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Research Article

Precision Targeting of Cancer Chemotherapy Using Non-Invasive Focused Resonance Nano-Permeabilization (FORN): Enhancing Drug Delivery to Limit Life-Threatening Systemic Toxicities and Eliciting Good Clinical Outcomes

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Abstract

Focused Resonance Nano-permeabilization (FORN) (US Patent 9,616, 245 B2-Apr 11th 2017) enables the'targeted' delivery of chemo-therapeutic molecules using a safe, non-invasive, whole-body therapeutic device. The prototype device houses a gantry with specialized, near field, radio-frequency (RF) antennae and guns to deliver instantaneous, magnetic resonance. Drug focusing and delivery was enabled using FORN in a patient with advanced, loco-regionally recurrent, metastatic, nasopharyngeal carcinoma (NPC). Non-ionizing, safe, extraneous-source radio-frequencies (RF) were delivered in the presence of an instantaneous magnetic field, to create temporary drug molecular weight-specific nano-pores in the cell membrane of target lesions, concurrently with systemic chemotherapy. The high frequency RF is timed and delivered to regions of interest (ROIs) to span peak plasma concentrations of infused chemotherapeutic drugs over multiple treatment cycles. FORN-enabled chemotherapy-related adverse event evaluation and tumor response based on PERCIST 1.0 reflected improved clinical, anatomical and metabolic outcomes and significantly reduced myelosuppression in the patient who received 6+1 Cycles of combination chemotherapy, over an extended period of time. Functional Assessment of Cancer Treatment-Head & Neck (FACT-H&N) / Quality of Life (QoL) and Karnofsky Performance Status (KPS) reflected overall patient well-being. Recurrent, loco-regional disease, nodal, hepatic and skeletal metastases showed dramatic response on PET-CT follow up. Concurrent chemo-radiotherapy (CCRT) as a treatment paradigm is the standard of practice in locally advanced nasopharyngeal carcinoma (NPC). Different chemotherapy regimens used in relapsed NPC with distant metastases, very often fail any attempts to treat or palliate. The severe cytotoxicity experienced with 'standard of care' palliative chemotherapy in end-stage disease has made patient compliance poor and survival statistics dismal. The role of concurrent chemotherapy with a drug focusing and delivery-enabling technology like FORN can help overcome dose-limiting cytotoxicity and improve therapeutic windows with existing and emerging chemotherapeutic regimens. Providing effective palliation that is largely lacking - while positively impacting therapeutic outcomes and progression free survival - fills a very large vacuum and unmet, urgent medical need today.

Keywords: Focused resonance nano-permeabilization, Non-invasive targeted cancer drug delivery, Therapeutic device, Chemotherapy-related systemic toxicity, Effective palliation and clinical response

Introduction

Targeting solid tumors - primary & metastatic - irrespective of their anatomical location in the body or pathological sub-type - and permeating drug molecules into the targeted tumor mass, will improve therapeutic outcomes and reduce life-threatening systemic toxicities induced by routinely administered chemotherapeutic regimens. Creating molecular dimension-specific temporary pores in the cell membrane using precisely computed, safe radiofrequencies (RF) from an external source, to non-invasively deliver the drug payload, is much less complicated and more cost-efficient than current or emerging invasive, drug delivery approaches. The short-comings of cancer chemotherapy plaguing the industry and patients that desperately need good drugs, can be circumvented with a patented technology called Focused Resonance Nano-permeabilization (FORN) [1].

Although on-going nanotechnology initiatives to deliver "targeted" nanoparticle-coupled drug pay-loads, or nano-variants of existing / new chemical entities are having

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transformational impact on drug-delivery, the field is fraught with technical and translational road-blocks. It is well documented that complex biological barriers are the major obstacles to treating diseases, and the challenges facing the development of nano-scale platforms to face the enormity of drug-induced toxicities are not simple to surmount [2].

FORN is a process by which the focused delivery of chemo-molecules can be enabled by its concurrent use with planned, systemic (and/or oral) chemotherapy. Drug targeting of the chemotherapeutic molecules - carboplatin and paclitaxel during Cycle 2 through 6 and an additional Cycle 7, in a case of advanced, recurrent, metastatic, nasopharyngeal carcinoma (NPC) as part of a proof of concept pilot study, is reported. Systemic chemotherapy was enabled by the concurrent use of non-ionizing, safe radio-frequencies (RF) using specialized antennae in the presence of instantaneous magnetic resonance (MR). FORN is used to create temporary, drug molecular weight-specific nano-pores in the cell membrane of target lesions that are identified in the whole-body, based on pre-treatment MRI-derived proton density (PD) evaluations. High frequency RF is timed and delivered to target lesions, spanning peak plasma concentrations of Carboplatin and Paclitaxel drug until drug wash-out time. The whole body device that delivers the precisely pulsed RF and MR, houses a gantry of RF guns with specialized antennae. The prototype FORN device is modelled after the CE marked, stand-alone, patented legacy device [3] - the Cytotron® used for Quantum Magnetic Resonance Treatment (QMRT®) applied for tissue regeneration in musculo-skeletal disorders like Osteoarthritis (OA), re-myelination in neuro-degenerative diseases like Multiple Sclerosis (MS) and the induction of apoptosis and degeneration of neoplastic tissues in cancer [4].

Loco-regional recurrence in the nasopharynx and metastases in the mediastinal lymph nodes, liver, dorsal vertebrae and iliac crest were simultaneously targeted with FORN in a carefully timed protocol. Base-line chemotherapy induced adverse event evaluation, before applying FORN, and tumor response criteria based on PET-CT scans, were compared with chemotherapy cycles combined with the FORN protocol. Considering that most therapies offered in advanced stages of cancer offer little to no overall survival benefit, the use of a sophisticated yet safe, non-invasive RF and MR-mediated drug delivery technology like FORN, enhanced the therapeutic efficacy of cytotoxic chemotherapy; improved treatment outcomes; dramatically mitigated adverse systemic toxicities and improved Quality of Life (QoL) in this report of an NPC patient presenting with loco-regional recurrence and advanced, multiple metastases**.**

Materials and Methods

Case presentation and standard of care chemotherapy

A forty-eight year old male patient of Anglo-Indian descent, under treatment for recurrent, metastatic, undifferentiated NPC at the Akika Center of the Japanese Cancer Research Foundation (JCRF), Japan, presented to the Manipal Hospital in Bangalore-India, in April 2013, with relapsed disease, following the 1st cycle of the 5thcourse of Carboplatin (CBDCA) + Paclitaxel (Total of 6 cycles were originally planned). Concurrent chemotherapy and FORN was initiated in consultation with the medical oncologists who afforded care for the patient in the study at the Akika Center of the JCRF, Japan and the Manipal Comprehensive Cancer Center (MCCC) and Hospital, in Bengaluru, India, together with the authors involved in the study. Detailed, anecdotal case history as well as Functional Assessment of Cancer Treatment-Head & Neck (FACT-H&N) questionnaires were initiated and maintained through the treatment period and follow up visits [5]. Karnofsky Performance Scale score (KPS/ K- score) [6] was used to assess QoL at specific time points in the study. Patient's clinical status was periodically recorded at baseline (before therapy) and at the completion of every chemo-cycle in the study.

Disease and prior treatment history

2005 (no details available from patient's medical record): A biopsy of a nasal polyp confirmed the diagnosis of locally confined, undifferentiated NPC. Patient was treated with CCRT in USA (6-Gy+weekly Cis-Diamminedichloride Platinum (CDDP) 33mg x 6 wks. (Cycle I)

2010 Nov: Palpable right neck node-confirmed as undifferentiated NPC. Treatment with Cisplatin (CCDP) x 6wks. (Cycle II) given at JCRF.

2011 Feb: Swollen right lymph node (LN) diagnosed in JCRF as relapsed disease with recurrence in the LN. Cycle III with Cisplatin was discontinued because of severe vomiting and diarrhoea. Cisplatin was replaced with Docetaxel. Subsequently received 4 (Cisplatin) of 6 chemo-cycles in the US concurrently with 6 weeks of radiation.

2011 Feb 22nd III Cycle: DC regimen: Docetaxel 75mg/m^2 and CDDP 75mg/ m^2

2011 Mar 15th: IV Cycle: Carboplatin (CBDCA) AUC 6 + Paclitaxel (PAX) #1-200ng/ m^2

2011 Nov 10th: PET-CT confirmed metastatic axillary LN, gradually increasing in size.

2012 March 5th: Presented with cramps and numbness in fingers and pain in upper right hand.

PET scan revealed enlarged right axillary LN. Biopsy confirmed relapse of undifferentiated NPC.

2012 March 28th to June 27th: 6 cycles of chemotherapy (carboplatin and paclitaxel) planned at the JCRF. Treatment discontinued after 4 cycles since CT scans after 2nd and 4th chemo-cycles showed no sign of tumor or lymphadenopathy. The CBDCA + PAX# 2-5 resulted in near complete response.

2013 Feb 18th: Pain in right hand combined with cramps and swelling in fingers. CT scan showed loco-regional recurrence of NPC (not ruled out), mediastinal lymph nodes, and multiple skeletal and liver metastases. (Report based on PET-CT of March 4th 2013 done at JCRF).

2013 Mar 27th: CBDCA + PAX # 6 started at JCRF. Significant adverse effects reported. Patient decided to travel to Bengaluru, India to receive un-interrupted chemotherapy +FORN

2013 April 23rd: Day 1: Suggested 6 cycles of Carboplatin (CBDCA+PAX #6) by the Consultant Medical Oncologist at the MCCC in Bengaluru, India.

2013 May14th to August 15th: Completed all planned chemo-cycles (once every 3 weeks) with adjuvant FORN.

2013 August 5th: PET-CT (1st) Outcome: Selected images compared with original PET in March 2013 and PET-CT at MCCC in August 2013 (2nd) after 1st round Chemotherapy.

2013 Sept (no date specified): Patient returned to work in Japan.

2013 Nov 11th: Disease recurrence in the liver was diagnosed on follow up PET-CT in Japan. Imaging revealed progressive liver metastases. Patient returned to Bengaluru, India for subsequent chemotherapy and FORN. He presented with massive hepatomegaly, anemia, thrombocytopenia, hepatic and renal dysfunction. Due to poor performance status, patient was initially started on weekly single agent Abraxane (nab-paclitaxel), however, as the parameters gradually improved clinically with reduced hepatomegaly, improved appetite and energy levels, and improvement in hematological parameters, liver and kidney dysfunction, weekly Cisplatin was added. He was also continued on Zoledronic acid monthly, in view of his bone metastases.

2014 Jan 31st: Follow up PET was done after 3 cycles of nab-paclitaxel (weekly dosing for 6 weeks with 1 week gap) + Cisplatin (weekly dosing for 5 weeks). Disease outcome was compared using PET CT (3rd) done in Japan in March 2013 and Nov 2013 with PET-CT (4th) at MCCC in Jan 2014. Treatment planned: 2 week treatment holiday followed by monthly nab-paclitaxel and Cisplatin as maintenance therapy, with adjuvant FORN.

2014 May 1st: Patient was hospitalized at the MCCC with liver failure / encephalopathy and succumbed after a few days of active medical management.

MRI /PD sequence protocol for FORN treatment planning and dosimetry

Dose-planning MRI-derived Proton Density (PD) sequence was obtained for the Region(s) of Interest (ROIs) to be targeted for chemo-drug delivery, in the whole body. The PD sequence-that is an integrated component of most 1.5T equipment - is derived for lesions to be targeted by FORN. TR value used is set at 4000msec and TE value at 11msec. Three millimeter (mm) contiguous sections with zero spacing are maintained. The use of a 'navigator' was used to improve the resolution and minimize imaging artefacts. Appropriate Field of View - around 400-450mm was used, with phase encoding in the anterior-posterior direction. The skin was included in planning as it is integral to FORN dosimetry and treatment planning. The Dosimetry planning film is marked on the MRI film (Fig 1) and transferred to a compact disc (CD) for use in the FORN device computer. Surface marking on the patient's skin were made, under Computer-aided Tomography (CT) for aligning and focusing the FORN RF guns. A transparent sheet template is prepared with body surface markings delineating the axes to be targeted by the FORN protocol, and used to position the patient in the gantry prior to RF / MR exposure (Supplemental Figure 1).

Note: Diffusion Weighted Imaging (DWI) sequences can also help to identify foci of restrictions, indicative of suspicious areas).

Forn protocol

The pathological diagnosis, tumor type and cellular morphology were used to determine the cell membrane thickness of target tumor cells. The cell membrane thickness of

Figure 1. The MRI-derived target lesion marking done by the radiologist/ radiology technician during PD sequence determination, is seen on the film transferred to a compact disc (CD) used for dose targeting. The region shown is the loco-regional recurrence in the nasopharynx.

the loco-regional un-differentiated naso-pharyngeal carcinoma NPC cells and distant metastases is ideally obtained from biopsy slides during pathological diagnosis. In this case, given the time from original diagnosis and the onset of metastatic disease, the membrane thickness of NPC cells of squamous origin was set at 4.55 microns. The drug molecular weight (g/mol), peak plasma concentration time (in minutes), drug wash out time (in minutes) or its known active metabolites was determined from available literature [7]. This information is fed into the device computer as seen in Figure 2.

Dosimetry is fixed using the gun paths planned to focus on each of the targeted ROIs. Individualized and precise RF gun-path files are programmed for all the ROI's targeted and 'mapped' as seen for each of the lesions to which the drug was driven and 'focused' for this patient (Figure 3).

E-planning for the dosimetry and the nanosecond pulses for the FORN protocol are determined using the dedicated machine intelligence and software for FORN on the device computer. The "Target Planning Films" derived from the PD sequences in the MRI for the ROIs, show the core of the tumor mass to be targeted. The number of guns/axes required to be fired for FORN depends on the cancer cell type and specific drug molecules to be permeated. A specially trained and certified FORN technologist enters specific inputs like drug / its metabolite, molecular weight (of the largest molecule), time to Peak Plasma Concentration (of the drug with the shortest peak plasma concentration time), Drug Washout Time of the drug and or its metabolites to be permeated, cell membrane thickness of the tumor tissue type and total tissue volume (cm^3) of respective lesions. On the day of scheduled treatment, the patient is administered the required dose of the drug to be permeated X-minutes before applying FORN (X=peak time taken (in minutes) for the drug to attain maximum

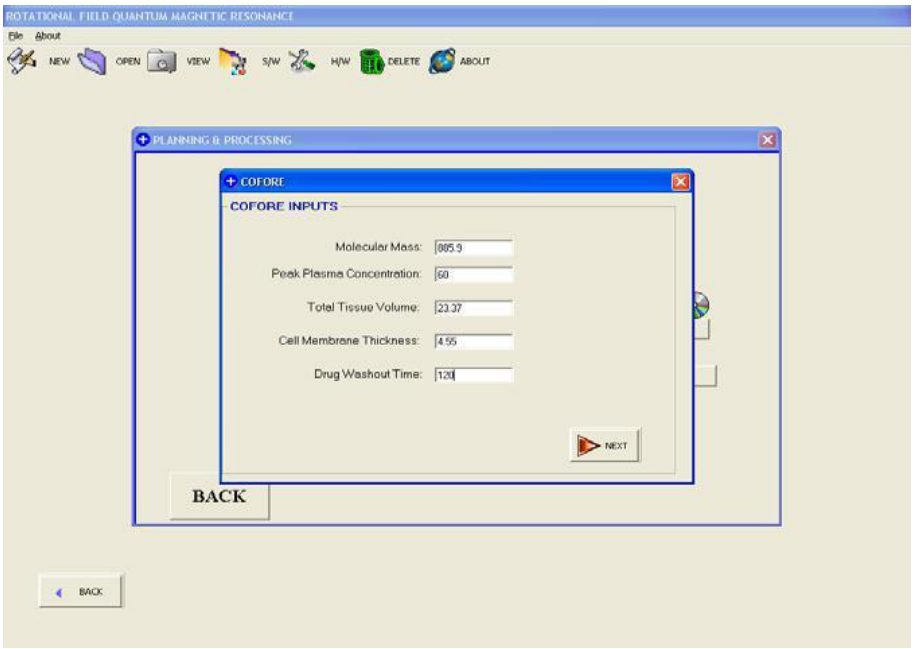
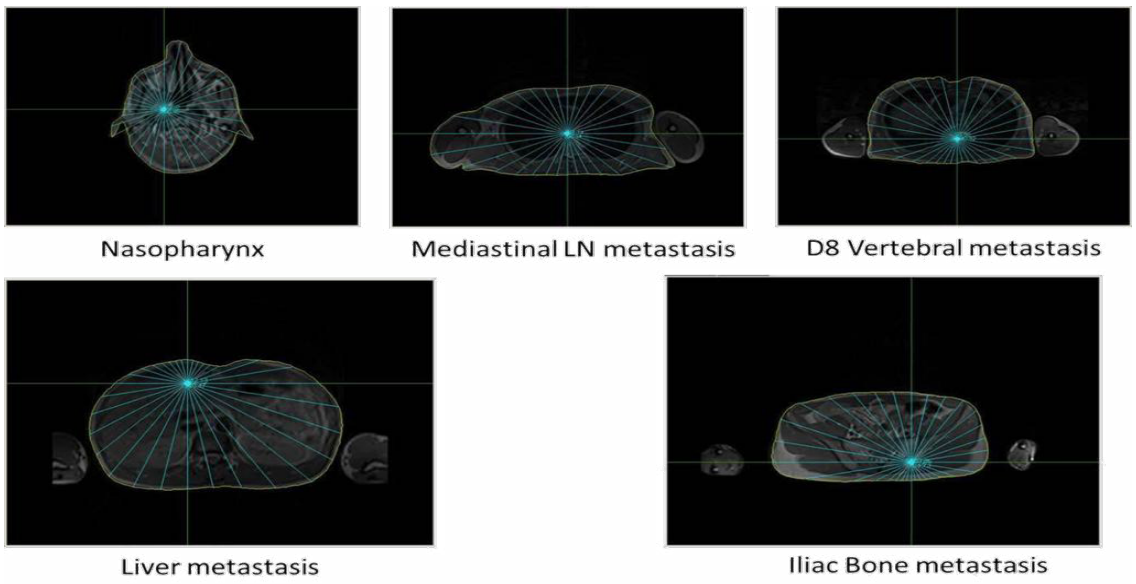


Figure 2. A screen shot from the device computer software used for dose planning and FORN protocol. Note: The total tissue volume determination is done using the MR imaging-based PD sequence for Regions of Interest (ROIs) to be targeted. These values remain unchanged during subsequent FORN cycles as it is the basis of PD sequence derived FORN dosimetry.



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concentration in circulation in the patient). Before exposure, the patient is made to lie down on the treatment transport bed and the patient is moved into the FORN device; the RF-guns are now focused on the target ROIs using a laser-guided system. The exposure is for Y- hours each day for Z-days, where Y is the time period required for the trans-permeabilization of maximum drug molecules infused and Z is the course or number of cycles of the drug on given days of drug infusion. When the planned FORN signals are withdrawn, the pores are closed and drug retained within the tumor (Figure 4).

FORN is targeted precisely to affected areas in the whole body, to transport and permeate the cancer drugs used in the treatment of the NPC patient described in this report, in a safe, non-invasive and precisely programmed and controlled manner. Baseline / PET-CT scan was obtained prior to chemotherapy planning at

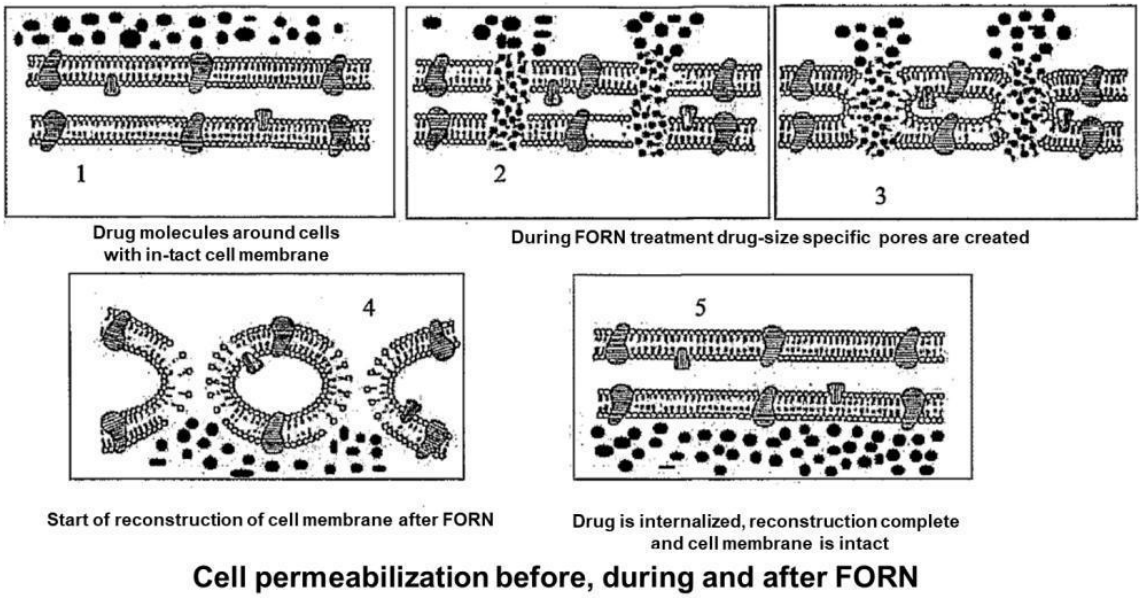

Figure 4. A schematic of the FORN process showing the state of pores in the cell membrane before, during and after guns are fired and planned RF/MR doses are pulsed and then withdrawn.

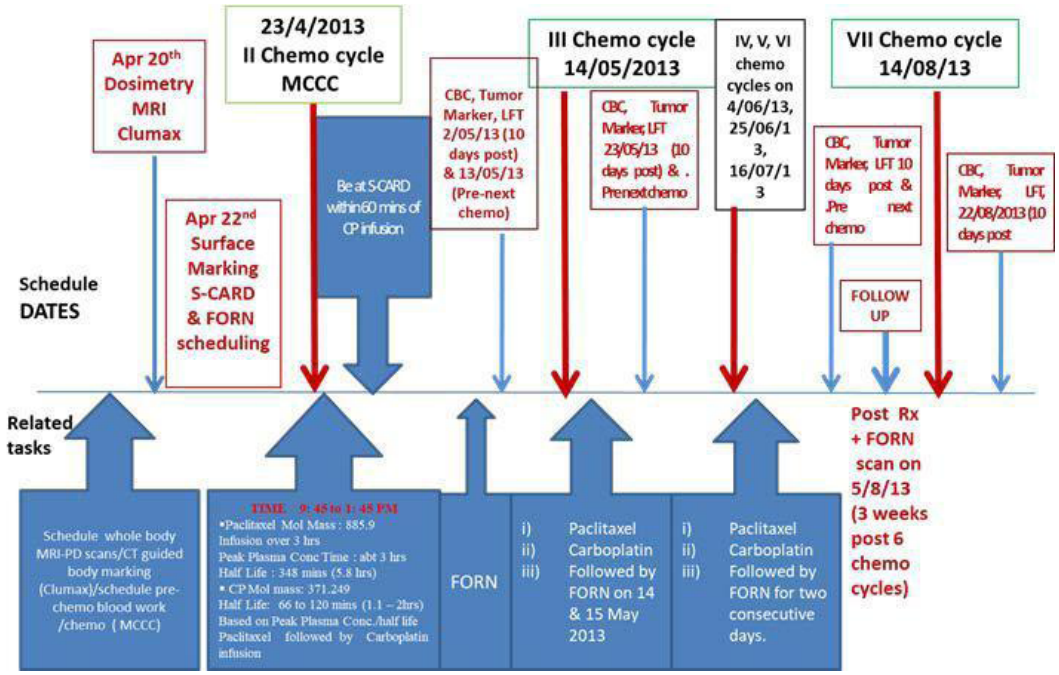

Figure 5. The chronological calendar days for different events during the chemo +FORN protocol is condensed in this reference schematic. The exact timing for chemotherapy cycles followed by FORN for each of 6 cycles administered as well as days for related blood work and PET-CT scans is shown.

the JCRF-Akika, Japan. Periodic post-chemotherapy and FORN assessments were done using ultrasound, CT/MRI or PET.

Chemotherapy infusion schedule and FORN

The first cycle of CBDCA + PAX course # 6 was given at JCRF, Japan. Significant adverse effects were reported by the patient. The patient travelled to Bengaluru, India to continue his chemotherapy schedule under the care of the oncologist at the MCCC and S-CARD for concurrent chemotherapy-enabled FORN. The route and time of administration of the Carboplatin and Paclitaxel was determined and fixed on Day 1 of chemo-cycle # 2 given at MCCC. After chemo was administered, patient was transferred to the FORN facility and treatment was administered as per protocol. The details of drugs administered in each of the chemo-cycles with respective pharmacokinetic details critical to the concurrent application of the FORN protocol, is summarized in Figure 5 and detailed in Supplemental Table 1.

A PET scan was repeated after Cycle # 6 was completed. Evaluation of tumor response was done using PERCIST 1.0 criteria [8,9]. Based on the residual marginal SUV in one mediastinal lymph node, Cycle 7 was planned with the oncologist and enabled with FORN. The patient returned to Japan in September 2013 to resume work.

Results

Improvements in symptoms of nausea, fatigue, weight loss, and other related events, determined with the use of patient interviews and FACT-H&N, QoL and KPS-S questionnaires, reflected very good responses. Patient consistently reported that the intensity of side effects commonly experienced in Japan during the course of treatment, was minimal when chemotherapy cycles were administered concurrently with FORN. No episodes of vomiting, diarrhoea or other major gastrointestinal (GI) symptoms were experienced. Patient had Grade 2-increase of 4-6 stools/day over the baseline - after routine chemotherapy without FORN, when assessed based on criteria laid down by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) [10]. More significantly, the patient's overall recovery from any side-effects, were faster. The blood work and adverse events/toxicity profile after the 1st course of the CBDCA/PAX # 6 cycles done at the JCRF, Japan, after the chemotherapy infusion without FORN, is shown in Supplemental Table 2 as an XL spread sheet on pages 2 and 3. All subsequent hematological work-ups and toxicity related parameters evaluated after each Chemotherapy + FORN cycle (# 2, #3, #4, #5, #6 and #7) is also seen in Supplemental Table 2. Tumor response criteria were evaluated comparing previously refractory lesions using PERCIST 1.0 for metabolic and metastatic disease as seen in PET-CT scans, after completion of planned therapy sessions. The images of pre-treatment PET-CT evaluation and the post chemotherapy + FORN treatment is seen in sequence in Figure 6. The radiology interpretation of PET-CT is abridged in Table 1.

Discussion

The majority of patients with squamous cell carcinomas of the head and neck present with locally advanced tumors. The first-line treatment for NPC consists of combined modality management [11,12]. Despite these aggressive protocols, many patients develop loco-regional recurrences with or without metastasis. New technology, more effective and less toxic chemotherapy regimens, and targeted therapy offer new opportunities for treating NPC patients who require multiple chemo-cycles during the course of the disease. Considering that most therapies offered in advanced stages of the disease offer little to no overall survival benefit in NPC [13], the use of an effective drug delivery method to enhance therapeutic efficacy and circumvent systemic side effects was considered. Using FORN concurrently with systemic chemotherapy, in an advanced case of NPC with metastatic lymph nodes, skeletal and liver metastases; dramatically improved survival, tumor response and very good QoL [14,15]. This case is being presented with the intent to disseminate the potential application of a concurrent, non-invasive drug delivery technology to trans-permeate drugs intra-tumorally, in routine clinical practice, along with planned cancer chemotherapy.

Electric field pulses reported as inducing transient permeabilization of drugs, have long been known, and extensively reported [16]. Probably the most important feature of a bio-membrane is that it is a selectively permeable structure. This means that the size, charge, and other chemical properties of the atoms and molecules attempting to cross it will determine whether they succeed in doing so. Selective permeability is essential for effective separation of a cell or organelle from its surroundings [17]. While electro-permeabilization is a technique using short pulses of electrical fields to cause temporary holes in the cell membrane *in vitro*, nano-permeabilization is a technique by which temporary pathways are precisely created for a specific molecule based on its molecular weight and size, *in vivo*. In nano-permeabilization, as described in the FORN protocol used in this patient study, specific cells in the ROI were resonated in a high, instantaneous magnetic field, followed by the delivery of nanosecond radio-pulses that penetrate only such resonating cells. This process is achieved non-invasively, within the cells natural environment. Like electro-permeabilization, nano-permeabilization can be widely used for the introduction of molecules such as DNA, antibodies, enzymes, and drugs into cells [1]. Research and development for use of the FORN protocol with concurrent chemotherapy, has facilitated the delivery of a variety

Table 1. Radiology reports of PET-CT findings are summarized over the time period of March 2013 to January 2014 showing remarkable disease-free survival for nodal, skeletal and liver metastases.

PREVIOUSLY NOTED NODES	PET CT FINDINGS ON		
LOCATION	04/03/2013	05/08/2013	31/01/2014
PREVASCULAR NODES	Measured size - 3.6x1.4 and SUV max uptake - 6.2	Measured size – 2.2x1.1 and SUV max uptake - 3.1	Not seen
PRECARINAL NODES	SUV max uptake - 5.2	Measured size – 1.7x1.2 and SUV max uptake- 2.1	Not seen
RIGHT HILAR NODES	Measured size -1.4X1.5 and SUV max uptake - 2.3	Measured size – 1.3X1.2 and SUV max uptake – 3.1	Not seen
SKELETAL LESIONS	Seen in D10, D3, D4, L5, L3	Resolved in metabolic activity and appears more sclerotic in this study.	Sclerotic lesions are seen in D4- D5, D10, L3, L5 vertebrae and also in Sacrum, left iliac bone and head of left femur
LIVER LESIONS	FDG avid lesion in right lobe of liver	Totally resolved in size and metabolic activity	Non FDG avid hypodense areas in segment VIII and anteriorly in the left lobe involving segment IV, II and III

1st row: FDG-PET/CT dated 4th March 2013 showing: FDG avid lesions in the right lobe of the liver and FDG avid mediastinal lymphadenopathy and one of the FDG avid skeletal lesions in the lower dorsal vertebrae (D 8-10 vertebra).
2nd row: FDG-PET/CT dated 5thAug 2013: Follow up FDG-PET/CT after 6 months, showing total resolution of all lesions with the exception of a pre-carinal node - good response.
3rd row: FDG-PET/CT dated 11th Nov 2013 showing disease recurrence in the liver with a large conglomerate lesion.
4th row: FDG-PET/CT shows complete resolution of FDG uptake with significant reduction in size of the liver lesion - complete metabolic response (good response).

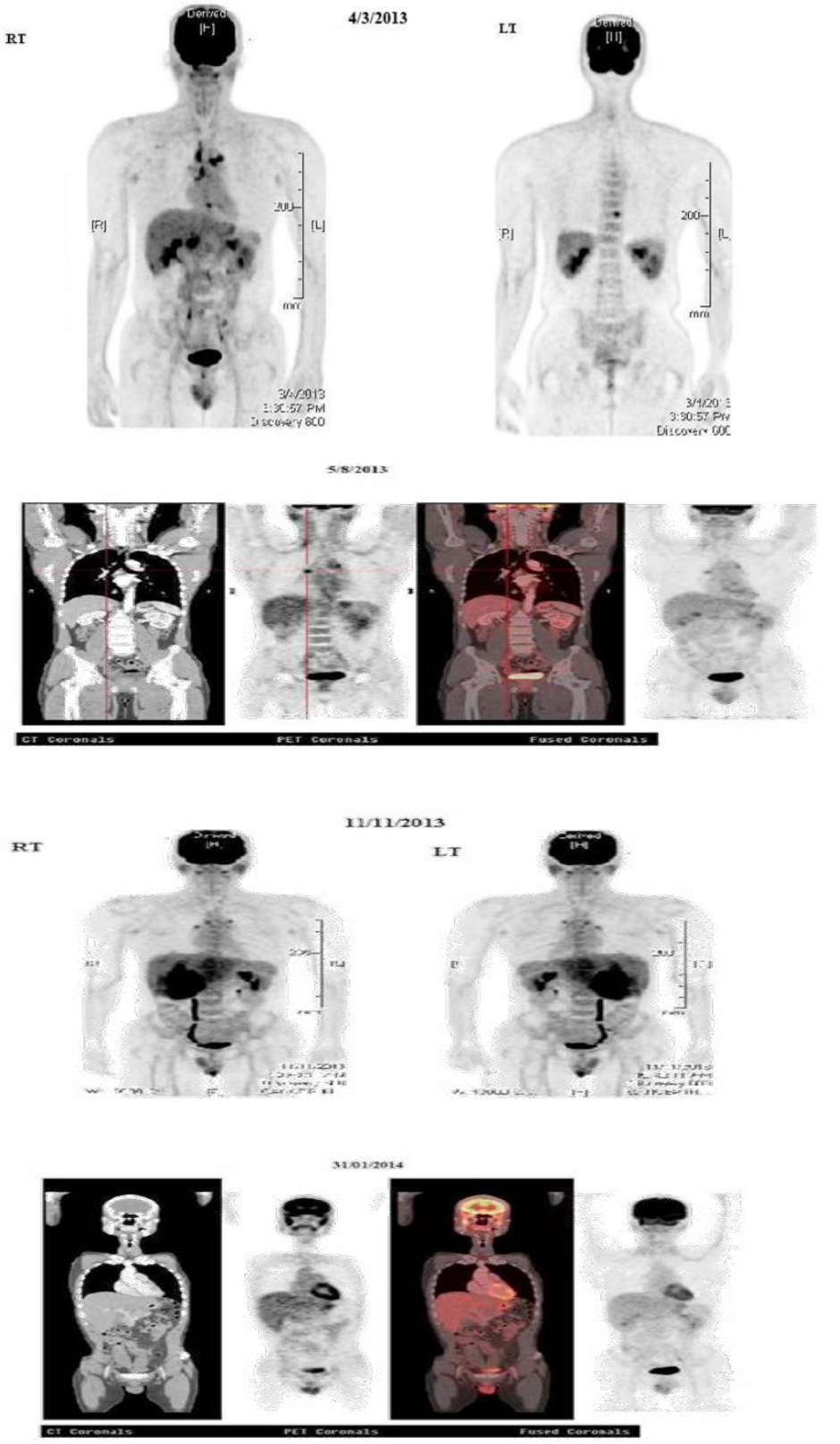

Figure 6: Clinical outcome based on PERCIST 1.0 at recurrence and post chemo+ FORN is presented along with the radiologist's interpretive report in Table 1.

of small and very large molecule drugs into target tissue, non-invasively, despite all normally restrictive size and permeability constraints.

Controlled drug delivery technology has advanced significantly in the last few decades, leading to the development of various clinical formulations improving patient compliance and convenience [18,19]. The critical intracellular target for cytotoxic drugs is dependent on intracellular concentrations of the drug moiety, and/or its metabolites, which in turn is dependent on membrane permeability [20]. Anti-tumoral drugs therefore need direct access to the cytosol to fully exert their cytotoxic potential. Lower doses than the ones required in classical protocols of chemotherapy regimens could also technically be used to achieve better therapeutic indices even with highly cytotoxic drugs [21]. Potentiating cytotoxicity of various chemotherapy agents and other targeted molecules can also be increased several fold by this 'focused' internalization process enabled by the FORN protocol, just as how the cytotoxicity of Cisplatin is potentiated up to 70 times more in suspended cell cultures using electric pulses *in* vitro [16]. Such `potentiation' can be highly controlled using FORN, by in-putting delivery parameters like molecular mass of the drug / active metabolite, peak plasma concentration, total tissue volume and cell membrane characteristics. FORN used concurrently with conventional chemotherapy in this patient with recurrent, metastatic NPC, very clearly potentiated the anti-tumor effectiveness of Carboplatin and Paclitaxel, based on reviewing the disease response and clinical outcome. Drug delivery could be timed and precisely localized *in vivo*, to achieve the desired therapeutic impact without concomitant cytotoxic adverse effects. The Institute for Safe Medication Practices (ISMP) using FDA data estimates the 2011 licensed drug death figure at 128,000. This excludes chemo drug deaths, which are classified as cancer deaths. Licensed drugs are the number 4 killer of human beings, according to the FDA's own figures. It is an epidemic. They refer to 2 million "Adverse Drug Reactions" which they call ADRs, and 100,000 deaths a year, with approved drugs. A startling study by Public Health England and Cancer Research UK has found that cancer treatment itself may be killing up to 50 percent of patients [22]. In a first of its kind study, the researchers on this study dug deeper into cancer patients who died within 30 days of beginning their treatment, indicating that the treatment caused the death, not the cancer. Across the nation, they found that 8.4 percent of those undergoing treatment for lung cancer, and 2.4 percent of those being treated for breast cancer, died within a month of beginning treatment. Results varied greatly based on the hospital however, as an alarming 50.9 percent of those in Milton Keynes Hospital – UK, beginning chemotherapy treatment for lung cancer died within 30 days. Researchers noted that the total number of patients treated at the hospital was much smaller than the norm, but the numbers remain eye-opening, and the list is endless. Efficient and effective drug delivery processes are being increasingly reported in the literature to circumvent issues related to traversing the blood brain barrier (BBB) and improving bioavailability to enhance therapeutic effect. Ideal delivery systems should allow targeting of the drug to tumors. Improving therapeutic efficacy while simultaneously mitigating toxic side effects of commonly used cancer drugs; as well as reducing the iteration of new drugs in the pipeline, due to failed drug trials, is the hope. Although many advances in treatment have been made, they have yielded only modest survival benefits for cancer patients [2]. A major factor contributing to limitations in systemic delivery is dose-limiting drug toxicity.

'Safe' Chemotherapy need not be an oxymoron. For the longest time, chemotherapy has been a double-edged sword, with the balance tipping heavily against it, due to the dangers of systemic toxicities accompanying even the best of molecularly target agents in this day and age of personalized, precision medicine. Reports and studies have flooded the 'playing' field with every possible combination of drug molecules being used to achieve even minimal survival advantage in very aggressive brain tumors [23-25] as well as in the more long-drawn out but equally aggressive, treatment refractory NPC being discussed here [26-29]. The problem remains that very little consideration is applied to the QoL in these patients being subjected to random drug combinations, with no real understanding of synergies or complicated drug-drug interactions that could induce even more severe systemic toxicities! The challenge has been that the treatment does not specifically target cancerous cells, and randomly destroys normal, healthy, fast-dividing cells in its wake.

"Most cancer patients die of chemotherapy. Chemotherapy does not truly eliminate breast, colon, or lung cancers despite all the years of research and trial designs applied to date. The immune system is hit particularly hard by chemotherapy and the body often does not recuperate enough to adequately protect from common illnesses, leading to death [22]." The fact that chemo only contributes on average about 2% to overall survival rate, is very alarming, and not often discussed. It is important to remember that the "2.1% average" can be deceptive. Some cancers do respond better to chemo than others. According to a 2004 report by Morgan et al. "The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies was estimated to be 2.3% in Australia and 2.1% in the USA [30]."

Technically speaking, an ideal delivery method would be one that achieves adequate coverage of tumor volume while minimizing unwanted toxicities. Optimal delivery requires three important components: 1) the ability to target the tumor while minimizing local and systemic effects; 2) applicability over a wide range of therapies, and 3) a safe, efficacious method of continuous delivery with non-invasive methods while monitoring volumes of distribution (Vd) of agents. Although promising results are now being reported with the use of NAB-paclitaxel combined with cisplatin (NAB-TP) for advanced NPC [31]; a drug used on our patient too, the anti-tumor efficacy in patients with locally advanced NPC needs to be viewed in the light of post-treatment quality of life in patients with multiple, severe metastatic disease as reported here, and managed with concurrent FORN. The toxicities induced by NAB-TP treatment were well tolerated and manageable in this patient, when it was administered concurrently with FORN. Given the protracted course of the disease and the many cycles of CCRT and multiple chemo-drugs over the survival span of the patient, it was not surprising that he was finally diagnosed with liver failure and encephalopathy. Ironically, although the death certificate assigned the cause of death as metastatic liver disease, a very thorough radiological review of the final PET scan did not show any residual 'metabolically active' disease in the liver (Figure 6 and Table 1).

Minimizing systemic exposure, thereby reducing the co-morbidities in patients with advanced disease, will allow for

significant improvements in quality of life and supportive care for the terminally ill. This outcome should also include improvement in symptoms and patient satisfaction, with reduced caregiver burden. The American Society of Clinical Oncology (ASCO) provided a provisional clinical opinion (PCO) that recommended that end of life counselling should be an integral component of treatment planning even at the earliest presentation of a patient diagnosed with cancer [32]. More often than not, systemic chemotherapies that are given to advanced cancer patients, although essentially hoping to achieve palliation of some kind, are excessively toxic in these patients who are already severely immune-compromised and weakened both by the disease and multiple cytotoxic chemotherapy regimens.

A very significant advantage of this process of concurrent chemotherapy with FORN is that it is not restricted to any specific type of drug molecule or solid tumor type. Drug "focusing" is achieved by MRI derived tissue proton density determinations of ROIs, and creating drug molecule and size-specific temporary nano-pores to accentuate cellular permeability. The NPC case study reported here for the first time, details the procedure in one patient in a pilot study series, who received FORN for 6 consecutive chemotherapy cycles and survived with very good QoL despite the very advanced status of the disease. The pilot study being conducted to clinically validate the technology, included several other patients with a variety of advanced solid tumors like Stage 1V Ovarian cancer on 1 cycle of systemic Carboplatin and Gemzar; advanced breast cancer with liver, lung and skeletal metastases on Ixempra + Capecitabine; Ca. Breast with liver, pelvic bone, left adrenal & brain metastasis on oral Lapatinib and Temozolamide; Herceptin-failed breast cancer, with multiple brain metastases on palliative chemotherapy; Anaplastic Astrocytoma on oral Temozolamide + natural, large molecule Physalis minima; pediatric, recurrent, medulloblastoma on systemic Cyclophosphamide & Etoposide; adult glioblastoma on Temozolamide and natural Curcuminoids; and advanced, radiation-induced secondary, relapsed metastatic osteosarcoma on oral Sorefinib. In all these cases of advanced solid tumor patients, receiving either 'curative' chemotherapy as part of 'standard of care' treatment regimens or palliative chemotherapy, showed significant reduction in drug-induced adverse effects, tolerating previously intolerable, chemotherapy and having very active, good quality of life for the duration of FORN treatment. More studies that combine the power of pharmaco-kinetic and pharmaco-dynamic toxicity criteria, alongside quantitative evaluation of blood, tissue and excretion of infused drug and it's active metabolites, over the period of a chemo-cycle, needs to be done. Parallel evaluation of criteria of myelosuppression and other adverse effects in a specific group of cancer patients with advanced solid tumors on different 'trial and error' chemotherapeutic regimens, would throw more light on the projected reduction of drug in systemic circulation during FORN. More importantly, improving and salvaging "failed' drug pipelines with novel drug moieties, vaccines, genetic materials or any other molecules of interest *in vivo*, can facilitate novel drug discovery and improve patient compliance using FORN-enabled concurrent chemotherapy, in routine clinical practice.

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Supplemental Table1

Name : **XXXXXXX** **D.O.B** : **06/01/1965**
Age / Gender : **48Yrs/ Male** **Diagnosis** : **Recurrent CA Nasopharynx with Metastasis**

2nd CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half -Life	Drug Wash Out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at S-CARD	Date
1.	Paclitaxel 6-α,3'-p-dihydroxy-paclitaxel (C47H51NO16)	885.9g/mol	260 mg	Infusion Over three Hours	About 3 hrs	348 mins (5.8 hrs)	348 mins	3 hrs (9:45 am to 12:45 pm)	2hrs (2:30pm to 3: 30 pm + 3: 40 pm to 4:45pm)	23/04/2013
2.	Carboplatin (cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II))	317.249g/mol	600 mg	Infusion Over One Hour	60 mins	66-120 mins	120 mins	1hr (12:45 pm to 1:45pm)	2hrs (2:30pm to 3: 30 pm + 3: 40 pm to 4:45pm)	23/04/2013

Note : Cell Membrane Thickness **4.55 microns** (squamous cell).

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	D & E
20/04/2013	3	Mediastinal LN	043	74.7	C
20/04/2013	6	Liver	044	50.96	B
20/04/2013	8	Left Ilium	045	59.04	A

Note : 1. Started pre-medication at 8: 45 am on 23/04/2013.

2. The treatment was given for 2 hrs with a break after 1 hr for about 10 mins.

Name : **XXXXXX** **D.O.B** : **06/01/1965**
Age / Gender : **48Yrs/ Male** **Diagnosis** : **Recurrent CA Nasopharynx with Metastasis**

3rd CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half -Life	Drug Wash Out Time	Infusion Time at Manipal Hospital	FONE Therapy Time at S-CARD	Date
1.	Paclitaxel 6-α,3'-p-dihydroxy-paclitaxel (C47H51NO16)	885.9g/mol	260 mg	Infusion Over Three Hours	About 3 hrs	348(5.8 hrs)	348 mins	3hrs (9:00 am to 12:00 pm)	2hrs (2:16pm to 4:35pm)	14/05/2013
									2 hrs (9:35 am to 11:50 am)	15/05/2013
2.	Carboplatin (cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II))	317.249g/mol	600 mg	Infusion Over One Hours	60 mins	66-120 mins	120 mins	1 hrs (12:00 pm to 1:00 pm)	2hrs (2:16pm to 4:35pm)	14/05/2013
									2 hrs (9:35 am to 11:50 am)	15/05/2013
3.	Zometa (Zoledronic acid)	272.09g/mol				146 hrs	146 hrs	20 mins (1: 00 to 1: 20 pm)	2hrs (2:16pm to 4:35pm)	14/05/2013
									2 hrs (9:35 am to 11:50 am)	15/05/2013

Note : Cell Membrane Thickness **4.55 microns** (squamous cell).

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	I
20/04/2013	3	Mediastinal LN	043	74.7	H

13/05/2013	2	Liver	046	43.411	G
13/05/2013	8	Left Ilium	045	59.04	F to A

Note : 1. Patient left MCCC at 1: 30 pm on 14/05/2013. Patient reached S-CARD at 2:05 pm on 14/05/2013.

2. The treatment was given for 2 hrs with a break after 1 hr for about 15-20mins.

3. All axes were fired since Zometa is expected to 'target' all bones.

Name : XXXXXX **D.O.B : 06/01/1965**
Age / Gender : 48Yrs/ Male **Diagnosis : Recurrent CA Nasopharynx with Metastasis**

4th CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half -Life	Drug Wash Out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at S-CARD	Date
1.	Paclitaxel 6-α,3'-p-dihydroxy-paclitaxel (C47H51NO16)	885.9g/mol	260 mg	Infusion Over Two Hours	About 3 hrs	348 mins (5.8 hrs)	348 mins	2 hrs (9:20 am to 11:20 pm)	2hrs (2:24pm to 4:44pm)	04/06/2013
									2 hrs (10:35 am to 12:47 pm)	05/06/2013
2.	Carboplatin (cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II))	317.249g/mol	600 mg	Infusion Over One Hour	60 mins	66-120 mins	120 mins	1hr 20 mins (11:40 pm to 1:00pm)	2hrs (2:24pm to 4:44pm)	04/06/2013
									2 hrs (10:35 am to 12:47 pm)	05/06/2013

Note : Cell Membrane Thickness **4.55 microns** (squamous cell).

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	E
20/04/2013	3	Mediastinal LN	043	74.7	D
01/06/2013	2	Liver	046	43.411	C
20/04/2013	8	Left Ilium	045	59.04	A & B

Note : 1. Started pre-medication at 8: 40 am.

2. Reported at S-CARD at 1: 50 pm on 4/06/2013

3. The treatment was given for 2 hrs with a break after 1 hr for about 10-15 mins.

Name : XXXXXXXX **D.O.B : 06/01/1965**
Age / Gender : 48Yrs/ Male **Diagnosis : Recurrent CA Nasopharynx with Metastasis**

5th CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half -Life	Drug Wash Out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at S-CARD	Date
1.	Paclitaxel 6-α,3'-p-dihydroxy-paclitaxel (C47H51NO16)	885.9g/mol	260 mg	Infusion Over Three Hours	About 3 hrs	348 mins (5.8 hrs)	348 mins		2hrs (1:57 pm to 4:30 pm)	25/06/2013
									2 hrs (9:00 am to 11:15 am)	26/06/2013
2.	Carboplatin (cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II))	317.249g/mol	600 mg	Infusion Over One Hours	60 mins	66-120 mins	120 mins		2hrs (1:57 pm to 4:30 pm)	25/06/2013
									2 hrs (9:00 am to 11:15 am)	26/06/2013
3.	Zometa (Zoledronic acid)	272.09g/mol							2hrs (1:57 pm to 4:30 pm)	25/06/2013
									2 hrs (9:00 am to 11:15 am)	26/06/2013

Note : Cell Membrane Thickness **4.55 microns** (squamous cell).

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	I
20/04/2013	3	Mediastinal LN	043	74.7	H
22/06/2013	1	D8 vertebraF	047	2.92	G
22/06/2013	2	Left Ilium	048	6.77	F to A

Note: 1. Reported to MCCC at 7: 30 am on 25/06/2013.

2. Patient's pre- medication started at 9 am.

3. Reported to S-CARD at 1:45 pm on 25/06/2013.

4. All axes were fired since Zometa is meant for all bones.

5. The treatment was given for 2 hrs with a break after 1 hr for about 10-20 mins.

Name : XXXXXX **D.O.B : 06/01/1965**
Age / Gender : 48Yrs/ Male **Diagnosis : Recurrent CA Nasopharynx with Metastasis**

6th CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half -Life	Drug Wash Out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at S-CARD	Date
1.	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9g/mol	260 mg	Infusion Over Three Hours	About 3 hrs	348 mins (5.8 hrs)	348 mins		2hrs (4:18 pm to 6: 35pm)	16/07/2013
									2 hrs (11:05 am to 1:15 pm)	17/07/2013
2.	Carboplatin (cis-Diammine(1,1-cyclobutanedicarboxylato)platinum(II))	317.249g/mol	600 mg	Infusion Over One Hours	60 mins	66-120 mins	120 mins		2hrs (2:16pm to 4:35pm)	16/07/2013
									2 hrs (11:05 am to 1:15 pm)	17/07/2013

Note : Cell Membrane Thickness **4.55 microns** (squamous cell).

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	E
20/04/2013	3	Mediastinal LN	043	74.7	D
15/07/2013	1	D8 vertebra	049	7.457	C
01/06/2013	2	Liver	046	43.411	B
15/07/2013	2	Left Ilium	050	11.791	A

Note : 1. Patient reported at MCCC at 7: 30 pm on 16/7/2013.

2. Reported to S-CARD at 4: 15 pm on 16/07/2013

3. The treatment was given for 2 hrs with a break after 1 hr for about 15- 20 mins.

Name : XXXXXXX **D.O.B : 06/01/1965**
Age / Gender : 48Yrs/ Male **Diagnosis : Recurrent CA Nasopharynx with Metastasis**

7th CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half -Life	Drug Wash Out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at S-CARD	Date
1.	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9g/mol	260 mg	Infusion Over Three Hours	About 3 hrs	348 mins (5.8 hrs)	348 mins		2hrs (3:48 pm to 5:00pm + 5:11 to 6:15 pm)	14/08/2013

									2 hrs (8:10 am to 9:10 pm + 9:25 + 10:25 pm)	15/08/2013
2.	Carboplatin	317.249g/mol	600 mg	Infusion Over One Hours	60 mins	66-120 mins	120 mins		2hrs (3:48 pm to 5:00pm + 5:11 to 6:15 pm)	14/08/2013
									2 hrs (8:10 am to 9:10 pm + 9:25 + 10:25 pm)	15/08/2013
3.	Zometa (Zoledronic acid)	272.09g/mol							2hrs (3:48 pm to 5:00pm + 5:11 to 6:15 pm)	14/08/2013
									2 hrs (8:10 am to 9:10 pm + 9:25 + 10:25 pm)	15/08/2013

Note : Cell Membrane Thickness **4.55 microns** (squamous cell).

First one hour with FORN

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	I & H
13/08/2013	1	Mediastinal LN	051	1.589	G
1/06/2013	2	Liver	046	43.411	F
13/08/2013	4	Left Ilium	053	10.283	E to A

Note: 1. FORN was applied for 2 hrs. with a break after 1 hr for about 10- 15 mins.

Second one hour with FORN

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis Fired
20/04/2013	1	Nasopharyngeal Area	042	23.37	I
13/08/2013	1	Mediastinal LN	051	1.589	H
13/08/2013	3	D8 vertebra	052	5.046	G
13/08/2013	4	Left Ilium	053	10.283	F to A

Note: 1. All axes were fired since Zometa is meant for all bones.

2. The treatment was given for 2 hrs with a break after 1 hr for about 20 mins.

3. Patient's pre- medication started at 8.50 am.

4. The patient was positioned for the first one hour targeting mediastinal LN. For the second hr patient was positioned targeting D8 vertebra.

Supplemental Table 2

Name : XXXXXXXXXX DOB : 06/01/1965

Age/ Gender : 48 yrs/ M Diagnosis: Recurrent CA Nasopharynx with Metastasis

2nd CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Adminstration	Peak Plasma Concentration Time	Half-Life	Drug Wash out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at CARD	DATE
1	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9 g/mol	260 mg	Infusion over three hours	About 3 hrs	348 (5.8 hrs)	348 mins	3 hrs (9: 45 am to 12: 45 pm)	2 hrs (2:45 pm to 4:45 pm)	23/4/2013
2	Carboplatin	371.249 g/mol	600 mg	Infusion over one hour	60 mins	66- 120 mins	120 mins	1 hr (12: 45 pm to 1: 45 pm)	2 hrs (2:45 pm to 4:45 pm)	23/4/2013

Note: Cell membrane thickness: **4.55 microns** (squamous cell)

PD Date	Image No.	Region	ID No.	Total Tissue Volume	Axis Fired
20/04/13	1	Nasopharyngeal area	042	23.37	D & E
20/04/13	3	Mediastinal LN	043	74.7	C
20/04/13	6	Liver	044	50.96	B
20/04/13	8	Left ilium	045	59.04	A

Name : XXXXXXXXX DOB : 06/01/1965

Age/ Gender : 48 yrs/ M Diagnosis: Recurrent CA Nasopharynx with Metastasis

Sl. No	Drug	Molecular Mass	Dose	Mode of adminstration	Concentration Time	Half-Life	Drug Wash out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at CARD	DATE
1	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9 g/mol	260 mg	Infusion over three hours	About 3 hrs	348 (5.8 hrs)	348 mins	3 hrs (9: 05 am to 12:05 pm)	2 hrs (2:16 pm to 4:35 pm) 2 hrs (9:35 am to	14/5/2013 15/5/2013
2	Carboplatin	371.249 g/mol	600 mg	Infusion over one hour	60 mins	66- 120 mins	120 mins	1 hr (12: 45 pm to 1: 45 pm)	2 hrs (2:16 pm to 4:35 pm) 2 hrs (9:35 am to 11:50 am)	14/5/2013 15/5/2013
3	Zomenta	272.09 g/mol				146 hrs	146 hrs	20 mins	2 hrs (2:16 pm to 4:35 pm) 2 hrs (9:35 am to 11:50 am)	14/5/2013 15/5/2013

Note: Cell membrane thickness: **4.55 microns** (squamous cell)

PD Date	Image No.	Region	ID No.	Total Tissue Volume	Axis Fired
20/04/13	1	Nasopharyngeal area	042	23.37	I
20/04/13	3	Mediastinal LN	043	74.7	H
13/05/13	2	Liver	046	43.411	G
20/04/13	8	Left ilium	045	59.04	F to A

Note 1. The treatment was given for 2 hrs with a break after 1 hr for about 15-20 mins.

Name : XXXXXXXXXXX DOB : 06/01/1965

Age/ Gender : 48 yrs/ M Diagnosis: Recurrent CA Nasopharynx with Metastasis

4th CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of adminstration	Peak Plasma Concentration Time	Half-Life	Drug Wash out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at CARD	DATE
1	Paclitaxel dihydroxy-paclitaxel (C47H51NO	885.9 g/mol	260 mg	Infusion over two hours	About 3 hrs	348 mins (5.8 hrs)	348 mins	2 hrs (9: 30 am to 11:30 am)	2 hrs (2:24 pm to 4:44 pm) 2 hrs (10:35 am to 12: 47 pm)	6/4/2013 6/5/2013
2	Carboplatin	371.249 g/mol	600 mg	Infusion over one hour	60 mins	66- 120 mins	120 mins	1 hr (12: 45 pm to 1: 45 pm)	2 hrs (2:24 pm to 4:44 pm) 2 hrs (10:35 am to 12: 47 pm)	6/4/2013 6/5/2013

Note: Cell membrane thickness: **4.55 microns** (squamous cell)

PD Date	Image No.	Region	ID	Total Tissue Volume	Axis Fired
20/04/13	1	Nasopharyngeal area	042	23.37	E
20/04/13	3	Mediastinal LN	043	74.7	D
01/06/13	2	Liver	046	43.411	C
20/04/13	8	Left ilium	045	59.04	A & B

Note: 1. Started premedication at 8: 40 am.
2. Reported at CARD at 2.00 pm on 4/06/2013
3. The treatment was given for 2 hrs with a break after 1 hr for about 10 -15 mins.

Name : XXXXXXXXXX DOB : 06/01/1965

Age/Gender: 48yrs/ M Diagnosis: Recurrent CA Nasopharynx with Metastasis

5th CHEMO CYCLE WITH FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of Administration	Peak Plasma Concentration Time	Half-Life	Drug Wash out Time	Infusion Time at Manipal Hospital	FORN Therapy Time at CARD	DATE
1	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9 g/mol	260 mg	Infusion over one hour	About 3 hrs	348 mins (5.8 hrs)	348 mins	1 hr (10: 38 am to 11:38 am)	2 hrs (1:57 pm to 4:30 pm) 2 hr (09:00 am to 11:15 pm)	25/6/2013 26/6/2013
2	Carboplatin	371.249 g/mol	600 mg	Infusion over one hour	60 mins	66- 120 mins	120 mins	45 pm to 12: 45 pm)	2 hrs (1:57 pm to 4:30 pm) 2 hrs (09:00 am to 11:15 pm)	25/6/2013 26/6/2013
3	Zomenta	272.09 g/mol				146 hrs	146 hrs	12: 50 pm to 1: 00 pm	2 hrs (1:57 pm to 4:30 pm) 2 hrs (09:00 am to 11:15 pm)	25/6/2013 26/6/2013

Note: Cell membrane thickness: **4.55 microns** (squamous cell)

PD Date	Image No.	Region	ID No.	Total Tissue Volume (cm3)	Axis fired
20/04/13	1	Nasopharyngeal area	042	23.37	I
20/04/13	3	Mediastinal LN	043	74.7	H
22-06-13	1	D8 vertb	047	2.92	G
22-06-13	2	Left ilium	048	6.77	A to F

Note: 1. All axis fired since Zomenta is meant for all bones.

2. The treatment was given for 2 hrs with a break after 1 hr for about 15 mins.

3. Patient's pre- medication started at 9 am.

Name : XXXXXXX DOB : 06/01/1965

Age/Gender: 48yrs/ M Diagnosis: Recurrent CA Nasopharynx with Metastasis

6th Chemo cycle with FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of adminstration	Peak Plasma Concentation Time	Half-Life	Drug Wash out time	Infusion Time at Manipal Hospital	FORN Therapy Time at CARD	Date
1	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9 g/mol	260 mg	Infusion over three hours	About 3 hrs	348 (5.8 hrs)	348 mins	3 hrs (9: 30 am to 12:30	2 hrs (2:24 pm to 4:44 2 hrs (10:35 am to 12: 47 pm)	16/7/2013 17/7/2013
2	Carboplatin	371.249 g/mol	600 mg	Infusion over one hour	60 mins	66- 120 mins	120 mins	1 hr (12: 45 pm to 1: 45 pm)	2 hrs (2:24 pm to 4:44 pm) 2 hrs (10:35 am to 12: 47 pm)	16/7/2013 17/7/2013

Note: Cell membrane thickness: **4.55 microns** (squamous cell)

PD Date	Image No.	Region	ID No.	Total Tissue Volume	Axis Fired
20/04/13	1	Nasopharyngeal area	042	23.37	E
20/04/13	3	Mediastinal LN	043	74.7	D
01/06/13	2	Liver	046	43.411	B
15/07/13	1	D8 vertb	049	7.457	C
15/07/13	2	Left ilium	050	11.791	A

Name : XXXXXXXXXX DOB : 06/01/1965

Age/Gender: 48yrs/ M Diagnosis: Recurrent CA Nasopharynx with Metastasis

7th Chemo cycle with FORN

Sl. No	Drug	Molecular Mass	Dose	Mode of adminstration	Peak Plasma Conc	Half-Life	Drug Wash out time	Time at Manipal Hospital	FORN therapy time at CARD	DATE
1	Paclitaxel 6-α,3′-p-dihydroxy-paclitaxel (C47H51NO16)	885.9 g/mol	260 mg	Infusion over 3 hrs 20 mins	About 3 hrs	348 (5.8 hrs)	348 mins	3 hr 20 mins (09: 30 am to 12:55 pm)	1+ 1 hrs (3:48 pm to 4:48 pm + 5:11 to 6:11 pm) 1+ 1 hrs (8: 10 to 9: 10 am+ 9: 25 to 10: 25 am)	14/08/2013 15/08/2013
2	Carboplatin	371.249 g/mol	600 mg	Infusion over 1 hr 20 mins	60 mins	66- 120 mins	120 mins	1 hr (1: 15 pm to 2:50 pm)	1+ 1 hrs (3:48 pm to 4:48 pm + 5:11 to 6:11 pm 1+ 1 hrs (8: 10 to 9: 10 am + 9: 25 to 10: 25 am)	14/08/2013 15/08/2013
3	Zometa	272.09 g/mol				146 hrs	146 hrs	12:55 pm to 1:15 pm	1+ 1 hrs (3:48 pm to 4:48 pm + 5:11 to 6:11 pm) 1+ 1 hrs (8: 10 to 9: 10 am+ 9: 25 to 10: 25 am)	14/08/2013 15/08/2013

		First one hour with FORN				Second one hour with FORN				
PD Date	Image No.	Region	ID	Total tissue vol (cm3)	Axis fired	Image No.	Region	ID	Total tissue vol (cm3)	Axis fired
20/04/13	1	Nasopharyngeal area	042	23.37	I and H	1 (PD dated 20-04-2013)	Nasopharyngeal area	042	23.37	I
13/08/13	1	Mediastinal LN	051	1.589	G	1(PD dated 13-08-2013)	Mediastinal LN	051	1.589	H
01/06/13	2	Liver	046	43.411	F	3(PD dated 13-08-2013)	D8 vertb	052	5.046	G
13/08/13	4	Left ilium	053	10.283	E to A	4(PD dated 13-08-2013)	Left ilium	053	10.283	F to A

Note :
1. All axis fired since Zometa is meant for all bones.
2. The treatment was given for 2 hrs with a break after 1 hr for about 20 mins.
3. Patient's pre- medication started at 8.50 am.
4. The patient was positioned for the first one hour targeting mediastinal LN. For the second hour patient was positioned targeting D8 vertb.

MRI – PET Biopsy Findings

Sl No	Investigation	Date (dd/mm/yyyy)	Period	Impression	Lesion Measurements	SUV
1	PET	11/10/11		Rt Axilla LN uptake		
2	Biopsy	03/05/12		Rt Axilla LN- Undifferentiated carcinoma, relapse		
3	CT	18/02/13		Mediastinal LN swelling, multiple liver tumor, bone metastases s/o		
4	PET-CT	03/04/13		Local (rt nasopharynx) recurrence not ruled out. LN mets, Hepatic & skeletal mets.		
5	MRI scan + PD (India)	20/04/13	Pre- 2nd chemo+ FORN	Small irregular lesion in segment II of liver (metastatic)	1.1 x 0.8 cms and 1.2 x 0.7 cms	
				Few mildly enlarged mediastinal LN's in Perivascular and sub carinal region. Possibly reactive nodes	27 x 9 mm and 15 x 9 mm respectively	
				Focal lesion in body of D4, D6, D10, L3 and L5 vertebrae (metastatic ?)		
				Focal metastasis in left ilium	12 x 13 mm postero-medial aspect	
6	PD sequence (India)	11/05/13	Pre- 3rd chemo+ FORN	Same lesions, with slight decrease in size of liver and D6 vertebrae mets. Size not mentioned.		
7	PD sequence (India)	01/06/13	Pre- 4th chemo+ FORN	Same lesions with slight decrease in size of liver. Size not mentioned.		
8	PD sequence (India)	22/06/13	Pre- 5th chemo+ FORN	Lesions in liver, mediastinum almost resolved. Lesion in D8 and left iliac bone persist.		
9	PD sequence (India)	15/07/13	Pre- 6th chemo+ FORN	Lesion in D8 and left iliac bone persist, but appear sclerotic		
10	PET-CT	05/08/13	Post 6th chemo+ FORN			
11	PD sequence (India)	13/08/13	Pre- 7th chemo+ FORN	Residual mediastinal nodes- reactive? Lesion in D8 and left iliac bone persist, but appear sclerotic		

Blood Work

		Low value	High value	Parameter																										
Scheduled date	Performed Date	Place	Period	WBC Total count	RBC	Hb	PCV	MCV	MCH	MCHC	Platelet	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	ESR	Creatinine	Total Bilirubin	Direct. Bilirubin	SGOT/AST	SGPT/ALT	ALP	Total protein	s. albumin	s. globulin	Albumin/ Globulin	CEA	squamous cell carcinoma related (SSC)
3/27/2013	3/27/2013	Japan	Pre- 1st chemo	6700 /cu.mm	4.64 m/cu.r	13.2 g/dl	41.10%	88.5 fl	28.5 pg	32.2 g/dl	225 x 10*3/	62.60%	18.80%	14.10%	4.20%	0.30%	----	0.79 mg/dl	0.4 mg/dl	----	23 IU/ml	12 IU/ml	455 U/L	----	4.3 g/dl	----	----	----	----
4/8/2013	4/8/2013	Japan	12 days post- 1st chemo	2400	4.19	12.2	36.7	87.5	29.1	33.2	206 x 10*3	45	29	13	7	0	----	0.77	0.2	----	28	18	387	----	3.7	----	----	1.9	0.8
4/18/2013	4/18/2013	Blore (Manipal)	Pre- 2nd chemo+ FORN	4820	4.7	13.3	39.8	84.5	28.2	33.4	243 x 10*3	60.6	28.8	7.3	2.7	60	----	0.92	0.51	0.10 mg/dl	26	21	92	7.1 g/dl	4.2	2.9 g/dl	1.4	----	0.7
5/2/2013	Not done	Blore	10 days post-2nd chemo+ FORN	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----
5/9/2013	5/9/2013	Blore (Manipal)	Pre- 3rd chemo+ FORN	3860	4.7	13.2	40.1	85.5	28.1	32.9	127 x 10*3	56.9	31.8	9.4	1.6	0.3	----	0.79	0.3	0.14	37	41	127	8	4.7	3.3	1.4	2.9	----
5/25/2013	5/25/2013	Blore (Clumax)	10 days post-3rd chemo+ FORN	6400	4.36	12.5	37.4	85.8	28.7	33.4	125 x 10*3	69	25	4	2	----	33	----	----	----	----	----	----	----	----	----	----	1.73	----
5/31/2013	5/31/2013	Blore (Manipal)	Pre- 4th chemo+ FORN	3740	4.6	13.5	40.8	88.5	29.3	33.1	150 x 10*3	52.1	34.8	11.8	0.8	0.5	----	0.86	0.61	0.1	41	41	105	7.3	4.2	3.1	1.4	----	----
6/14/2013	6/14/2013	Blore (Clumax)	10 days post-4th chemo+ FORN	4800	4.27	12.6	37.4	88	29.5	33.7	130 x 10*3	69	24	6	1	0	24	----	----	----	----	----	----	----	----	----	----	2.26	----
6/21/2013	6/21/2013	Blore (Manipal)	Pre- 5th chemo+ FORN	4540	4.6	13.5	41.2	89.6	29.3	32.8	113 x 10*3	59.7	28.9	9.7	1.3	0.4	----	0.84	0.4	0.14	32	31	110	8	4.7	3.3	1.4	----	
7/4/2013	7/7/2013	Blore (Clumax)	13 days post-5th chemo+ FORN	3500	4.26	12.9	38.5	90	30.3	33.5	78 x 10*3	49	44	6	1	0	36	----	----	----	----	----	----	----	----	----	----	2.01	----
7/15/2013	7/15/2013	Blore (Manipal)	Pre- 6th chemo+ FORN	3430	4.4	13	40.5	91.6	29.4	32.1	115 x 10*3	54.2	34.4	9.6	1.5	0.3	----	----	----	----	----	----	----	----	----	----	----	----	----
7/26/2013	7/27/2013	Blore (Clumax)	10 days post-6th chemo+ FORN	4100	4.01	12.3	36.9	92	30.7	33.3	61 x 10*3	61	32	5	2	0	31	1.1	----	----	----	----	----	----	----	----	----	2.13	----
8/13/2013	8/10/2013	Blore (Clumax)	Pre- 7th chemo+ FORN	3600	4.12	13	37.7	92	31.6	34.5	150 x 10*3	46	42	8	4	0	18	----	----	----	----	----	----	----	----	----	----	2.42	----
8/22/2013	8/24/2013	Blore (Clumax)	10 days post-7th chemo+ FORN	4000	4.03	12.7	37.3	93	31.5	34	65 x 10*3	62	33	4	1	0	34	----	----	----	----	----	----	----	----	----	----	2.45	----

Adverse Events Post Chemo

Adverse events post chemo						
Post 1st cycle chemo (in Japan on 27/03/2013)	**Post 2nd cycle + FORN (in Bengaluru on 23/04/2013)**	**Post 3rd cycle + FORN (in Bengaluru on 14/05/2013)**	**Post 4th cycle + FORN (in Bengaluru on 04/06/2013)**	**Post 5th cycle + FORN (in Bengaluru on 25/06/2013)**	**Post 6th cycle + FORN (in Bengaluru on 16/07/2013)**	**Post 7th cycle + FORN (in Bengaluru on 14/08/2013)**
Nausea, Vomiting G2, diarrhea G2,	**Slight fatigue**, Pain in legs (slight improvement with ginger tea)	**May 14** after reaching home: **Slight fatigue, slight pain in legs** (subsided with ginger tea). **No other side effects, had a good night sleep**.	**June 4 Slight fatigue/ tiredness**. Slight pain in both legs. Slight fever during later part of the evening.	**June 25** Slight fatigue/ tiredness. Slight pain in legs. Had a good night sleep	**July 16** Slight pain in legs. **No other side effects.**	**Aug 14** Felt slightly feverish. Slight headache. Slight pain in legs. Had a **good night's sleep**.
Severe pain in both legs on 1st day	**Apr 24**: Took prescribed meds *- led to slight stomach ache and mild diarrhea. **Slight nausea, loss of taste**, Hiccups all day, **slight tiredness, able to move around and walk.**	May 15: Very slight pain in legs. Slight feverish, but subsided later. Loss of taste but appetite was fine. Slight hiccups (every now and then), slight fatigue, uneasiness in stomach. Around 10 pm he noticed veins on left hand from the point of infusion to elbow had turned red.	**Jun 5**: Slight fever in morning. Fatigue during day. No taste, appetite is fine. Slight fever in evening. No nausea. Hiccups all morning only.	**June 26** Slight hiccups in the morning. **Slight fatigue/ tiredness. No taste but appetite fine**. Felt slightly feverish during the evening.	**July 17 Slight fatigue/ tiredness**. Hiccups only in the morning. No taste from afternoon but appetite fine. Slight uneasiness in the stomach. Face turned a little reddish in the evening. Able to sleep well.	**Aug 15** Felt slightly feverish in the evening. Slight stomach ache in the evening. Had hiccups all day. No bowel movements. Redness in face during the evening. Slight fatigue. No taste/ appetite fine. Able to sleep well.
Severe Fatigue/ tiredness/ lack of energy	**Apr 25**: **Fatigue**, didn't feel like doing anything. Hiccups, **loss of taste sensation/ appetite.** Slight stomach ache. **Able to sleep**	May 16: Slight fever (99.8) all day- got worse during the evening. Fatigue/ tiredness/ pain in throat. No taste/ lower than normal appetite. Continued redness in left hand veins with redness in right hand as well. Called Dr. Patil around 8 pm and was advised to take tab Augmentin 1000mg.	**Jun 6:** Fatigue all day. No taste/ lower than normal appetite. No bowel movements.	**June 27** Fatigue/ tiredness all day. Slight nausea. Felt constipated. No taste/ appetite.	**July 18** Slight fatigue/ tiredness. No Hiccups at all. No taste/ lower than normal appetite. No bowel movements. Slight stomach ache in the evening. Heaviness in the chest in the evening. Started Neupogen today.	**Aug 16** Felt slightly feverish. Pain in the throat- salt water gargle. Slight pain in the stomach and right ear. No taste and appetite. Slight fatigue + tiredness. No hiccups. Bowel movements fine. Was able to sleep well.
Loss of sensation, Reduced appetite	**Apr 26**: All of above- hiccups subsided.	May 17: Woke up with slight fever and body ache. Didn't feel too good. No taste, but appetite was fine. Continued redness in both hands. Advised to continue with Augmentin and Crocin (Paracetamol). Fever subsided by evening, but slight uneasiness in stomach. Doctor suggested it might be viral infection.	**Jun 7:** Continued fatigue. **No taste, appetite is fine. Bowel movements is fine.**	**June 28** Fatigue/ tiredness continues. **No taste, but appetite getting better. Bowel movement fine**. Slight pain in stomach during afternoon. Slight nausea towards evening.	**July 19 Slight fatigue/ tiredness**. No taste/ lower than normal appetite. Slight stomach ache all day. Bowel movement fine. Slight lack of energy today.	****Aug 17** Slightly feverish during the day. Pain in throat and right ear continued all day. Slight pain in stomach. No taste or appetite. Slight fatigue and tiredness. No bowel movements. Was able to sleep well.
	Apr 27: All of above, no problem sleeping	**May 18:** Fever subsided. Uneasiness/heaviness in stomach. **Slight fatigue**. No taste but appetite is fine. Cramps, sometimes pain in index finger (rt.). Continued with Augmentin and Neupogen. Reduced redness in hands.	**June 8:** Fatigue. No taste, appetite is fine. Bowel movement fine.	**June 29 Slight fatigue/ tiredness**. No taste but appetite fine. No nausea or stomachache today. Able to go out and feeling a lot better.	**July 20 Slight fatigue/ tiredness. No taste. Appetite better**. Slight lack of energy. Stomach feels a little better. No bowel movement.	**Aug 18** Slight pain in the stomach only during the day. Pain in throat and ear continue. No taste or appetite. Slight fatigue and tiredness. Bowel movement fine. No fever today.
	Apr 28: **Reduced fatigue, feels a lot better**, slight stomach ache, no nausea, **still no taste, appetite slightly better**.	**May 19:** No fever, redness in hands. Still no taste, but appetite is fine. Cramps and prickly sensation in right hand fingers. **Slight fatigue**. Continued with Augmentin+ Neupogen. Slight pain in throat (only when he goes out).	**June 9:** Feeling better. Slight taste, appetite is fine. Bowel movement fine.	***June 30** Slight fatigue but feeling much better. Taste better and appetite fine. Overall feeling lot better.	**July 21** Woke up with slight stomach ache. Slight heaviness in chest. Energy levels better during the evening. Taste seems a little better. Appetite fine. **Bowel movements normal**. Didn't feel too tired.	**Aug 19** Slight uneasiness in stomach in the morning. No taste. Appetite little better. Slight fatigue and tiredness. No pain in throat or ear. No fever, no bowel movements
	Apr 29 till date: no complaints	**May 20:** Still no taste. Cramps and prickly sensation in right index finger. Continued with Augmentin+ Neupogen.	**June 10:** Feeling good. Taste and appetite improving. Bowel movements fine.	**July 1 Completely fine. Energy level up.** Taste and appetite fine. Bowel movement fine. No nausea or stomach ache	**July 22** Feeling good. **Tastes getting better**. Appetite fine. **Bowel movement normal. Energy level normal**. No stomach ache.	**Aug 20** No fever, throat pain, ear ache or stomach ache. Bowel movements fine. Felt slight fatigue and tiredness. No taste but appetite getting better.
		May 21 onwards: All normal	**June 11: Taste and appetite improving further. Feeling a little energized.**			**Aug 21** Feeling a lot better. No fever/ throat pain/ ear ache/ stomach ache. Felt slight fatigued but better than previous days. Bowel movements fine. Slight taste sensation and appetite fine. Had a good nights sleep.
	* Tab Pantodac DSR 1-0-0, Tab Perinorm 1-1-1, Tab Emeset 8mg 1 SOS 1/2 hr. BF, Tab Levoflox 500mg					
				*He was out the whole day at cousins place for lunch. Played a little cricket on the terrace.		** Called Dr. Patil in the afternoon. Was advised Tab Combiflam 1- 0- 1. Cetirizine 10 mg once a day for 3 days. Started medication in the evening. Salt and warm gargle before bed. Continued with prescribed medication on Aug 18 and 19 also and salt water gargle (twice a day). Was able to sleep well.

Supplemental Figure 1

Body surface markings based on the location of the ROIs in the MRI -derived PD sequence films used in the Dosimetry planning are maintained on a plastic template sheet for precisely focusing the guns for FORN delivery