Abstract # 2498

THE MVA VIRAL PLATFORM FOR THE TREATMENT OF CANCER AND CHRONIC INFECTIOUS DISEASES: CLINICAL EXPERIENCE FROM FOUR RANDOMIZED CONTROLLED PHASE II STUDIES.

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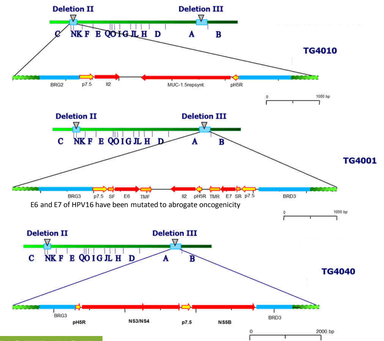
MVA PLATFORM

MVA virus (Modified attenuated Vaccinia virus, strain Ankara)

- Induces mainly cellular immunity
- Non-integrative and non-propagative virus in most mammalian cells
- Extensive history of safety
- Used for smallpox eradication campaign in more than 150,000 immuno-compromised individuals



ABSTRACT

The modified vaccinia strain Ankara (MVA) is attenuated and non-propagative but retains infectivity and immunogenicity, its large DNA genome allows the insertion of several full-length coding sequences for disease associated antigens or other transgenes of interest. MVA based targeted immunotherapeutics are designed to induce a cytolytic cellular immune response.

TG4010 expresses the full-length sequences of MUC1 and IL2 and was tested in combination with first line platin-based chemotherapy in stage IV non-small cell lung cancer (NSCLC) versus chemotherapy alone (NCT00415818 and NCT01383148); 10^8 plaque forming units (pfu) was given S/C weekly for 6 weeks then every three weeks up to progression. TG4001 expressing E6 and E7 of HPV16, and IL2 was assessed versus placebo in women with cervical intra-epithelial neoplasia (CIN2/3) (NCT01022346) at the dose of 5.10^7 pfu, three S/C injections a week apart. TG4040 expresses the HCV antigens NS3, NS4 and NS5B and was evaluated in combination with peg-interferon-α and ribavirin versus the same treatment alone in treatment-naïve patients with chronic hepatitis C, (10^7 pfu), two distinct schedules of administration were evaluated: with or without immunotherapy run-in phase (NCT01055821).

A total of 729 patients were included and randomized in these four studies: 443 in active arms (185 NSCLC, 136 CIN2/3, 122 HCV) and 286 in control arms. In all studies the repeated S/C administration of the MVA vectors alone or in combination therapies appeared feasible and well tolerated, neither dose reduction nor modification of the schedules of administration have been necessary. Injection site reactions have been the most frequent adverse events associated with treatment, mild to moderate in the majority of cases. Despite lower doses they seemed more prevalent for vectors expressing xenoantigens (TG4001 99% pts, TG4040 42% pts) than for TG4010 (31%).

The phase II studies with TG4010 met their primary endpoints based respectively on 6 month progression free survival (PFS) and overall PFS. The primary endpoint of improved complete early viral response (cEVR) was also achieved in the study with TG4040. These studies had in common 1/ to combine the MVA from the beginning of standard of care and 2/ to use a schedule of administration with a run-in phase of 6 or more weekly injections followed by at least monthly injections. The study with TG4001 did not meet its threshold-based primary endpoint of complete response but significantly more women in the experimental arm had a clearance of their cervical lesions at a conization performed 6 months later.

Three MVA-based immunotherapeutics have shown meaningful activity in different clinical settings. Their favorable safety profile allows the combination of these products with standard of care therapies and also with immune checkpoint inhibitors (ongoing).

TG4010.09: Phase 2b Randomized Study in Non-Small Cell Lung Cancer

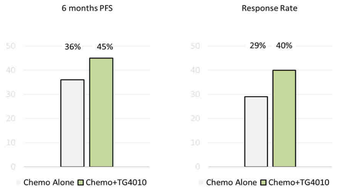
148 NSCLC patients
- Stage IIIB with effusion or IV
- PS 0-1
- Treatment naïve for advanced disease
- MUC1+ tumors by IHC (25% positive cells)

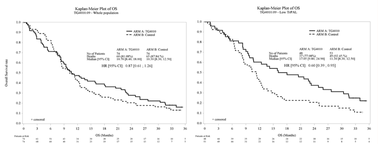
1:1

- TG4010 SC injection ($1.0x10^8$ PFU) weekly for 6 weeks then once every 3 weeks up to progression + Cisplatin + Gemcitabine, Every 3 weeks up to 6 cycles
- Cisplatin + Gemcitabine, Every 3 weeks up to 6 cycles

- Primary objective: improved progression free survival (PFS) at 6 months
- Fleming design, endpoint achieved if PFS at 6 months >40%
- Secondary objectives : response rate, overall survival, Immunology
- Randomization stratified on PS and stage (minimization)

	Chemotherapy N=74	TG4010 + chemotherapy N=74
Age : median (years)	58.5	58.5
Gender: Male	73%	72%
PS = 1	73%	73%
Tumor stage III B « wet » IV	8% 92%	8% 92%
Tumor histology: Adenocarcinoma	70%	61%
Squamous cells	15%	25%
Other	15%	15%





Lancet Oncol. 2011 Nov;12(12):1125-33

- Study TG4010.09 met its primary endpoint based on 6 months PFS
- The biomarker program identified a low pre-treatment level of triple positive activated lymphocytes (TrPAL, CD16+CD56+CD69+) as predictive of efficacy
- 75% of the patients have a low level of TrPAL at baseline

TG4010.14: Randomized Phase 2b Part of the Study "TIME" in NSCLC

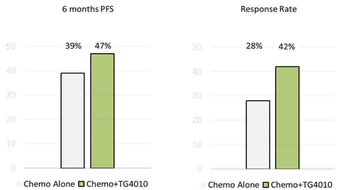
222 NSCLC patients
- Stage IV
- PS 0-1
- Treatment naïve for advanced disease
- MUC1 + tumors by IHC (50% positive cells)
- Albuminemia >30g/l

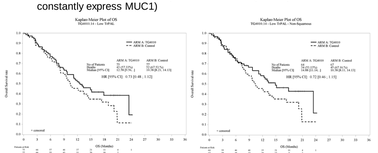
1:1

- TG4010 SC injection ($1.0x10^8$ PFU) weekly for 6 weeks then every 3 weeks up to progression + Cisplatin + Pemetrexed or Cisplatin + Gemcitabine or Carboplatin+ Paclitaxel, Every 3 weeks up to 6 cycles, Bevacizumab and maintenance allowed
- Placebo SC injection weekly f or6 weeks then every 3 weeks up to progression + Cisplatin + Pemetrexed or Cisplatin + Gemcitabine or Carboplatin + Paclitaxel, Every 3 weeks up to 6 cycles, Bevacizumab and maintenance allowed

- Primary objective: improvement in PFS
- Bayesian analysis, efficacy endpoint achieved if P(HR<1 in Normal TrPAL patients)>95%.
- Secondary objectives : response rate, overall survival, safety, immunology,
- Randomization stratified on TrPAL, histology, chemotherapy, bevacizumab and center (minimization)

	Placebo N=111	TG4010 N=111
Gender : Male	63%	65%
Median age (yrs)	59	63
(Former) Smoker	89%	94%
PS=1	68%	69%
Stage IV at diagnosis	98%	91%
Squamous	12%	12%
Adenocarcinoma	81%	86%
Others	7%	3%





- The Bayesian analysis of PFS in patients with a normal level of TrPAL at baseline showed that P(HR<1 in Normal TrPAL patients) is 98.6% meeting the primary endpoint for efficacy in those patients
- Analysis of OS shows that TG4010 is active in patients with low TrPAL (75% of the patients at screening), and especially in patients with both low TrPAL and a non-squamous tumor (non-squamous tumors constantly express MUC1)

NV25025 Randomized Phase 2b in CIN2/3

Roche

206 patients
- CIN2/3
- High-risk HPV based on Roche Linear Array® test
- At least one quadrant involved

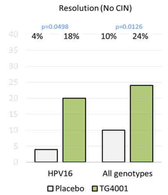
2:1

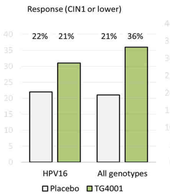
- TG4001 SC ($5x10^7$ pfu), Weekly three times (Day 1, 8 and 15)
- Placebo SC (formulation buffer), Weekly three times

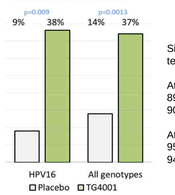
D1 D8 D15 D29 M3 M6 M30

- Primary objective: resolution at the conization performed at 6 months in HPV16 monoinfected patients
- Endpoint achieved if >60% resolutions and at least two times the % in the control arm
- Secondary endpoints : viral clearance, safety, immunology, histologic response in HP16 mono infected, histologic resolution and response in all HPV genotypes
- Randomization stratified on HPV16 single infection only or other HR-HPV single/multiple infections

	Placebo N=70	TG4001 N=136
CIN Grade (after review)		
- CIN2	43%	39%
- CIN3	47%	56%
- <CIN2	9%	4%
- >CIN3	1%	<1%
- Indeterminate	-	<1%
Single Genotype	62%	63%
Multiple Genotypes	38%	37%







Similar viral clearance during long-term follow up in the two groups :

At 12 months :
89% in the TG4001 group
90% in the placebo group

At 30 months patients, Month 30:
95% in the TG4001 group
94% in the placebo group

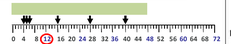
TG4040.02 (HCVac) Randomized Phase 2b in chronic hepatitis C

153 patients
- Chronic hepatitis C
- Non-cirrhotic
- Treatment naïve

2:2:1

- TG4040 SC (10^7 pfu) 13 injections, started first Weekly 6 times then monthly 7 times After 12 weeks PegIFN/Ribavirin for 48 weeks

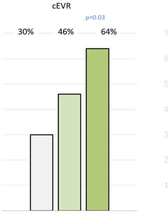
- PegIFN/Ribavirin for 48 weeks started first After 4 weeks TG4040 SC (10^7 pfu) 6 injections Weekly 3 times then every 3 months 4 times

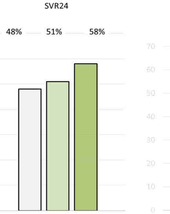


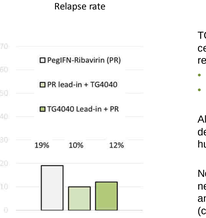
- Control arm PegIFN/ribavirin for 48 weeks

- Primary endpoint : improvement of complete early viral response rate (cEVR) defined as undetectability of HCV RNA after 12 weeks of PegIFN and Ribavirin
- Three outcome one stage design, Endpoint achieved if cEVR >55%
- Secondary endpoints : safety, end-of-treatment response (ETR), sustained viral response (SVR)

	Control N=31	PegIFNα2a/RBV Lead-in N=63	TG4040 Pre-Treatment N=59
Mean Age in years	41	44	43.6
Gender, male	52%	57%	54%
HCV genotype, 1a	19%	19%	25%
1b	81%	79%	75%
1a/b	-	2%	-
IL28B non C-C	76%	69%	66%
F3 Fibrosis (Biopsy or FibroScan®)	3%	9%	12%
ALT ≥ 2 ULN	16.1%	24%	27%







Gastroenterology. 2014 Jul;147(1):119-131

TG4040 induced HCV-specific T-cell ELISpot IFN-gamma responses:
- 46% NS3-specific
- 71% NS3, NS4, NS5B

All TG4040 treated patients developed detectable anti-MVA humoral responses

No significant correlation between neither total nor neutralizing antibodies and virological response (cEVR and/or SVR24)

SAFETY

- Injection site reactions (ISRs) usually of mild or moderate intensity are the most frequent adverse events observed with MVA vectors given sub-cutaneously

	Active Arm	Placebo or Control Arm
TG4010.09	8%	-
TG4010.14	31%	4%
NV25025 (TG4001)	99%	37%
TG4040.02	42%	-

- The frequency and intensity of ISRs appears higher for MVA expressing xenoantigens (TG4001 and TG4040) than for TG4010 which expresses MUC1.
- Depending on the context of the study the frequency of ISRs varies for a same vector (TG4010) or for the same placebo (TG4010.14 and NV25025 studies)
- Fever was reported more frequently in the open label studies (24% vs 8% in TG4010.09 study and 36% vs 23% in TG4040.02 study) however fever was not more frequent in the active arms than with the placebo in the placebo controlled studies (TG4040.14 and NV25025)
- Fatigue did not differ significantly between active and control arms and was more related to the underlying disease (60% vs 51%, 57% vs 56%, 4% vs 1% and 36% vs 23% respectively)
- In studies TG4010.09 and TG4010.14 NSCLC patients received TG4010 with concommitant chemotherapy and the hematogical tolerance of chemotherapy was not significantly altered
- In study TG4040.02 severe peripheral thrombocytopenia was reported in 3 patients (2 in PR lead-in arm, 1 in TG4040 pre-treatment arm). These events were considered by the investigators to be related to both TG4040 and PEG-Ribavirin. All three patients shared the HLA group DRB1*04 know to be associated with a risk of auto-immune thrombopenia.

CONCLUSION

- MVA are attenuated though immunogenic vectors for therapeutic vaccination
- The usual dose per SC injection ranges from 10^7 to 10^8 plaque forming units (pfu)
- At these doses minor to moderate injection site reactions are the most frequent side effects
- Three positive randomized clinical trials, two in non-small cell lung cancer and one in chronic hepatitis C had in common:
  - The administration of the therapeutic vaccine from the beginning of standard of care
  - A weekly schedule of administration for at least 6 weeks followed by injections every 3 to 4 weeks
- The ability of MVA vectors to be easily combined with other therapies and the strong rationale to combine them with immune checkpoint inhibitors calls for clinical trials associating these two classes of drugs.

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