INDUCTION-COMBINED TREATMENT (ICT) AS AN RADICAL TREATMENT APPROACH FOR INOPERABLE, LOCALLY VERY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA (LVAHNSSC) PATIENTS

Krzysztof Skladowski, MD, PhD, Lukasz Michalecki, MD, Tomasz Rutkowski, Md, PhD, Marcin Hutnik, MD, Beata Lukaszczyk-Widel, MD, Boleslaw Pilecki, MD, PhD, Andrzej Wygoda, MD, PhD, Marek Kentnowski, MD; The Institute of Oncology - Maria Sklodowska-Curie Memorial Cancer Centre in Gliwice, Poland

Purpose. TPF (docetaxel, cisplatin, 5-fluorouracil) induction chemotherapy followed by radiation (with or without carboplatin) is an EB front-line therapy of locally advanced HNSCC currently recommended. Our experience is that is specially dedicated to HNSCC patients with bulky tumor(s) or with multiple neck node metastases. In spite of the relatively high treatment response (OR ≈ 75%, CR ≈ 50%) TPF induction is rather low effective for very advanced (inoperable) tumors, i.e. T4B and N3. Though majority of patients with that disease is only palliated, some of them remarkably recover and some other still have had a good performance status, lack of weight loss and expectation of radical therapy. Therefore we decided to combine the TPF chemotherapy and radiation in one induction treatment - ICT for LVAHNSCC patients.

Material and Methods. Patients with T4B or N3 HNSCC of oropharynx (OPC) or hypopharynx (HPC) were selected to the ICT on the base of following criteria: KPS 0-1, weight loss less than 5%, HGB level in reference range, no significant comorbidities. Over the year 2010 ten patients in average age 58 (range 45-64) have been qualifying and treating according to the study protocol. The ICT consisted of: 20 Gy given in 5 fractions at days 1-5 as an upfront boost delivered in high-precision IMRT (RapidArc™) to all GTVs (named: Hypofractionated Upfront High-Precision Radiation Boost - HUHPRB) and TPF chemotherapy (docetaxel 75 mg/m2/d on day 1, cisplatin 100 mg/m2/d on day 1, 5-fluorouracil 1000 mg/m2/d for 4 days) administered at days 6-9, 27-30 and 48-51. After the end of TPF chemotherapy treatment response was scored. Patients with complete (CR) or partial response (PR) had to be consolidated by RT alone (50-54 Gy in 25-30 fractions) either chemoradiation (54 Gy in 30 fractions + 2 courses of cisplatin 100 mg/m2/d on days 1 and 22), respectively.

Results. The median follow-up is 25 months. From 10 patients (7 male, 3 female; 6 OPC, 4 HPC, 5 T4B and 5 N3) who had entered to the study, 3 patients have no received any further TPF course, 3 have received 1 and 4 have received 2 courses (40% compliance of the ICT). From 8 patients who have been scored to ICT response, 6 had CR (75%) and 2 PR (25%) of the disease and they have further received consolidated RT alone and RT + cisplatin, respectively (100% compliance). Two-year results are as follows: all 8 patients have had LRC; 3 patients (37%) died due to distant metastases (all had received less than 3 courses of TPF); actually 5 patients are alive (63%) with no evidence of disease.

Conclusions. The poor (40%) compliance have indicated that investigated ICT was "too hot" for the patients. But idea of ICT seems to be very promising for selected patients with LVAHNSCC. The study is continued now with modified ICT protocol.
**S336 CANCER-TESTIS ANTIGEN EXPRESSION IN A PHASE II TRIAL OF INDUCTION CHEMOTHERAPY FOLLOWED BY CHEMORADIATION**

**Authors:** Simon Laban, MD; Djordje Atanackovic, MD, PhD; Chia-Jung Busch, MD; Till S Clauditz, MD; Thomas K Hoffmann, MD, PhD; Gerd Ritter, PhD; Giulio Spagnoli, PhD; Alexander Knuth, MD, PhD; Adrian Münscher, MD; Rainald Knecht, MD, PhD; University Medical Center Ulm, University Medical Center Hamburg, Ludwig Institute for Cancer Research, National Center for Cancer Care & Research Qatar, University of Basel

**Introduction:** Cancer-testis antigens (CTA) are immunogenic proteins expressed specifically in cancer tissue with the exception of testis and germline cells. In a tissue microarray (TMA) of 453 surgically treated patients with head and neck squamous cell carcinoma, we have identified pan-MAGE, MAGE-A3/A4 and NY-ESO-1 as prognostic markers associated with a significantly poorer survival, especially if simultaneously expressed in the cytoplasm and nucleus. We now set out to determine the impact of CTA expression on response to treatment and outcome in patients treated with induction chemotherapy (ICT) followed by chemoradiation therapy (CRT).

**Material and Methods:** In this prospective German phase II larynx preservation trial (Laryngoprotect), 278 stage III/IV larynx and hypopharynx cancer patients received ICT with docetaxel (75mg/m2; d1), cisplatin (100mg/m2; d1, d22, d43) and 5-FU (1000mg/m2; d1-4 continuous infusion), followed by chemoradiation with cisplatin (100mg/m2, d1, d22, d43). A TMA was constructed with pre- and posttherapeutic biopsies. Pretherapeutic biopsy material was available from 73 patients and corresponding biopsies after ICT from 13 patients. MAGE-A family and MAGE-C family CTA and NY-ESO-1 were stained immunohistochemically and scored separately for cytoplasmic and nuclear expression.

**Results:** Rates of pretherapeutic positivity were pan-MAGE: 22/52; MAGE-A3/A4: 18/52; MAGE-C1: 4/46; MAGE-C2 0/50; NY-ESO-1: 2/51. Expression rates of MAGE-C2 and NY-ESO-1 were considered too low for further analysis. No significant influence of CTA positivity on treatment response to ICT or CRT could be found. With a mean follow-up of 28 months patients with complete response (CR) to ICT or CR to CRT had significantly improved median overall survival (OS) (CR_{ICT} 57 vs. 23 months, p=0.01; CR_{CRT} 53 vs. 21 months, p=0.01) and median progression-free survival (PFS) (CR_{ICT} 53 vs. 12 months, p=0.01; CR_{CRT} 43 vs. 7 months, p<0.001). No significant differences comparing OS or PFS of CTA positive vs. negative patients could be found. Updated survival data will be presented at the meeting.

**Conclusion:** No correlation of CTA expression with treatment response could be found, but CR to ICT or to CRT was significantly correlated with improved OS and PFS. In contrast to our results in the primary surgical treatment setting, CTA expression could not be identified as a marker for poor prognosis. This may be due to an immunological response to CTA in the ICT/ CRT setting diminishing the negative influence of CTA expression on survival. These are preliminary results, since data with longer follow-up are currently being prepared and will be available at the time of presentation.
**S337 PRIMARY (CHEMO-) RADIOTHERAPY AND CONCOMITANT EGFR-INHIBITOR ZALUTUMUMAB TO PATIENTS WITH SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK. RESULTS OF THE RANDOMIZED PHASE III TRIAL, DAHANCA19**

Jesper Grau Eriksen, Christian Maare, Jørgen Johansen, Hanne Primdahl, Jan Evensen, Claus Andrup Kristensen, Lisbeth Juhler Andersen, Jens Overgaard; on behalf of the DAHANCA-group (Depts. of Oncology in Copenhagen, Herlev, Odense, Aarhus, Aalborg, Denmark and Oslo, Norway)

**Background:** Monoclonal antibodies against the Epidermal Growth Factor receptor (EGFR-I) have been reported to increase tumor control and survival of patients with Head and Neck Squamous Cell Carcinomas (HNSCC) when combined with radiotherapy (RT). This study was conducted by the Danish Head and Neck Cancer group (DAHANCA) and aimed to evaluate if concurrent treatment with the EGFR-I zalutumumab during RT improved outcome in patients with HNSCC.

**Material and methods:** 619 pts with biopsy-verified HNSCC entered the study from November 2007 to June 2012. The majority of tumors were of oropharyngeal origin (69%) whereas other sites were less represented: oral cavity (4%), hypopharynx (12%) and larynx (14%). Stratification was done by tumor-site, stage (554 (89%) patients were st. 3-4), p16-status (75% of oropharyngeal carcinomas were positive) and use of concurrent cisplatinum (70%). Patients were randomized to control-arm or zalutumumab-arm. The control-arm was primary accelerated RT predominantly 66-68Gy, 2Gy/fx, 6fx/wk and concomitant daily hypoxic radiosensitisation with nimorazole. St. 3-4 carcinomas received weekly cisplatinum 40 mg/m2 during RT. Elective neck-dissection was not performed. The zalutumumab-arm was identical with the control-arm plus zalutumumab 8 mg/kg. First dose was given the week before start of RT and continued weekly during irradiation. Analyses were performed as intention-to-treat. Primary endpoint was Locoregional Control (LRC). Secondary endpoints were Disease-Specific Survival (DSS) and Overall Survival (OS).

**Results:** Median observation time was 36 month (12-67 months). 309 pts were in the control-arm and 310 in the zalutumumab-arm. Patient and tumor parameters were well balanced. At time of analysis 126 LRC were verified, 71 pts were dead of disease and 45 were dead of other causes. The 3-year LRC rate was 78% in the zalutumumab-arm vs. 79% in the control-arm, HR: 0.8 [95% CI: 0.6-1.2]. This outcome was reflected in DSS: HR 1.0 [0.7-1.7] and in OS: HR 0.9 [0.6-1.3]. Median number of doses zalutumumab given per patient was 5. LRC was not better when having more than 5 doses compared to less than 5 doses (HR 1.3 [0.7-2.1]) nor was DSS and OS. Treatment was generally well tolerated, but 94% of the pts in the zalutumumab-arm experienced a skin-rash (29% had grade 3-4 rash). The degree of rash did not influence LRC (HR: 1.5 [0.9-2.7]) or the other outcome parameters. Finally, the effect of zalutumumab was not influenced by p-16 positivity (HR 1.0 [0.6-1.8]) nor p-16 negativity (HR 0.8 [0.5-1.4]).

**Conclusion:** Treatment with zalutumumab was generally well tolerated, but the addition of concomitant zalutumumab to primary (chemo-) RT and nimorazole for HNSCC did not increase locoregional control nor disease-specific or overall survival at 3 years.
Purpose: E2303 evaluated induction therapy, then chemoradiation (CRT) with cetuximab, paclitaxel and carboplatin in patients with stage III/IV head and neck squamous cell carcinoma (HNSCC) focusing on pathologic complete response, event-free survival, toxicity, and disease.

Methods: Patients with resectable stage III/IV HNSCC underwent induction therapy with planned primary site restaging biopsies (at week 8 in clinical complete responders and at week 14 if disease persisted). Chemoradiation with weekly cetuximab, paclitaxel and carboplatin began week 9. If week 14 biopsy was negative, patients completed CRT (68-72 Gy); otherwise, resection was performed. p16 protein expression status was assessed using automated quantitative protein analysis (AQUA) and was correlated with response/survival. Results: Seventy-four patients were enrolled; 63 were eligible. Forty-four (70%) were free of surgery to the primary site, progression, and death 1-year post treatment. Following induction 41 (23 complete response (CR)) underwent week 8 primary site biopsy of whom 24 (59%) had no tumor (pathologic CR). Week 14 biopsy during CRT (50 Gy) in 34 (15 previously positive biopsy and 19 no prior biopsy) was negative in 33. Thus 90% of eligible patients completed radiation. Neck dissection was positive in 11/30 (37%) patients. Overall survival (OS) and event-free survival (EFS) were 78% and 55% at 3 years, respectively. Disease progression in 23 patients (37%) was local only in 10 (16%), regional in 5 (8%), combined (LR) in 2 (3%), and distant in 5 patients (8%). There were no treatment-related deaths. Toxicity was primarily hematologic or radiation-related. p16 AQUA score was not associated with response/survival.

Conclusions: Induction cetuximab, paclitaxel and carboplatin followed by same drug chemoradiation is safe and induces high primary site response and promising survival.
Background: Concurrent chemoradiation is the standard treatment for inoperable LA-SCCHN. Gemcitabine and cetuximab are potent, synergistic radiosensitizers. The aim was to study the feasibility of the gemcitabine, cetuximab, and radiotherapy combination in SCCHN.

Material and methods: Eligible were patients with LA-SCCHN who qualified for definitive chemoradiation. Cetuximab 400 mg/m$^2$ was started 1 week before radiotherapy. Gemcitabine 10 mg/m$^2$ and cetuximab 250 mg/m$^2$ were administered weekly for the duration of radiotherapy (32 fractions, 5 fractions/week, up to 69.12 Gy, simultaneous integrated boost technique). Induction chemotherapy prior to RAGE was allowed. During RAGE, toxicity was scored weekly according to NCI-CTC version 4.

Results: 25 patients (22 male) were treated between April 2010 and November 2013. Median age: 63 (range: 47-74). Tumor sites: hypopharynx: 9; oropharynx: 9; supraglottis: 3; maxillary sinus: 2, tongue, unknown: each 1. Stage: T4N2c: 4; T3N2b: 4; T4N2b: 3; T2N2b: 2; T2N1: 2; Tu2b, TxN3, T2N3, T3N0, T3N1, T3N2c, T3N3, T4N1, T4N3, recurrence after prior surgery and RT: each 1. In 21 patients, RAGE was preceded by induction chemotherapy: 6 x weekly carboplatin (AUC 2)/paclitaxel (70 mg/m$^2$): 3; TPF: 17 (4 cycles: 13; 3 cycles: 1; 3 patients switched to weekly carboplatin/paclitaxel after 1 or 2 cycles because of renal toxicity); 4 x docetaxel, 5-FU, carboplatin: 1. Duration of radiotherapy: median: 44 days (range:42-50); < 47 days in 24 of the 25 patients, 50 days in 1. 24 patients received the planned radiotherapy dose (one patient refused further treatment after 18 fractions of 2.16 G; he also refused treatment for limb ischemia and requested euthanasia on day 35). 22 of the 25 patients received all planned gemcitabine and cetuximab. Patients received 97 % of planned gemcitabine and cetuximab without delays. Toxicity during RAGE (maximum grade, number of patients): radiodermatitis: grade 1: 1, grade 2: 7, grade 3: 15, grade 4: 2; mucositis: grade 2: 1, grade 3: 23, grade 4: 1. Weight loss: 5-10%: 9, 10-20%: 10. No toxicity-related deaths. 15 patients needed temporary tube feeding and/or parenteral nutrition, 15 needed hospitalization(s) (23 episodes, median duration: 11 days). 23 received opioids. 2 patients (T3N3 and T4N2c at diagnosis) were rendered tumor-free by salvage lymphadenectomy. 2 patients had persistent unresectable local disease at the end of RAGE. Lung metastases developed in 2 patients (1 with persistent local persistent unresectable local disease), a local recurrence in 1. Median follow-up since enrollement is 25.3 months (range: 2.6-44.2). The Kaplan-Meier estimated 2-year disease-free survival rate is 60.5 %. 18 patients are alive without evidence of SCCHN disease: 16/18 are feeding-tube independent, 2/18 are feeding-tube dependent (< 6 months after treatment).

Conclusions: With adequate support, the concomitant administration of cetuximab, gemcitabine and radiotherapy in SCCHN patients is feasible, both with and without induction chemotherapy, without treatment interruptions, with patients receiving 97 % of planned cetuximab and gemcitabine dose, and 100 % of planned radiotherapy dose. After a median follow-up of 25.3 months, the Kaplan-Meier estimated 2-year disease-free survival rate is 60.5 %.
Background: Concurrent chemoradiotherapy has now been established as the standard treatment of care for unresectable head and neck squamous cell carcinoma (HNSCC). However, locoregional failure and distant metastasis remain common. Induction chemotherapy is frequently used in clinical practice and may have a role in organ preservation and in reducing distant metastasis. We previously reported that weekly cisplatin at a dose of 40 mg/m$^2$ could be easier to manage than three-weekly cisplatin (100mg/m$^2$), which is recognized as standard regimen. In this study, we evaluated the feasibility of induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy followed by concurrent weekly cisplatin chemoradiotherapy for the patients with locally advanced HNSCC.

Patients and methods: Between 2009 and 2013, 30 patients with Stage III-IV M0 HNSCC were treated in Hokkaido University Hospital with three cycle of induction chemotherapy (docetaxel 75mg/m$^2$ and cisplatin 75mg/m$^2$, day 1, and 5-fluorouracil 750mg/m$^2$/day 120h continuous infusion, every 3 weeks) followed by concurrent weekly cisplatin (40mg/m$^2$, on weeks 1,2,3,5,6 and 7) chemoradiotherapy.

Results: Median age was 59 years (range, 40-69 years). The number of the patients with oropharyngeal carcinoma, hypopharyngeal carcinoma and laryngeal carcinoma were 16 (53%), 12 (40%), and 2 (7%), respectively. StageIII, IVA, and IVB were 2 (7%), 24 (80%), and 4 (13%) patients, respectively. A median follow-up period was 18 months (range, 5-38 months). Three courses of induction chemotherapy were performed in 24 patients (80%). Grade 3-4 toxicities during induction chemotherapy were observed in 22 patients (73%). The major toxicities were hematologic, with 21 cases (70%) of grade 3-4 neutropenia. Grade 3 diarrhea was experienced in 3 patients (10%). The overall response rate after induction chemotherapy was 83%; one patient (3%) had complete response, 24 patients (80%) had partial response, 4 patients (13%) had stable disease. One patient was withdutumor progression. Radiotherapy was fully received (70Gy) in 29 patients (97%). A total of 19 patients (63%) completed five (12 patients) or six (7 patients) courses of the chemotherapy. Six patients (20%) received four courses, 4 patients (13%) received three courses, and one patient (3%) received two courses of the chemotherapy. During concurrent chemoradiotherapy, no grade 4 hematological toxicities were observed. Grade 4 dermatitis was observed in one patient, and grade 3 mucositis was observed in 11 patients. There were no treatment-related deaths during induction chemotherapy and concurrent chemoradiotherapy. After completion of concurrent chemoradiotherapy, 26 patients (87%) achieved a complete response. Two patients (7%) had partial response. One patient (3%) had stable disease, and 1 (3%) had progressive disease. One- and 2-year progression-free survival and overall survival were 86%, 72%, and 89%, 81%, respectively.

Conclusion: The sequential therapy composed of induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy followed by concurrent weekly cisplatin chemoradiotherapy is feasible with encouraging efficacy in patients with locally advanced HNSCC. Concurrent weekly cisplatin chemoradiotherapy
following induction chemotherapy appears to be a suitable alternative to three-weekly high-dose cisplatin.
ORGAN PRESERVATION FOR PATIENTS WITH ADVANCED LARYNGEAL CANCER WHO RESPONDED TO INDUCTION CHEMOTHERAPY WITH DOCETAXEL, CISPLATIN, AND 5-FUOROURACIL (TPF) FOLLOWED BY CISPLATIN CONCOMITANT WITH RADIATION THERAPY: A PHASE II TRIAL

Aron Popovtzer, MD, Salomon Stemmer, MD, Dror Limon, MD, Ohad Hilly, MD, Gideon Bachar, MD, Hannna Burnstien, MD, David Groshar, MD, Fienmesser I Rafael, MD, Jacob Shvero, MD; Rabin Medical Center

INTRODUCTION: The optimal treatment of patients with advanced laryngeal cancer remains controversial. For T3 patients, standard treatment includes laryngectomy or organ preservation (OP) which consists of induction chemotherapy (IC) followed by radiotherapy or concomitant chemoradiotherapy (CCRT). For T4 patients, the standard treatment is total laryngectomy. Previous studies suggest that response to IC could serve as an in-vivo predictive tool to select patients for an OP approach. We conducted a phase II OP trial in stage III/IV laryngeal cancer to determine whether larynx preservation rates (LPR) could be improved without compromising overall survival (OS) in patients who responded to a single IC cycle.

PATIENTS/METHODS: Patients received TPF-based IC (docetaxel 75 mg/m² on day 1, followed by cisplatin 75 mg/m² on day 1, and continuous-infusion 5-fluorouracil 1,000 mg/m²/d for 5 days), with prophylactic ciprofloxin and a pegfilgrastim injection. Response was determined after the first IC cycle by PET-CT and a second laryngoscopy with biopsies. Patients with >50% tumor reduction were treated according to tumor stage at diagnosis: Stage III, CCRT; stage IV, treatment with 2 additional TPF cycles followed by CCRT. Nonresponders had immediate laryngectomy. Patients with residual disease after chemoradiotherapy had planned salvage surgery.

RESULTS: Twenty-three patients (T3, 11; T4, 12) were enrolled in this study. Median age was 59 (range) 49-74) years, 19 (83%) were males. After a single TPF cycle, 5 patients had complete response, 12 had a >50% tumor shrinkage, 4 were nonresponders, and 2 died from neutropenic sepsis. Two patients underwent immediate laryngectomy and 2 underwent laryngectomy upon recurrence. One patient experienced acute renal failure that developed into chronic renal failure. Two-year OS and LPR were 76% and 81%, respectively. The disease-specific survival rate was 87%. Response after a single TPF cycle was positively associated with survival (2-year OS of 92% vs. 50%, P=0.02). T stage was not predictive of survival in patients who responded to 1 TPF cycle.

CONCLUSIONS: Our findings suggest that response to a single TPF-based IC cycle could serve as a tool to select patients with locally advanced laryngeal cancer for an OP treatment.
**S342** UPDATED ANALYSIS OF A PHASE II TRIAL OF E10A (ENDOSTATIN ADENOVIRUS) IN RECURRENT/METASTATIC HEAD AND NECK CANCER

George Yoo, MD, Changchuan Pan, Ye Wen, Liu Wenqing, Cui Yu, Liu Bo, George Thomas, PhD, Nancy Stewart, PhD, Bob Choy, Wenlin Huang; Wayne State University, Guangzhou Double Bioproducts Ltd, Marsala Biotech Inc., CAS Key Laboratory of Pathogenic Microbiology and Immunology

**Purpose**: To determine the safety and efficacy of E10A and chemotherapy in treating head and neck cancer in a randomized phase II trial.

**Background**: Recombinant human endostatin non-replicating adenovirus (E10A) is a novel anti-tumor gene therapy agent. E10A expresses human endostatin, which inhibits vascular endothelial cell proliferation and tumor angiogenesis, thereby blocking tumor blood supply.

**Methods**: In a Phase II trial, a total of 140 subjects were enrolled with recurrent or metastatic head and neck cancer to receive either E10A/chemotherapy or chemotherapy in a 1:1 ratio.

**Results**: The objective response rate (ORR), disease control rate (DCR), median progression free survival (PFS) and median overall survival (OS) in E10A/chemotherapy or chemotherapy arms were:

<table>
<thead>
<tr>
<th></th>
<th>E10A/Chemo</th>
<th>Chemotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>45.8%</td>
<td>32.3%</td>
<td>NS</td>
</tr>
<tr>
<td>DCR</td>
<td>89.8%</td>
<td>75.8%</td>
<td>0.035</td>
</tr>
<tr>
<td>PFS</td>
<td>7.0 Mo</td>
<td>3.6 Mo</td>
<td>0.006</td>
</tr>
<tr>
<td>OS</td>
<td>19.1 Mo</td>
<td>14.5 Mo</td>
<td>NS</td>
</tr>
</tbody>
</table>

[ORR = complete response (CR) + partial response (PR); DCR = CR+PR+ stable disease (SD); Month (Mo)].

E10A-related adverse events were fever, flu like symptoms, and reactions at injection site which were minor and reversible. There was no significant difference in other adverse events between the E10A/chemotherapy and chemotherapy.

**Discussion**: These overall survival data are encouraging since 19.1 month survival is better than historical data (5 -10 months). Furthermore, the absolute difference in overall survival between the treatment groups of 4.6 months is superior to a previously reported trial with chemotherapy vs. Erbitux + chemotherapy (2.7 months). These E10A-related adverse events are similar to previously reported adenovirus-related toxicities.

**Conclusion**: These data support the development of a phase III trial with appropriate statistical power and the adequate sample size to detect an improvement in overall survival. A phase III trial is being initiated to demonstrate the benefit of E10A in treating patients with Recurrent/Metastatic Squamous Cell Carcinoma of the head and neck when combined with currently available chemotherapeutic agents. This study is designed to confirm the efficacy (OS, PFS) and safety of E10A in combination with chemotherapy for treatment of head and neck cancer.
1. Wayne State University Medical Center, Detroit, MI, USA;

2. Guangzhou Double Bioproducts Ltd., Guangzou, China;

3. Marsala Biotech Inc., 7-1250 Waverley Street, Winnipeg R3T6C6, Manitoba, Canada;

4. CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Science, Beijing 100054, People’s Republic of China