



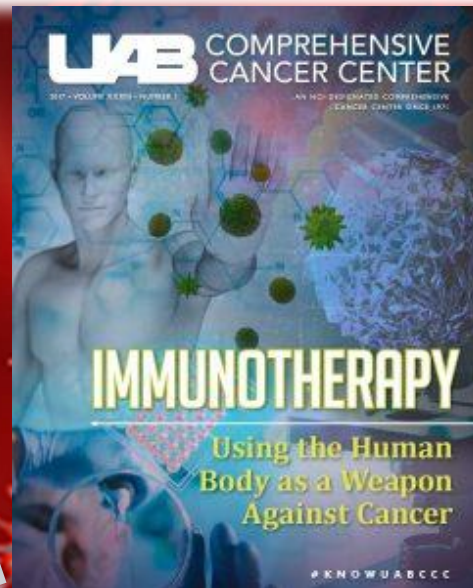
Off the shelf DCs for cancer immunotherapy

Sandra van Wetering

December 15, 2017

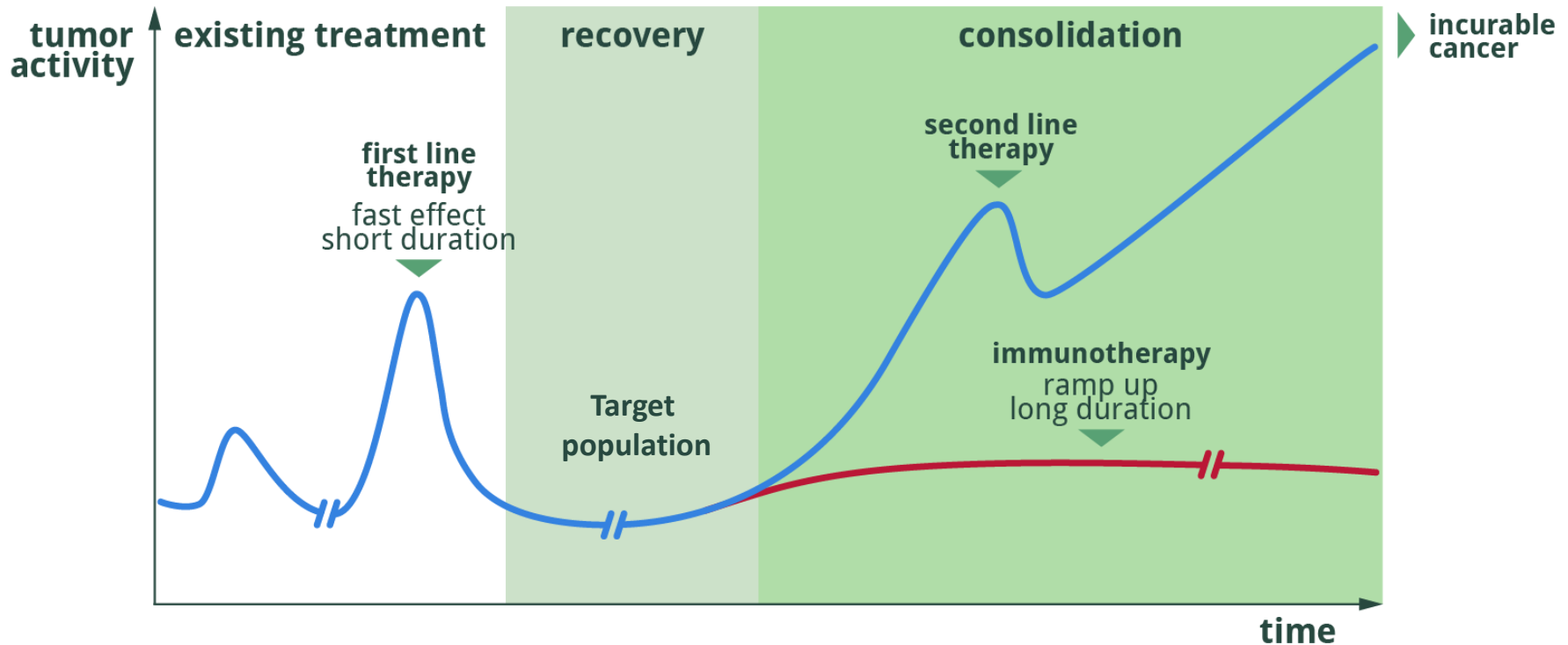


Immune therapy: Future for cancer treatment

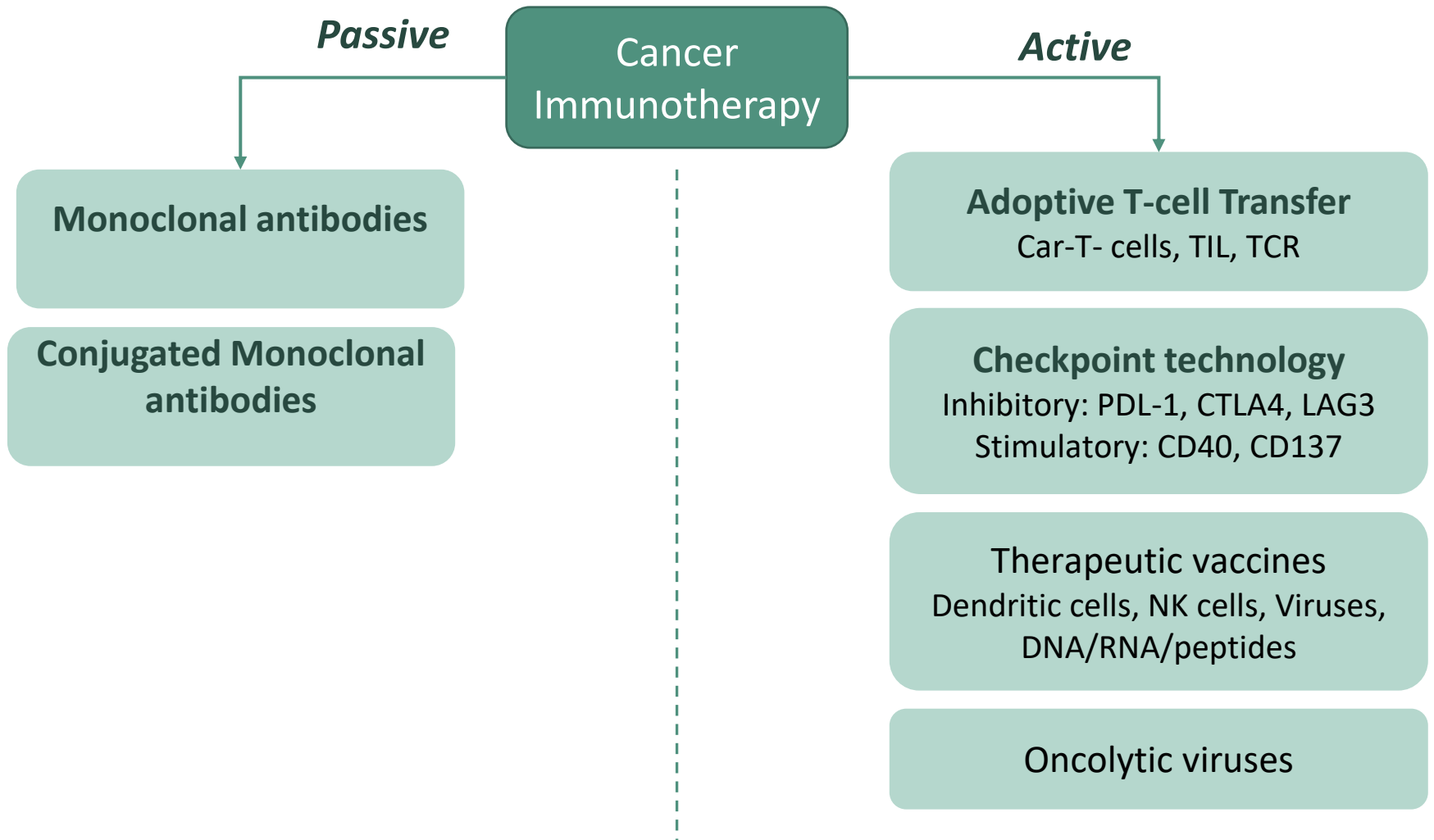


Vaccines for post-remission treatment

Prolong consolidation by targeting different pathways

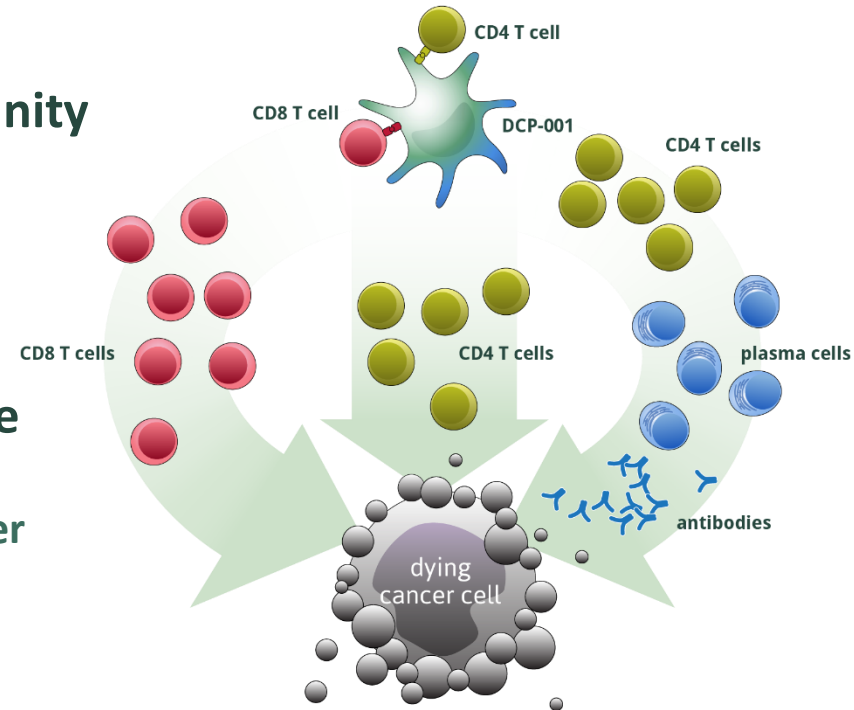


Immunotherapy: approaches & Combinations



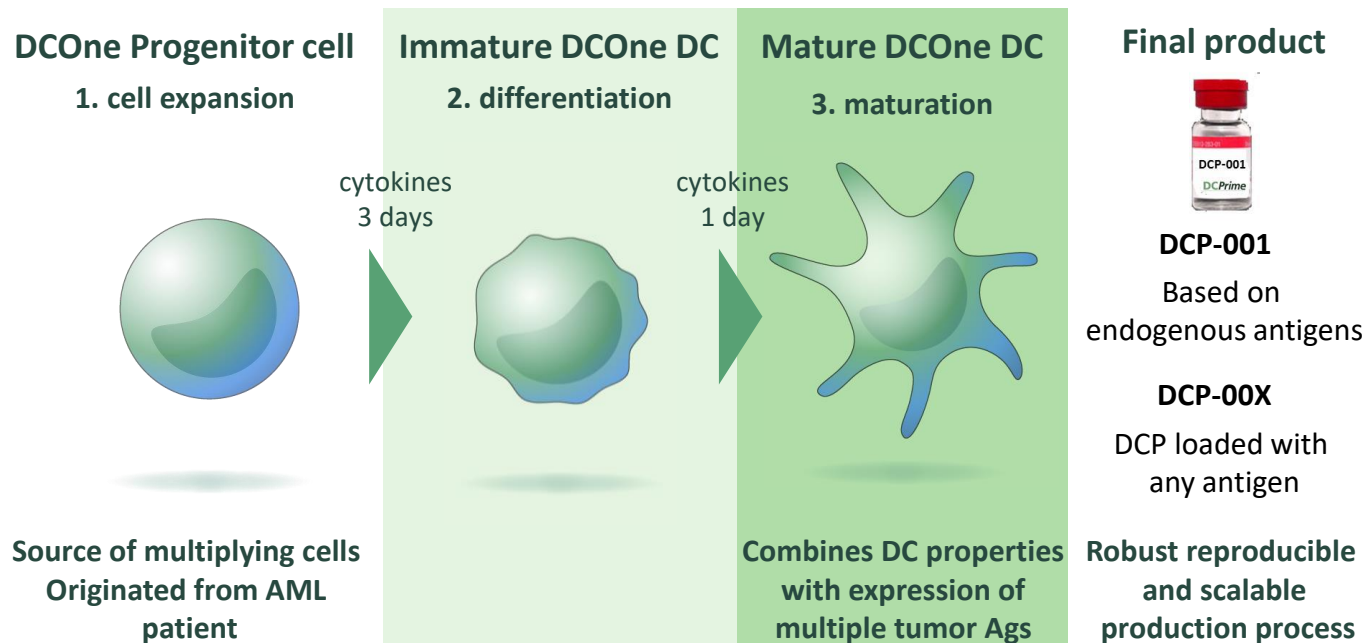
DC therapy rationale

- **DCs have a pivotal role in adaptive immunity**
 - Presentation of antigens
 - Co stimulation of T cell response
 - Induction of pro-inflammatory cytokines
- **T cells are a major contributor to immune surveillance of malignancies**
 - Hampered cellular immunity leads to cancer
 - Tumors develop T cell inhibitory pathways
- **DCs provide multiple inroads to cancer immunotherapy**
 - Overcoming tumor ignorance
 - (Re)directing cellular immunity towards relevant antigens
 - Providing co stimulation to boost T cell immunity
 - Prevent/overcome T cell exhaustion

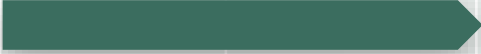


An unique allogeneic off-the-shelf Dendritic cell platform based on DCOne cell line

- DCPrime is developing dendritic cell based cancer vaccines based on the proprietary DCOne cell line, generated from a patient with AML
- DCOne cell line is a precursor cell for dendritic cells, and offers the unique opportunity to generate *'Allogeneic off the shelf'* dendritic cell vaccines



DCPrime product pipeline

Indication	Product	Research	Preclinical	Phase I/IIa	Phase II
AML	DCP-001				
MM	DCP-001				
Solid cancers	DCP-00x				

- **Lead program in AML based on DCOne expressing endogenous antigens (DCP-001)**
 - Patients in CR with MRD, not eligible for HSCT
 - Phase I/IIa successfully completed
 - PhII trial to start in 2018Q1
 - Orphan Medicinal Product (OMP) in the EU (EU/3/12/969)
- **MM program with DCP-001 based on immunogenic overlap**
 - Combination therapy with lenalidomide in post HSCT patients with controlled tumour burden
 - PhI/IIa to start in 2018Q2
- **Solid tumour programs based on immunogenic overlap and introduction of novel antigens**

Phase I/IIa safety and feasibility study DCP-001 in AML

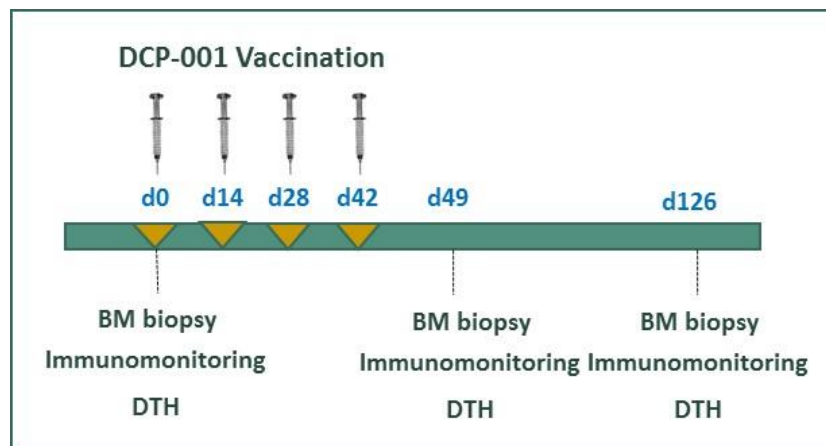
Dose-escalating setting in standard 3 + 3 design

12 AML patients
Mean (SD) 68 (5)
Not Eligible for any standard
AML therapy

Cohort 1
10 million
cells/vaccination
N=3

Cohort 2
25 million
cells/vaccination
N=3

Cohort 3
50 million
cells/vaccination
N=6



Endpoints

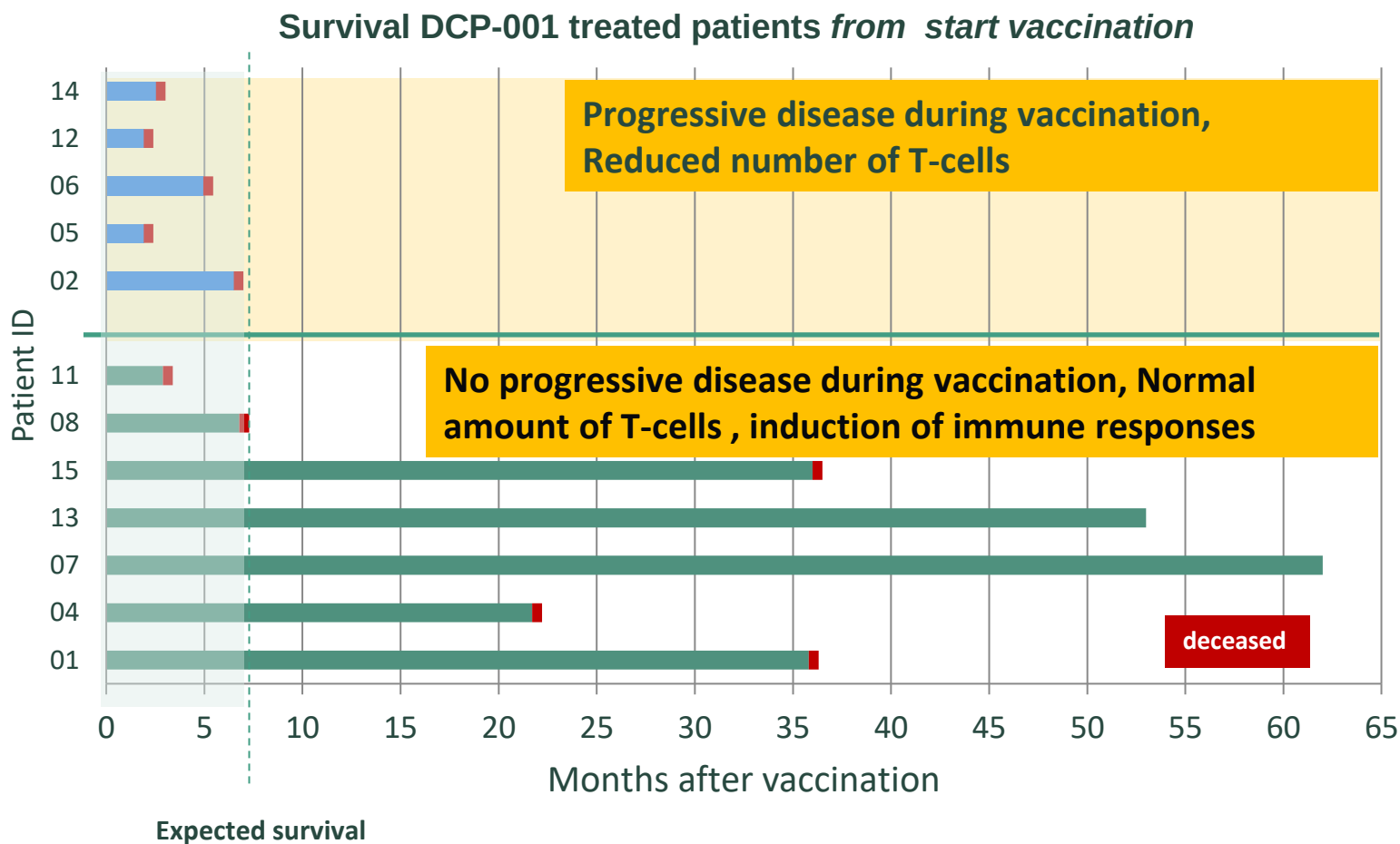
Primary

- Safety & feasibility

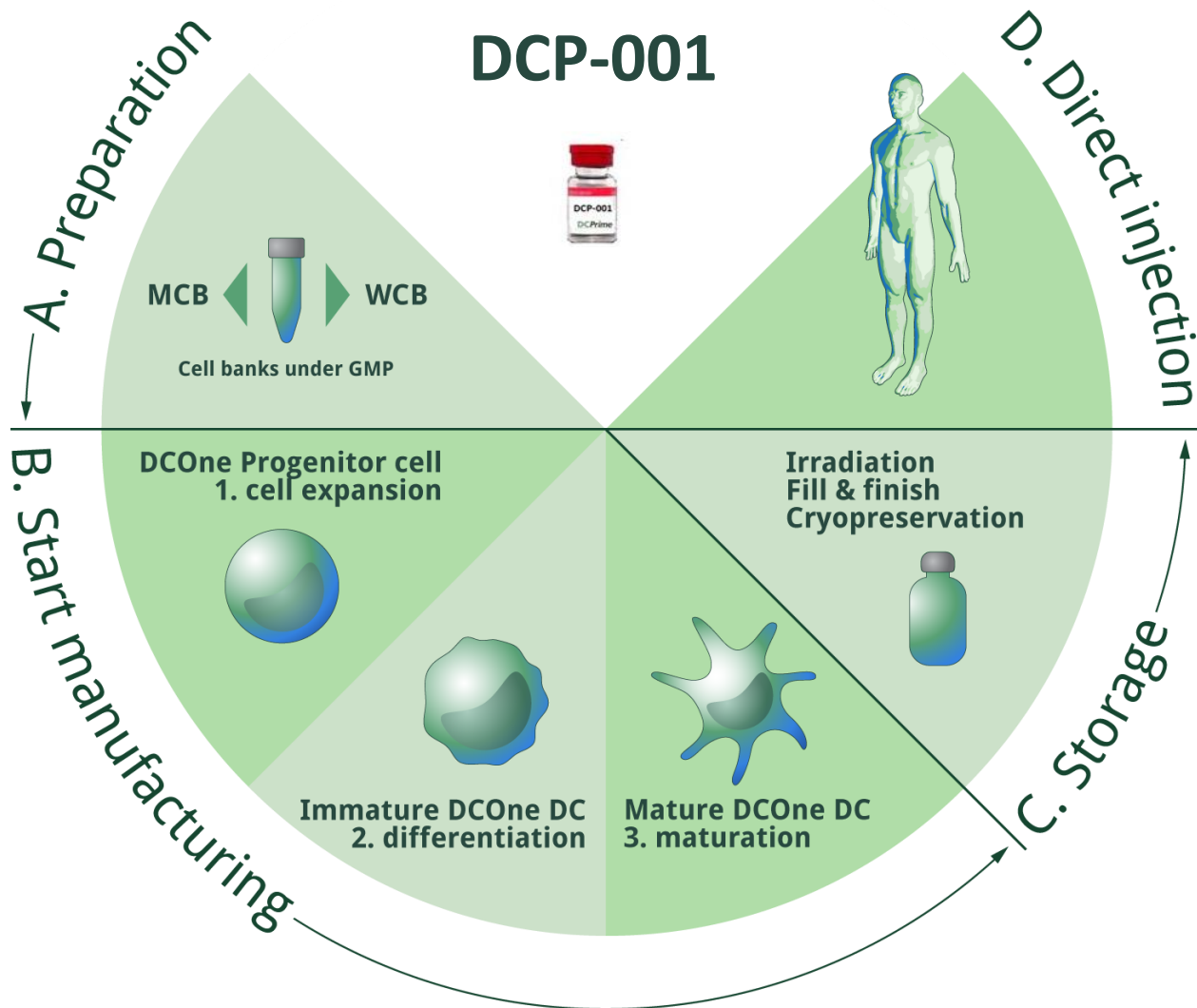
Secondary

- Clinical & immunological responses

DCP-001 Vaccination in late stage AML patients not eligible for any SoC treatment



Production flow DCP-001

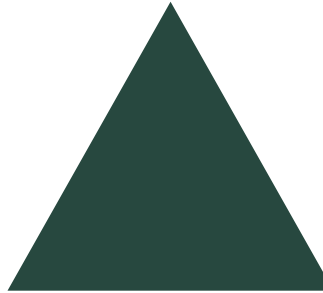


Manufacturing Process Clinical phase I trial

Development of small scale culture process in Cell Stack Culture chambers

Advantages

- Conventional culture method
- Compatibility culture flasks with DCs is well known
- *Opportunity to identify critical process and product parameters*
- Relative fast manufacturing process suitable for clinical batch production at early stage

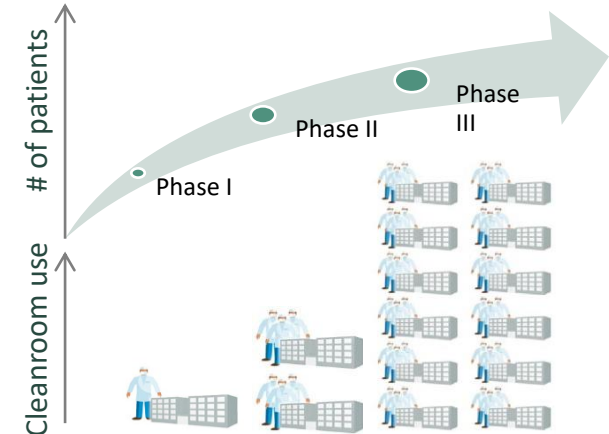


Disadvantages

- Large no of open handlings
- High risk of infection
- Highly trained people required
- Not suitable for upscaling

Future Clinical supply Requirements

Example	No of patients	Total clinical batches needed	No of production runs	Time (mo)
Phase I	12	60	3	9
Phase II	60	280	15	45
Phase III	120	560	30	



- Need for a culture system suitable for large scale production
- Acceptable Costs of Goods

Investment in developing a scalable manufacturing process

Phase I/IIa



Open system - Manual

Large scale expansion
/differentiation

Media prep, Seeding,
Feeding

Manual Harvesting
Centrifugation

Fill & Finish

Phase II



Phase III and beyond



Closed system - Automatic

Large scale expansion /differentiation in
closed systems

Media bags, seeding and feeding via
tubings

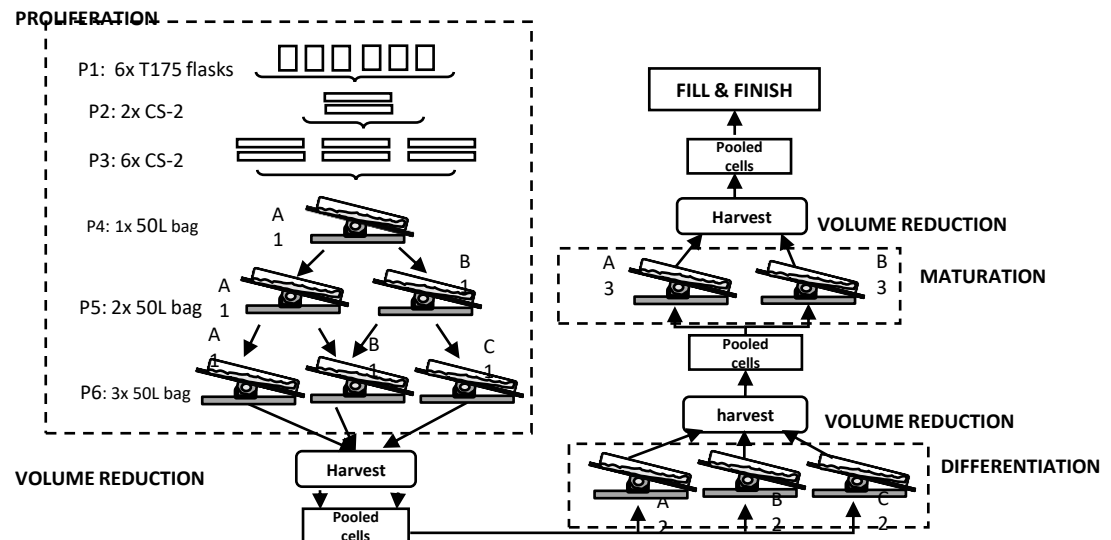
Automated harvest procedure

Automated Fill and Finish procedure

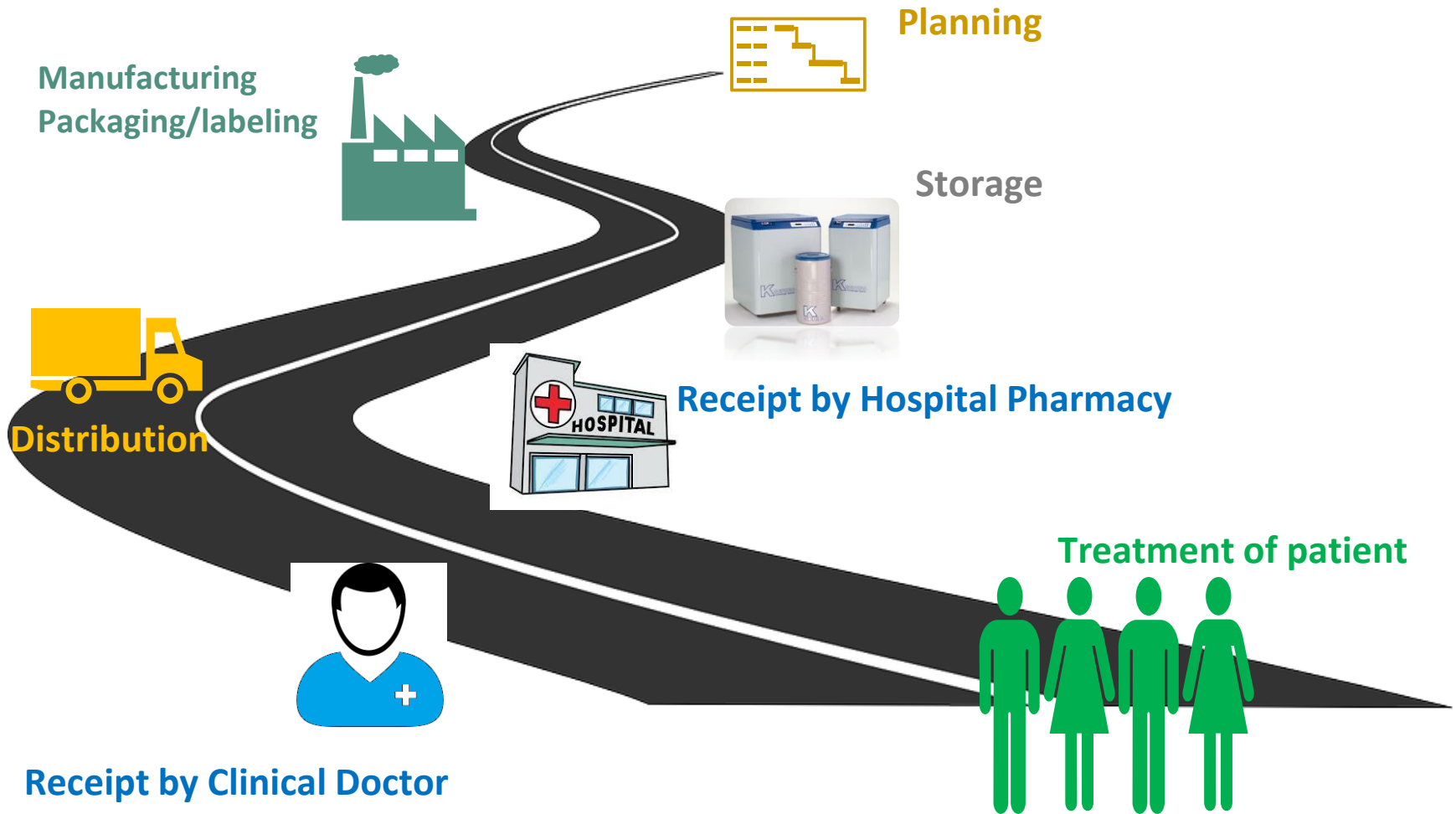


Bioreactor system for large scale cultures

- Upscaling and outscaling process -> 5 Liter scale to 25 L scale/system
- Outscale to 3 wave systems (75 L, ~450 dosages)
- Currently, the largest DC based manufacturing system
- Per run, supply for 45 patients



Clinical supply chain management

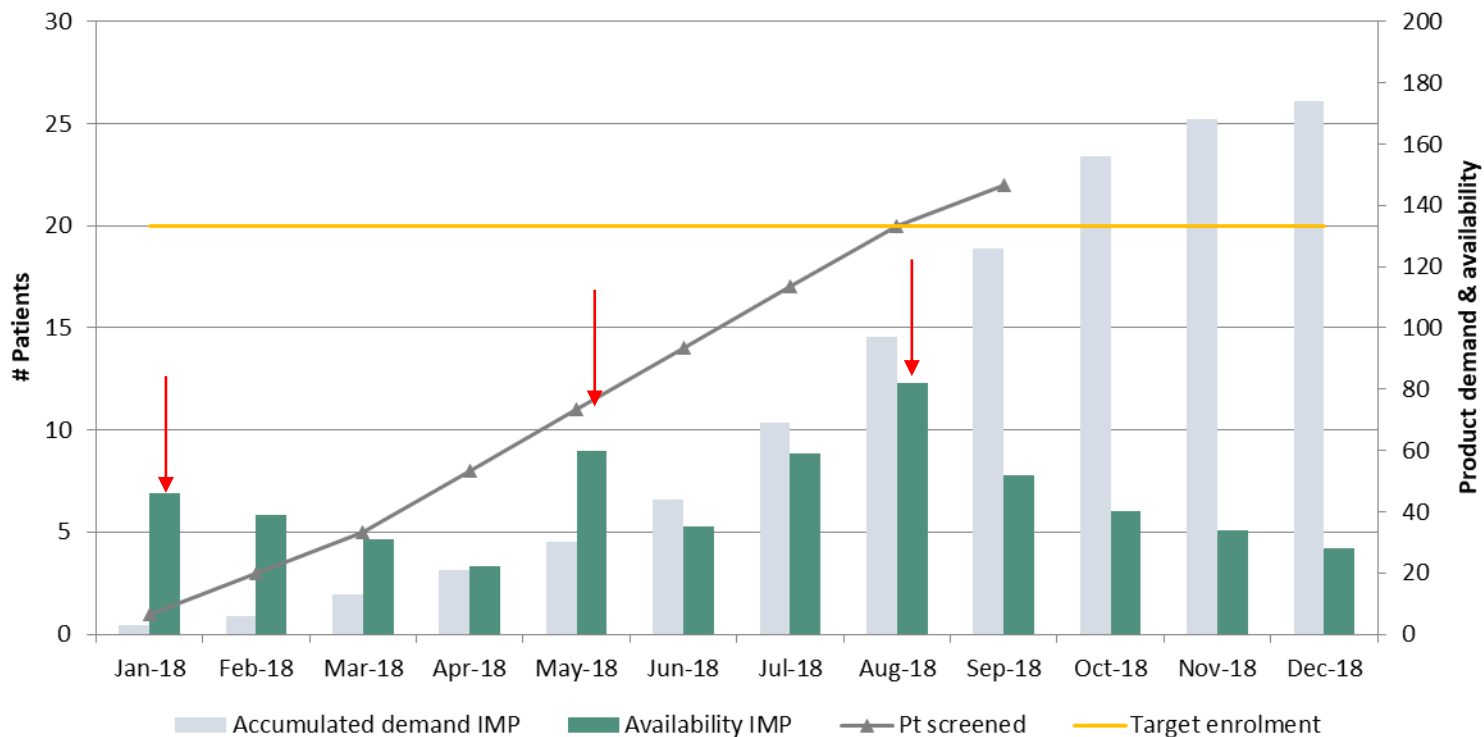


Planning

- Determined by production capacity
- Clinical trial product demand
- Enrollment rate
- Shelf life/stability product

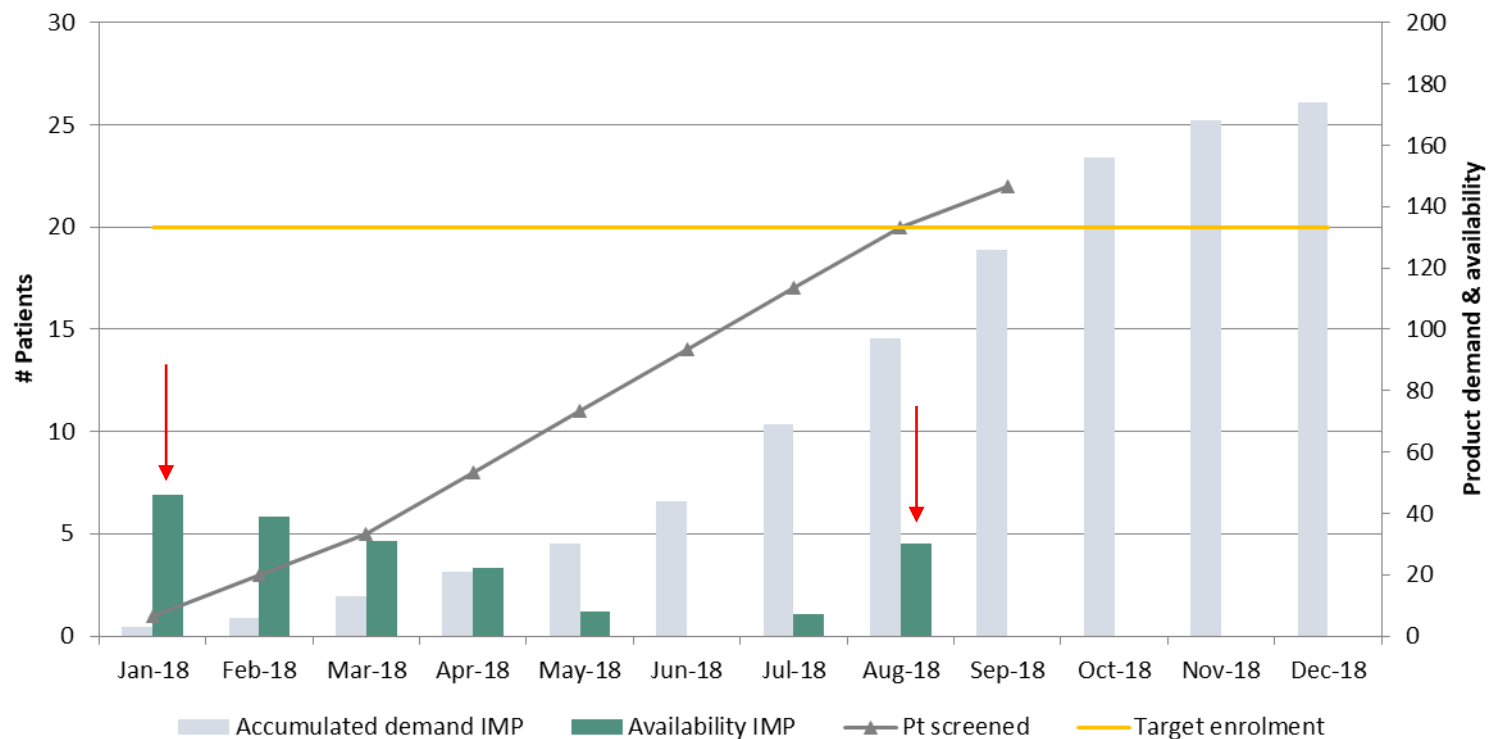
Product demand

- 2 treatment dosages: after first dose demand increases
- Treatment time per patient: 5 mo
- Per production run: 60 dosages available



Product demand

- Poor planning or risk management may lead to clinical hold
- Efficient contingency planning is a must



Manufacturing

- Mostly one production site in early clinical development (Phase I/II)
- Mostly outsourced to specified CMO
- Planning is essential due to availability of slots
- Requires start production planning 1-2 years prior to start clinical study.
 - At that time clinical plans, enrollment and number of patients are often unclear.
 - Plan for success, the highest known dosages and implement contingency planning.
- Cell therapeutic products have a limited shelf life (1 - 24 mnd)
 - Producing and building up large storage is not an option

Labeling, packaging and Storage

- Cell therapeutic products are stored in gas phase N2 containers
- Controlled storage most often at CMO but storage time is mostly short
- Labeling part of the manufacturing process.
 - Post thawing labeling is not an option
- Packing is performed as soon as request for IMP is obtained
- Request for IMP is done by sponsor/CRO

Transport to clinical sites

- Currently transport is done by courier service specialized in cold chain management
- Transport is done using LN2 dry ship containers
- Transport includes temp log and GPS
- Transport is on a on-call basis performed by sponsor/CRO

Receipt by clinical trial

- Hospital pharmacies does not have N2 storage capacity
- Short local storage using N2 dry shippers max 2 days prior to patient treatment
- Administration
- Request from clinical site for product release
- Release to clinical site

Patient treatment

- Specified oncology centre's
- Trained oncologists and research nurses
- Training product handling/thawing
- Most products need to be administered 1 hour post thawing

Start to end supply chain

