July 23, 2012

Tesaro

(TSRO-NASDAQ)

Stock Rating: **Outperform**
Industry Rating: **Outperform**

Biotechnology

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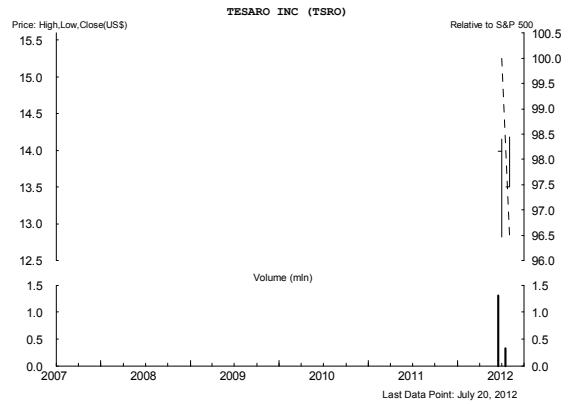
Initiating Coverage With OUTPERFORM Rating

Securities Info

Price (23-Jul)	**$13.90**	**Target Price**	**$22**
52-Wk High/Low	--	Dividend	--
Mkt Cap (mm)	$4,108	Yield	--
Shs O/S (mm, BASIC)	295.5	Float O/S (mm)	286.3
Options O/S (mm)	na	ADVol (30-day, 000s)	3,976

Price Performance



Valuation/Financial Data

(FY-Dec.)	2010A	2011A	2012E	2013E
EPS GAAP	-$7.61	-$9.12	-$2.12	-$2.30
P/E			nm	nm
First Call Cons.				
FCF	-$1.29	-$14.24	-$47.73	-$66.00
P/FCF			nm	nm
EBITDA ($mm)	-$8	-$15	-$48	-$64
EV/EBITDA			nm	nm
Rev. ($mm)	$0	$0	$0	$0
EV/Rev			na	nm

Quarterly EPS	**1Q**	**2Q**	**3Q**	**4Q**
2011A	-$1.64	NA	NA	NA
2012E	-$0.70A	-$0.46	-$0.47	-$0.49

Balance Sheet Data (31-Mar)

Net Debt ($mm)	-$89	TotalDebt/EBITDA	nm
Total Debt ($mm)	$0	EBITDA/IntExp	na
Net Debt/Cap.	nm	Price/Book	-0.5x

Notes: Quarterly EPS may not sum due to share count. All values in US$.

Source: BMO Capital Markets estimates, Bloomberg, Thomson Reuters, and IHS Global Insight.

Investment Thesis

We are initiating coverage of Tesaro Inc (TSRO) with an **OUTPERFORM** rating and $22 price target. We believe that TSRO offers a unique combination of late-stage, lower-risk asset development for downside protection, with earlier stage, higher risk-reward targeted therapeutics for cancer and significant upside potential. With primary focus on novel NK-1 antagonist rolapitant for chemotherapy-induced nausea and vomiting (CINV), we believe that validation of the target with Merck's Emend and potential best-in-class attributes for rolapitant offer an attractive risk-reward proposition into phase 3 data in 2H13. We believe that phase 2 data suggest a more rapid and broader effect on nausea and vomiting with rolapitant and that high bioavailability, extended half-life and lower potential for drug interactions provide dosing advantages for the oral formulation and ease of transition to the more important IV formulation. With perhaps greater upside potential from earlier stage targeted therapeutics we believe that ALK inhibitor TSR-011 and PARP-inhibitor niraparib offer potential features of differentiation that could leap-frog more advanced competitors, particularly in the area of PARP inhibition where competitors have stumbled. To the extent that execution will be critical, we believe that management success in creating shareholder value historically is an important consideration here.

Forecasts

Our 2012 forecast is for a loss per share of $2.12.

Valuation

$22 price target is based on 20x our 2017E EPS of $2.35 discounted 25%.

Recommendation

We rate Tesaro **OUTPERFORM**.

Investment Thesis

We believe that TSRO offers a relatively lower-risk, higher-reward proposition as compared to other small-cap, development stage biopharmaceutical companies. With initial focus on NK-1 antagonist rolapitant we believe that likelihood of success is relatively high and that risk-adjusted value provides downside support, with upside potential retained in the event that phase 2 data are replicated in phase 3. Relative to NCCN treatment guidelines we believe that NK-1 antagonists are under-utilized for chemotherapy induced nausea and vomiting (CINV) and believe that a drug with more rapid effects on vomiting, broader affect on nausea, and with dosing advantages in going from oral to intravenous could dramatically expand the market and command dominant share. We estimate peak sales for rolapitant at $335 million with an estimated NPV of $14/share, assuming 70-75% likelihood of success, with upside potential to $18/share on full phase 3 success.

While the supportive care opportunity in CINV is attractive we believe that greater upside potential may exist from earlier stage cancer therapeutics focused on key oncogenic proteins and mediators of aberrant cancer cell growth. While the area of ALK inhibition has been getting crowded since the approval of Pfizer's XALKORI (crizotinib) we believe that the market is under-penetrated and suffering from sub-optimal features of this first-generation inhibitor. Success of second-generation ALK inhibitors will be driven by higher potency, activity against key resistance mutations, including the important xx gatekeeper mutation, activity against CNS disease and limitation of prominent toxicities, in particular adverse ocular and liver effects seen with XALKORI. With IND filing for TSRO's TSR-011 expected by YE12 we believe that higher affinity for ALK and 100-200x fold activity against the gatekeeper mutation should be leverageable into a path to accelerated development. We estimate the market opportunity for ALK inhibition at $1.8 billion and believe that there will be potential for multiple market entrants, used in sequence, like BCR:ABL inhibitors in CML and anti-VEGF agents in renal cell cancer (RCC). We estimate TSR-011 peak sales of roughly $300 million as a treatment for resistant ALK+ NSCLC with 33% penetration of the primary resistance market and estimate an NPV of $6/share assuming 40% likelihood of success.

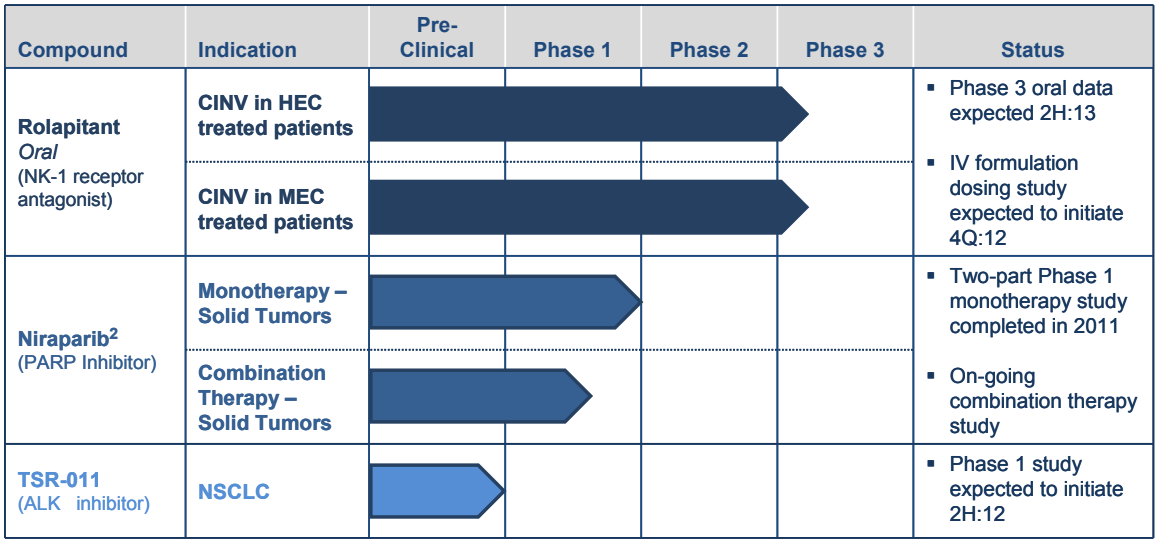
Where a larger window may exist for differentiation, in perhaps a larger category of drug is for PARP inhibitor niraparib following stumbles for more advanced competitors. With focus of PARP inhibition on defects of DNA repair, particularly in tumors with well-defined mutations in DNA repair, like the BRCA mutation found in breast cancer, ovarian cancer and other solid tumors. To the extent that there is a complex calculus involved in establishing optimal dose, dose schedule, proximity and timing to DNA-damaging chemotherapy as well as patient sub-population we believe that TSRO is ideally positioned to learn from results of competitor trials, including several setbacks that may provide a path to more rational development. As with other TSRO drugs, niraparib was identified for several potential best-in-class attributes including selectivity for PARP-1/2 over other PARP family members and extended half-life and durable affect on PARP activity. With phase 1 data establishing clear activity for in breast cancer and ovarian cancer we believe that niraparib is well positioned to establish greater proof-of-concept in phase 2. Value is not yet attached to niraparib pending initiation of a development path.

Tesaro Overview

Tesaro is a development-stage biopharmaceutical company focused on in-licensing, development, and commercialization of therapeutics for cancer. Tesaro has in-licensed three programs to date:

- Rolapitant to prevent chemotherapy induced nausea and vomiting (CINV) currently completing phase 3 testing
- Niraparib a PARP inhibitor to treat cancers with certain DNA repair defects currently entering phase 2 testing, and
- TSR-011 an ALK inhibitor to treat tumors with translocations making ALK an oncogene currently approaching an IND.

Exhibit 1: Tesaro Pipeline



Source: Tesaro Inc and BMO Capital Markets Research.

Tesaro's strategy is to identify compounds that have best-in-class and or first-in-class potential with a primary focus on oncology-supportive care and targeted therapeutics. Thus in the chemotherapy-induced nausea and vomiting (CINV) market, rolapitant, a neurokinin-1 (NK-1) antagonist would compete with one incumbent, Merck's Emend, and seek to establish an enhanced therapeutic benefit profile. NK-1 antagonist use is proven for delayed emesis, but Emend has not shown a benefit to treat acute emesis or decrease the rate of nausea. In phase 2 testing, rolapitant has shown the expected benefit against delayed emesis but has also demonstrated clinically and statistically significant benefits for both acute emesis and nausea. Tesaro is currently in the process of completing three phase 3 trials in patients receiving both highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (HEC) with an oral formulation of rolapitant with plans to conduct bioequivalence trials with an intravenous (IV) formulation by YE12. Phase 3 data for rolapitant are expected by 2H13 with potential approval of the oral formulation by 2H14.

In the area of targeted drug development for cancer, PARP inhibitor niraparib has completed phase 1 testing and has established that the compound has a long half life permitting once-daily dosing. Pre-clinical testing suggests that niraparib preferentially accumulates in the tumor tissue, further suggesting that niraparib can effectively suppress PARP activity with once-daily dosing. The PARP field is highly competitive, but leaders Sanofi (SNY) and AstraZeneca (AZN) have run into problems. Sanofi's (SNY's) iniparib has a different mechanism of action (MOA) to other PARP inhibitors and failure in a phase 3 trial in triple negative breast cancer, is not necessarily representative of the potential for PARP inhibition in this disease. AstraZeneca's olaparib has shown significant activity in BRCA+ve ovarian cancer; however, the current capsule formulation is not suitable for phase 3 testing. Tesaro has developed a commercially suitable formulation for niraparib and as such may be in a position to "leap frog" competitors. Of the other PARP inhibitors in early stage development, Abbott's (ABT's) velaparib is perhaps the most noteworthy, mainly owing to a broad development program including selection by CTEP for inclusion in NCI trials. However, velaparib is dosed twice daily versus once daily niraparib, giving niraparib a distinct advantage.

A third oncology asset of note is TSR-011, a late stage preclinical ALK inhibitor in-licensed from Amgen (AMGN). TSR-011 is more active against ALK than Pfizer's approved ALK inhibitor Xalkori and 200-fold more active against the gatekeeper L1996M mutation. Tesaro plans to initiate clinical testing of TSR-011 in 2H12. The competitive landscape for second-generation ALK inhibitors is brisk and on its 2Q12 earnings call, Novartis announced its intention to start phase 3 trials for ALK inhibitor LDK378 in 2H12. The ALK field is made more competitive by the potential use of heat shock protein 90 inhibitors as ALK drive tumors are very sensitive to Hsp90 inhibition. Key considerations in assessing the potential for TSR-011 to differentiate will be dosing interval, ability to avoid prominent ocular and liver toxicities associated with XALKORI, clinical activity against key resistance mutations including the L1996M gatekeeper mutation, activity in patients failing XALKORI, durability of response and in particular activity on brain metastases, where XALKORI failures are often seen.

Rolapitant – Best in Class NK-1 Antagonist

Rolapitant is a potent selective neurokinin-1 (NK-1) antagonist developed by Schering Plough (SGP) for the prevention and control of chemotherapy-induced nausea and vomiting (CINV). Rolapitant was divested upon acquisition of SGP by Merck (MRK) which developed and sells the only approved NK-1 antagonist, Emend. Key features of rolapitant include a long half life of 180 hours and an absence of activity against cytochrome P450 3A4. Phase 2 data suggest the expected risk reduction benefit of an NK-1 antagonist on delayed emesis, but in addition unexpected benefits on acute emesis and rates of nausea.

At the 2012 American Society of Clinical Oncology (ASCO) meeting, Tesaro presented data from a randomized phase 2 trial of rolapitant in patients receiving highly emetogenic chemotherapy (HEC). The trial randomized 454 subjects to a 5HT-3 antagonist with dexamethasone and one of four dose levels of rolapitant (10mg, 25mg, 100mg or 200mg) or placebo. Rolapitant or placebo was administered on day 1 of each cycle of cisplatin-based HEC. Subjects recorded nausea, emesis and use of rescue therapy in the Nausea Vomiting Subject Diary daily on days 1 through 6 of cycle 1 with the primary endpoint of complete response, i.e. no emesis or use of rescue medication between 0 and 120 hours of cycle 1.

Data presented at ASCO focused on the 200mg rolapitant cohort and are summarized in Exhibit 2:

Exhibit 2: Rolipitant Efficacy at Preventing Nausea and Vomiting from HEC

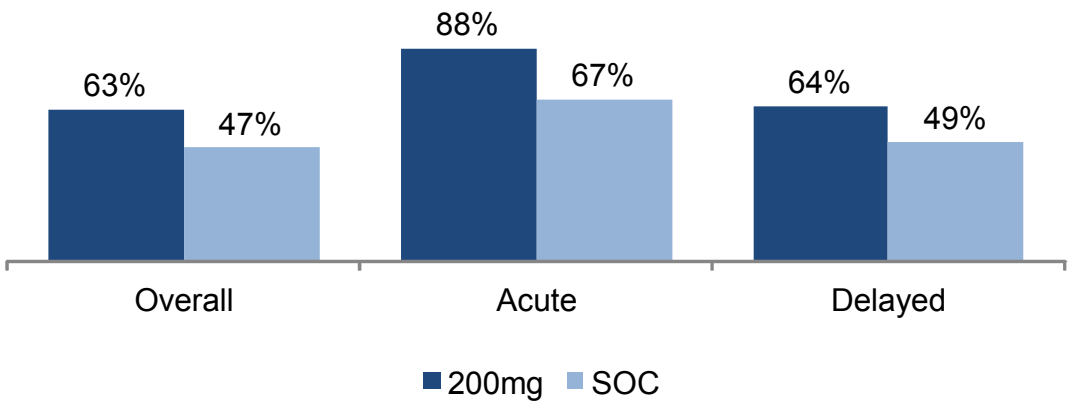
	Placebo	200mg	p value
No emesis & no use of rescue therapy			
0-120h	46.7%	62.5%	0.032
0-24h	66.7%	87.6%	<0.001
>24-120h	48.9%	63.6%	0.008
No emesis			
0-120h	46.7%	67.0%	0.006
0-24h	67.8%	91.0%	<0.01
>24-120h	48.9%	68.2%	0.008
No signficant nausea			
0-120h	42.2%	63.2%	0.005
0-24h	73.3%	86.5%	0.029
>24-120h	47.8%	64.4%	0.026

Sources: ASCO and BMO Capital Markets Research.

For the primary endpoint the addition of 200mg rolapitant on day 1 of cycle 1 increased the probability that patients recorded no emesis or rescue therapy use over 120 hours. In the control group just under half the patients reported no emesis or use of rescue therapy increasing to 62.5% in the rolapitant 200mg cohort. The 0-120 hour improvement in the primary endpoint data were clinically and statistically significant as was the effect on acute emesis/rescue therapy use (0-24h) as well as delayed emesis (>24 – 120h).

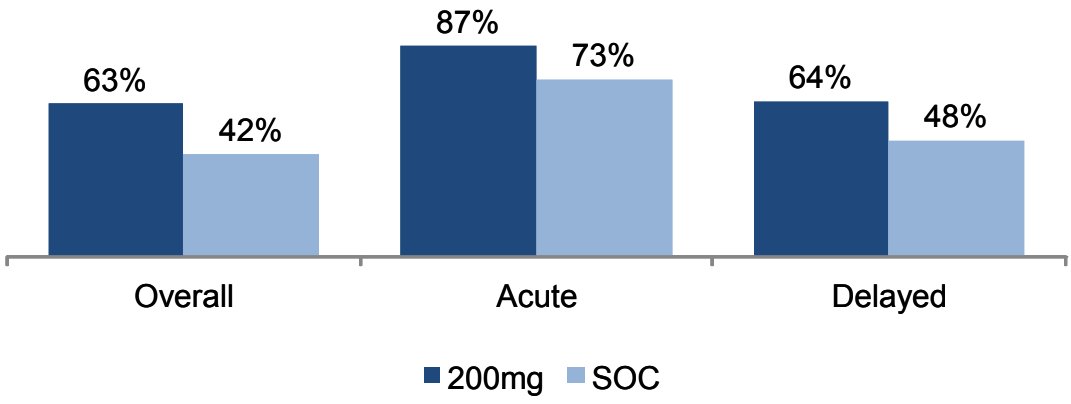
Relaxing the endpoint to just no emesis increased the magnitude of difference between 200mg rolapitant and placebo, while changing the endpoint to a visual analog scale (VAS) for nausea showed the same statistically significant benefits favoring rolapitant over placebo for all three time ranges. The ASCO poster noted that the same magnitude of rolapitant benefits were observed in cycles 2-6.

Exhibit 3: Rolapitant Complete Response Rate



Sources: Tesaro Inc and BMO Capital Markets Research.

Exhibit 4: Rolapitant Nausea Rates



Sources: Tesaro Inc and BMO Capital Markets Research.

Tesaro is currently conducting three phase 3 trials of an oral formulation of rolapitant, including two trials in HEC (n=530) and one trial in moderately emetogenic chemotherapy (MEC) (n=1350). The trials will compare standard of care 5HT-3 based anti-emesis therapy with placebo or a single 200mg dose of rolapitant. The primary outcome for all three trials is absence of emesis and rescue medication use in the delayed emesis phase with overall emesis and acute emesis phase response as secondary outcomes. Additional secondary outcomes include the incidence and intensity of nausea, as well as safety and tolerability. Data from these trials are expected by 2H13. In 4Q12 Tesaro will initiate IV dosing trials designed to demonstrate bioequivalence between oral and IV formulations of rolapitant.

Chemotherapy-Induced Nausea and Vomiting Primer

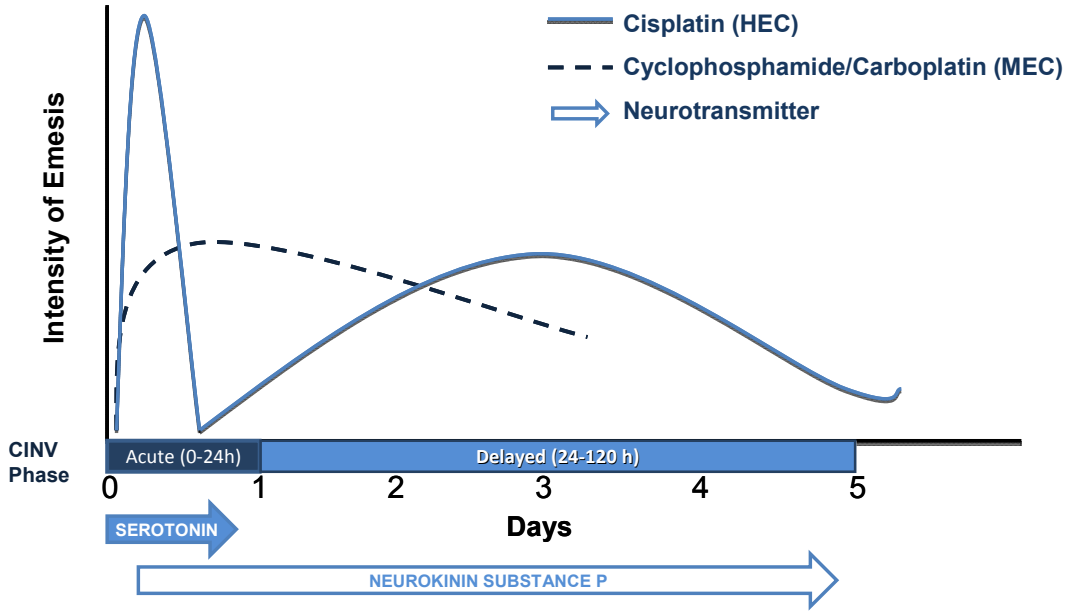
Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of chemotherapy. The National Comprehensive Cancer Network (NCCN) has developed a guideline detailing when and how to use antiemetic agents. The guideline is prefaced by the following principles:

- Risk for nausea and vomiting lasts at least three days after the use of highly emetogenic chemotherapy (HEC) has been completed and two days after the last dose of moderately emetogenic chemotherapy (MEC).
- Oral and IV 5-HT3 antagonists have equivalent efficacy.
- Toxicity of specific agents needs to be considered.
- Choice of anti-emetic should be based on emetic risk, prior experience with antiemetics and patient factors.

NCCN notes that chemotherapy-induced nausea and vomiting (CINV), can affect patient quality of life (QOL) and can interfere with compliance to therapy. Persistent nausea and vomiting can lead to metabolic imbalance, nutritional depletion, anorexia, decreased performance status and functional outcome, which ultimately can affect survival.

NCCN notes that different chemotherapies have different propensities to cause CINV and in general NCCN classifies individual chemotherapeutic agents as highly emetogenic (>90% risk), moderately emetogenic (30-90% risk), low risk emetogenic (10-30%) and minimal risk emetogenic (<10%), Exhibit 6. Several chemotherapeutic agents can appear in more than one category dependent on dose. With the exception of IL-2 and IFN-alpha, all approved biologic agents carry a minimal risk rating. Exhibit 7 summarizes NCCN classification of highly and moderately emetogenic risk therapies.

Exhibit 5: Patterns of Emesis: Highly vs. Moderately Emetogenic Chemotherapy



Source: Adapted from Martin M. *Oncology.* 1996;53 (suppl 1):26-31.

Exhibit 6: NCCN Classification of Highly and Moderately Emetogenic Chemotherapy

- HEC (>90% risk) - IV
  - Anthracycline (doxorubicin or epirubicin) with cyclophsophamide
  - Carmustine <250mg/m^2
  - Cisplatin ≥50mg/m^2
  - Cyclophosphamide > 1500mg/m^2
  - Dacarbazine
  - Doxorubicin >60mg/m^2
  - Eiprubicin >90mg/m^2
  - Ifosfamide ≥10mg/m^2
  - Mechlorethamine
  - Streptozocin
- HEC/MEC - Oral
  - Hexalen
  - Busulfan (≥ 4mg/d)
  - Cyclophosphamide ≥ 100mg/m^2/d
  - Emcyt
  - Etoposide
  - Lomustine
  - Procarbazine
  - Temodar (>75mg/m^2/d)
- MEC (30-90% risk) - IV
  - IL-2 >12-15 million IU/m^2
  - Amifostine >300
  - Arsenox
  - Vidaza
  - Treanda
  - Busulfan
  - Carboplatin
  - Carmustine ≤350
  - Cisplatin <50
  - Clolar
  - Cyclophosphamide ≤ 1500mg/m^2
  - Cosmegen
  - Daunorubicin
  - Doxorubicin ≤ 1500mg/m^2
  - Epirubicin ≤ 1500mg/m^2
  - Idarubicin
  - Ifosphamide ≤ 1500mg/m^2
  - IFN-alpha > 10 M IU, M2
  - Irinotecan
  - Melphalan
  - Cyclophosphamide ≥ 250mg/m^2
  - Oxaliplatin
  - Temodar

Sources: NCCN and BMO Capital Markets Research.

As noted in the preface, NCCN's goal is to initiate antiemetic therapy before starting chemotherapy and Exhibit 7 details the consensus strategies for HEC IV chemotherapy, MEC IV chemotherapy and HEC/MEC oral chemotherapy.

Exhibit 7: NCCN Consensus for Prevention of Chemotherapy Induced Nausea and Vomiting

- HEC IV chemotherapy
  - 5-HT3 antagonist + Steroid + NK-1 antagonist
    - Emend PO 125mg d1, 80mg d2-3 Emend IV 150mg d1
    - Emend IV 115mg d1, Emend PO 80mg d2-3
- Oral HEC/MEC chemo
  - 5-HT3
- MEC IV chemo D1
    - 5-HT3 antagonist + steroid +/- NK-1 antagonist
  - Emend PO 125mg d1, 80mg d2-3 Emend IV 115mg d1
- MEC IV chemo D2-3
  - 5-HT3 OR steroid OR NK-1
    - Emend PO 80mg +/- dex

Sources: NCCN and BMO Capital Markets Research.

NCCN recommends that a 5HT-3 antagonist be administered prior to the first dose of MEC or HEC and then dexamethasone is recommended for 2-3 days following initiation of steroid-free chemotherapy as once-daily therapy. For agents or regimens where delayed emesis is a concern in terms of delivering the next cycle of therapy on time, a neurokinin-1 (NK-1) antagonist can be used. NCCN notes that Category 1 evidence exists for the use of Emend with single-day chemotherapy regimens where Emend dosing occurs on days 1-3. NCCN notes that phase 2 data support that Emend use on days 4 and 5 of multi-day chemotherapy regimens is safe but evidence for prevention of nausea is lacking. As an alternative to three days of oral Emend, NCCN notes that a high dose of IV Emend can be given on day 1. With respect to efficacy, NCCN comments that the prophylactic use of antiemetic therapy with HEC decreases the risk for vomiting from >90% to ~30%. However, while antiemetic therapy is effective at reducing vomiting, NCCN notes that control of nausea is much harder.

Physiology of Nausea and Vomiting

Vomiting is triggered when chemoreceptor sensors in the chemoreceptor trigger zones found in pharynx, GI tract and cerebral cortex signal the vomiting center in the medulla. The principal neuroreceptors used by chemoreceptor sensors are the serotonin 5HT-3 and dopamine receptors. In the vomiting center of the brain numerous receptors have been implicated including neurokinin-1 (NK-1).

The two principal antiemetic receptor antagonist agents target different parts of the emetic pathway and combination therapy is recommended by NCCN as no single agent can protect from the various phases of emesis. NCCN describes three phases of chemotherapy-induced nausea and vomiting (CINV).

1. Acute-onset – occurs minutes to several hours after administration of emetogenic chemotherapy and resolves over 24 hours. Intensity peaks 5-6 hours after administration. Risk of acute onset CINV is influenced by age and gender with younger females (<50 years of age) at highest risk.

2. Delayed onset – develops more than 24 hours after administration of chemotherapy. Most common with the use of a platinate, cyclophosphamide and/or doxorubicin. Cisplatin associated emesis peaks 48-72 hours after administration and can last 6-7 days.

3. Anticipatory – occurs before patients receive their next round of chemotherapy. Associated with a negative prior experience of CINV. Incidence ranges from ~ 20% to 60%, with nausea more common than vomiting. Younger patients are more susceptible to anticipatory CINV due to more frequent use of aggressive chemotherapy.

In addition to the three common subclasses of CINV, NCCN recognizes breakthrough emesis which occurs despite prophylaxis and requires the use of rescue antiemetic agents and perhaps most disturbingly refractory emesis, which reflects failure of both prophylaxis and rescue antiemetics.

Antiemetic agents can be delivered by a variety or routes including oral, rectal, IV, intramuscular, or transdermal. For patients unable to swallow, intravenous (IV) administration is preferred. NCCN notes that while studies show comparability between antiemetic agents, individual patient responses vary and therapy may need to be individualized.

Emend is the only approved NK-1 antagonist, in contrast to numerous approved 5HT-3 antagonists. Emend acts by preventing substance P from binding to the NK-1 receptor. This mechanism is different but complementary to other antiemetic agents. The two phase 3 trials of Emend added to a 5HT-3 antagonist and a steroid are summarized in Exhibit 8:

Exhibit 8: Control of Acute and Delayed Emesis in Emend Phase 3 HEC Trials

	5HT-3/Dex	Emend 5HT-3/dex
Study 1 n=519		
Acute emesis control	78%	89%
Delayed emesis control	56%	75%
Study 2 n=523		
Acute emesis control	68%	83%
Delayed emesis control	47%	68%

Sources: NCCN and BMO Capital Markets Research.

As noted in the phase 3 trials, and confirmed by a meta-analysis of seven randomized controlled trials (RCTs), Emend used alone or with other anti-emetic agents does not increase protection against acute nausea but is effective at improving protection from delayed nausea from HEC. With respect to MEC, a phase 3 trial enrolling 866 patients, showed that the addition of Emend

to a 5HT-3/dexamethasone doublet was more effective at controlling vomiting in the 120 hours following chemotherapy but that nausea rates remained unchanged at 40%.

NCCN states that antiemetic therapy needs to be individualized and that part of the equation is taking into account potential drug-drug interactions. Emend is simultaneously a substrate, moderate inducer and moderate inhibitor for cytochrome P450 3A4, and also induces CYP2C9. The effects of Emend on other drugs are more significant for the oral formulation. The Emend prescribing information warns of serious or life-threatening reactions occurring with Emend administration in the context of the oral antipsychotic Orap, and three drugs no longer on the US market, Seldane, Hismanal and Propulsid. NCCN notes that many commonly used chemotherapy agents are metabolized by CYP3A4 including taxanes, etoposide, vinorelbine and vinca alkaloids and caution is urged when using Emend with one of these agents. Further, NCCN notes that Emend interacts with several non chemotherapy drugs including Warfarin where clinically significant reductions in INR are a risk.

Rolapitant Analysis

Rolapitant has a long half life and like Emend a single IV dose would be expected to provide coverage for a full 120 hours after a single day of chemotherapy. However, unlike Emend, Rolapitant does not interact with CYP3A4 and thus the level of concern for unwanted interaction with both chemotherapy and non-chemotherapy drugs is lower.

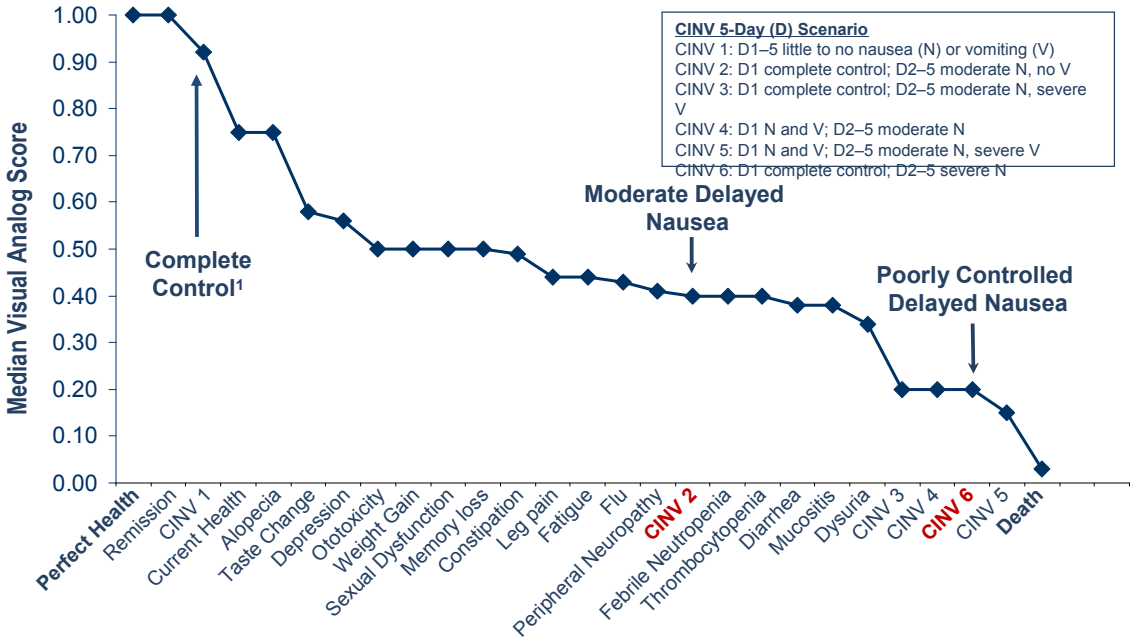
Exhibit 9: Rolapitant Features of Differentiation

Product / Product Candidate	Status	Single Dose Oral	Single Dose IV	Low CYP 3A4 DDI Potential	Potential to Prevent Nausea[2]
Rolapitant	**Phase 3 (oral)**	✓	✓	✓	✓
EMEND® (aprepitant Oral & fosaprepitant IV)	Oral 3-Day; 2003 IV 150 mg; 2010		✓		
Netupitant - palonosetron combo	Phase 3	✓			NA
Casopitant	NDA Withdrawn	✓	✓		

[1]No head-to-head clinical trials have been conducted
[2]Based upon the secondary endpoint of "No Significant Nausea"; P3 data and the product label (aprepitant, fosaprepitant), P3 data (casopitant), and P2 data (rolapitant)
"NA": unknown
Sources: Tesaro Inc and BMO Capital Markets Research

The rolapitant phase 2 trial showed as expected an effect of rolapitant on delayed emesis resulting from HEC. However, a statistically significant effect was observed for acute emesis, which if repeated in the phase 3 trial would be the first time an NK-1 antagonist has had a significant effect on acute emesis. In addition the phase 2 rolapitant trial also showed a benefit in nausea control favoring rolapitant, again a benefit not seen with Emend. Focus at a recent supportive care meeting in New York City with roughly 1,500 oncologists suggests that persistent nausea remains a significant unmet need and an area of tremendous morbidity.

Exhibit 10: Patient Ranking of Chemotherapy Side Effects



Source: Adapted from Charlotte C. Sun et al., Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer, Support Care Cancer (2005).

Casopitant – A Cautionary Tale

GSK filed casopitant for approval in 2Q08, but received a complete response letter (CRL) from FDA in 3Q09. GSK subsequently withdrew the application as it became clear that regulators required additional safety data. While GSK did not state the nature of safety concerns, GSK researchers recently published data from long term (6 months) and dog (9 month) toxicology studies. In both species and both genders a consistent finding was the development of cardiomyopathy and cardiovascular changes at a median exposure of ≥50 µg h/mL. Incidence of cardiac changes were time and dose dependent and were accompanied by an increase in plasma levels of biomarkers of cardiac damage including troponin I and creatinine kinase-MB. Moreover, transmission electron microscopy revealed evidence of ultrastructural changes in the hearts of treated animals consistent with phospholipidosis. While phospholipidosis was not an unexpected finding for casopitant, the myocardium is not a common target of phospholipidosis. The major metabolite of casopitant, M200 was found at increasing levels over time in dog

myocardium. However, the inability to use plasma levels of M200 to predict tissue levels means that monitoring of M200 to provide a margin of safety could not be easily performed with a blood test.

Long-term toxicology testing for rolapitant was performed by SGP and none of the pathogenic changes observed with casopitant were observed for rolapitant.

TSR-011 – A Potential Best in Class ALK Inhibitor

Tesaro's ALK inhibitor (ALKi) program was developed by Amgen and acquired by Tesaro in 1Q11. The lead compound was renamed TSR-011, although Tesaro has also published data for a related compound TSR-012. Tesaro's ALKi program is in the late pre-clinical stage with a targeted IND submission date of 2H12. At the 2012 AACR meeting, Tesaro published *in-vitro* characterization data of TSR-011 including comparative data to Pfizer's Xalkori. In both kinase inhibition assays and cell based assays, TSR-011 was considerably more active at inhibiting ALK than Xalkori.

The IC_{50} of TSR-011 was approximately 10nM or less across different cells lines with an NPM-ALK, EML4-ALK translocation or ALK amplification. By comparison, Xalkori activity across the same cell lines ranged from 16 – 108nM. Against the gatekeeper L1196M Xalkori resistance mutation, TSR-011 is 100-200 fold more active than Xalkori.

In xenograft tumor models, TSR-012, a related Tesaro ALKi, completely suppressed phosphorylation of ALK 8 hours post dosing at a dose of 30mg/kg. Increasing the dose to 60mg/kg provided over 90% inhibition of ALK phosphorylation for at least 24 hours. Partitioning of TSR-12, and we assume TSR-011 between plasma and tumor compartments suggests preferential accumulation of the drug in tumors as the compound is cleared from plasma between 8 and 15 hours, yet ALK inhibition is observed beyond 24 hours.

Tesaro currently plans to evaluate TSR-011 in ALK+ve non small-cell lung cancer (NSCLC) patients who are ALKi naïve as well as those who have been progressed on an ALK inhibitor. Beyond NSCLC, Tesaro plans to evaluate TSR-011 in patients with ALK amplification, ALK activating mutations or other ALK fusions across other tumor types.

ALK Biology

ALK or anaplastic lymphoma kinase is a largely silent gene in normal lung tissue, however when a translocation of a part of the EML-4 gene occurs juxtaposed to ALK, ALK expression is turned on constitutively and in the case of NSCLC, ALK becomes oncogenic. The fusion of EML-4 with ALK is causative in approximately 5% of NSCLC, making EML4-ALK one of the top 5 molecularly driven causes of NSCLC identified to date. The discovery of an EML4-ALK fusion in NSCLC was preceded by the discovery of a nucleoplasmin or NPM fusion with ALK in anaplastic large-cell lymphoma (ALCL). Beyond ALCL and NSCLC, ALK fusions have been found in inflammatory myofibroblastic tumor, diffuse large B-cell lymphoma, breast cancer, colorectal cancer and squamous cell carcinoma (SCC) of the esophagus. In parallel to the development of ALKi, has been a companion diagnostic. Detection of tumors bearing the EML-4 ALK fusion has been enabled by a 2 color FISH kit such that positioning of a green and red probe next to each other or overlapping to produce a yellow signal indicates a fusion.

Signaling of ALK fusions occurs via the RAS/RAF/MEK/ERK pathway and PI3k/AKT/mTOR pathways predominantly. These are the same pathways used by the EGF and MET receptors and in this context Pfizer repurposed a MET antagonist, crizotinib, as an ALKi leading to its development and approval in NSCLC under the brand name Xalkori. ALK +ve NSCLC is a distinct subtype of NSCLC associated with a younger age of onset than in the general NSCLC population and also with non-smoking or light smoking status.

Xalkori was evaluated in a large phase 1 trial and a follow-on phase 2 trial enrolling 119 and 136 ALK+ve NSCLC patients respectively. Xalkori efficacy is summarized in Exhibit 11.

Exhibit 11: Xalkori Efficacy in NSCLC

	Phase 1	Phase 2
n	119	136
ORR %	61	50
DoR (range) wk	48 (4+ - 77+)	42 (6+ - 42+)
Median PFS	10	NR
6 mo OS	90%	NR
12 mo OS	81%	NR

Sources: Scagliotti et al and BMO Capital Markets Research.

In both trials the majority of responses were rapid occurring within the first eight weeks of therapy. Overall RECIST defined response rates were high but waterfall plots of target lesions in individual patients demonstrate that >90% of ALK+ve patients derived clinical benefit from Xalkori. These data clearly indicate that EML4-ALK is the dominant oncogene in the tumor. The duration of Xalkori benefit is approximately 10 months with some patients continuing to receive Xalkori after two years.

While the two completed Xalkori trials were uncontrolled, an assessment of Xalkori effectiveness can be obtained by comparing each patient's response to the therapy immediately preceding Xalkori to that on Xalkori. With respect to the phase 1 trial, the median duration of response to the therapy immediately prior to Xalkori in 3rd or later line patients was 14 weeks, versus 31.1 weeks for Xalkori. Similarly in phase 2, the median duration or response to Xalkori was 10 weeks longer (22.3 versus 12.1 weeks) than the response duration for the immediately preceding therapy.

Data from large randomized studies against standard of care therapies in the front and second line setting are maturing, and trial designs are summarized in Exhibit 12.

Exhibit 12: Ongoing Phase 3 trial of Xalkori in ALK+ve NSCLC

Disease	Patients	Trial Design	N	1ary EP	Milestone
NSCLC	Frontline	Xalkori versus Alimta/platinum doublet	334	PFS	Data 4Q13
NSCLC	Asian front line ALK+ve	Xalkori versus Alimta/platinum doublet	200	PFS	Data 3Q15
NSCLC	2nd line	Xalkori versus Alimta or Taxotere	318	PFS	Data 1Q12

Sources: clinicaltrials.gov and BMO Capital Markets Research.

Given the absence of randomized data in the frontline setting, analysis of Xalkori activity relative to chemotherapy in front line patients relies on retrospective analyses from small case series. Acknowledging caveats associated with case series analysis, published data suggest that ALK+ve NSCLC patients achieve a higher overall response rate (ORR) when treated with Xalkori than 1st line unselected NSCLC patients treated with chemotherapy (~60% vs. 10-20%) and that both progression free survival (PFS) and overall survival (OS) in the advanced setting with Xalkori exceed those observed in front line patients treated with chemotherapy. The ongoing studies listed in Exhibit 12 will clarify the role of chemotherapy in treating ALK+ve disease, and while available data for chemotherapy in ALK+ve disease are scant they suggest that ALK+ve disease may be more sensitive to Alimta than other chemotherapeutic agents, perhaps suggesting a role for combination therapy with an ALKi.

The safety profile of Xalkori will be defined by a large ongoing registry; however data from clinical trials and reported at medical meetings suggest that Xalkori is well tolerated and that serious adverse events (SAEs) are few and far between. Grade 3 or higher adverse events (AEs) occurred in 16% of patients in phase 1 and 26% in phase 2, however most AEs were deemed unrelated to treatment. The Xalkori studies have identified some common AEs associated with Xalkori which include:

- Visual effects - ~60% incidence mostly grade 1 occurring around 2 weeks
- GI effects – acute (day 2) and common
- Edema – delayed onset usually occurring after 2-3 months

Treatment failure to Xalkori is almost universal and while only a few case series have been analyzed, it is estimated that approximately 50% of failures occur via an ALK dominant pathway and 50% through a non-ALK-dominant pathway. In the case of ALK dominant resistance, the most commonly observed mechanisms are development of additional ALK mutations that confer resistance to Xalkori or ALK overexpression to an extent that Xalkori's ability to control ALK signaling is overpowered. In the case of ALK non-dominant progression, ALK is replaced as the driver of tumor growth by an alternate pathway.

Mutations conferring resistance to Xalkori are numerous and while a gatekeeper mutation has been described, L1996M, it accounts for perhaps 20% of resistance to Xalkori. The broad pattern of resistance development to ALK in the context of new EML4-ALK mutations is reminiscent of the pattern observed to another first-in-class drug used to treat a translocation driven cancer, Gleevec in CML. In the case of CML, patterns of resistance mutations to more potent inhibitors show a reduction in breadth of mutation types and this has led to more potent, but equally well tolerated agents rapidly replacing Gleevec as the front line agent of choice.

With 50% of Xalkori failures due to the development of Xalkori resistance mutations, the opportunity to develop more potent inhibitors of ALK has not gone unnoticed by industry. Novartis, Roche (Chugai), Ariad and Astellas have reported or will report phase 1 data in 2012 for compounds that are more potent than Xalkori including activity to the L1196M gatekeeper mutation. Behind these clinical candidates are several companies with late-stage pre-clinical candidates including Tesaro.

At the recent American Society of Clinical Oncology (ASCO) meeting, Roche and Novartis presented first in man phase 1 data for ALK inhibitors CH5424802 and LDK378 respectively. Key points from each presentation are highlighted below.

- Roche evaluated twice daily CH5424802 in 24 patients with ALK positive NSCLC. Among 20 patients evaluable for response, an 85% overall response rate (ORR) was observed increasing to 100% for 15 patients treated at a higher dose of 240mg/day.
- Novartis evaluated LDK378 in patients with advanced solid tumors including Xalkori failures. The headline data from the phase 1 trial was an 80% overall response rate (ORR) in Xalkori-resistant patients; however, absent ALK sequencing data, it is hard to establish how active LDK378 is; a priori, in a random selection of Xalkori failures, one would expect the response rate to be no more than the proportion of ALK dominant patients, which is estimated to be 50%. Further compounding the difficulty of assessing the activity level of LDK378, only 1 of 7 Xalkori-naïve patients responded.

Overlaying the nature of the development of resistance to Xalkori is the organ where progression occurs. The brain is often the first site of progression in patients treated with Xalkori. Because Xalkori does not effectively cross the blood brain barrier, CNS progression can occur independently of systemic control and does not necessarily reflect development of resistance to Xalkori. The clinical implications of progression depend on the nature of the CNS lesion(s). A single small lesion can often be treated with radiation therapy while the patient continues to benefit from Xalkori. However, more complex CNS progression or recurrence of CNS lesions following cranial irradiation may lead to Xalkori discontinuation despite evidence for continued systemic control. Thus in addition to new ALK inhibitors being more potent at inhibiting ALK and decreasing the likelihood and diversity of resistance mutation development, inhibitors that effectively cross the blood-brain-barrier (BBB) would be expected to reduce the development of CNS progression potentially further prolonging the duration of ALKi treatment. With respect to data reported at ASCO, we note that investigators for NVS's LDK378 reported data for a patient that was entered into the phase 1 trial with a CNS lesion at baseline. Preliminary data suggest that the lesion responded to LDK378.

Is Xalkori Suitable for Use in Adolescent Patients?

While the focus of Xalkori development has been in non small-cell lung cancer (NSCLC), there are many tumors where ALK translocation is oncogenic. Some of these tumors predominate in pediatric and adolescent populations, but recent observations of a near universal effect of Xalkori on testosterone suppression may lead to reluctance for Xalkori use in peri-pubescent/pubescent patients. Serum testosterone is not routinely measured in NSCLC patients according to experts we have spoken with and the effect of Xalkori on serum testosterone came to light in one clinic after a younger male patient complained of sexual dysfunction. Following this case, the clinic broadened their review of testosterone levels for patients receiving Xalkori noting a rapid and near-universal suppression. Whether this is an on target or off target effect of ALK inhibition remains to be seen but clearly offers another potential point of differentiation for next generation inhibitors.

Second Generation Inhibitors May Not Be the Only Solution

Research has suggested that ALK is a client of heat shock protein 90 (HSP90) and that Hsp90 is critical to maintaining viability of ALK+ve NSCLC cells. Synta pharmaceuticals (SNTA) has developed ganetespib as an Hsp90 inhibitor that in pre-clinical studies appears to be very effective at inhibiting both native and mutated ALK. The latter may have particular relevance in the clinic as pre-clinical data presented at AACR for 4 unidentified second generations ALK inhibitors suggest that each has its own profile of activity against the panoply of mutations that have been observed to develop in the context of Xalkori. In some cases, the second generation inhibitors were less effective than Xalkori and key opinion leaders have suggested that at the point of confirmed Xalkori failure due to development of a resistance mutation, selection of the second line ALK inhibitor will be dependent on its specific activity to the Xalkori resistance mutation developing in the progressing lesion(s). A simpler approach could be to use an Hsp90 inhibitor, as its activity is not dependent on mutation status, that is to say the activity of Hsp90 inhibitors such as ganetespib is independent of mutation status suggesting that ganetespib offers a simpler approach to 2nd line therapy.

While Hsp90 inhibitors such as SNTA's ganetespib can be considered as competitive to ALK inhibitors, their use is not mutually exclusive to direct specific ALK inhibition. Studies are ongoing combining Xalkori and ganetespib in newly diagnosed ALK+ve patients with a view to increasing progression free survival (PFS) by reducing the rate of development of resistance mutations; clearly development of more potent inhibitors may obviate the need for Hsp90 combination therapy.

TSR-011 Analysis

At this stage it is too early to determine how competitive Tesaro's ALKi is to the handful of other clinical candidates. While some characteristics such as the ability to cross the blood brain barrier and cross reactivity to newly identified oncogenic drivers in NSCLC such as ROS1 that are sensitive to Xalkori can be clarified short term, key safety and efficacy characteristics can only be assembled after large randomized clinical studies.

Tesaro's development of an ALKi is clearly behind the programs at Novartis, Roche, Astellas and Ariad, and it is incumbent on Tesaro to accelerate development and to narrow the lead of these companies; on their 2Q12 earnings call, NVS announced their intention to start pivotal studies of LDK378 before YE12. Currently ALKi development is straightforward since Xalkori was approved for approval by the CHMP in Europe only in late July 2012 and even in the US, investigators are comfortable randomizing Xalkori-naïve ALK+ve NSCLC patients to trials that do not include a Xalkori arm.

The pool of post-Xalkori ALK-dominant patients is growing and will service the growing number of post-Xalkori trials that we expect to begin in the next 12-18 months. In this context we believe that to remain competitive, Tesaro needs to conduct a rapid, perhaps healthy volunteer trial of TSR-011 and move straight to registration enabling trials. In parallel, Tesaro needs to clearly differentiate TSR-011 from the burgeoning competitive landscape. The preliminary data suggesting a long half life and preferential accumulation in tumor tissue are encouraging but once-daily ALKi are in the clinical and as a class the compounds appear to be relatively well tolerated.

Niraparib – First to market PARP Inhibitor

Niraparib was developed by Merck (MRK) where the product was known as MK-4827. It is an orally active PARP 1/2 inhibitor with IC_{50} for PARP1/2 ranging from 2-4nM versus >100nM potency against other PARP family members. Pre-clinical data show that niraparib has activity in BRCA deficient tumors with 50% cell kill (CC_{50}) concentrations ranging from 10-90nM. Niraparib activity is specific for BRCA deficient tumors as the CC_{50} for BRCA proficient tumors is >1500nM. Pre-clinical data also show that niraparib is somewhat effective in tumors that are BRCA proficient but have defects in other parts of the homologous recombination DNA repair pathway, displaying a so-called BRCA-ness phenotype. Niraparib CC_{50} concentrations range from 100nM to 800nM for tumor cell lines deficient in DNA repair enzymes such as PTEN or ATM.

Phase 1 data for daily oral niraparib were reported at the 2010 American Society of Clinical Oncology (ASCO) meeting. The phase 1 trial was enriched for patients with cancers likely to have homologous recombination (HR) DNA repair defects including patients with known BRCA mutations as well as tumors with a high likelihood of sporadic HR repair defects such as high grade serous ovarian tumors. The phase 1 trial evaluated once daily oral doses of niraparib ranging from 30mg to 400mg in 60 patients and was followed by dose expansion cohorts (300mg/day) in patients with platinum resistant ovarian cancer and castrate resistant prostate cancer (CRPC).

In the breast cancer dose escalation phase, 12 partial responses (PRs) were observed for an overall response rate (ORR) of 20% with the majority of activity (n=10) restricted to patients with BRCA mutations. An additional 24 patients showed prolonged stable disease (SD) including both BRCA and non-BRCA mutation carriers. Of the 39 evaluable patients with ovarian cancer, a 46% clinical benefit rate (CBR) was observed, increasing to 58% in patients with a BRCA mutations

Niraparib was well tolerated with grade 1 constitutional symptoms commonly observed including nausea, vomiting, diarrhea, fatigue and anorexia in 20-45% of patients. Grade 3 non-hematologic events however were rare. Grade 3 hematologic toxicity was observed in the single digit range and only for thrombocytopenia were grade 4 events observed (6%). Thrombocytopenia was deemed dose limiting, with niraparib maximal tolerated dose (MTD) established at 300mg/day.

An analysis of niraparib pharmacokinetics (PK) show an accumulation of product over 21 days after which a steady state is observed with a terminal half life ranging from 37-42 hours. Pharmacodynamic (PD) studies of PARP activity in peripheral blood mononuclear cells (PBMC) suggest that at doses of 80mg/day and above significant PARP activity is inhibited. Accumulation of double strand breaks in DNA from pre and post niraparib tumor samples was observed using gamma H2AX, a member of the histone H2A family of proteins as a pharmacodynamic (PD) marker. A significant up-regulation of H2AX in tumor samples from a BRCA breast cancer patient suggests that niraparib inhibits homologous recombination DNA repair.

The phase 2 development plan for niraparib is in development, but Tesaro plans both monotherapy and combination therapy trials in solid tumors with a high likelihood of both germ line and sporadic DNA repair defects including breast, ovarian, lung and gastric cancers.

DNA Repair Primer

All cells are at risk for genetic instability, leading to DNA damage which is manifest in the production of non-functional proteins. Such proteins can have a deleterious effect on the control of cellular metabolism. While genetic instability can result randomly, exposure of cells to damaging agents such as excessive sunlight or genotoxic chemicals for example can lead to an increased rate of DNA damage. Perhaps not unsurprisingly, several detection and signaling pathways are activated by damaged DNA and initiate a cascade of pathways to repair damaged DNA. The two most common pathways lead to cell cycle arrest, to allow for DNA repair to occur or programmed cell death known as apoptosis.

Since one outcome of damaged DNA is to turn a normal cell into a cancer cell, the genes responsible for repairing damaged DNA can be considered to play a role in tumor suppression. Consequently, mutations in a gene involved in DNA repair would be expected to increase the capability of the cell to become cancer promoting. As noted earlier there are several DNA repair pathways and each pathway is specific for a particular type of DNA damage. Following is a brief list:

- Non-homologous end joining – repair double strand breaks and crosslinked DNA
- Homologous recombination – as above
- Base excision or single strand break repair – removes incorrect bases and repair
- Nucleotide excision repair – repair missing bases
- Mismatch repair – detects and repairs base mismatches, insertions and deletions

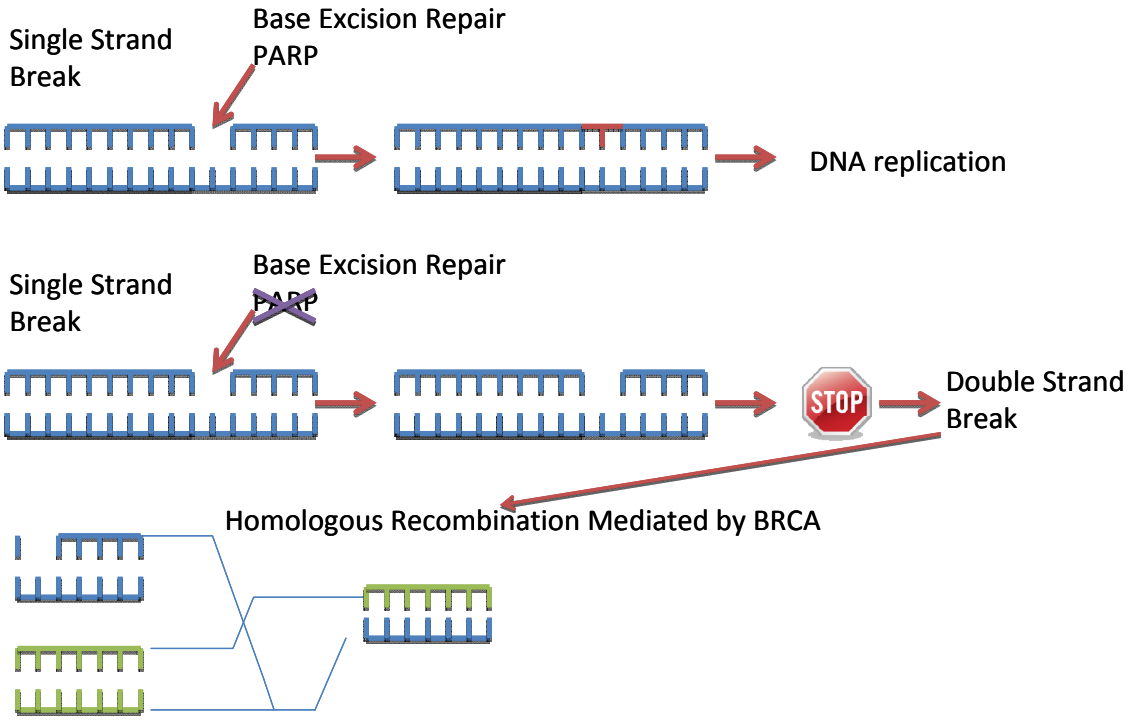
In cancer cells that have mutations to one or more components of a DNA repair pathway, cells can become overly reliant on the remaining pathway(s). This raises the possibility that targeting the dominant pathway could lead to cell death.

Targeting Base Excision and Single Strand Break

The best known DNA repair genes associated with cancer are BRCA1 and BRCA2, which are involved in the repair of double-strand DNA breaks. Cells with germ line mutations in the BRCA genes become overly reliant on the base excision and single strand break repair mechanisms and thus targeting genes involved in this pathway becomes a viable strategy to target tumors with BRCA mutations. A critical enzyme in base excision or single strand break repair is poly (ADP-ribose) polymerase or PARP. At least 16 members of the PARP family have been identified, but only PARP-1 and PARP-2 appear to be involved in DNA repair.

In normal cells PARP-1 activity is low but is upregulated in response to DNA damage. PARP-1 over expression has also been documented in several cancers. PARP-1 is not essential to maintain cell viability as knockout mice are normal, however knocking out PARP-1 and PARP-2 leads to embryonic lethality.

Exhibit 13: Cartoon of DNA Repair and the Role of PARP



Source: BMO Capital Markets

Clinical Development – The Concept of Synthetic Lethality

In classical cancer drug development, single agent activity is required to proceed from small proof-of-concept studies to larger definitive one, however, because there are many pathways involved in DNA repair, it is unlikely that inhibiting a single pathway will lead to cell death. In the case of drugs targeting DNA repair pathways therefore; patients need to be selected who have an existing DNA repair defect, where the use of a drug to inhibit a second pathway may lead to cell death. The concept that two independent mechanisms alone do not affect cell viability but combined, lead to cell death is referred to as synthetic lethality.

PARP inhibitors have been developed in three distinct areas:

- In patients with known non-base excision or single strand break repair DNA repair mutations
- With DNA damaging agents, where PARP inhibition serves to sensitize the tumor to a platinate for example.
- With radiation therapy where PARP also serves as a sensitizing agent.

A number of PARP inhibitors have entered the clinic and are currently at different stages of clinical development as noted in Exhibit 14.

Exhibit 14 PARP Inhibitor Development Summary

Sponsor	Drug	Phase
SAN	Iniparib	3
AZN	Olaparib	2
ABT	Velaparib	2
CLO*	Rucaparib	2
BMRN	BMN673	1
TEVA	CEP-9722	1
Eisai	E7016	1
Tesaro	Niraparib	1

Sources: clinicaltrials.gov and BMO Capital Markets Research; Licensed from Pfizer.

Sanofi's iniparib reached phase 3 testing following a successful phase 2 trial in patients with triple negative breast cancer (TNBC) that has been reported in the *New England Journal of Medicine* (NEJM), O'Shaughnessy et al., 20;364(3):205-14. While TNBC patients were not selected on the basis of a BRCA mutation, their physiology is considered to be BRCA-like based on the genetic profile of TNBC. However, the 520 patient phase 3 trial failed to confirm the benefit for iniparib shown in phase 2. Sanofi (SNY) has concluded that while iniparib does have effects on DNA repair, it does not have the activity profile of a typical PARP inhibitor. This can be explained in part because iniparib targets the zinc finger domain of PARP rather than compete with NAD for the PARP catalytic site as is the case for all other PARP inhibitors

in clinical development. While Sanofi is currently completing a phase 3 trial in NSCLC the development of iniparib will not be a template for other PARP inhibitors.

Behind Sanofi are several earlier stage inhibitors but for the most part published peer reviewed data are largely limited to AZN's olaparib. In comparison to iniparib, AstraZeneca has taken a more biomarker drive approach to developing the PARP inhibitor olaparib. In early phase 1 testing AZN enrolled 60 patients with advanced disease for a multiple ascending dose (MAD) trial at olaparib doses ranging from 10mg/day to 600mg bid dosed 14 of 21 days. A dose of 200mg bid was selected for further evaluation in a cohort of 23 patients with BRCA mutations, comprising mostly breast, ovarian and pancreatic tumors. A partial response (PR) was observed in 9 patients for a response rate of 39%. Following phase 1 testing, two multicenter randomized phase 2 trials were conducted in chemotherapy-refractory breast or ovarian cancer patients with BRCA mutations. Two doses were evaluated, including 400mg bid in the first cohort and 100mg bid in a second cohort. As noted in Exhibit 15, breast cancer patients receiving the higher dose had a greater chance of achieving a response (41% vs. 22%) and benefited from a longer time to tumor progression – 5.7 mo. vs. 3.8 mo. The ovarian cancer patients showed a similar dose response.

Exhibit 15: Phase 2 Olaparib data in BRAC Mutation +ve Patients

	Breast		Ovarian
	ORR	TTP	ORR
400mg BID	41%	5.7 mo.	33%
100mg BID	22%	3.8 mo.	12.50%

Sources: Fong et al, JCO, 2010 and BMO Capital Markets Research.

Fong and colleagues published additional data from the ovarian cancer dose ranging expansion cohort in the *Journal of Clinical Oncology* (JCO), 2010, 28: 15, 2512-19, showing that responses to olaparib were higher in platinum sensitive patients (61.5%) versus platinum resistant patients (15.4%).

Additional evidence of olaparib activity in high grade serous ovarian cancer was reported at the 2010 ASCO meeting by Gelmon and colleagues from a phase 1 Canadian trial. Of the 64 patients enrolled, 10 patients were known BRCA mutation carriers and an overall response rate (ORR) of 40% was observed compared to 26% in the non-BRCA cohort.

In addition to monotherapy trials, data have been reported for a trial combining pegylated doxorubicin (PLD) with olaparib in patients with less than a 12 month PFS following platinate front line therapy. While PLD had not been studied in BRCA+ve ovarian cancer the investigators assumed its activity would be similar to that observed in a general population, that is to say an ORR of ~ 20% and PFS of ~ 4 months.

In the Kaye trial, patients were randomized to PLD (n=33), PLD + olaparib 400mg BID (n=32) or olaparib 200mg BID (n=32). Overall, the treatments were well tolerated with 1-3 patients across the three arms discontinuing therapy due to an adverse event (AE). As shown in Exhibit

16, an overall response rate (ORR) of ~ 20% was observed in the PLD arm increasing to 25-30% in the olaparib arms; these increases did not achieve statistical significance.

Exhibit 16: Phase 2 Pegylated doxorubicin /- Olaparib data in BRAC Mutation +ve Ovarian Cancer

		Olaparib	
	PLD	PLD + 200mg bid	PLD + 400mg BID
ORR	18%	25%	31%
DoR - mo.	6	6.8	5.5
Deaths - n	13	9	11
%Δ ↓in target lesion size -%	14.3%	15.9%	24.6%
Patient with new lesions - %	45.5%	28.1%	34.4%

Sources: Kaye et al, JCO 2012 and BMO Capital Markets Research.

With 11 months of follow-up reported in the JCO manuscript deaths favored olaparib arms numerically, but perhaps more convincing of efficacy was a larger benefit in target lesion size reduction and a concomitant reduction in development of new lesions both favoring olaparib. But with ORRs limited to 20-40%, clinical data suggest that olaparib has activity in an as yet to be defined subset of BRCA mutation +ve ovarian cancer patients. Further evidence for the subset benefit comes from patients crossing over from PLD to olaparib where 8/25 received long-term olaparib treatment.

In the Kaye et al trial, any safety and tolerability effects of olaparib 200mg/day or 400mg/day over and above those of PLD were hard to distinguish and thus it is not surprising that olaparib has been evaluated as maintenance therapy. At the recent ASCO meeting, Oza and colleagues presented data evaluating olaparib (400mg bid) or observation following carbo/taxol + olaparib (200mg bid) induction in patients with platinum-sensitive recurrent serous ovarian cancer. The trial enrolled 156 patients, 121 of whom entered a maintenance phase of observation or olaparib. A statistically significant increase in PFS was observed in favor of patients receiving olaparib maintenance therapy (12.2 vs. 9.6 months; p=0.0012). During maintenance, nausea and vomiting were more commonly observed in the olaparib arms at 50% vs. 6% and 29% vs. 7% respectively with 8% vs. 0% discontinuing due to an adverse event (AE).

In addition to these data, Ledermann and colleagues published data for olaparib (400mg BID) maintenance in serous ovarian cancer patients with platinum sensitive disease, NEJM,; 366: 1382-92. In this trial, 265 patients achieving a partial or complete remission in the second or third line setting were randomized to olaparib (n=136) or placebo (n=129) maintenance therapy. The trial was designed to show a 33% increase in PFS from 9-12 months. While this trial did not restrict enrollment to patients with BRCA mutations, it is estimated that about 50% of high grade serous tumors have deficiencies in DNA repair, specifically homologous recombination due to mutations of BRCA, epigenetic silencing of BRCA or dysfunction in BRCA-related genes – so called BRCA-ness. Baseline demographics showed that of the 100 or so patients for which BRCA status was known about 60% had a BRCA mutation.

Following 153 progression events, the median PFS for the placebo group was 4.8 months increasing to 8.4 months in the olaparib group, a hazard ratio of 0.35. Using CA-125 as an additional marker of progression further widened the gap between the two cohorts. Following 21 months of follow up no differences in overall survival have been observed; however, 21 patients remain on olaparib compared to 4 on placebo.

Exhibit 17: Phase 2 Olaparib Maintenance Data in High Grade Serous Ovarian Cancer

	Placebo	Olaparib
PFS - mo.	4.8	8.4
PFS/CA-125 mo.	3.7	8.3
ORR	4%	12%
Deaths n	49	52
OS - mo.	29.9	29.7

Sources: Ledermann et al, NEJM Mar12 and BMO Capital Markets Research.

As noted in the Oza trial, nausea and vomiting were commonly observed in the olaparib arm of the Ledermann trial and around 1/4 of patients either had a dose reduction or interruption.

Data for overall survival (OS) from both the Oza and Ledermann studies are not yet mature. Given relatively low ORRs for targeted therapy in selected patients we are encouraged to see that AZN will conduct a biomarker analysis combining patient samples form the OZA and Ledermann studies which in total will include over 350 patient biopsies. In addition to AZN identifying a subset of patients where a more profound benefit to olaparib can be expected, AZN needs to complete development of the tablet formulation. As noted by Oza at ASCO, the current capsule dose is unacceptable for continued development and a tablet formulation is required for further development.

With respect to breast cancer, Gelmon presented data at the 2010 ASCO meeting described data from a Canadian OL trial of olaparib in triple negative breast cancer (TNBC) or high grade serous ovarian cancer. The TNBC cohort included 25 patients initially (15 with unknown BRCA status) with a plan to add 20 more patients with unknown BRCA status if a response was observed in the original cohort of 15. However, no objective responses were observed in either the known or unknown BRCA TNBC cohorts.

Velaparib – Broadest Development Program

Velaparib, formerly known as ABT-888 is an oral PARP 1/2 inhibitor developed by Abbott (ABT). Velaparib is not a substrate for p-glycoprotein pump, induction of which has been postulated as a mechanism of resistance to long term treatment with olaparib. The NCI's CTEP program has focused on velaparib as their lead PARP inhibitor and has a number of single agent and combination approaches across a number of different tumors. Currently the clinicaltrials.gov website lists 64 clinical studies of velaparib including 28 phase 2 trials.

At the 2010 ASCO meeting, first in man data were presented for velaparib in combination with cyclophosphamide. While the trial did limit the number of prior therapies a patient could have received, they were all cyclophosphamide naïve. The trial enrolled 30 patients; with breast and ovarian cancer the most commonly represented tumor type. Of the 13 breast cancer patients enrolled, 3 had a BRCA mutation as did 3 of 8 ovarian cancer patients. The trial dose escalated velaparib from 10mg/m^2 BID to 200mg/m^2 BID on days 1-3 with cyclophosphamide dose escalated from to 450mg/m^2 to 750mg/m^2on day 3 in cohorts of 3 patients per dose level. At two dose levels dose limiting hematologic toxicities were observed leading to the addition of 3 additional patients but no further dose limiting toxicities (DLT's) were observed to the maximum tested dose of 200mg/m^2 BID velaparib plus 750mg/m^2 cyclophosphamide.

A single partial response (PR) was observed in a prostate cancer patient with liver metastatic disease of unknown BRCA status and in addition five patients showed stable disease as best response including male breast cancer, BRCA mutation +ve female breast cancer, bladder cancer, NSCLC and colon cancer. The combination was well tolerated with one case each of grade 3 fatigue and anemia, four cases of neutropenia, and two cases of febrile neutropenia; in addition, two cases of grade 4 neutropenia were observed.

The average plasma half life of velaparib was 4h and consistent with this, the activity of velaparib on PARP activity in PBMC showed a >50% reduction of PAPR activity 4h after dosing on day 3 in 75% of patients evaluated.

Niraparib Analysis

While PARP is a highly competitive space, Tesaro believes that it has the potential to be first to market with an inhibitor that has a highly competitive profile including once daily oral dosing. Specifically, Tesaro believes that niraparib has a formulation advantage over AZN's olaparib that allows for rapid deployment of a commercially scalable formulation into the clinic. Tesaro believes the major benefit of niraparib over ABT's velaparib is that niraparib has a much longer half life allowing for once daily dosing versus twice daily for velaparib.

While PARP inhibitors target genetic mutations associated with cancer, they clearly do not produce the same dramatic results as EGFR inhibitors in EGFR+ve NSCLC or BCR-ABL +ve inhibitors in CML. Response rates in PARP trials in patients with BRCA mutations are in the 20%-40% range and while these may increase in the treatment naïve setting, it is clear that clinical development would be aided by the identification of additional biomarkers.

Use of PARP inhibitors as monotherapy and maintenance therapy in patients with BRCA mutations appears feasible, but for larger populations of patients combination of a PARP inhibitor with a DNA damaging agent will likely be required. Currently, there remain many unanswered questions:

Not all commonly used DNA damaging chemotherapies appear to work with PARP inhibition, with anthracyclines as an example.

Even with sensitive chemotherapy agents scheduling of the agent with a PARP inhibitor needs to be resolved, in terms of whether the PARP inhibitor should be used before, simultaneously or after chemotherapy and how is this influenced by the stage of the cell cycle that the chemotherapy acts upon?

Some tumors display shortcuts to bypass homologous recombination as a mechanism to repair single strand breaks and in these tumors additional DNA repair pathway targeting agents will need to be added.

In summary, niraparib has a potential best in class profile for a new class of therapy that is regarded as having the potential to change the paradigm for treating tumors that have DNA repair deficiencies. Longer-term the use of biomarkers may allow for segmentation of larger populations of patients such as those with lung or prostate cancers into BRCA-like and non-BRCA-like expanding the potential for PARP inhibition. As with all therapies safety and tolerability will be a key factor to success and absent data from large randomized trials it is hard to identify distinguishing features between, although the thrombocytopenia observed with niraparib has not been seen with other agents to date.

Tesaro Management

Lonnie Moulder Jr.

Mr. Moulder is the co-founder, CEO and Chairman of the Board of Tesaro. Prior to forming Tesaro, Mr. Moulder was president, CEO and vice chairman of the board of Abraxis from 4/09 to 1/10, prior to the company's acquisition by Celgene. Between 1/08 and 1/09 Mr. Moulder served as vice chairman and executive vice president of Japanese pharma Eisai Co. Ltd following its acquisition of MGI PHARMA. Mr. Moulder joined MGI Pharma in 1999 becoming President and COO in 2002. During this time, MGI developed Aloxi, a 5HT-3 antagonist for the prevention of chemotherapy induced emesis.

Mary Lynne Hedley, PhD

Dr Hedly is the co-founder, president and CSO of Tesaro and serves on the board for directors. Prior to Tesaro, Dr Hedley held senior management positions at Abraxis, Eisai and MGI PHARMA. Prior to joining MGI PHARMA in 2004, Dr Hedly co-founded and served as president and CSO of ZYCOS prior to its acquisition by MGI PHARMA.

Rick Rodgers

Mr. Rodgers has served as Executive Vice President, Chief Financial Officer, Secretary and Treasurer since co-founding TESARO. Mr. Rodgers held executive positions at Abraxis, Eisai and MGI PHARMA prior to co-founding Tesaro.

Exhibit 18: TSRO Income Statement 2011A-2015E

INCOME STATEMENT ($M)	2011A	1Q12A	2Q12E	3Q12E	4Q12E	2012E	2013E	2014E	2015E
REVENUES									
Product Revenues	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 43.3
Collaborative Revenues/Milestones	-	-	-	-	-	-	-	-	-
Total Revenues	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ -**	**$ 43.3**
EXPENSES (GAAP)									
Cost of Goods Sold (COGS)	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ 0.2
R&D Expense	11.8	8.2	11.0	11.5	12.0	42.7	54.0	66.0	78.0
SG&A Expense	3.2	1.2	1.3	1.3	1.4	5.1	10.0	14.5	53.0
Acquired In-Process R&D	0.5	-	-	-	-	-	-	-	-
TOTAL EXPENSES	15.4	9.3	12.3	12.8	13.4	47.7	64.0	80.5	131.2
Operating Income	**(15.4)**	**(9.3)**	**(12.3)**	**(12.8)**	**(13.4)**	**(47.7)**	**(64.0)**	**(80.5)**	**(87.9)**
Depreciation and Amortization	-	-	-	-	-	-	-	-	-
EBIT	(15.4)	(9.3)	(12.3)	(12.8)	(13.4)	(47.7)	(64.0)	(80.5)	(87.9)
Interest Income	0.0	0.0	-	-	-	0.0	-	-	-
Interest Expense	-	-	-	-	-	-	-	-	-
Other Expense	(1.0)	-	-	-	-	-	-	-	-
Interest and Other (net)	$ (1.0)	$ 0.0	$ -	$ -	$ -	$ 0.0	$ -	$ -	$ -
Pre-Tax Income	(16.4)	(9.3)	(12.3)	(12.8)	(13.4)	(47.7)	(64.0)	(80.5)	(87.9)
Income Taxes	-	-	-	-	-	-	-	-	-
Net Income (GAAP)	**(16.4)**	**(9.3)**	**(12.3)**	**(12.8)**	**(13.4)**	**(47.7)**	**(64.0)**	**(80.5)**	**(87.9)**
EPS (GAAP) (basic)	$ (9.12)	$ (0.70)	$ (0.46)	$ (0.47)	$ (0.49)	$ (2.12)	$ (2.30)	$ (2.51)	$ (2.54)
EPS (GAAP) (diluted)	**$ (9.12)**	**$ (0.70)**	**$ (0.46)**	**$ (0.47)**	**$ (0.49)**	**$ (2.12)**	**$ (2.30)**	**$ (2.51)**	**$ (2.54)**
Reconciliation of Reported GAAP to Non-GAAP									
COGS Stock Compensation Expense	-	-	-	-	-	-	-	-	-
R&D Stock Compensation Expense	-	-	1.0	1.0	1.0	3.0	4.0	4.0	4.0
SG&A Stock Compensation Expense	-	-	1.0	1.0	1.0	3.0	4.0	4.0	4.0
Other Adjustments	-	-	-	-	-	-	-	-	-
Total of Reconciliation Items	-	-	2.0	2.0	2.0	6.0	8.0	8.0	8.0
Net Income (Non-GAAP)	$ (16.4)	$ (9.3)	$ (10.3)	$ (10.8)	$ (11.4)	$ (41.7)	$ (56.0)	$ (72.5)	$ (79.9)
Impact of Adjustments to EPS	-	-	0.07	0.07	0.07	0.22	0.29	0.25	0.23
EPS (Non-GAAP) (basic)	$ (0.49)	$ (0.20)	$ (0.38)	$ (0.40)	$ (0.42)	$ (1.40)	$ (2.01)	$ (2.26)	$ (2.31)
EPS (Non-GAAP) (diluted)	$ (0.49)	$ (0.20)	$ (0.38)	$ (0.40)	$ (0.42)	$ (1.40)	$ (2.01)	$ (2.26)	$ (2.31)
Weighted average shares outstanding (basic)	1.8	13.3	26.7	27.0	27.3	23.6	27.9	32.0	34.6
Weighted average shares outstanding (diluted)	1.8	13.3	26.7	27.0	27.3	23.6	27.9	32.0	34.6

Source: Company reports and BMO Capital Markets.

Exhibit 19: TSRO Balance Sheet 2011A-2015E

BALANCE SHEET ($M)	2011A	1Q12A	2Q12E	3Q12E	2012E	2013E	2014E	2015E
ASSETS								
Cash and cash equivalents	$ 39.8	$ 88.6	$ 75.9	$ 137.7	$ 108.8	$ 57.8	$ 25.3	$ 35.4
Marketable securities	-	-	-	-	-	-	-	-
Restricted cash	0.2	0.2	0.2	5.0	20.0	20.0	20.0	20.0
Total cash, cash equivalents, and short-term investments	$ 40.0	$ 88.8	$ 76.1	$ 142.7	$ 128.8	$ 77.8	$ 45.3	$ 55.4
Accounts receivable	-	-	-	-	-	-	-	-
Inventory	-	-	-	-	-	-	-	-
Prepaid expenses and other current assets	2.6	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Total Current Assets	$ 42.6	$ 91.5	$ 78.8	$ 145.4	$ 131.5	$ 80.5	$ 48.0	$ 58.1
Plant, property, and equipment, net	0.1	0.1	0.6	1.1	1.6	3.6	5.6	7.6
Other assets	0.1	1.3	1.3	1.3	1.3	1.3	1.3	1.3
TOTAL ASSETS	**$ 42.9**	**$ 93.0**	**$ 80.8**	**$ 147.8**	**$ 134.4**	**$ 85.4**	**$ 54.9**	**$ 67.0**
Current Liabilities								
Accounts payable	0.6	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Accrued expenses	3.0	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Deferred revenue	-	-	-	-	-	-	-	-
Current portion of long-term debt	-	-	-	-	-	-	-	-
Investor rights obligation	-	-	-	-	-	-	-	-
Other current liabilities	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Current Liabilities	$ 3.6	$ 4.5	$ 4.5	$ 4.5	$ 4.5	$ 4.5	$ 4.5	$ 4.5
Notes payable	-	-	-	-	-	-	-	-
Convertible preferred stock warrant liability	-	-	-	-	-	-	-	-
Convertible preferred stock	-	-	-	-	-	-	-	-
Other liabilities	0.0	-	-	-	-	-	-	-
TOTAL LIABILITIES	**$ 3.6**	**$ 4.5**	**$ 4.5**	**$ 4.5**	**$ 4.5**	**$ 4.5**	**$ 4.5**	**$ 4.5**
Shareholder's Equity								
Common stock	-	-	-	-	-	-	-	-
Preferred stock	64.3	122.7	122.7	122.7	122.7	137.7	137.7	137.7
Additional paid-in capital	0.3	0.5	0.5	80.3	80.3	80.3	130.3	180.3
Accumulated other comprehensive income	-	-	-	-	-	-	-	-
Accumulated deficit	(25.4)	(34.7)	(47.0)	(59.7)	(73.1)	(137.1)	(217.6)	(255.5)
TOTAL SHAREHOLDER'S EQUITY (DEFICIT)	$ 39.3	$ 88.5	$ 76.3	$ 143.3	$ 129.9	$ 80.9	$ 50.4	$ 62.5
TOTAL LIABILITIES AND SHAREHOLDER'S EQUITY	**$ 42.9**	**$ 93.0**	**$ 80.7**	**$ 147.8**	**$ 134.4**	**$ 85.4**	**$ 54.9**	**$ 67.0**

Source: Company reports and BMO Capital Markets

Exhibit 20: TSRO Cash Flow Statement 2011A-2015E

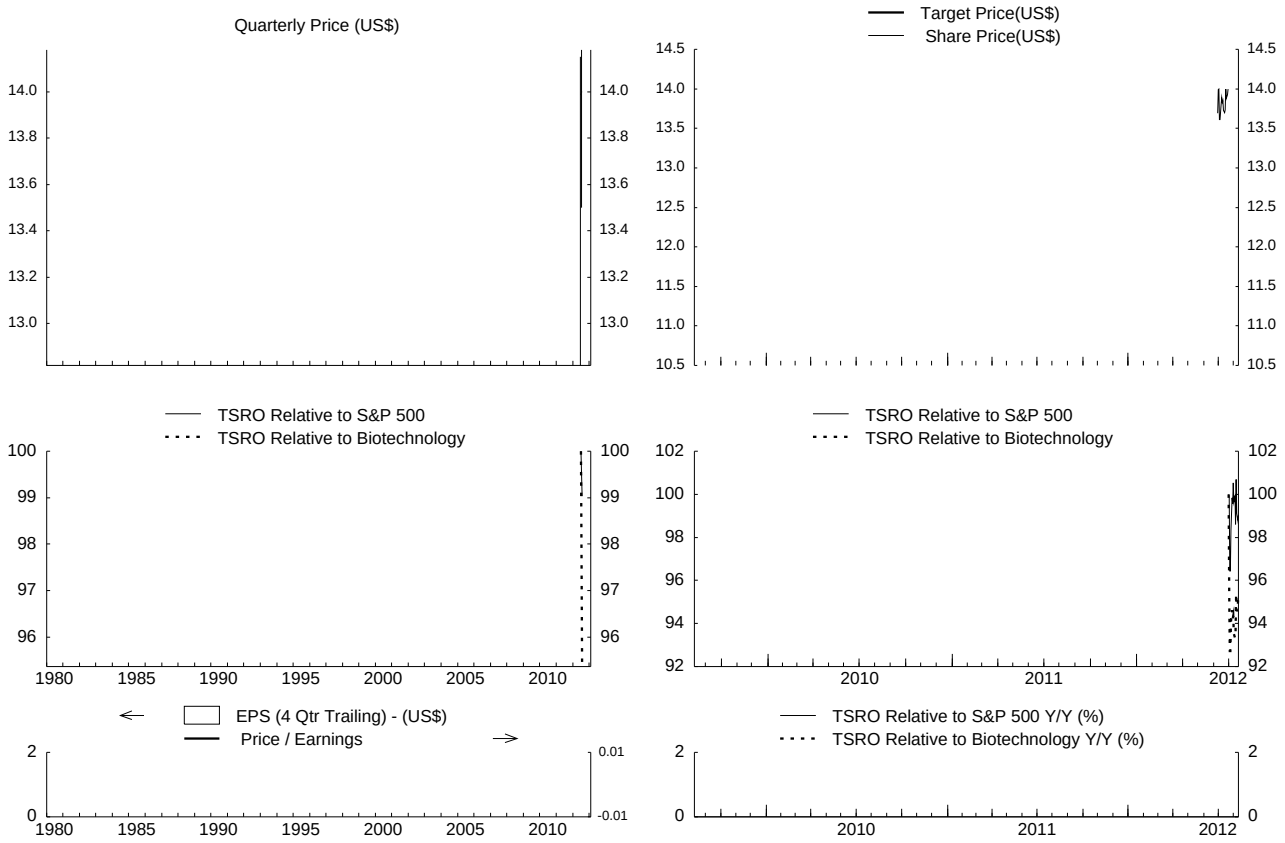
CASH FLOW STATEMENT ($M)	2011A	1Q12A	2Q12E	3Q12E	2012E	2013E	2014E	2015E
Cash Flow From Operating Activities								
Net Income	$ (16.4)	$ (9.3)	$ (12.3)	$ (12.8)	$ (13.4)	$ (18.0)	$ (22.0)	$ (24.2)
Depreciation & Amortization	0.0	0.0	(0.0)	-	-	-	-	-
Stock-based compensation	0.3	0.2	(0.2)	-	-	-	-	-
Loss on disposal of equipment	-	-	-	-	-	-	-	-
Issuance of stock options for services	-	-	-	-	-	-	-	-
Deferred Taxes and Other	1.5	-	-	-	-	-	-	-
Working Capital Adjustments								
Accounts receivable	-	-	-	-	-	-	-	-
Inventory	-	-	-	-	-	-	-	-
Prepaid expenses and other current assets	(2.7)	-	-	-	-	-	-	-
Accounts payable	0.5	0.2	(0.2)	-	-	-	-	-
Accrued expenses	2.6	0.7	(0.7)	-	-	-	-	-
Deferred rent	-	-	-	-	-	-	-	-
Deferred revenue	-	-	-	-	-	-	-	-
Collaboration payable	-	-	-	-	-	-	-	-
Other assets/liabilities	0.0	(0.2)	0.2	-	-	-	-	-
Total Working Capital (Decrease)	$ 0.4	$ 0.7	$ (0.7)	$ -	$ -	$ -	$ -	$ -
TOTAL CASH FROM OPERATIONS	**$ (14.1)**	**$ (8.5)**	**$ (13.1)**	**$ (12.8)**	**$ (13.4)**	**$ (18.0)**	**$ (22.0)**	**$ (24.2)**
Cash From Investing Activities								
Purchases of marketable securities	-	-	-	-	-	-	-	-
Sales and maturities of marketable securities	-	-	-	-	-	-	-	-
Capital expenditures	(0.1)	(0.0)	0.0	-	-	(0.5)	(0.5)	(0.5)
Other	(0.6)	-	-	-	-	-	-	-
TOTAL CASH FROM INVESTING	(0.7)	(0.0)	0.0	-	-	(0.5)	(0.5)	(0.5)
Cash From Financing Activities								
Proceeds from issuance of common stock	52.1	(1.1)	1.1	-	-	-	-	50.0
Proceeds from exercise of stock options	-	-	-	-	-	-	-	-
Proceeds from exercise of warrants	-	-	-	-	-	-	-	-
Proceeds from sales of preferred stock	-	58.4	(0.7)	74.5	(15.5)	-	-	-
Payment of capital lease obligations	-	-	-	-	-	-	-	-
Proceeds from (payments on) long-term debt	-	-	-	-	-	-	-	-
TOTAL CASH FROM FINANCING	52.1	57.3	0.4	74.5	(15.5)	-	-	50.0
Increase (decrease) in cash and cash equivalents	37.3	48.8	(12.7)	61.8	(28.9)	(18.5)	(22.5)	25.3
Cash and cash equivalents at beginning of quarter	2.5	39.8	88.6	75.9	137.7	76.3	47.8	10.1
Cash and cash equivalents at end of quarter	$ 39.8	$ 88.6	$ 75.9	$ 137.7	$ 108.8	$ 57.8	$ 25.3	$ 35.4
Supplemental disclosures of non-cash operating, investing and financing activities								
Issuance of Series O convertible preferred stock	-	-						
Settlement of investors rights obligation	3.8	-						

Source: Company reports and BMO Capital Markets

Other companies mentioned (priced as of the close on July 23, 2012):

Amgen (AMGN, $77.53, **MARKET PERFORM**)
AstraZeneca (AZN, $46.15, Not Rated)
Merck (MRK, $43.27, **MARKET PERFORM**)
Pfizer (PFE, $23.60, Not Rated)
Sanofi (SNY, $37.55, Not Rated)

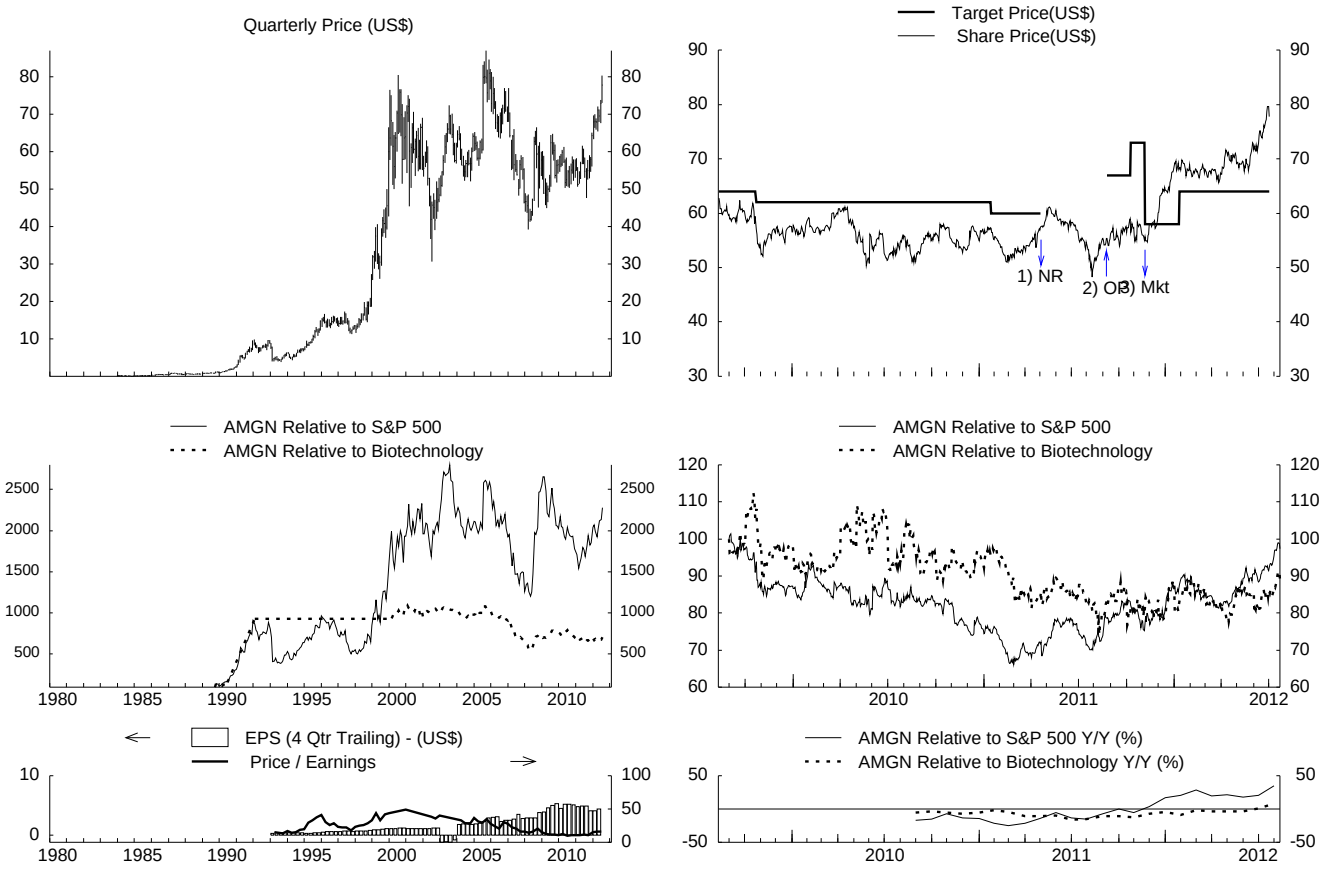
TESARO INC (TSRO)



TSRO - Rating as of 30-Dec-11 = NR

Last Daily Data Point: July 19, 2012

AMGEN INC (AMGN)

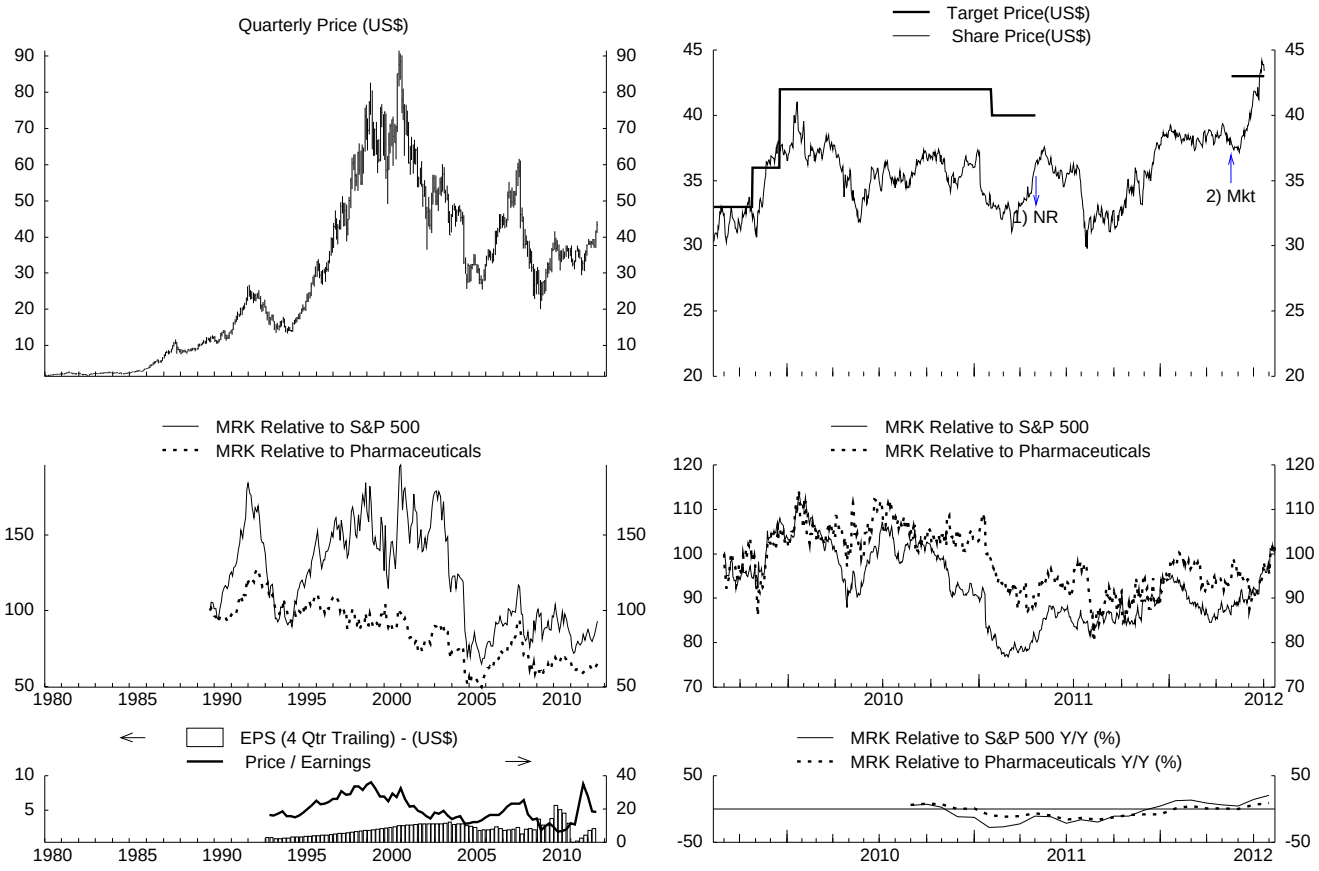


AMGN - Rating as of 11-Aug-09 = NR

	Date	Rating Change	Share Price
1	3-May-11	Mkt to NR	$57.38
2	7-Sep-11	NR to OP	$54.52
3	22-Nov-11	OP to Mkt	$54.97

Last Daily Data Point: July 20, 2012

MERCK & CO INC NEW (MRK)



MRK - Rating as of 11-Aug-09 = NR

	Date	Rating Change	Share Price
1	3-May-11	OP to NR	$36.31
2	17-May-12	NR to Mkt	$38.23

Last Daily Data Point: July 20, 2012

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Methodology: We arrive at our price target by applying a 20x multiple to 2017 GAAP EPS estimate of $2.35 and discounting 25%.
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Rating Category	BMO Rating	BMOCM US Universe*	BMOCM US IB Clients**	BMOCM US IB Clients***	BMOCM Universe****	BMOCM IB Clients*****	Starmine Universe
Buy	Outperform	39.2%	14.2%	66.0%	39.7%	49.1%	55.7%
Hold	Market Perform	58.8%	4.6%	31.9%	57.1%	48.6%	39.3%
Sell	Underperform	2.0%	9.1%	2.1%	3.2%	2.3%	5.0%

* Reflects rating distribution of all companies covered by BMO Capital Markets Corp. equity research analysts.
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(S) = speculative investment;
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