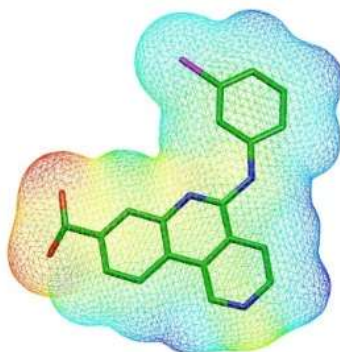


## CX-4945

Oral Small Molecule Inhibitor of CK2 Protein Kinase  
Enables Diverse Drug Combinations with Improved  
Treatment Outcomes for Cancer Patients



### ***Substantial Market Potential***

- Combination with diverse approved agents
- Combination in multiple indications

### ***Targeted Cancer Agent***

- CK2 is a newly validated target that drives multiple oncogenic pathways
- Excellent profile for combination agent
- Highly differentiated from other therapies

### ***Attractive Clinical Qualities***

- Clearly defined patient populations

### ***Robust IP Position***

- Patent allowed by USPTO

### ***Clinical Trial***

- Phase I trial nearing completion
- Safe and well tolerated
- Linear and predictable PK
- CK2 target hit, key pathways suppressed
- Dose-dependent biomarker movement
- Stable Disease Observed
- Extended Duration on Treatment
- Positioned for Phase II combination trials

## Market for CK2 Inhibitor as a Combination Agent

Combination therapy for cancer has become an everyday reality for physicians and their patients and will continue to be employed into the future to treat the vast majority of cancer indications. The traditional development route for combinations is to demonstrate single agent activity in a sensitive indication and subsequently seek practical combinations in an empirical manner. This approach is time consuming, expensive and ultimately results in many missed opportunities. A more rational approach is to create a new drug directed against a target protein that is essential in multiple cancer signaling pathways. Such an agent simultaneously impacts multiple pathways and acts synergistically with numerous approved agents that also act through those pathways.

CK2 protein kinase represents a prime target for this approach, as it promotes multiple cancer-driving pathways and modulates many processes critical to tumor growth. It is essential for cancer cell survival, up-regulated in many different cancers, is not mutated and as such it is an excellent target for the design of a potent combination agent. Cylene's small molecule CX-4945 is a potent and selective CK2 inhibitor and an innovative anticancer agent. The market for CX-4945, which successfully combines with numerous approved therapies, is substantial and could exceed \$2 billion in annual sales.

	Sales 2010 (USD Millions)	Lung	Breast	Colorectal	Bladder	Pancreatic	Head and Neck	Brain	Ovarian	Gastric	Multiple Myeloma	Combination Pathway
<b>US Incidence 2009 (All Cancers 1,529,560)</b>		240,610	209,060	142,570	70,530	43,140	36,540	22,020	21,880	21,000	20,180	
<b>CX-4945 (CK2 inhibitor)</b>											Phase I	CK2 Inhibitor
Gemcitabine (Gemzar)	1,149								Phase II			DNA Repair
Platinum Agents (Cis and Carbo)	162								Phase II			DNA Repair
Radiotherapy												DNA Repair
Erlotinib (Tarceva)	1,412	Phase II										EGFR
Gefitinib (Iressa)	334											EGFR
Cetuximab (Erbix)	1,802											EGFR
Panitumumab (Vectibix)	305											EGFR
Bevacizumab (Avastin)	6,303											Angiogenesis
TBD												PI3K/Akt/mTOR

Table 1: 2010 market and indications for agents that combine well with CX-4945. Indications in which each drug is currently used are marked in yellow, those where CX-4945 is planned for trials in red.

Strong mechanistic and *in vivo* drug combination data confirm that CX-4945 combines synergistically with EGFR antagonists and with DNA damaging agents and such combinations are planned in Cylene's upcoming Phase II trials. The 2010 market for such agents to be used in combination is outlined above (Table 1). CX-4945 acts in concert with both small molecule and biological therapies and their range of applicability spans many indications. By combining with currently approved agents that act through different mechanistic pathways, CX-4945 enables pharmaceutical companies to expand their portfolios and extend the efficacy, lifecycle and reach of current cancer therapies.



During the Phase I trial, CX-4945 has been safe and well-tolerated, demonstrated linear and predictable pharmacokinetic properties and presented a clear dose-dependent pharmacodynamic response. Measurement of mechanism and tumor-related biomarkers in patients demonstrate that CX-4945 hits the CK2 target and suppresses the expected downstream markers and pathways (Figure 2), and measurement of circulating tumor cells demonstrated the ability of CX-4945 to kill tumor cells in patients. Moreover, CX-4945 achieved clinical benefit as a single agent CK2 inhibitor, demonstrating anticipated disease stabilization and extended duration on treatment in several patients (Figure 3). Additionally, research support studies identified a potential genetic signature that provides cancer cells with greater sensitivity to CX-4945, and many of the patients receiving clinical benefit in the trial have indications that are reported possess that genetic signature. Findings from the successful Phase I trial results highlight CX-4945 as a promising therapeutic agent with the characteristics necessary for positive Phase II combination trials.

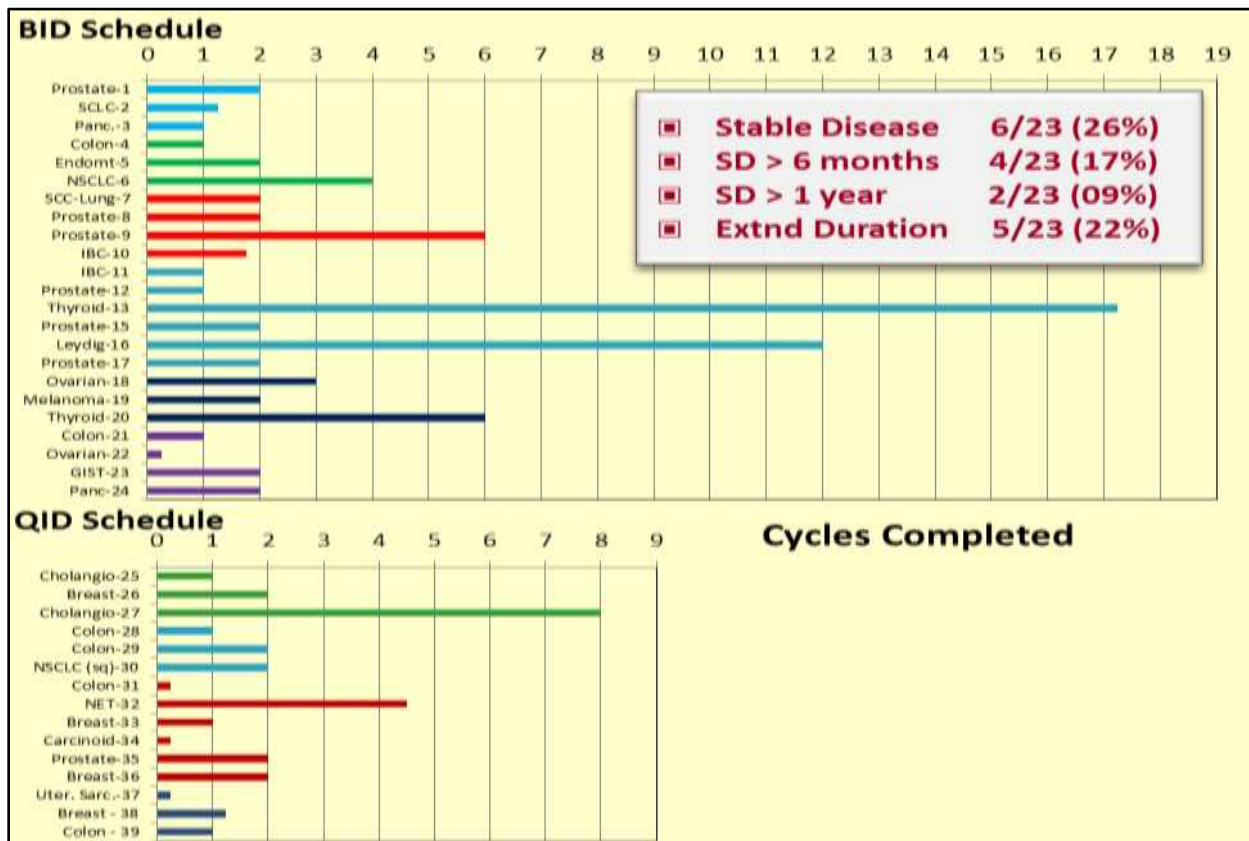


Figure 3: Depiction of the length on study for each patient in the Phase I solid tumor trial. Patients left the study upon appearance of disease progression. Several patients (26% on the BID schedule) had stable disease at first examination and this continued for over 6 months for 17% of patients, with two patients on study for over a year.

## Mechanistic Rationales for Drug Combination Trials

Protein Kinase CK2 is essential for cancer cell survival because it drives multiple critical pathways (Figure 4). When a CK2 inhibitor is combined with an agent that acts through one of these pathways synergy is expected occur. As CX-4945 is transitioned from Phase I into randomized Phase II drug combination trials, we have explored which combination of pathways/drugs are most suitable for combination with CX-4945, and in which cancer indications these combinations will be most effective.

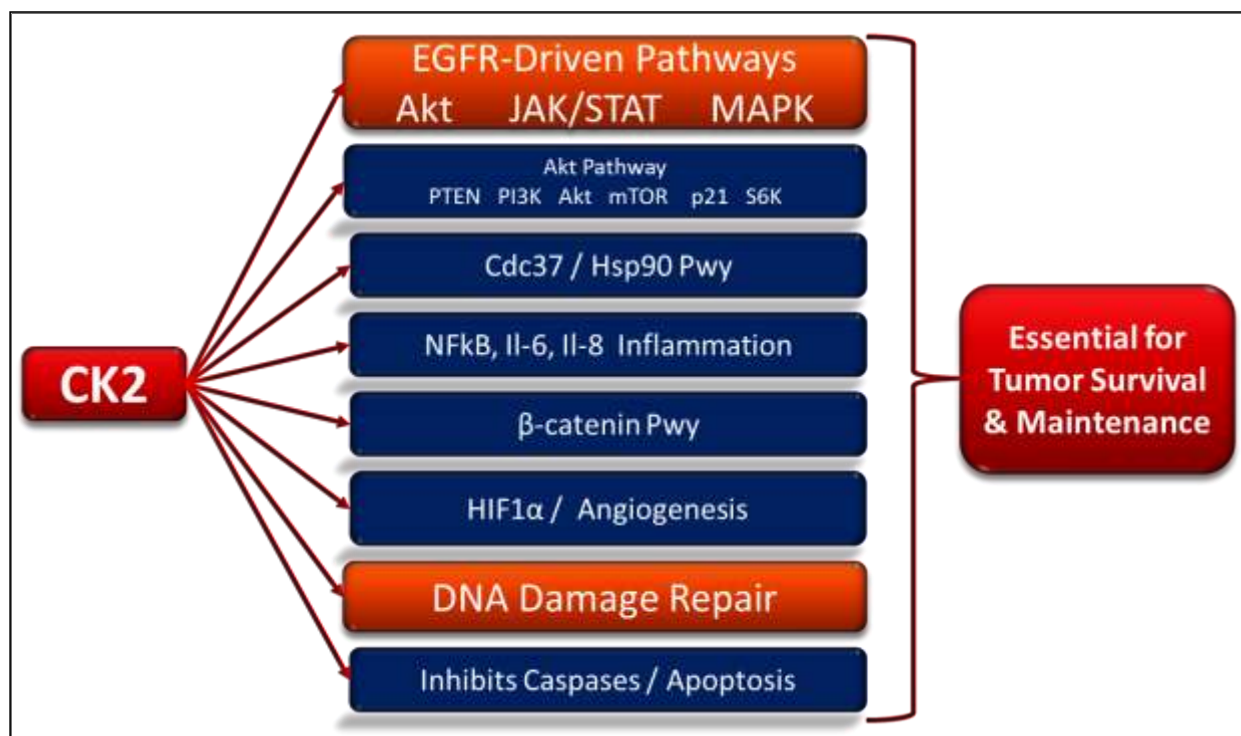


Figure 4: Protein Kinase CK2 is essential for cancer cell survival by driving multiple pathways. When combined with an agent that acts through one of these pathways synergy is observed.

*In vitro* mechanistic studies and literature revealed that EGFR and CK2 signaling cooperate to promote oncogenic signaling. This finding is confirmed by many experiments which show that CX-4945 exerts synergistic activity when combined with EGFR antagonists (cetuximab, erlotinib, gefitinib, panitumumab). Likewise, CK2 is central to many pathways involved in DNA repair and therefore when CX-4945 is combined with DNA damaging agents (gemcitabine, cisplatin or carboplatin) the cancer cells are unable to repair the damaged DNA and the cell killing effect is enhanced. Synergistic combination of CX-4945 with both EGFR antagonists and also DNA damaging agents was seen *in vitro* and further demonstrated *in vivo* murine xenograft studies.

These compelling mechanistic rationales underpin the design of two separate Phase II trials where CX-4945 will be combined with an EGFR antagonist and with DNA damaging agents in the appropriate cancer indications.

## CK2 and EGF-Receptor in Cancer

Due to the importance of EGFR in cancer, many agents that inhibit its activities are currently approved. It has been shown that EGF stimulation increases CK2 activity as seen by direct elevation of kinase activity (Figure 5A) or by evaluation of the phosphorylation status of the CK2 specific site, Akt S129 (Figure 5B). Figure 5B shows p-Akt S129 phosphorylation dramatically increases upon stimulation of starved A341 cells with EGF. Further, CX-4945 abolishes EGF stimulated CK2 activity as shown by absence of phosphorylation of Akt S129.

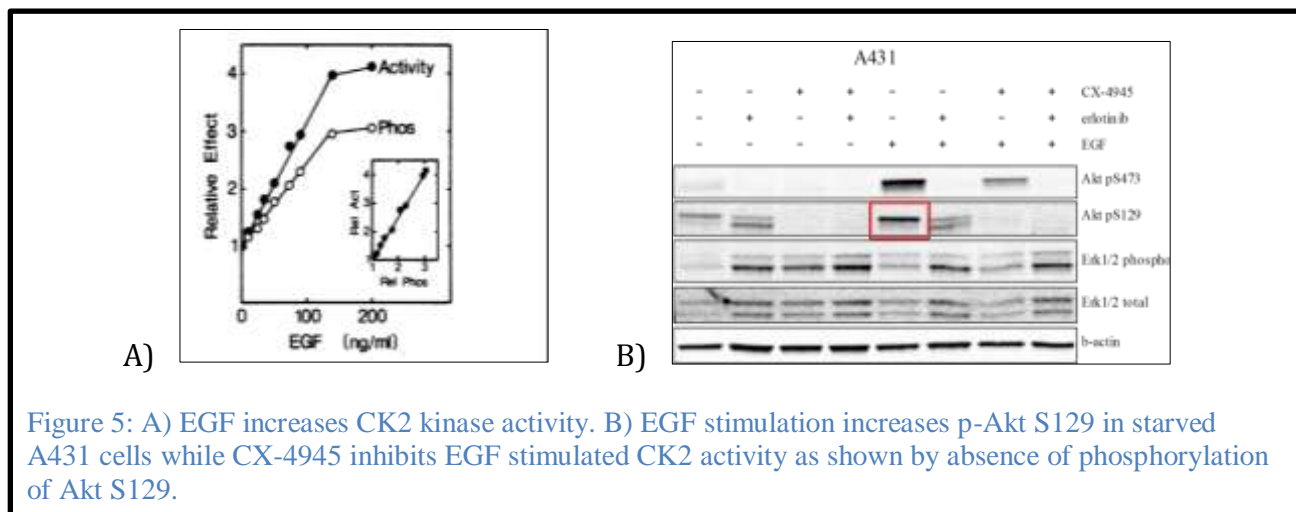


Figure 5: A) EGF increases CK2 kinase activity. B) EGF stimulation increases p-Akt S129 in starved A431 cells while CX-4945 inhibits EGF stimulated CK2 activity as shown by absence of phosphorylation of Akt S129.

## CX-4945 Shows Synergy with EGFR Antagonists

In EGFR dependent human tumors in murine xenograft models, CX-4945 was combined with cetuximab (Figure 6A) or erlotinib (Figure 6B and C). Significant synergy was seen in both models. Each combination considerably decreased tumor growth and increased time to endpoint compared to the individual treatments alone. These demonstrated that synergy with EGF-Receptor antagonists occurs in combination both with small molecule and biological agents.

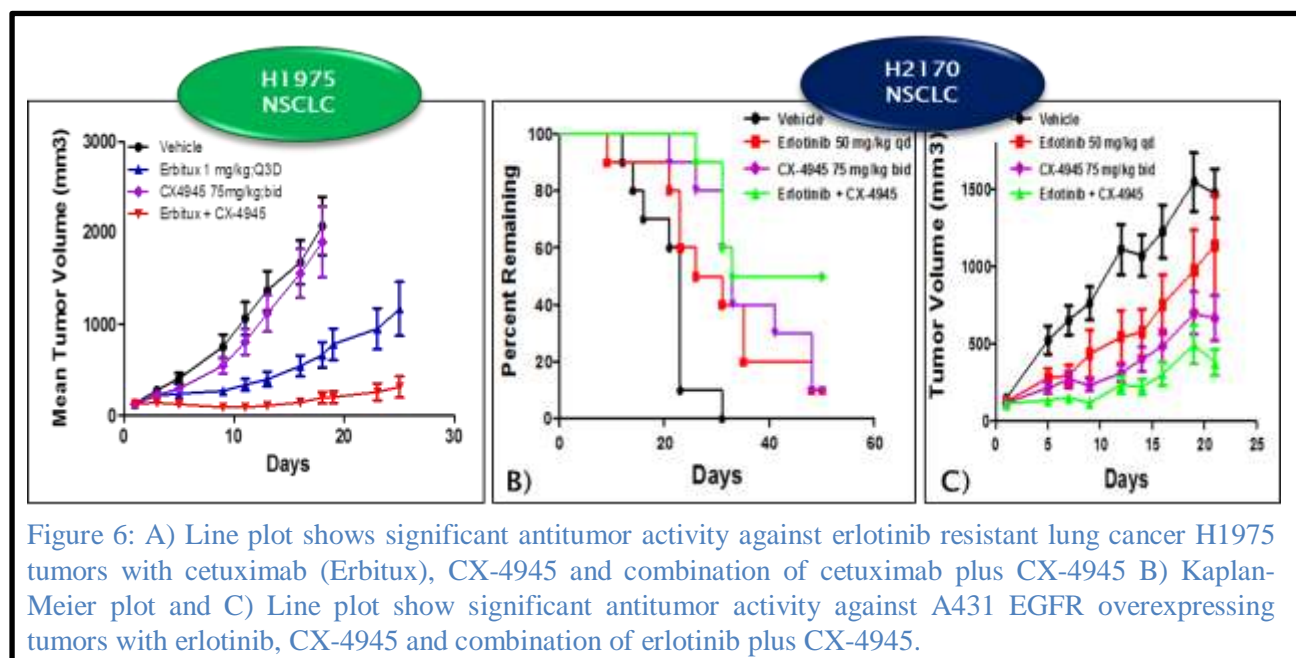


Figure 6: A) Line plot shows significant antitumor activity against erlotinib resistant lung cancer H1975 tumors with cetuximab (Erbix), CX-4945 and combination of cetuximab plus CX-4945 B) Kaplan-Meier plot and C) Line plot show significant antitumor activity against A431 EGFR overexpressing tumors with erlotinib, CX-4945 and combination of erlotinib plus CX-4945.

## CK2 and DNA Damage Repair in Cancer

CK2 is intimately involved in several DNA repair pathways (Figure 7). DNA damaging chemotherapeutics like gemcitabine are commonly used to treat solid tumors but are limited in their application by side effects and by recovery of cancer cells from the genotoxic insult. Our mechanistic studies demonstrate that inhibition of CK2 prevents DNA repair, and improves the antitumor activity of gemcitabine.

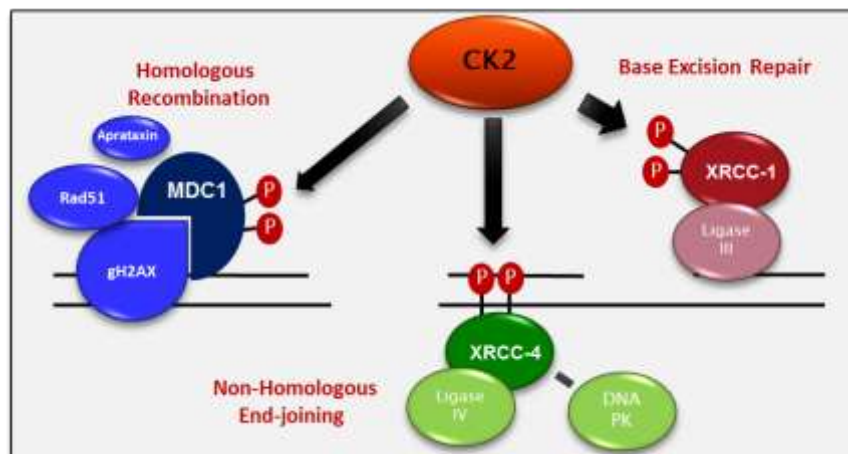


Figure 7: CK2 regulates DNA repair signaling through multiple interactions.

## CX-4945 Shows In Vivo Synergy with DNA Damaging Agent Gemcitabine

In the A2780 ovarian tumor model, a significant increase in time to endpoint was demonstrated with a combination of gemcitabine and CX-4945 (green line in Figure 8A), following only 4 doses, as compared to administration of each as single agent. The Colo-205 colorectal cancer model is resistant to each individual agent alone (Figure 8B). However, gemcitabine and CX-4945 in combination significantly reduce tumor growth, suggesting this combination may be effective in indications where gemcitabine alone is not approved.

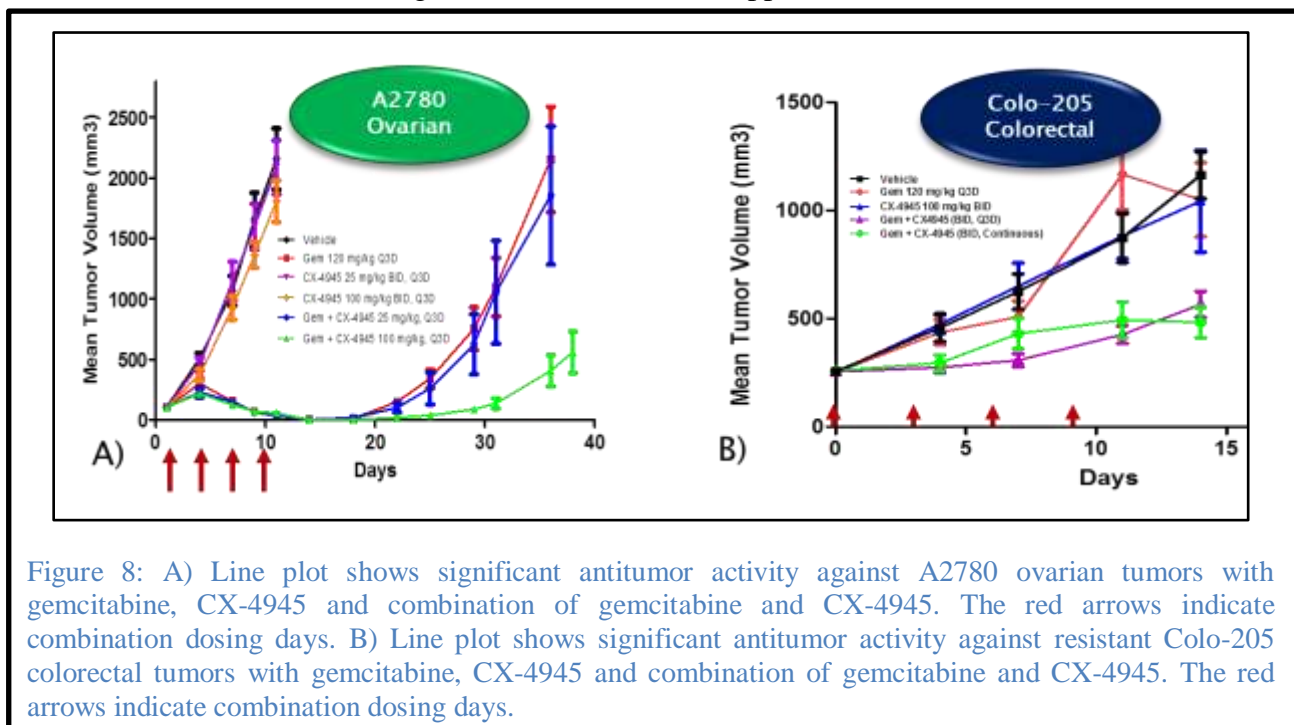


Figure 8: A) Line plot shows significant antitumor activity against A2780 ovarian tumors with gemcitabine, CX-4945 and combination of gemcitabine and CX-4945. The red arrows indicate combination dosing days. B) Line plot shows significant antitumor activity against resistant Colo-205 colorectal tumors with gemcitabine, CX-4945 and combination of gemcitabine and CX-4945. The red arrows indicate combination dosing days.

## ***CK2 inhibitor CX-4945***

Protein Kinase CK2 is a newly validated cancer target ideally suited for the development of a dynamic combination agent. Therefore Cylene's small molecule CK2 inhibitor CX-4945 has been positioned for combination with multiple approved agents and therapies. By augmenting the effectiveness of diverse therapeutics, CX-4945 will extend and expand the markets of currently approved and future cancer treatments.

CX-4945 is a potent and selective inhibitor of CK2 to which Cylene owns all intellectual property and has patents granted by the USPTO. As a small molecule with drug-like physicochemical properties and ease of synthesis, it has flexible routes and schedules of administration. A successful Phase I clinical trial demonstrated that it has favorable safety, pharmacokinetic and pharmacodynamic characteristics. CX-4945 hits the CK2 target and it modulated the expected pathways without displaying toxicity. The monitoring of circulating tumor cells demonstrated the ability of CX-4945 to kill tumor cells in patients which supports the observation that CX-4945 achieved clinical benefit as a single agent CK2 inhibitor, demonstrating stable disease and extended duration on treatment in a several patients. These findings positions CX-4945 for success in upcoming Phase II combination trials.

The Phase II randomized drug combination trials are supported by compelling mechanistic rationales which guide selection of indications and shape trial designs. As such Cylene is initiating a trial with gemcitabine/carboplatin in ovarian cancer (DNA damage repair) and also initiating a trial with erlotinib in NSCLC (EGFR pathway). CX-4945 has created physician excitement and acceptance due to its novel mechanisms of action and the fact that it was designed for combinability to meet real-world need.

Cylene's leadership in exploiting CK2 pathways enables multiple drug combinations for improved treatment outcomes. This unique approach enables pharmaceutical companies to expand their portfolio and extend the efficacy, lifecycle and reach of current cancer therapeutics.

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