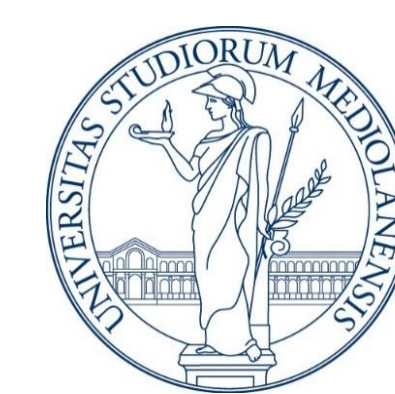


STABILITY OF NIVOLUMAB SOLUTIONS AFTER TRANSPORT THROUGH PNEUMATIC TUBE SYSTEMS



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DI MILANO

Francesca Selmin¹; Laura Camuffo²; Francesca Vasile³; Greta Mangoni²; Mariantonietta Piccoli²; Melania Rivano²; Luca Cancanelli²; Paola Minghetti^{1*}

¹ Dept. Pharmaceutical Sciences, University of Milan, Via G. Colombo 71, Milan (I) ² School in Hospital Pharmacy, University of Milan, Via G. Colombo 71, Milan (I) ³ Dept. Chemistry, University of Milan, Via Golgi 19, Milan (I) - Corresponding Author: paola.minghetti@unimi.it

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PNEUMATIC TUBE SYSTEM in HOSPITALS...

- ... not recommended for active substances that could undergo **physical alterations** [1].
- ... could promote plasticizer nanodroplets **extraction** in saline polyvinyl chloride bags, with activation of the complement system in in-vitro assay [2].
- ... could produce signs of **aggregation** in diluted solution of rituximab in presence of air into the bag, probably due to the air-liquid interface [3].

This work **AIMS** to investigate:

- the stability of diluted solutions of nivolumab after PTS delivery;
- the effect of residual air inside the bag upon storage.



Characterization of compounded mAb

| Quality attributes | Target | Justification | Is it critical? | Methods |
|----------------------|-------------------------|---|-----------------|-------------------|
| Appearance | Limpid | Indicative of formation of visual aggregates | YES | Turbidimetry |
| pH | 5.5-6.0 | The buffer system assure the stability, solubility and tolerability of the mAb. | YES | pHmeter |
| Osmolality | 300 mOsm/kg | Variation in osmolality can induce physical instability and pain at the injection site | YES | Osmolality |
| Aggregation | No aggregates | Low levels of aggregates potentially can cause immunogenicity in patients. | YES | DLS, NTA SEC-HPLC |
| High-order structure | Native folded structure | Higher order structure (HOS) comprises the 3D structure necessary for function. Changes in HOS can affect safety, efficacy and pharmacokinetics | YES | SDS-PAGE NMR, CD |

Stability indicating methods were applied based on results of a forced degradation study consisting of different stress conditions (i.e. high temperature, shear and mechanical stress)

Nivolumab

2.4 mg/mL
in physiologic solution
(bags: 100 mL pre-filled
polyolefin infusion bag)



With residual air



Single pass in
PTS



Without residual air



Two-station,
bidirectional,
SITRAIN
MC2/160 system



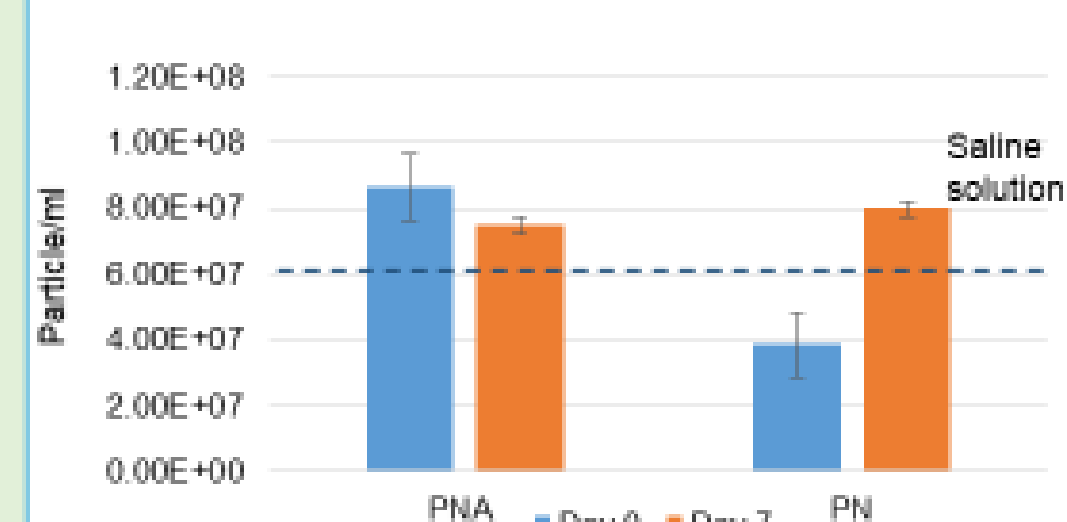
Control sample

Larger aggregates (i.e. > 5 µm) were not observed upon 7 days

Osmolality did not undergo to variation ranging from 283 to 297 mOsm/Kg during storage.

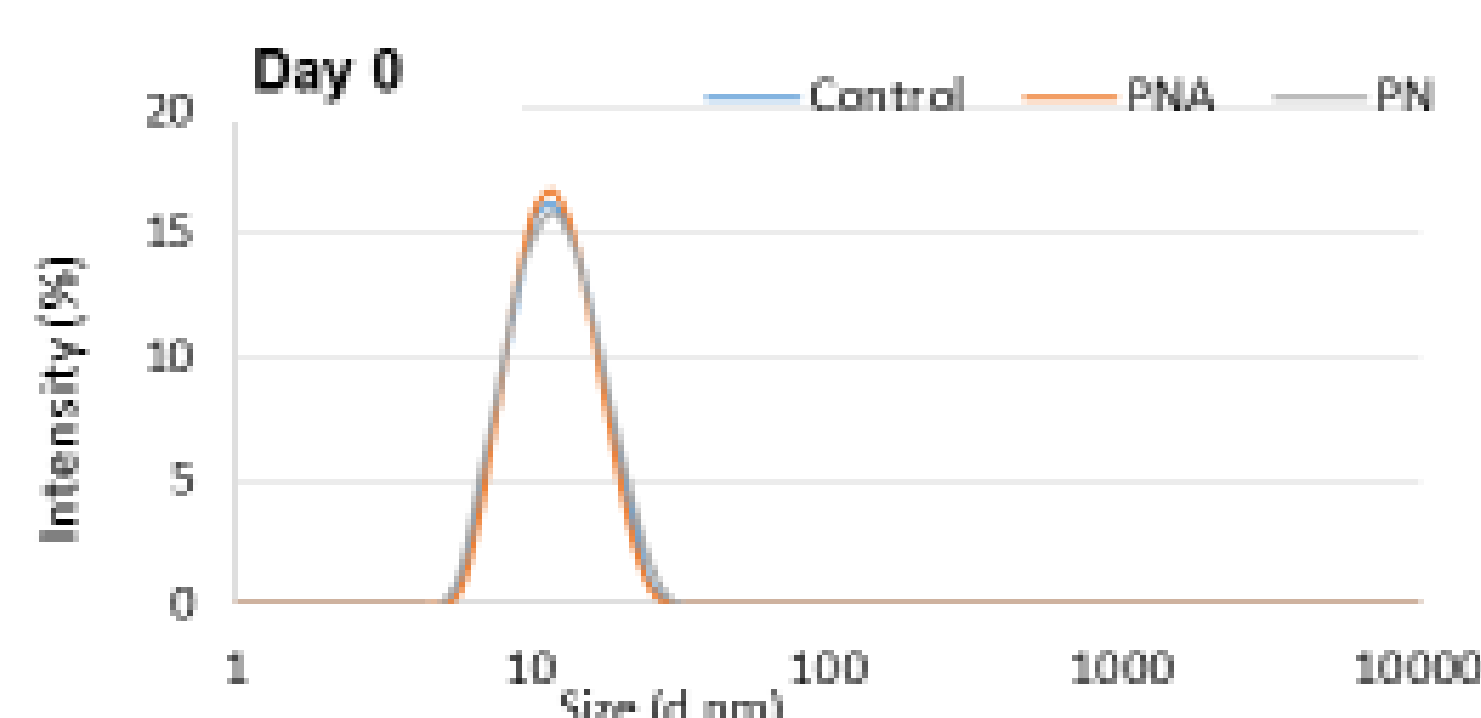
In all solutions **pH** ranged from 5.8-6.0 over time, in agreement to manufacturer's pH range.

Nanoparticle Tracking Analysis (NTA)

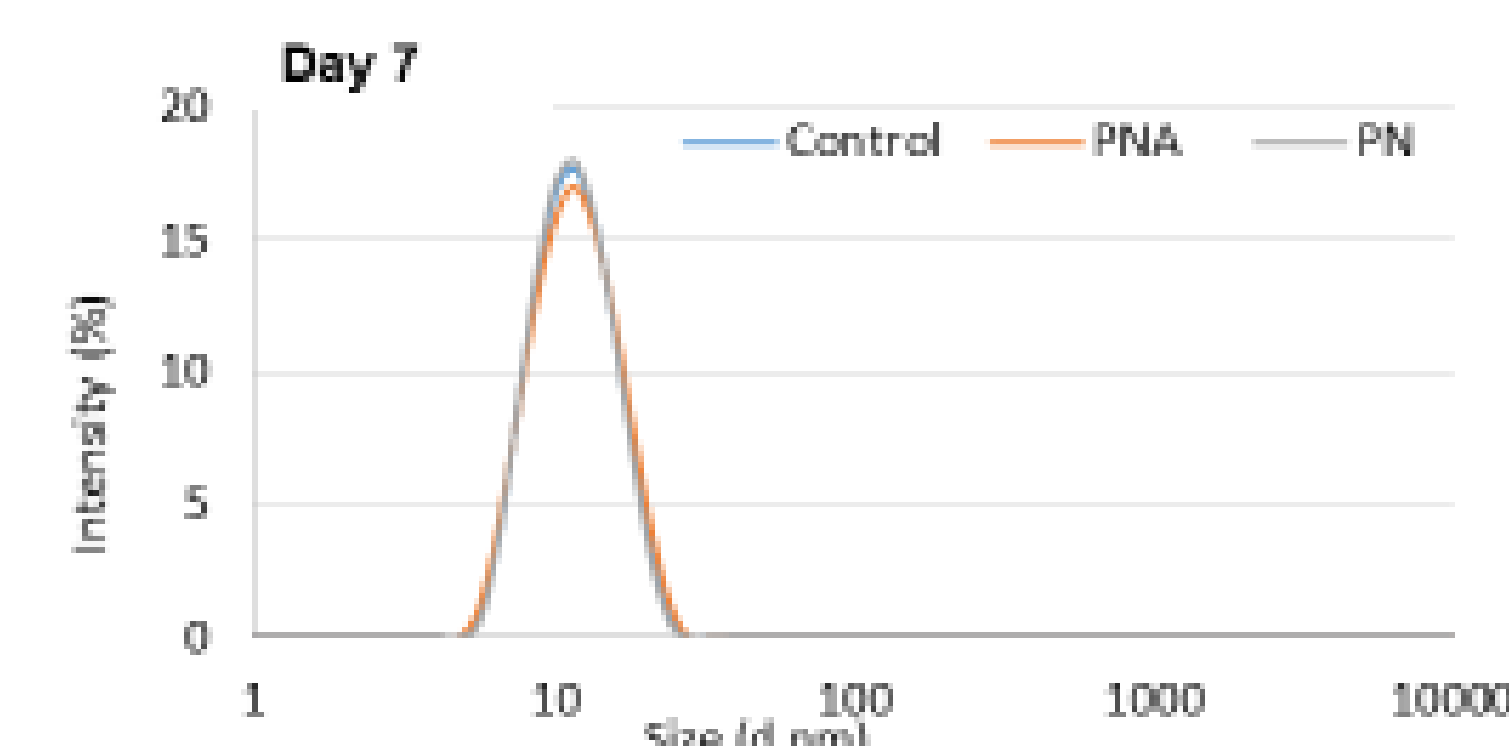


- At day 7 the concentration was in the same range of the 0.9% NaCl.
- The determined size mean value remained stable for "with air" (PNA) and "no air" (PN) samples

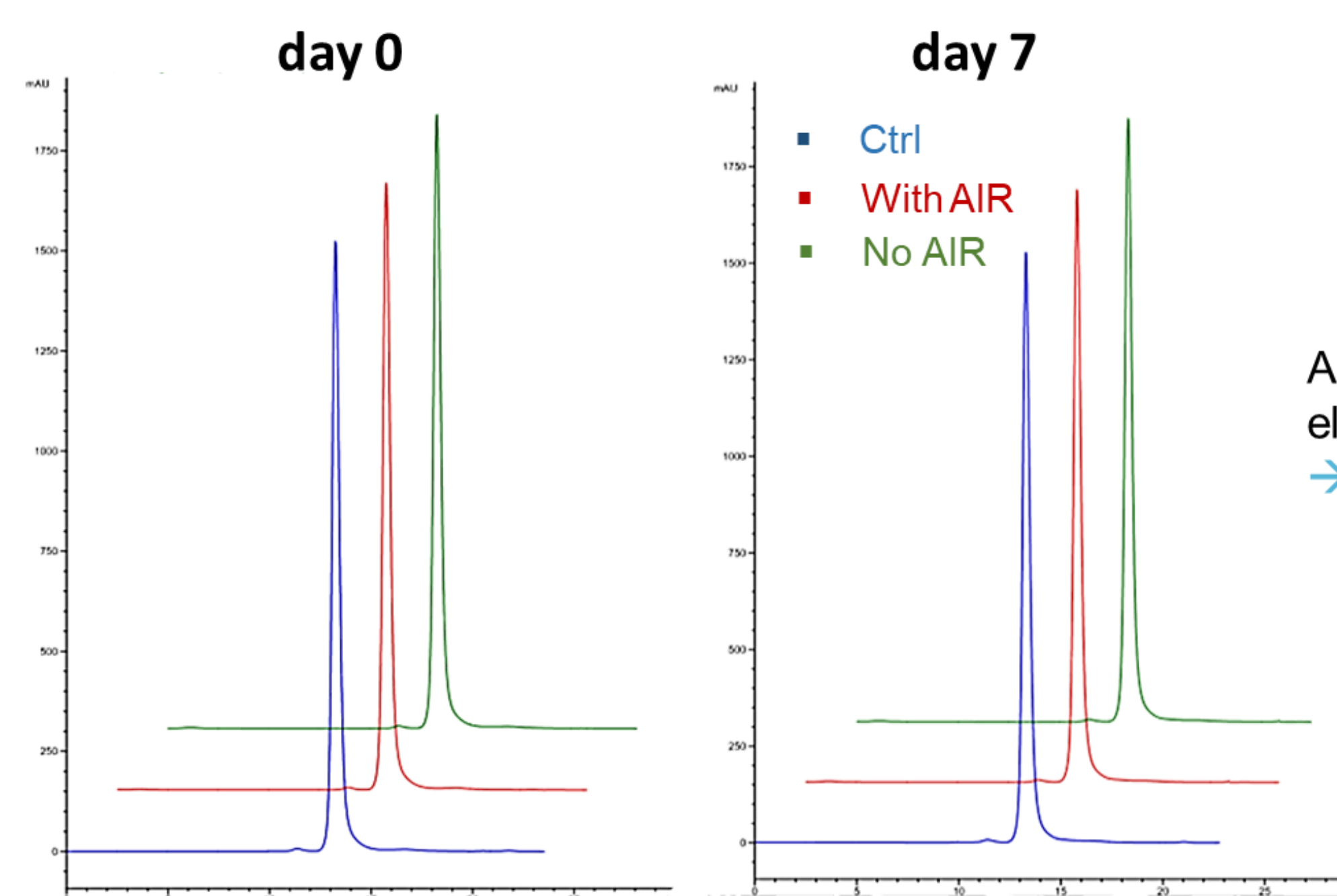
Dynamic Light Scattering (DLS)



→ Absence of submicronic aggregates after 7 days (monodisperse peak 12 nm)



Size exclusion chromatography (SEC)

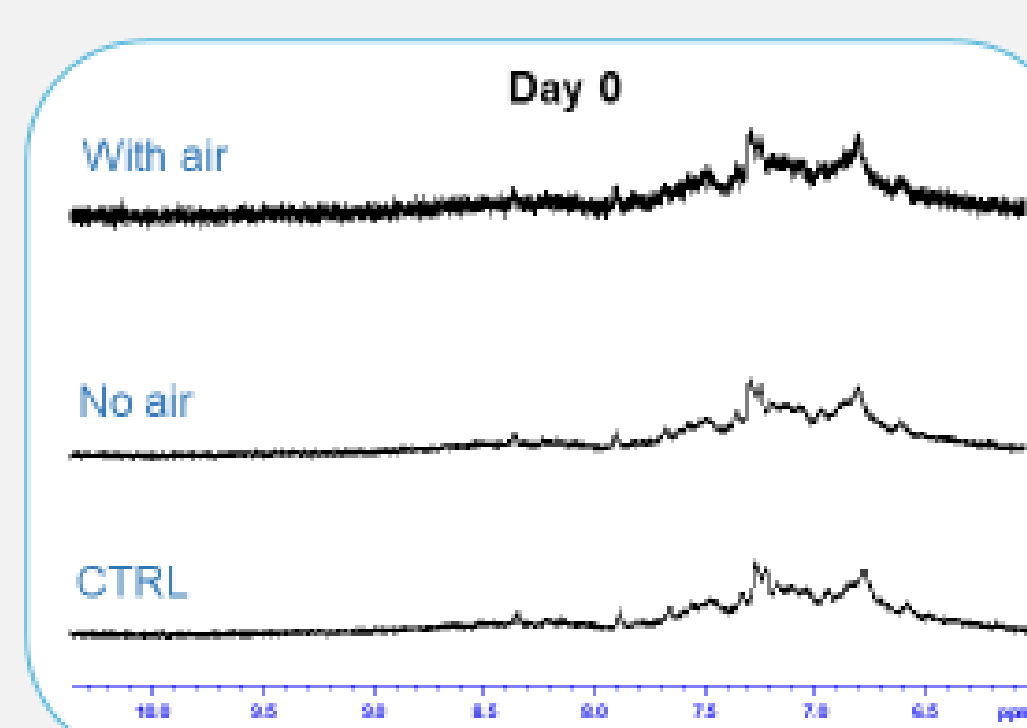


In all chromatograms:
Rt= 13 min the main peak
Rt= 11 min minor signal

All samples presented the identical elution profile as the Ctrl
→ Absence of aggregation after PTS

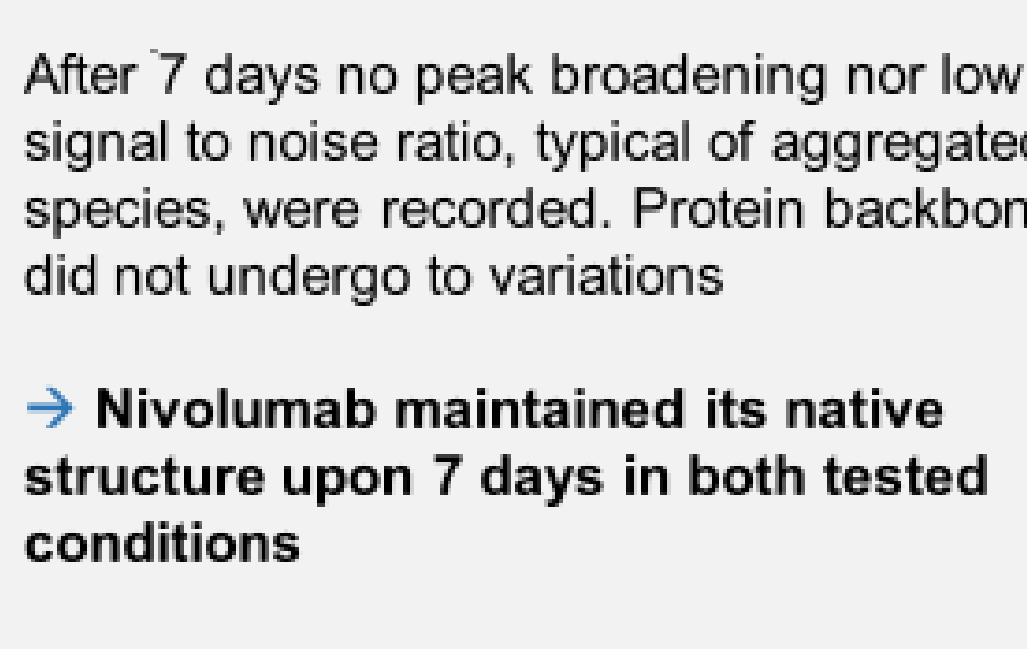
No new peaks were observed upon 7 days.
→ Absence of aggregates or fragments during storage

NMR spectra



Peaks did not collapse toward chemical shifts associated to random coils (7-7.5 ppm)

→ The native conformation of nivolumab conserved after PTS in both conditions



After 7 days no peak broadening nor low signal to noise ratio, typical of aggregated species, were recorded. Protein backbone did not undergo to variations

→ Nivolumab maintained its native structure upon 7 days in both tested conditions

CONCLUSIONS

- No differences in the main physical and chemical properties were observed in compounded nivolumab solutions after a single pass in PTS for at least 7 days of storage.
- The presence of air-liquid interface inside the bag was not risk determining for protein stability.
- These results support the possible use of PTS to deliver bags to clinical services.

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