	Phase I/II
MK2206	Merck	AKT	BC, pancreatic cancer, GC, NSCLC, lymphoma, solid tumors	Phase II
RX-0201	Rexahn	AKT	Pancreatic cancer	Phase II
GSK2110183	GSK	AKT	MM, OC, CLL, hematologic malignancies, and Langerhans cell histiocytosis	Phase I/II
GSK2141795	GSK	AKT	CC, CRC, melanoma, OC,lymphoma and solid tumors	Phase I/II
LY2780301	Eli Lily	P70S6K/ AKT	BC, NHL	Phase I/II

PBI-05204	Phoenix Biotechnology	AKT	Solid tumors	Phase I
VD-0002	VioQuest	AKT	Solid tumors and hematologic malignancies	Phase I
BAY1125976	Bayer	AKT	Solid tumors	Phase I
SR13668	NCI	AKT		Phase I
MKC-1	EntreMed	AKT/ mTOR	EC, OC, NSCLC, BC, pancreatic cancer, and CRC	Phase II

Table 1: Inhibitors targeting PI3K/AKT pathway in clinical development CC, Cervical cancer, CLL, chronic lymphocytic leukemia; CRC, colorectal carcinoma; EC, endometria cancer; ER, estrogen receptor; GC, gastric cancer, GBM, glioblastoma; HCC, hepatocellular carcinoma; Her2, human epidermal growth factor receptor-2; HNSCC, head and neck squamous cell carcinoma; HR, hormone receptor; mBC, metastatic breast cancer; MM, multiple myeloma; NHL, Non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PI3K, phosphatidylinositol 3-kinase; PNET, pancreatic neuroendocrine tumors; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma.

mTOR Inhibitors

Everolimus is a mTORC1 selective inhibitor and has been tested in GC patients in phase II and phase III trials. In the recent phase II trial, everolimus demonstrated anti-tumor activity with a response rate of 3.7% (2/44) and a disease control rate (DCR) of 38.9% (17/44) [53]. However, a everolimus phase III study failed to achieve a survival benefit in comparison with the best supportive care (BSC) in previously treated advanced GC cases [54]. Although the phase II trial failed to achieve its primary objective, the observed association between high levels of pS6 expression (Ser240/4) at baseline and higher DCR and prolonged PFS warrant further trials with a molecular-stratification-based patient selection strategy. Because eveolimus suppresses only mTORC1 and the feedback activation of MAPK may limit its anti-tumor potency [55], a few inhibitors of both mTORC1 and mTORC2 with improved potency (e.g., OSI-027, BEZ235, XL765, AZ8055, and Ink128) are being currently evaluated in phase I/II trials for patients with solid tumors.

PI3KCA Inhibitors

There are two types of PI3K inhibitors targeting the p110 catalytic subunit that are currently under clinical development: pan-PI3K inhibitors and isoform-specific PI3K inhibitors.Pan-PI3K inhibitors are active against all family members of PI3K, whereas isoform specific inhibitors selectively inhibit p110α, β, or δ. These include the pan-PI3K inhibitors BKM120 (Novartis), PX-886 (Oncothyreon), XL147 (SAR245408; Sanofi) and the p110a selective inhibitors BYL719, GDC0032, and INK1117 etc. [56].Because the catalytic domains of p110 and mTOR are structurally similar and mTOR activation is the downstream event of the PI3K/AKT pathway, it is expected that the dual inhibition of these targets may be more effective. Some of the dual PI3K/mTOR inhibitors currently being investigated in clinical trials include BEZ235, XL765, GDC-0980, GDC0084, SF1126, and PF-46915 etc. [57]. The clinical anti-tumor activity of some of these inhibitors has been reported [58].

AKT Inhibitors

AKT plays a central role in the activation of the PI3K/AKT pathway to facilitate cellular survival and suppress cell apoptosis. A number of AKT inhibitors have entered clinical trials. These include the allosteric inhibitors perifosine (Keryx Biopharmaceuticals) and MK-2206 (Merck) and the ATP competitive inhibitors AZD5363, GSK690693 and GDC0068 etc. Previously, we reported the development of AZD5363 and demonstrated its activity in GC cell lines [31,44]. Recent phase I data indicated that AZD5363, as a monotherapy, led to partial responses in two patients harboring tumor mutations in either AKT1 or PI3KCA [59].

Future Direction

For patients with metastatic or recurrent GC, the evidence supports the use of chemotherapy to prolong survival and maintain quality of life. However, the long-term outcomes of chemotherapy treatments are poor, suggesting the need for novel targeted agents that may confer a greater survival benefit. The critical role of the activation of the PI3K/AKT signaling pathway in both tumorigenesis and drug resistance has been well-documented. A number of small molecule inhibitors of PI3K, AKT, or mTOR are at various stages of drug development for the treatment of solid tumors, including GC (Table 1). Because the activations of AKT and mTOR have been commonly detected in human GC, it is expected that agents against the PI3K/AKT pathway alone or in combination with current therapies will provide viable options for the treatment of advanced GC.However, there are still challenges ahead in terms of their clinical application. First, the results of the phase III everolimus trial in GC cases without patient selection were disappointing. Second, the preclinical data indicated that only PI3KCA mutations were predictive of a response to AKT inhibitor (31).Thus, it is critical to validate and implement biomarkers and assays for the selection of patients with a predictive response to the therapy. Another approach for improving efficacy is to combine the inhibitors of the PI3K/AKT pathway with chemo or other targeted agents. Preclinical translational studies based on rational design and the safety profiles of the inhibitors will help in choosing the right agents and combinations.

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